Received: 16 July 2021 | Revised: 15 September 2021 | Accepted: 7 October 2021

DOI: 10.1002/jhet.4383

ARTICLE

JOURNAL OF HETEROCYCLIC CHEMISTRY WILEY

Effective synthesis of new benzo-fused macrocyclic and thiamacrocyclic dilactams and related pyrazolo-fused macrocycles

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Abstract

In the current study, we examined the synthetic potential of new bis(aldehydes), linked to aliphatic spacers via phenoxy linkage, as versatile building blocks for the synthesis of new macrocyclic dilactams. The target macrocycles were prepared, in 65%–72% yields, by the cyclocondensation of *N*,*N*′-(alkane-1,ω-diyl)bis (2-cyanoacetamide) with the appropriate bis(aldehydes) in dioxane in the presence of few drops of piperidine at reflux for 4 h. Using the precursors for bis (2-cyanoacetamide), linked to aliphatic cores via thioethers, a new series of thiamacrocyclic dilactams were prepared, in 60%–66% yields, under the previous reaction conditions and at reflux for 5 h. Next, we examined the synthetic potential of the new dilactams derivatives as key synthons for the preparation of new dipyrazolo-fused macrocycles. After treating the appropriate dilactams with hydrazine hydrate in DMF at reflux for 6 h, the previous macrocycles were prepared in 50%–57% yields.

1 | INTRODUCTION

Over the last few years, there has been a lot of interest in the synthesis and study of macrocyclic derivatives [1]. They are an interesting chemical category for targeting difficult targets such as interactions of protein–protein, protein–nucleic acid, and transcription factors [2,3]. Macrocycles have been defined to contain one or more rings of at least 12 atoms, which results in the preorganization and a semi-rigid character of this chemical class [3–5]. They can contain a variety of donor atoms such as oxygen, nitrogen, sulfur, and others, and thus they play a key role in the metal ions complexation, as well as selective ion separation and detection [6–10].

Macrocycles combine the therapeutic benefits of small molecules as well as larger biomolecules with their lack of immunogenicity as well as high potency, selectivity, and reasonably low manufacturing costs [11–13]. Macrocycles have the ability to reduce the amount of entropy lost when the target binding conformation is adopted [11,14]. Because of their effective interactions at large-shallow surfaces, they were shown to be able to interact more efficiently with challenging target classes [15]. It was found that disk- and sphere-like macrocycles are better binders of flat binding sites, whereas rod-like macrocycles prefer groove-shaped binding sites [15].

Furthermore, macrocycles have the ability to mimic some of the structural properties of protein interfaces, so the physicochemical and pharmacokinetic properties of macrocyclic scaffolds are better than expected [16–21]. This demonstrates the versatility of macrocycles as potential drugs. About a hundred drugs and clinical candidates comprising macrocyclic units are currently commercially marketed or in drug discovery projects [22–25]. In the past few decades, many biologically active natural product macrocycles have been discovered, including vancomycin, romidepsin, sirolimus, and amphotericin B [26]. Despite the fact that macrocyclic scaffolds with a typical molecular weight greater than 500 Da may violate the "Lipinski's rule of five" [27], several orally available macrocyclic drugs

have been approved, including cyclosporin A, desmopressin, alisporivir, and linaclotide [15].

Because macrocyclic lactams have important biological applications, including antitumor activity [28], and promising Hsp90 inhibitory activity [29], as well as antimicrobial activity [30], several publications have been dedicated to their synthesis [31–34]. It was previously reported that dibenzo-fused macrocyclic dilactams were synthesized through the base-mediated reaction of bis(phenols) with dihalo-derivatives [35,36]. They could also be obtained by the amidation of diacid derivatives with diamines [37,38]. Additionally, they could also be synthesized by the Grubbs catalyzed-ring closure metathesis of bis(2-(allyloxy)benzamides) [39].

In connection with our efforts to design facile synthetic routes for the preparation of bis-linked and macrocyclic hybrids [40–51], we report herein effective procedures for the synthesis of new dibenzo-fused macrocyclic and tetrabenzo-fused thiamacrocyclic dilactams and related dipyrazolo-fused macrocycles (see Figure 1).

2 | RESULTS AND DISCUSSION

To begin our study, bis(aldehydes) **5**, linked to aliphatic spacers via phenoxy linkage, were prepared and taken as versatile building blocks for the synthesis of the target macrocycles. Therefore, one equivalent of each of benzenethiol derivatives **1a,b**, 5-(chloromethyl)-2-hydroxybenzaldehyde **2** [52] and potassium hydroxide were allowed to react in ethanol at reflux for 3 h to afford the corresponding salicylaldehyde derivatives **3a,b** in 88%–91% yields [53,54]. Next, the bis-alkylation of the previous salicylaldehydes afforded the precursors **5**. Thus, two equivalents of **3a,b** were reacted with one equivalent of the appropriate 1,ω-dibromoalkanes **4** in *N*,*N*-dimethylformamide (DMF) in the presence of anhydrous potassium carbonate. The prior mixture was stirred at room temperature (rt) for 8 h to afford the corresponding bis(aldehydes) **5** in 84%–87% yields (see Scheme 1 and Experimental section) [54].

Three different strategies were developed for the synthesis of the target macrocyclic dilactams **1**. In the first strategy, one equivalent of bis(aldehyde) **5a** condensed with two equivalents of ethyl cyanoacetate **6** in dioxane containing a catalytic amount of piperidine at reflux for 2 h to afford the corresponding bis(2-cyanoacrylate) **7** in 85% yield (see Experimental section) [55]. After that, the bis(2-cyanoacrylate) **7** should be cyclocondensed with the appropriate diamines **8** to give the target macrocyclic dilactams **9**. Unfortunately, our trials to prepare the target macrocycles **9** by the amidation of the diester **7** were failed. Instead, the reaction afforded a mixture of products that were difficult to separate and have yet to be characterized (Scheme 2).

In search of an effective strategy to prepare the target macrocyclic dilactams **9**, we focused on the precursors *N*,*N*′-(alkane-1,ω-diyl)bis(2-cyanoacetamide) **10**. The previous derivatives **10** were prepared by the reaction of ethyl cyanoacetate **6** with the appropriate diamines **8** [56]. Next, bis(2-cyanoacetamide) **10a,b** cyclocondensed

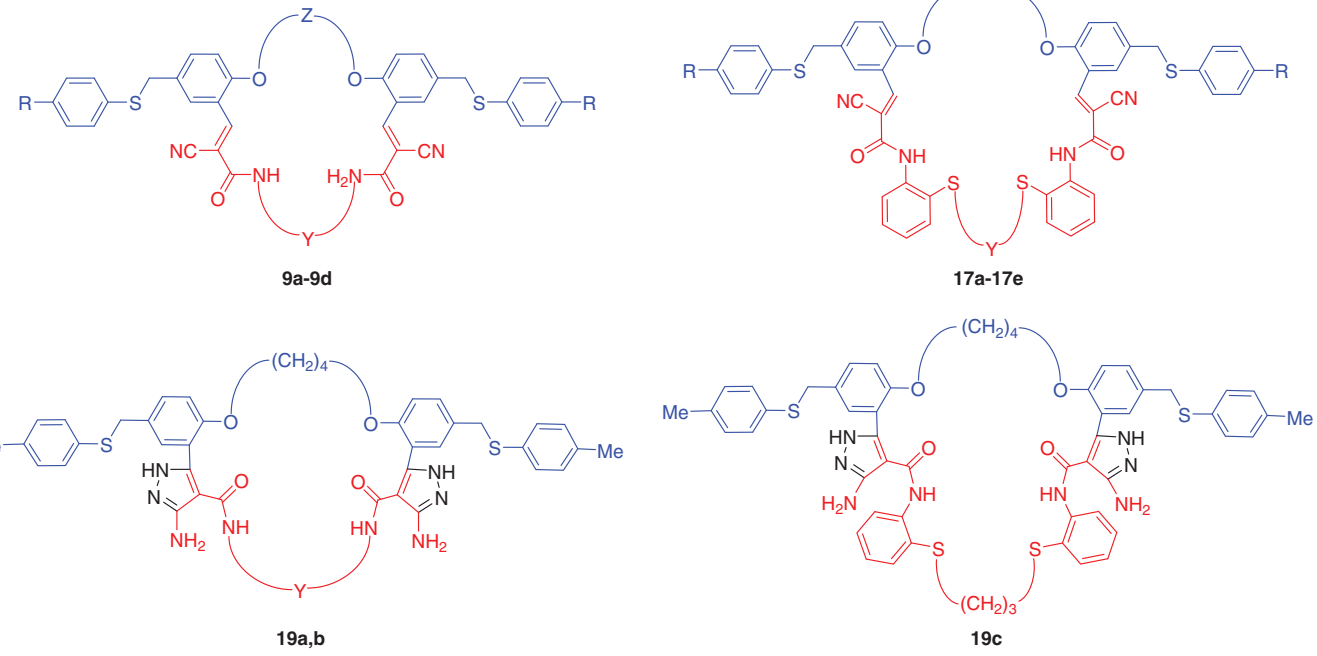
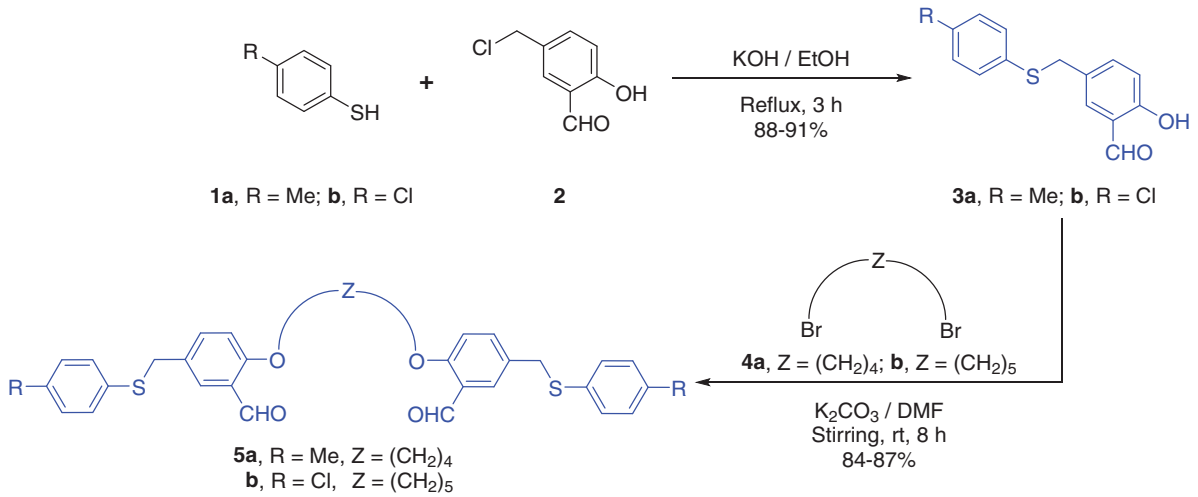
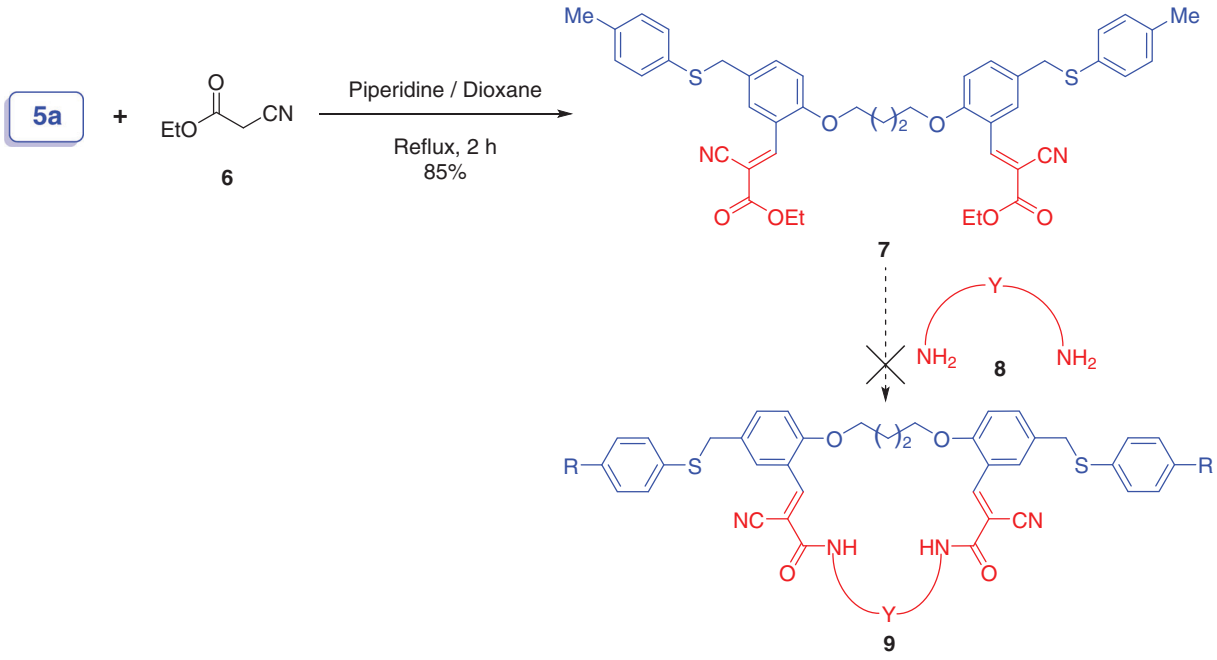


FIGURE 1 Structure of the target macrocycles **9**, **17**, and **19**



SCHEME 1 Synthesis of bis(aldehydes) **5**, linked to aliphatic spacers via phenoxy linkage

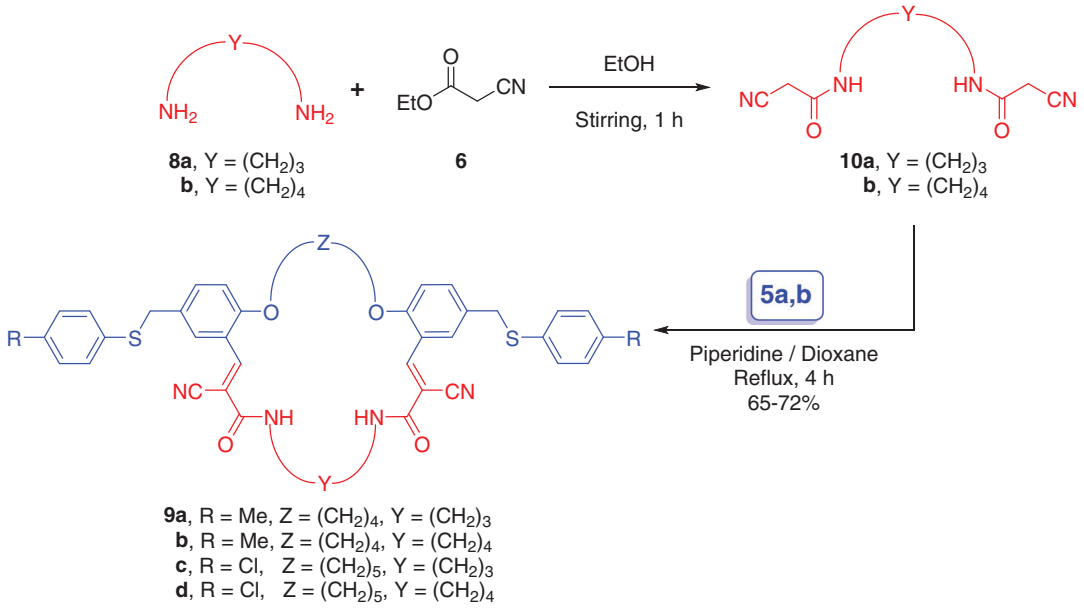


SCHEME 2 The first strategy to prepare the target macrocyclic dilactams **9**

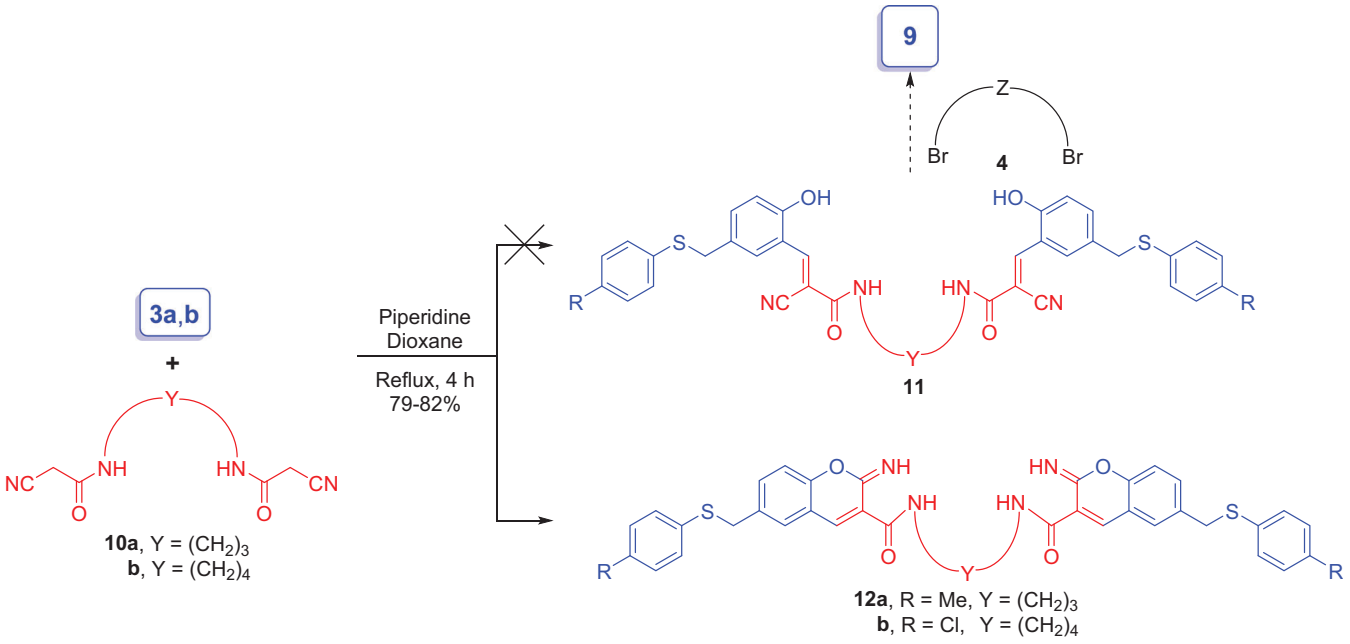
with the appropriate bis(aldehydes) **5a,b** in dioxane in the presence of few drops of piperidine at reflux for 4 h to afford the desired macrocycles **9a–9d** in 65%–72% yields (Scheme 3) [51]. The ^{1}H-NMR spectrum of **9c**, as a typical example, revealed five broad singlet signals at δ 1.61, 1.73, 1.82, 3.29, and 4.04 owing to the protons of five sets of methylene groups at propane and pentane spacers. Furthermore, it showed three singlet signals at δ 4.22, 8.27, and 8.43 corresponding to SCH_2, NH, and methine-H protons, respectively. In addition, it revealed the presence of signals corresponding to 14 aromatic protons at δ 6.78–7.36. Its ^{13}C-NMR exhibited five signals at δ 21.9, 26.8, 28.0, 35.1, and 67.9 owing to five sets of methylene carbons at propane and pentane linkers. Also, it showed five signals at δ 35.3, 105.9, 116.6, 145.3, and 161.7 ppm, respectively, corresponding to SCH_2, *C*-CN, CN, methine-C, and CO carbons. Additionally, it revealed 10 signals ranging between δ 114.6 and 158.2 corresponding to aromatic carbons (see Experimental section). Regarding the configuration of macrocyclic dilactams **9a–9d**, it is noteworthy to mention that the presence of methine-H group at δ 8.39–8.47 indicated that both methine-H and cyano groups were in *trans* position to each other [57].

Furthermore, we examined the synthesis of macrocyclic dilactams **9** by an alternative strategy. This pathway

involved the reaction of bis(2-cyanoacetamide) **10** with salicylaldehyde derivatives **3** to give the corresponding bis(3-(2-hydroxyphenyl)acrylonitrile) **11**. Subsequent base-mediated bis-alkylation of the previous bis(phenols) with the appropriate dihaloalkanes **4** should afford the desired macrocycles **9**. Unfortunately, we were unable to isolate pure samples of **11** after treating **10** with **3** in DMF in the presence of piperidine at reflux for 4 h. Instead, the bis(2-imino-2*H*-chromene-3-carboxamides) **12a** and **12b** were obtained (see Scheme 4 and Experimental section) [58]. The reaction may proceed by an initial condensation of the aldehyde functions in two molecules of **3** with the two methylene groups in **10** to give bis(3-(2-hydroxyphenyl)acrylonitrile) **11**, followed by subsequent nucleophilic attack of the hydroxy groups on the neighboring nitrile functions to produce **12a** and **12b**. The absence of any nitrile functions from the IR spectra of **12a** and **12b** confirmed its participation in the



SCHEME 3 Synthesis of the target macrocyclic dilactams **9** utilizing bis(2-cyanoacetamide) **10**



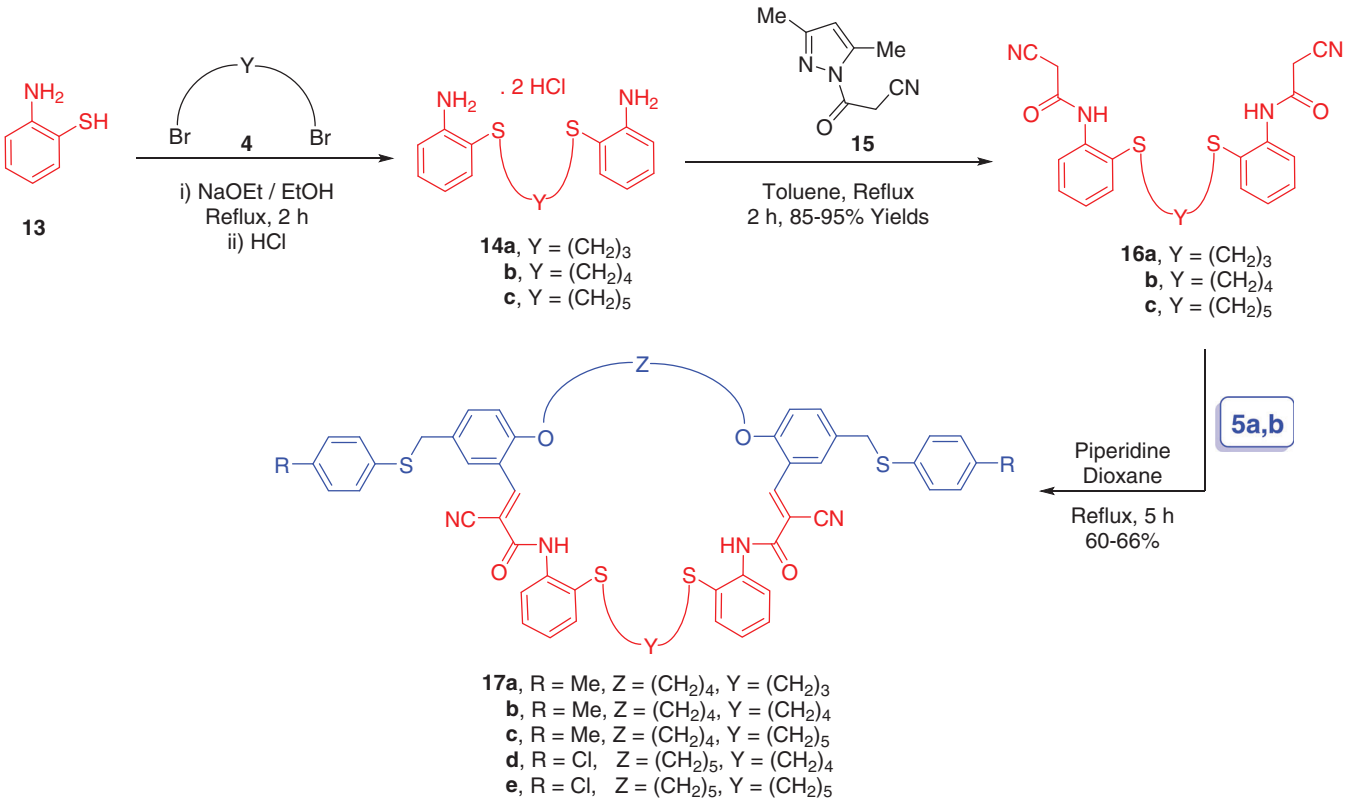
SCHEME 4 Synthesis of bis(2-imino-2*H*-chromene-3-carboxamides) **12**

cyclization. Furthermore, isolating intermediates **12a** and **12b** from the previous reaction confirmed the presence of the intermediate **11** as (*E*)-isomer, in which nitrile function is in a *trans* position to the methine-H, as only this isomer can conduct cyclization to the corresponding bis (2-imino-2*H*-chromene-3-carboxamides) **12**.

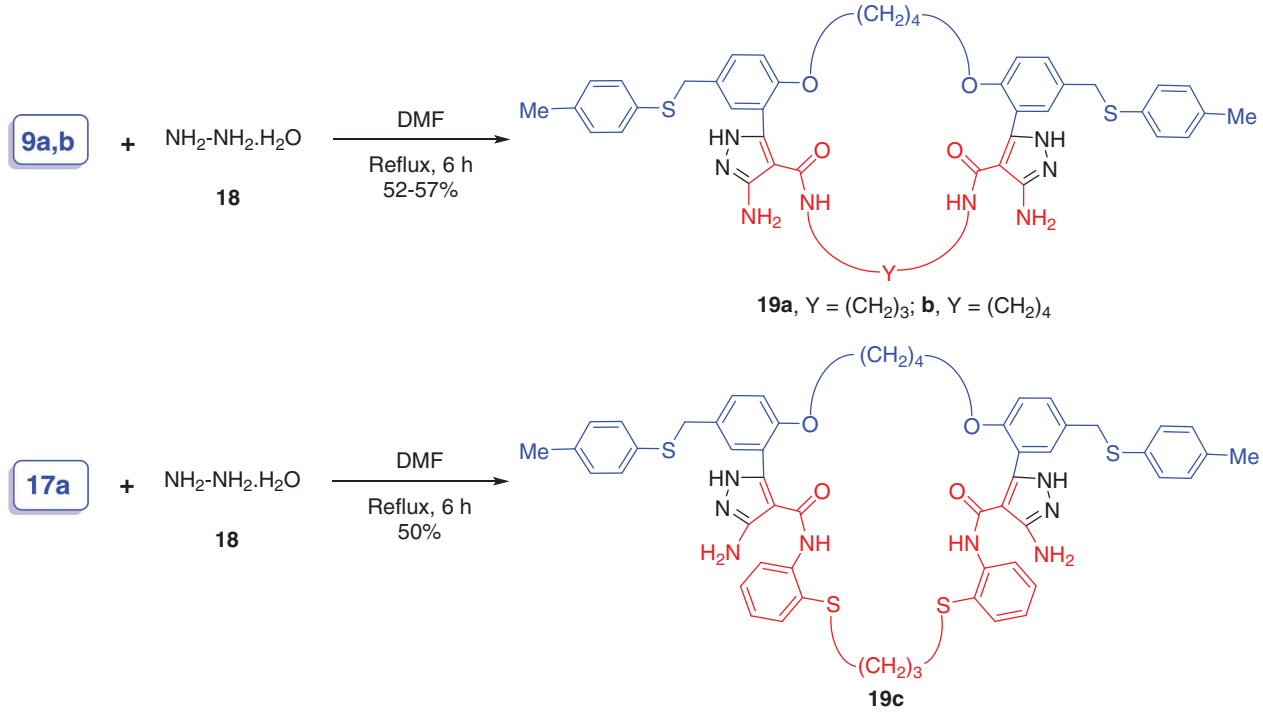
Inspired by the aforementioned findings, we extended our study to prepare a new series of thiamacrocyclic dilactams utilizing the appropriate bis(2-cyanoacetamide) **16**, linked to S_2-set of donor atoms. Thus, the bis (2-aminophenylthio)alkanes **14** were prepared by the reaction of 2-aminothiophenol **13** with the appropriate 1,ω-dibromoalkanes **4** in ethanolic sodium ethoxide solution at reflux [59]. Cyanoacylation of **14** in toluene with 3-(3,5-dimethyl-1*H*-pyrazol-1-yl)-3-oxopropanenitrile **15** at reflux resulted in the formation of bis(cyanoacetamides) **16**, linked to aliphatic cores via thioethers (Scheme 5) [60,61]. Next, the precursors **16a–16c** cyclocondensed with the appropriate bis(aldehydes) **5a,b** in dioxane in the presence of few drops of piperidine at reflux for 5 h to afford the desired macrocycles **17a–17e** in 60%–66% yields (Scheme 5) [60]. The ^{1}H-NMR spectrum of **17b**, as a representative example, showed four triplet signals at δ 1.66, 1.89, 2.86, and 4.07 owing to the protons of four sets of methylene groups at two butane linkers. Moreover, it revealed four singlet signals at δ 2.22, 4.14, 8.72, and 9.64 corresponding to *p*-CH_3, SCH_2, methine-H, and NH protons, respectively. In addition, it revealed the presence of signals corresponding to 22 aromatic protons at δ 6.76–7.83. Its ^{13}C-NMR exhibited four signals at δ 25.4, 27.5, 31.1, and 67.9 owing to four sets of methylene carbons at two butane spacers. It also showed six signals at δ 20.4, 35.8, 104.6, 115.5, 151.2, and 161.2 ppm, respectively, corresponding to CH_3, SCH_2, *C*-CN, CN, methine-C, and CO carbons. Additionally, it revealed 16 signals in the range between δ 114.0 and δ 158.0 corresponding to aromatic carbons (see Experimental section).

Encouraged by the presence of two acrylonitrile units in macrocycles **9** and **17**, we examined their synthetic potential as key synthons for the preparation of new dipyrazolo-fused macrocycles **19**. Therefore, the macrocyclic derivatives **19a–19c** were synthesized, in 50%–57% yields, after treating each of **9a**, **9b,** and **17a** with hydrazine hydrate **18** in DMF at reflux for 6 h (Scheme 6) [57,62].

The reaction may proceed via an initial hetero-Michael addition of NH_2 group in two molecules of hydrazine hydrate to olefinic bond in the two acrylonitrile units in **9** or **17**. Following that, the other hydrazine-NH_2 groups were added to the cyano groups in acrylonitrile units, followed by auto-oxidation to yield **19a–19c** as final isolable products. Once more, the disappearance of the absorption bands owing to nitrile functions in the IR spectra of



SCHEME 5 Synthesis of the target thiamacrocyclic dilactams **17**



SCHEME 6 Synthesis of the dipyrazolo-fused macrocycles **19**

19a–19c indicated their participation in the cycloaddition. In addition, their IR spectra revealed the characteristic absorption bands at 3405–3140 cm^{-1} owing to the NH and NH_2 groups. Also, the ^{1}H-NMR spectra of macrocycles **19a–19c** revealed a broad singlet signal at δ 6.40–6.55 corresponding to NH_2 protons. In addition, it showed two singlet signals at the regions δ 8.03–8.12 and 8.49–8.54 owing to two NH groups (see Experimental section).

3 | CONCLUSION

We reported herein the synthesis of new benzo-fused macrocyclic and thiamacrocyclic dilactams upon the cyclocondensation of the appropriate bis(2-cyanoacetamide) with bis(aldehydes). The target macrocycles were prepared, in good yields, in dioxane in the presence of few drops of piperidine at reflux for 4–5 h. Furthermore, a new series of pyrazolo-fused macrocycles were obtained, in moderate to good yields, by treating the appropriate dilactams with hydrazine hydrate in DMF at reflux for 6 h.

4 | EXPERIMENTAL

"Unless otherwise stated, all solvents were obtained from commercial sources and used exactly as received. All of the other chemicals were purchased from Merck or Aldrich. These chemicals were used without being purified further. All melting points are uncorrected. The melting points were determined using a Stuart digital advanced SMP30 melting point apparatus with a maximum temperature of 400°C (Stuart-equipment, Staffordshire, UK). Thermo Scientific Smart iTX ATR sampling accessory was used to standardize sample preparation and IR result quality. IR spectra were recorded using a Thermo Scientific Nicolet iS10 FT-IR spectrometer with a spectral range of 7800 to 350 cm^{-1} optimized, mid-infrared KBr beamsplitter (Thermo Fisher Scientific, Massachusetts, USA). NMR spectra were recorded on a 2-channel Bruker Avance III HD 400 MHz spectrometer with Z-gradient and equipped for gradient shimming (Bruker Scientific Instruments, Massachusetts, USA). ^{1}H-NMR and ^{13}C-NMR spectra were measured using 400 and 100 MHz, respectively, with a superconducting UltraShield 400 MHz magnet, TMS as an internal standard, DMSO-d_6 as a solvent and chemical shift were expressed as δ ppm units. Mass spectra were recorded on a GC-MS-QP1000EX spectrometer using inlet type at 70 eV. Elemental analyses were performed on a EuroVector EA3000 CHNS elemental analyzer including Callidus software (EuroVector Srl, Pavia, Italy)." [44]

4.1 | General procedure for the synthesis of alkane-linked bis(aldehydes) 5

A mixture of the appropriate salicylaldehydes **3a,b** (2 mmol), 1,ω-dibromoalkanes **4** (1 mmol) and

anhydrous potassium carbonate (4 mmol) in DMF (15 ml) was stirred at rt for 8 h. The mixture was poured onto 100 g of ice, filtered off, thoroughly washed with water, and then recrystallized from the suitable solvent.

4.2 | 6,6′-(Butane-1,4-diylbis(oxy))bis (3-((*p*-tolylthio)methyl)benzaldehyde) (5a)

Colorless solid (dioxane/ethanol mixture, 87%); m.p. 138–140°C; IR (υ cm^{-1}): 1668 (CO); ^{1}H-NMR (DMSO-d_6): δ 1.94 (br s, 4H, 2 OCH_2CH_2), 2.23 (s, 6H, 2 *p*-CH_3), 4.16 (s, 8H, 2 OCH_2 and 2 SCH_2), 7.08 (d, J = 8.0 Hz, 4H, ArH), 7.13 (d, J = 8.8 Hz, 2H, ArH), 7.21 (d, J = 8.0 Hz, 4H, ArH), 7.54 (d, J = 8.8 Hz, 2H, ArH), 7.61 (s, 2H, ArH), 10.31 (s, 2H, 2 CHO); ^{13}C-NMR (DMSO-d_6): δ 20.5 (CH_3), 25.1 (OCH_2CH_2), 36.1 (SCH_2), 68.0 (OCH_2), 113.5, 123.8, 127.6, 129.2, 129.5, 130.0, 131.8, 135.6, 136.6, 159.9, 188.9; Anal. for $C_{34}H_{34}O_4S_2$ (570.7): C, 71.55; H, 6.00; found: C, 71.29; H, 6.25%.

4.3 | 6,6′-(Pentane-1,5-diylbis(oxy))bis (3-(((4-chlorophenyl)thio)methyl) benzaldehyde) (5b)

Colorless solid (dioxane/ethanol mixture, 84%); m.p. 114°C; IR (υ cm^{-1}): 1666 (CO); ^{1}H-NMR (DMSO-d_6): δ 1.62 (br s, 2H, $OCH_2CH_2CH_2$), 1.83 (br s, 4H, 2 OCH_2CH_2), 4.11 (br s, 4H, 2 OCH_2), 4.23 (s, 4H, 2 SCH_2), 7.14 (d, J = 8.8 Hz, 2H, ArH), 7.32 (s, 8H, ArH), 7.59 (d, J = 8.8 Hz, 2H, ArH), 7.64 (s, 2H, ArH), 10.32 (s, 2H, 2 CHO); ^{13}C-NMR (DMSO-d_6): δ 22.0 ($OCH_2CH_2CH_2$), 28.1 (OCH_2CH_2), 35.6 (SCH_2), 68.3 (OCH_2), 113.6, 123.9, 127.6, 128.8, 129.4, 130.2, 130.6, 134.7, 136.6, 160.1, 188.8; Anal. for $C_{33}H_{30}Cl_2O_4S_2$ (625.6): C, 63.36; H, 4.83; found: C, 63.52; H, 4.91%.

4.4 | Synthesis of diethyl 3,3′-((butane-1,4-diylbis(oxy))bis(5-((*p*-tolylthio)methyl)-2,1-phenylene))(2*E*,2′*E*)-bis (2-cyanoacrylate) (7)

A mixture of bis(aldehyde) **5a** (1 mmol) and ethyl cyanoacetate **6** (2 mmol) in dioxane (15 ml) containing two drops of piperidine was heated at reflux for 2 h. The mixture was evaporated to its half volume, cooled, filtered off, washed with ethanol, and then recrystallized from dioxane/ethanol mixture as pale yellow solid (85%); m.p. 144°C; IR (υ cm^{-1}): 2217 (CN), 1719 (CO); ^{1}H-NMR (DMSO-d_6): δ 1.25 (t, J = 6.4 Hz, 6H, 2 OCH_2CH_3), 1.93 (t, J = 6.4 Hz, 4H, 2 OCH_2CH_2), 2.23 (s, 6H, 2 *p*-CH_3), 4.15 (br s, 8H, 2 OCH_2 and 2 SCH_2), 4.26 (q, J = 6.4 Hz, 4H, 2 OCH_2CH_3), 7.07–7.12 (m, 6H, ArH), 7.21 (d, J = 8.0 Hz, 4H, ArH), 7.52 (d, J = 8.8 Hz, 2H, ArH), 8.06 (s, 2H, ArH), 8.49 (s, 2H, 2 methine-H's); ^{13}C-NMR (DMSO-d_6): δ 13.8 (OCH_2CH_3), 20.5 (CH_3), 25.1 (OCH_2CH_2), 36.4 (SCH_2), 62.2 (OCH_2CH_3), 68.2 (OCH_2), 101.9, 113.0, 115.4, 119.5, 128.4, 129.1, 129.6, 130.0, 131.8, 135.5, 135.9, 148.1, 157.2, 161.9 (COO); MS *m/z* (%): 760 (M^+, 47.5); Anal. for $C_{44}H_{44}N_2O_6S_2$: C, 69.45; H, 5.83; N, 3.68; found: C, 69.27; H, 5.93; N, 3.37%.

4.5 | General procedure for the synthesis of macrocyclic dilactams 9 and 17

A solution of the appropriate bis(2-cyanoacetamide) **10a,b** or **16a–16c** (1 mmol) in dioxane (100 ml) was added to a solution of the appropriate bis(aldehydes) **5a,b** (1 mmol) in dioxane (100 ml) in the presence of piperidine (1.0 ml). The mixture was heated at reflux for 4–5 h. The mixture was reduced to 15 ml, cooled, and then 10 ml of ethanol was added in portions. The resulting solid was filtered, washed with ethanol, and recrystallized from the appropriate solvent.

4.6 | Macrocycle 9a

Pale yellow solid (dioxane/ethanol mixture, 70%); m.p. 260–263°C; IR (υ cm^{-1}): 3272 (NH), 2210 (CN), 1648 (CO); ^{1}H-NMR (DMSO-d_6): δ 1.77 (br s, 2H, NCH_2CH_2), 1.90 (t, J = 6.4 Hz, 4H, 2 OCH_2CH_2), 2.23 (s, 6H, 2 *p*-CH_3), 3.28 (br s, 4H, 2 NCH_2), 4.09 (t, J = 6.4 Hz, 4H, 2 OCH_2), 4.17 (s, 4H, 2 SCH_2), 6.77 (d, J = 8.8 Hz, 2H, ArH), 7.08 (d, J = 8.0 Hz, 4H, ArH), 7.20 (d, J = 8.0 Hz, 4H, ArH), 7.24 (d, J = 8.8 Hz, 2H, ArH), 7.35 (s, 2H, ArH), 8.33 (s, 2H, 2 NH), 8.47 (s, 2H, 2 methine-H); ^{13}C-NMR (DMSO-d_6): δ 20.4 (CH_3), 25.3 (OCH_2CH_2), 26.9 (NCH_2CH_2), 35.1 (NCH_2), 35.6 (SCH_2), 68.0 (OCH_2), 105.8, 114.2, 116.8, 118.8, 125.0, 125.6, 128.6, 129.7, 132.5, 137.1, 137.8, 145.3, 157.8, 161.5; MS *m/z* (%): 742 (M^+, 36.4); Anal. for $C_{43}H_{42}N_4O_4S_2$: C, 69.52; H, 5.70; N, 7.54; found: C, 69.35; H, 5.44; N, 7.69%.

4.7 | Macrocycle 9b

Pale yellow solid (dioxane, 65%); m.p. 266°C; IR (υ cm^{-1}): 3275 (NH), 2209 (CN), 1651 (CO); ^{1}H-NMR (DMSO-d_6): δ 1.50 (br s, 4H, 2 NCH_2CH_2), 1.91 (t, J = 6.4 Hz, 4H, 2 OCH_2CH_2), 2.24 (s, 6H, 2 *p*-CH_3), 3.21 (br s, 4H, 2 NCH_2), 4.08 (t, J = 6.4 Hz, 4H, 2 OCH_2), 4.16 (s, 4H, 2 SCH_2), 6.78 (d, J = 8.8 Hz, 2H, ArH), 7.08 (d,

J = 8.0 Hz, 4H, ArH), 7.21 (d, J = 8.0 Hz, 4H, ArH), 7.25 (d, J = 8.8 Hz, 2H, ArH), 7.34 (s, 2H, ArH), 8.33 (s, 2H, 2 NH), 8.44 (s, 2H, 2 methine-H); ^{13}C-NMR (DMSO-d_6): δ 20.4 (CH_3), 25.4 (OCH_2CH_2), 26.3 (NCH_2CH_2), 35.7 (SCH_2), 39.3 (NCH_2), 68.1 (OCH_2), 107.2, 114.0, 116.3, 118.9, 125.2, 125.7, 128.7, 129.6, 132.4, 137.0, 137.5, 144.9, 157.6, 161.8; MS m/z (%): 756 (M^+, 27.8); Anal. for $C_{44}H_{44}N_4O_4S_2$: C, 69.81; H, 5.86; N, 7.40; found: C, 70.05; H, 6.11; N, 7.13%.

4.8 | Macrocycle 9c

Pale yellow solid (dioxane/ethanol mixture, 69%); m.p. 274–276°C; IR (υ cm^{-1}): 3263 (NH), 2211 (CN), 1650 (CO); ^{1}H-NMR (DMSO-d_6): δ 1.61 (br s, 2H, $OCH_2CH_2CH_2$), 1.73 (br s, 2H, NCH_2CH_2), 1.82 (br s, 4H, 2 OCH_2CH_2), 3.29 (br s, 4H, 2 NCH_2), 4.04 (br s, 4H, 2 OCH_2), 4.22 (s, 4H, 2 SCH_2), 6.78 (d, J = 8.8 Hz, 2H, ArH), 7.25 (d, J = 8.8 Hz, 2H, ArH), 7.32 (s, 8H, ArH), 7.36 (s, 2H, ArH), 8.27 (s, 2H, 2 NH), 8.43 (s, 2H, 2 methine-H); ^{13}C-NMR (DMSO-d_6): δ 21.9 ($OCH_2CH_2CH_2$), 26.8 (NCH_2CH_2), 28.0 (OCH_2CH_2), 35.1 (NCH_2), 35.3 (SCH_2), 67.9 (OCH_2), 105.9, 114.6, 116.6, 118.4, 124.8, 125.5, 129.0, 130.5, 130.9, 135.0, 137.5, 145.3, 158.2, 161.7; Anal. for $C_{42}H_{38}Cl_2N_4O_4S_2$ (797.8): C, 63.23; H, 4.80; N, 7.02; found: C, 63.01; H, 5.04; N, 7.26%.

4.9 | Macrocycle 9d

Pale yellow solid (dioxane, 72%); m.p. 280–283°C; IR (υ cm^{-1}): 3263 (NH), 2211 (CN), 1650 (CO); ^{1}H-NMR (DMSO-d_6): δ 1.49 (br s, 4H, 2 NCH_2CH_2), 1.62 (br s, 2H, $OCH_2CH_2CH_2$), 1.81 (br s, 4H, 2 OCH_2CH_2), 3.20 (br s, 4H, 2 NCH_2), 4.03 (br s, 4H, 2 OCH_2), 4.20 (s, 4H, 2 SCH_2), 6.79 (d, J = 8.8 Hz, 2H, ArH), 7.26 (d, J = 8.8 Hz, 2H, ArH), 7.31 (s, 8H, ArH), 7.36 (s, 2H, ArH), 8.22 (s, 2H, 2 NH), 8.39 (s, 2H, 2 methine-H); ^{13}C-NMR (DMSO-d_6): δ 22.0 ($OCH_2CH_2CH_2$), 26.2 (NCH_2CH_2), 27.9 (OCH_2CH_2), 35.4 (SCH_2), 39.1 (NCH_2), 67.9 (OCH_2), 107.3, 114.4, 116.2, 118.3, 124.7, 125.7, 129.1, 130.4, 130.8, 134.9, 137.3, 144.7, 158.4, 161.9; Anal. for $C_{43}H_{40}Cl_2N_4O_4S_2$ (811.8): C, 63.62; H, 4.97; N, 6.90; found: C, 63.38; H, 4.73; N, 7.12%.

4.10 | Macrocycle 17a

Yellow solid (dioxane/ethanol mixture, 66%); m.p. 266–268°C; IR (υ cm^{-1}): 3316 (NH), 2205 (CN), 1680 (CO); ^{1}H-NMR (DMSO-d_6): δ 1.76 (br s, 2H, SCH_2CH_2), 1.89 (t, J = 6.4 Hz, 4H, 2 OCH_2CH_2), 2.23 (s, 6H, 2 p-CH_3), 3.00 (br s, 4H, 2 SCH_2CH_2), 4.09 (t, J = 6.4 Hz, 4H, 2 OCH_2), 4.17 (s, 4H, 2 SCH_2), 6.79 (d, J = 8.8 Hz, 2H, ArH), 7.09 (d, J = 8.0 Hz, 4H, ArH), 7.15–7.22 (m, 6H, ArH), 7.25 (d, J = 8.8 Hz, 2H, ArH), 7.30 (t, J = 8.0 Hz, 2H, ArH), 7.36 (s, 2H, ArH), 7.49 (d, J = 8.0 Hz, 2H, ArH), 7.86 (d, J = 8.0 Hz, 2H, ArH), 8.79 (s, 2H, 2 methine-H's), 9.66 (s, 2H, 2 NH); ^{13}C-NMR (DMSO-d_6): δ 20.3 (CH_3), 25.2 (OCH_2CH_2), 27.8 (SCH_2CH_2), 31.6 (SCH_2), 35.7 (SCH_2), 68.1 (OCH_2), 104.3, 114.4, 115.8, 118.5, 120.6, 120.7, 125.3, 125.8, 126.4, 128.7, 129.4, 129.6, 130.5, 132.2, 135.6, 137.0, 137.6, 151.5, 157.5, 161.0; MS m/z (%): 959 (M^+, 19.3); Anal. for $C_{55}H_{50}N_4O_4S_4$: C, 68.87; H, 5.25; N, 5.84; found: C, 69.13; H, 5.02; N, 6.06%.

4.11 | Macrocycle 17b

Yellow solid (dioxane, 60%); m.p. 254°C; IR (υ cm^{-1}): 3319 (NH), 2207 (CN), 1676 (CO); ^{1}H-NMR (DMSO-d_6): δ 1.66 (br s, 4H, 2 SCH_2CH_2), 1.89 (t, J = 6.4 Hz, 4H, 2 OCH_2CH_2), 2.22 (s, 6H, 2 p-CH_3), 2.86 (br s, 4H, 2 SCH_2CH_2), 4.07 (t, J = 6.4 Hz, 4H, 2 OCH_2), 4.14 (s, 4H, 2 SCH_2), 6.76 (d, J = 8.8 Hz, 2H, ArH), 7.09 (d, J = 8.0 Hz, 4H, ArH), 7.15–7.22 (m, 6H, ArH), 7.25 (d, J = 8.8 Hz, 2H, ArH), 7.31 (t, J = 8.0 Hz, 2H, ArH), 7.35 (s, 2H, ArH), 7.50 (d, J = 8.0 Hz, 2H, ArH), 7.83 (d, J = 8.0 Hz, 2H, ArH), 8.72 (s, 2H, 2 methine-H's), 9.64 (s, 2H, 2 NH); ^{13}C-NMR (DMSO-d_6): δ 20.4 (CH_3), 25.4 (OCH_2CH_2), 27.5 (SCH_2CH_2), 31.1 (SCH_2), 35.8 (SCH_2), 67.9 (OCH_2), 104.6, 114.0, 115.5, 118.7, 120.5, 120.6, 125.1, 125.5, 126.1, 128.4, 129.3, 129.5, 130.4, 132.4, 135.7, 136.9, 137.4, 151.2, 158.0, 161.2; Anal. for $C_{56}H_{52}N_4O_4S_4$ (973.3): C, 69.11; H, 5.39; N, 5.76; found: C, 69.36; H, 5.14; N, 5.97%.

4.12 | Macrocycle 17c

Yellow solid (dioxane/ethanol mixture, 62%); m.p. 264°C; IR (υ cm^{-1}): 3313 (NH), 2207 (CN), 1679 (CO); ^{1}H-NMR (DMSO-d_6): δ 1.47 (br s, 2H, $SCH_2CH_2CH_2$), 1.54 (br s, 4H, 2 SCH_2CH_2), 1.88 (t, J = 6.4 Hz, 4H, 2 OCH_2CH_2), 2.22 (s, 6H, 2 p-CH_3), 2.85 (br s, 4H, 2 SCH_2CH_2), 4.07 (t, J = 6.4 Hz, 4H, 2 OCH_2), 4.16 (s, 4H, 2 SCH_2), 6.78 (d, J = 8.8 Hz, 2H, ArH), 7.08 (d, J = 8.0 Hz, 4H, ArH), 7.16–7.21 (m, 6H, ArH), 7.25 (d, J = 8.8 Hz, 2H, ArH), 7.31 (t, J = 8.0 Hz, 2H, ArH), 7.37 (s, 2H, ArH), 7.49 (d, J = 8.0 Hz, 2H, ArH), 7.83 (d, J = 8.0 Hz, 2H, ArH), 8.78 (s, 2H, 2 methine-H's), 9.70 (s, 2H, 2 NH); ^{13}C-NMR (DMSO-d_6): δ 20.5 (CH_3), 25.2 (OCH_2CH_2), 27.1 ($SCH_2CH_2CH_2$), 27.8 (SCH_2CH_2), 31.6 (SCH_2), 35.7 (SCH_2), 68.0 (OCH_2), 104.3, 114.4, 115.6, 118.6, 120.5, 120.7, 125.2, 125.7, 126.3, 128.5, 129.2, 129.5, 130.4, 132.3, 135.5, 137.0, 137.5, 151.2, 157.6, 161.1; MS m/z (%): 987 (M^+, 30.1);

Anal. for $C_{57}H_{54}N_4O_4S_4$: C, 69.34; H, 5.51; N, 5.67; found: C, 69.08; H, 5.78; N, 5.43%.

4.13 | Macrocycle 17d

Yellow solid (dioxane, 60%); m.p. 254°C; IR (υ cm^{-1}): 3317 (NH), 2205 (CN), 1675 (CO); ^{1}H-NMR (DMSO-d_6): δ 1.58 (br s, 2H, $OCH_2CH_2CH_2$), 1.66 (t, J = 7.2 Hz, 4H, 2 SCH_2CH_2), 1.80 (br s, 4H, 2 OCH_2CH_2), 2.86 (t, J = 7.2 Hz, 4H, 2 SCH_2CH_2), 4.04 (br s, 4H, 2 OCH_2), 4.16 (s, 4H, 2 SCH_2), 6.80 (d, J = 8.8 Hz, 2H, ArH), 7.16 (t, J = 8.0 Hz, 2H, ArH), 7.26–7.34 (m, 12H, ArH), 7.37 (s, 2H, ArH), 7.49 (d, J = 8.0 Hz, 2H, ArH), 7.83 (d, J = 8.0 Hz, 2H, ArH), 8.67 (s, 2H, 2 methine-H's), 9.66 (s, 2H, 2 NH); ^{13}C-NMR (DMSO-d_6): δ 22.1 ($OCH_2CH_2CH_2$), 27.5 (SCH_2CH_2), 28.2 (OCH_2CH_2), 31.1 (SCH_2), 35.4 (SCH_2), 67.9 (OCH_2), 104.7, 114.3, 115.7, 118.6, 120.4, 120.6, 125.3, 125.6, 126.3, 129.2, 129.5, 130.5, 130.7, 131.0, 135.2, 135.8, 137.2, 151.0, 157.8, 161.4; Anal. for $C_{55}H_{48}Cl_2N_4O_4S_4$ (1028.1): C, 64.25; H, 4.71; N, 5.45; found: C, 64.01; H, 4.96; N, 5.19%.

4.14 | Macrocycle 17e

Yellow solid (dioxane, 64%); m.p. 270°C; IR (υ cm^{-1}): 3322 (NH), 2209 (CN), 1679 (CO); ^{1}H-NMR (DMSO-d_6): δ 1.49 (br s, 6H, $SCH_2CH_2CH_2$ and 2 SCH_2CH_2), 1.59 (br s, 2H, $OCH_2CH_2CH_2$), 1.80 (br s, 4H, 2 OCH_2CH_2), 2.82 (br s, 4H, 2 SCH_2CH_2), 4.03 (br s, 4H, 2 OCH_2), 4.18 (s, 4H, 2 SCH_2), 6.79 (d, J = 8.8 Hz, 2H, ArH), 7.17 (t, J = 8.0 Hz, 2H, ArH), 7.25 (d, J = 8.8 Hz, 2H, ArH), 7.27–7.34 (m, 10H, ArH), 7.36 (s, 2H, ArH), 7.51 (d, J = 8.0 Hz, 2H, ArH), 7.82 (d, J = 8.0 Hz, 2H, ArH), 8.65 (s, 2H, 2 methine-H's), 9.68 (s, 2H, 2 NH); ^{13}C-NMR (DMSO-d_6): δ 22.0 ($OCH_2CH_2CH_2$), 27.1 ($SCH_2CH_2CH_2$), 27.8 (SCH_2CH_2), 28.1 (OCH_2CH_2), 31.7 (SCH_2), 35.6 (SCH_2), 68.1 (OCH_2), 104.6, 114.4, 115.8, 118.6, 120.4, 120.6, 125.5, 125.7, 126.2, 129.0, 129.2, 130.2, 130.6, 131.0, 135.1, 135.3, 136.9, 150.9, 157.6, 160.8; Anal. for $C_{56}H_{50}Cl_2N_4O_4S_4$ (1042.1): C, 64.54; H, 4.84; N, 5.38; found: C, 64.27; H, 5.10; N, 5.15%.

4.15 | General procedure for the synthesis of bis(2-imino-2*H*-chromene-3-carboxamides) 12

A mixture of bis(2-cyanoacetamide) **10a,b** (1 mmol) and salicylaldehydes **3a,b** (2 mmol) in dioxane (15 ml) containing two drops of piperidine. The mixture was heated at reflux for 4 h. The mixture was evaporated to its half volume, cooled, filtered off, washed with ethanol, and then recrystallized from the suitable solvent.

4.16 | *N,N′*-(Propane-1,3-diyl)bis(2-imino-6-((*p*-tolylthio)methyl)-2*H*-chromene-3-carboxamide) (12a)

Yellow solid (dioxane/ethanol mixture, 82%); m.p. 250–252°C; IR (υ cm^{-1}): 3312, 3228 (2 NH), 1652 (CO); ^{1}H-NMR (DMSO-d_6): δ 1.73 (br s, 2H, NCH_2CH_2), 2.22 (s, 6H, 2 p-CH_3), 3.51 (br s, 4H, 2 NCH_2), 4.13 (s, 4H, 2 SCH_2), 7.11 (d, J = 8.0 Hz, 4H, ArH), 7.20 (d, J = 8.0 Hz, 4H, ArH), 7.35 (d, J = 8.4 Hz, 2H, 2 H7), 7.60 (d, J = 8.4 Hz, 2H, 2 H8), 7.73 (s, 2H, 2 H5), 8.47 (s, 2H, 2 H4), 8.85 (s, 2H, 2 NH), 10.41 (br s, 2H, 2 NH); ^{13}C-NMR (DMSO-d_6): δ 20.4 (p-CH_3), 29.3 (NCH_2CH_2), 35.8 (SCH_2), 37.9 (NCH_2), 113.2, 118.4, 123.2, 124.7, 129.2, 129.8, 131.4, 131.7, 132.6, 135.4, 144.0, 151.2, 158.4, 164.1; MS m/z (%): 688 (M^+, 45.9); Anal. for $C_{39}H_{36}N_4O_4S_2$: C, 68.00; H, 5.27; N, 8.13; found: C, 68.27; H, 5.04; N, 7.89%.

4.17 | *N,N′*-(Butane-1,4-diyl)bis(6-(((4-chlorophenyl)thio)methyl)-2-imino-2*H*-chromene-3-carboxamide) (12b)

Yellow solid (dioxane, 79%); m.p. 258°C; IR (υ cm^{-1}): 3316, 3226 (2 NH), 1647 (CO); ^{1}H-NMR (DMSO-d_6): δ 1.52 (br s, 4H, 2 NCH_2CH_2), 3.46 (br s, 4H, 2 NCH_2), 4.16 (s, 4H, 2 SCH_2), 7.32–7.38 (m, 10H, 8 ArH and 2 H7), 7.63 (d, J = 8.4 Hz, 2H, 2 H8), 7.76 (s, 2H, 2 H5), 8.49 (s, 2H, 2 H4), 8.90 (s, 2H, 2 NH), 10.46 (br s, 2H, 2 NH); ^{13}C-NMR (DMSO-d_6): δ 26.1 (NCH_2CH_2), 36.0 (SCH_2), 39.1 (NCH_2), 113.4, 118.7, 123.5, 124.8, 129.7, 130.9, 131.4, 131.6, 132.7, 135.9, 144.3, 151.0, 158.7, 164.3; Anal. for $C_{38}H_{32}Cl_2N_4O_4S_2$ (743.7): C, 61.37; H, 4.34; N, 7.53; found: C, 61.12; H, 4.09; N, 7.77%.

4.18 | General procedure for the synthesis of pyrazolo-fused macrocycles 19

A mixture of the appropriate dilactams **9a,b** or **17a** (1 mmol) and hydrazine hydrate **18** (4 ml) in DMF (15 ml) at reflux for 6 h. The mixture was evaporated to its half volume, cooled, filtered off, washed with ethanol, and then recrystallized from the suitable solvent.

4.19 | Macrocycle 19a

Yellow solid (dioxane, 52%); m.p. 180–183°C; IR (υ cm^{-1}): 3390, 3242, 3145 (NH_2, NH), 1630 (CO); ^{1}H-NMR

(DMSO-d_6): δ 1.89 (br s, 2H, NCH_2CH_2), 2.02 (t, J = 6.4 Hz, 4H, 2 OCH_2CH_2), 2.23 (s, 6H, 2 p-CH_3), 4.20 (br s, 4H, 2 NCH_2), 4.25 (s, 4H, 2 SCH_2), 4.35 (t, J = 6.4 Hz, 4H, 2 OCH_2), 6.55 (br s, 4H, 2 NH_2), 6.75 (d, J = 8.8 Hz, 2H, ArH), 7.09 (d, J = 8.0 Hz, 4H, ArH), 7.20 (d, J = 8.0 Hz, 4H, ArH), 7.25 (d, J = 8.8 Hz, 2H, ArH), 7.33 (s, 2H, ArH), 8.07 (s, 2H, 2 NH), 8.49 (s, 2H, 2 NH); ^{13}C-NMR (DMSO-d_6): δ 20.4 (CH_3), 25.4 (OCH_2CH_2), 26.8 (NCH_2CH_2), 36.0 (SCH_2), 39.2 (NCH_2), 67.6 (OCH_2), 106.5, 113.3, 120.4, 124.7, 125.2, 128.7, 128.9, 129.4, 132.1, 136.6, 137.5, 149.0, 158.4, 171.0; MS m/z (%): 803 (M^+, 19.7); Anal. for $C_{43}H_{46}N_8O_4S_2$: C, 64.32; H, 5.77; N, 13.95; found: C, 64.07; H, 5.52; N, 13.71%.

4.20 | Macrocycle 19b

Yellow solid (dioxane, 57%); m.p. 176–178°C; IR (υ cm^{-1}): 3392, 3248, 3140 (NH_2, NH), 1632 (CO); ^{1}H-NMR (DMSO-d_6): δ 1.73 (br s, 4H, 2 NCH_2CH_2), 1.92 (t, J = 6.4 Hz, 4H, 2 OCH_2CH_2), 2.24 (s, 6H, 2 p-CH_3), 4.05 (br s, 8H, 2 OCH_2 and 2 NCH_2), 4.23 (s, 4H, 2 SCH_2), 6.40 (br s, 4H, 2 NH_2), 6.74 (d, J = 8.8 Hz, 2H, ArH), 7.10 (d, J = 8.0 Hz, 4H, ArH), 7.22 (d, J = 8.0 Hz, 4H, ArH), 7.27 (d, J = 8.8 Hz, 2H, ArH), 7.36 (s, 2H, ArH), 8.03 (s, 2H, 2 NH), 8.51 (s, 2H, 2 NH); ^{13}C-NMR (DMSO-d_6): δ 20.3 (CH_3), 25.3 (OCH_2CH_2), 25.7 (NCH_2CH_2), 36.1 (SCH_2), 39.1 (NCH_2), 67.5 (OCH_2), 106.8, 113.5, 120.5, 124.8, 125.0, 128.5, 128.8, 129.5, 132.3, 136.8, 137.8, 149.2, 158.7, 171.2; MS m/z (%): 817 (M^+, 28.6); Anal. for $C_{44}H_{48}N_8O_4S_2$: C, 64.68; H, 5.92; N, 13.71; found: C, 64.45; H, 6.14; N, 13.93%.

4.21 | Macrocycle 19c

Yellow solid (dioxane, 50%); m.p. 166–168°C; IR (υ cm^{-1}): 3405, 3240, 3156 (NH_2, NH), 1627 (CO); ^{1}H-NMR (DMSO-d_6): δ 1.92 (br s, 6H, 2 OCH_2CH_2 and SCH_2CH_2), 2.24 (s, 6H, 2 p-CH_3), 3.02 (br s, 4H, 2 SCH_2CH_2), 4.12 (t, J = 6.4 Hz, 4H, 2 OCH_2), 4.24 (s, 4H, 2 SCH_2), 6.52 (br s, 4H, 2 NH_2), 6.73 (d, J = 8.8 Hz, 2H, ArH), 7.08 (d, J = 8.0 Hz, 4H, ArH), 7.15 (t, J = 8.0 Hz, 2H, ArH), 7.21 (d, J = 8.0 Hz, 4H, ArH), 7.27–7.31 (m, 4H, ArH), 7.38 (s, 2H, ArH), 7.47 (d, J = 8.0 Hz, 2H, ArH), 7.82 (d, J = 8.0 Hz, 2H, ArH), 8.12 (s, 2H, 2 NH), 8.54 (s, 2H, 2 NH); ^{13}C-NMR (DMSO-d_6): δ 20.4 (CH_3), 25.4 (OCH_2CH_2), 27.6 (SCH_2CH_2), 31.5 (SCH_2), 36.2 (SCH_2), 67.4 (OCH_2), 106.5, 113.3, 120.1, 120.3, 120.4, 124.7, 125.2, 126.2, 128.7, 128.9, 129.0, 129.4, 130.2, 132.1, 135.3, 136.6, 137.5, 149.0, 158.4, 167.4; Anal. for $C_{55}H_{54}N_8O_4S_4$ (1019.3): C, 64.81; H, 5.34; N, 10.99; found: C, 65.04; H, 5.56; N, 10.75%.

DATA AVAILABILITY STATEMENT

The data that supports the findings of this study are available in the supplementary material of this article.

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How to cite this article: A. A. M. Ahmed, A. E. M. Mekky, S. M. H. Sanad, *J. Heterocycl. Chem.* **2022**, *59*(2), 286. https://doi.org/10.1002/jhet.4383