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ORIGINAL PAPER

Effective synthesis of new benzo-fused macrocyclic and heteromacrocyclic bis(Schiff bases)

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Abstract

In this study, the synthons 2-hydroxy-5-((arylthio)methyl)benzaldehydes were reacted with 1,*ω*-dihaloalkanes to produce the corresponding bis(aldehydes). The previous precursors were reacted with the appropriate alkane-1,*ω*-diamines in glacial acetic acid to yield a new series of macrocyclic bis(Schiff bases). Following that, a new series of thiamacrocyclic bis(Schiff bases) were synthesized in glacial acetic acid via sodium acetate-mediated cyclocondensation of the appropriate of 2,2'-(alkane-1,*ω*-diylbis(sulfanediyl))dianiline dihydrochloride with bis(aldehydes). Moreover, bis(4-amino-4*H*-1,2,4-triazole-3-thiol), linked to propane core via thioether, was cyclocondensed with bis(aldehydes) in glacial acetic acid to prepare new *S*-triazole-fused thiamacrocyclic bis(Schiff bases). The previous macrocycles were reacted with two equivalents of iodomethane in methanolic sodium methoxide solution to give macrocyclic bis(methylthio) derivatives. Surprisingly, the reaction of thieno[2,3-*b*]thiophene-linked bis(4-amino-3-phenyl-4*H*-1,2,4-triazole) with the appropriate bis(aldehydes) in glacial acetic acid resulted in a new series [1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine-fused macrocycles. All of the new macrocycles were synthesized with good to excellent yields, and their structures were deduced using elemental and spectral data.

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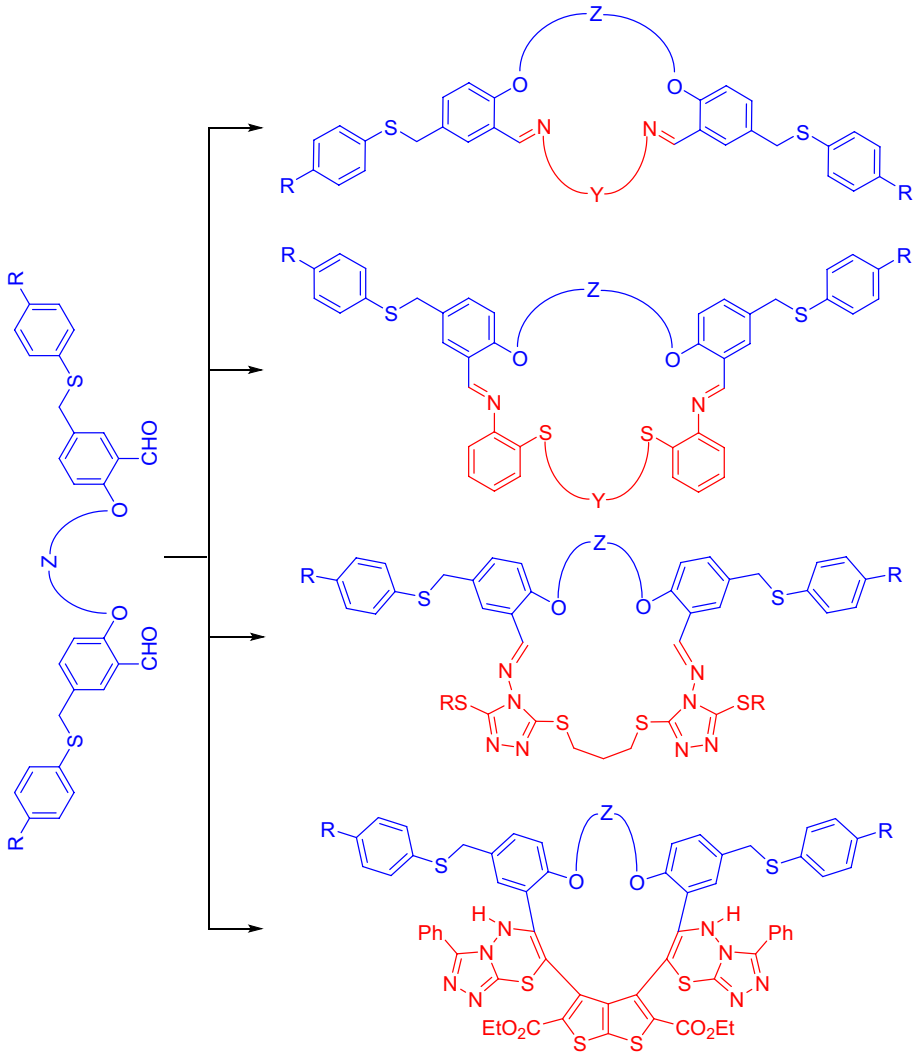
Graphic abstract



Keyword Benzo-fused macrocycle · Cyclocondensation · Heteromacrocycle · Schiff base · [1,2,4]triazolo[3,4-*b*][1,3,4] thiadiazine

Introduction

Macrocyclic compounds are an intriguing chemical class that comprised of one or more rings with at least 12 atoms resulting in preorganization and a semirigid character [1–3]. Because macrocyclic ligands can a variety of hetero-donor atoms, including oxygen, nitrogen, and others, they are ideal candidates for metal ions complexation, selective ion detection and separation [4–8]. The previous scaffolds combine small ligands' therapeutic potential with the ability to mimic some of the structural properties of protein interfaces [9–14]. As a result, they show promising efficacy, selectivity, and low manufacturing expenses [15–17]. This demonstrates macrocycles' adaptability as drug candidates. Currently, approximately a hundred drugs containing macrocyclic moieties are being promoted commercially or are in development. [18–21]

Macrocyclic Schiff bases have played a significant role in both macrocyclic and supramolecular chemistry [22, 23]. Although the vast majority of macrocyclic Schiff bases are synthetic compounds, there is some important naturally occurring macrocycles such as corrin. The prior heteromacrocycle represents the core structure of vitamin B_{12}. [24] Generally, macrocyclic Schiff bases are effective chelating agents capable of forming a wide range of complexes with metal ions. [25] By introducing suitable groups into the

aliphatic and/or aromatic chains of the precursors dicarbonyl derivatives as well as diamines, macrocyclic Schiff bases can be functionalized [26, 27]. These functionally substituted Schiff bases, linked to additional donor groups, are the most important class of hetero-polydentate ligands capable of forming a diverse spectrum of complexes with transition or non-transition metals [28, 29].

Several attempts have been made over the last two decades to develop macrocyclic Schiff bases based on the reaction between dicarbonyl derivatives and diamines, linked to various aliphatic [30–32], arene [33, 34], and *S*-triazole units [35, 36]. Actually, one of the most common strategies for preparing macrocyclic Schiff bases is the metal-promoted one-step condensation process [37–39]. The previous method necessitates the active participation of a metal ion that used as a template to induce the orientation of the reacting groups of linear substrates in the required conformation for the ring to close [40]. The previous strategy directly produces the corresponding macrocyclic Schiff base metal complexes [41–43] which have significant biological activity including good antibacterial [44, 45], antifungal [22], antioxidant [46], and anticancer activity [47, 48]. In addition, these complexes exhibit promising magnetic properties [49], as well as catalytic activity [50].

In the context of our ongoing efforts to prepare bis-linked and macrocyclic hybrids [51–62], the goal of this study was to develop efficient procedures for the synthesis of new heteroarene and/or arene-fused macrocyclic bis(Schiff bases) as well as [1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine-fused macrocycles (see Fig. 1).

Results and discussion

To begin our study, the starting materials 2-hydroxy-5-((arylthio)methyl)benzaldehydes 3a-3c were prepared and taken as key precursors [63–65]. The prior synthons were prepared, in good yields, by the reaction of benzenethiol derivatives 1a-1c with 5-(chloromethyl)-2-hydroxybenzaldehyde 2 [66] in ethanolic potassium hydroxide solution (Scheme 1).

To avoid the formation of undesired by-products, we conducted the synthesis of the target macrocycles in a high dilution condition. All reactions were followed up by TLC analyses. In each case, the reaction was stopped when TLC revealed the presence of a sole product with only minor contaminations. Following that, recrystallization was conducted to purify each isolated product.

Two strategies were examined to prepare the desired macrocyclic bis(Schiff bases) containing an O_2N_2-donor set and fused with two benzene units. At first, we investigated the utility of aldehydes 3 as key synthons. Therefore, alkane-1,ω-diamine 4a,b reacted with 3b,c in glacial acetic acid at reflux for 3 h to afford the corresponding bis(Schiff bases) 5a,b in 85% and 88% yields, respectively [67]. The prior compounds should react with the appropriate 1,ω-dihaloalkanes **6** to prepare the target macrocycles **7**. Unfortunately, our attempts to conduct this bis-alkylation using various reaction conditions failed (see Scheme 2 and Experimental section).

Motivated by the aforementioned findings, we designed another strategy for the synthesis of the target macrocycles 7. Therefore, the precursors 3a-3c were reacted with 1,ω-dihaloalkanes 6 in DMF in the presence of anhydrous potassium carbonate to give bis(aldehydes) 8a–c in 82–86% yields [68]. Next, we conducted the reaction between bis(aldehyde) 8a and propane-1,3-diamine 4a in

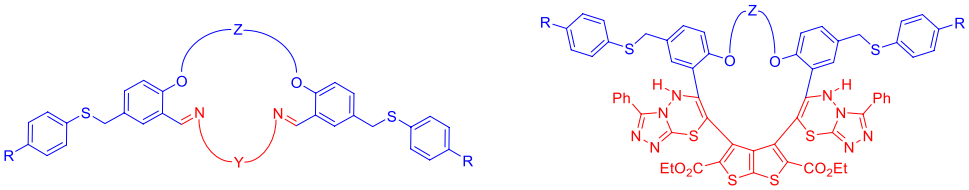
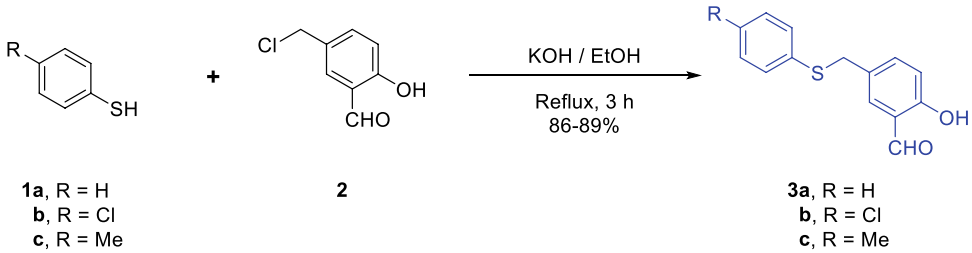


Fig. 1 Structure of the target macrocycles



1a, R = H
b, R = Cl
c, R = Me

2

3a, R = H
b, R = Cl
c, R = Me

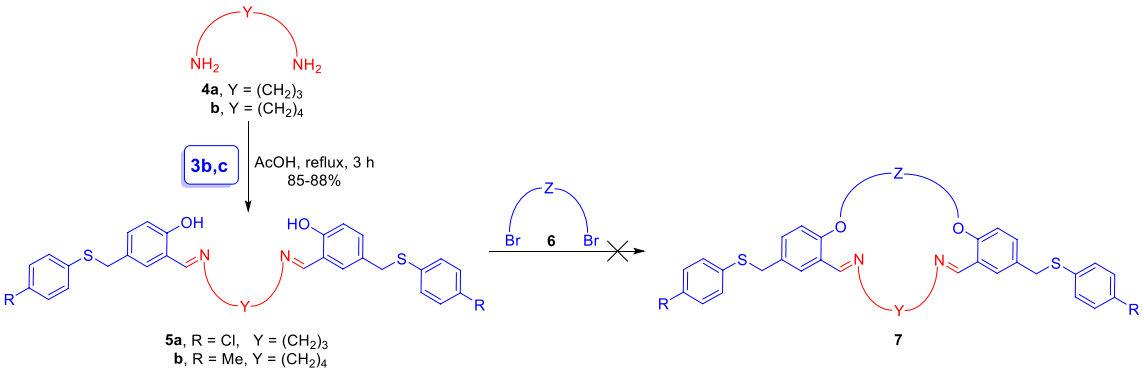
Scheme 1 Synthesis of precursors 2-hydroxy-5-((arylthio) methyl)benzaldehydes 3

glacial acetic acid. The prior mixture was heated at reflux for 5 h to afford the target macrocyclic bis(Schiff base) 7a in 75% yield (see Scheme 3 and Experimental section) [69].

In a similar manner, the precursors 8b and 8c were reacted with the appropriate of bis(amines) 4a or 4b in glacial acetic acid to afford the desired macrocyclic bis(Schiff bases) 7b–d in 72–76% yields (see Scheme 4 and Experimental section) [69].

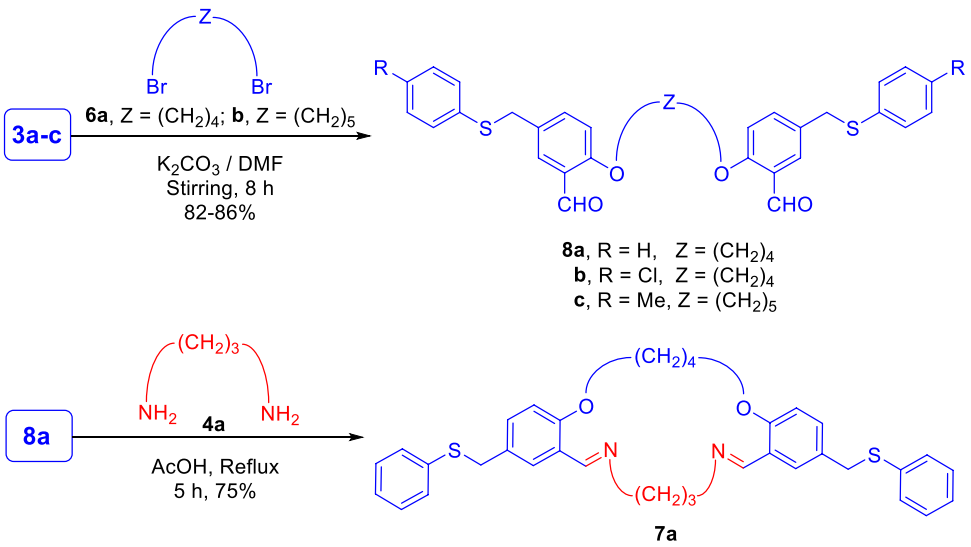
It is worth noting that ^{1}H-NMR spectrum of 5a, b revealed the presence of OH groups at δ 13.44–13.52 indicating the intramolecular H-bonding with the N_2-donor atoms. In addition, ^{1}H-NMR spectrum of both 5 and 6 revealed the presence of methine-H at δ 8.49–8.51 and δ 8.60–8.68, respectively. The above findings indicated the formation of both 5 and 6 in the (*E*)-configuration (see Fig. 2) [70, 71].

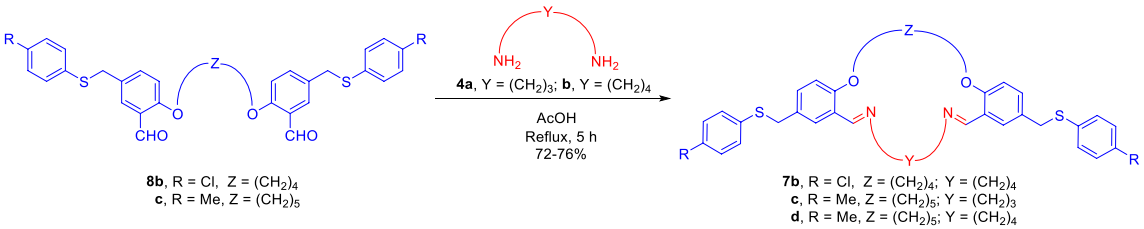
Next, we investigated the synthesis of thiamacrocyclic bis(Schiff bases) containing an N_2O_2-donor set and fused



Scheme 2 The unsuccessful strategy for preparing the desired macrocyclic bis(Schiff bases) 7

Scheme 3 Synthesis of macrocyclic bis(Schiff base) 7a





Scheme 4 Synthesis of macrocyclic bis(Schiff bases) 7b–7d

with four benzene units. According to the *literature* procedure [72, 73], the bis(amines) 9, linked to aliphatic cores via thioether linkage, were prepared and taken as versatile precursors for the prior purpose. Thus, the desired thiamacrocycles 10a-10c were prepared, in 67–70% yields, by the sodium acetate-mediated cyclocondensation of the appropriate of bis(amines) 9a,b with bis(aldehydes) 8a–c in glacial acetic acid at reflux for 5 h (Scheme 5). Once again, the thiamacrocycles 10 are formed in (*E*)-configuration as concluded by observing their ^{1}H-NMR spectra that revealed a singlet signal at δ 8.67–8.71 corresponding to methine-H protons (see Experimental section) [74].

Our study was extended to prepare new macrocyclic bis(Schiff bases) with fused two benzene as well as two *S*-triazole units and containing $N_4O_2S_2$-set of donor atoms inside the macrocyclic ring. Therefore, bis(aldehydes) 8 cyclocondensed with bis(4-amino-4*H*-1,2,4-triazole-3-thiol), linked to propane core via thioether, 11 [75] in glacial acetic acid to afford the desired macrocycles 12 in 63–68% yields (Scheme 6) [71]. The ^{1}H-NMR spectra of 12a–c revealed two singlet signals at δ 10.47–10.54 and δ 13.88–13.97 corresponding to methine-H and SH protons, respectively (see Experimental section).

The reaction potential of macrocyclic bis(Schiff bases) 12 with halogen containing reagents has also been investigated. Thus, one equivalent of each of 12a–c reacted with two equivalents of iodomethane 13 in methanolic sodium methoxide solution to give bis(methylthio) derivatives 14 in 84–87% yields (Scheme 7) [71]. The ^{1}H-NMR spectra of 14a–14c revealed a singlet signal at δ 2.65–2.67 corresponding to SCH_3 protons (see Experimental section). Moreover, compound 14c was alternatively prepared, in 72% yield, by the cyclocondensation of bis(4-amino-3-methylthio-4*H*-1,2,4-triazole) 15 with bis(aldehyde) 8c in glacial acetic acid (Scheme 7).

Finally, we examined the utility of thieno[2,3-*b*]thiophene-linked bis(4-amino-3-phenyl-4*H*-1,2,4-triazole) 16 in the synthesis of the corresponding macrocyclic bis(Schiff bases) [70]. Thus, we conducted the reaction between the prior bis(amine) with bis(aldehyde) 8b in glacial acetic acid to afford a sole reaction product in each case as detected by TLC analyses (Scheme 8). The ^{1}H-NMR spectra of the prior reaction products revealed

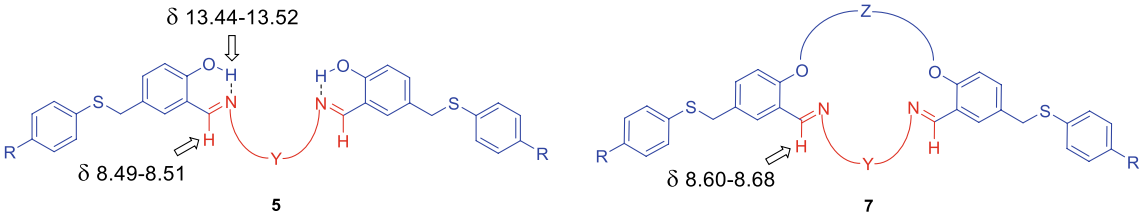
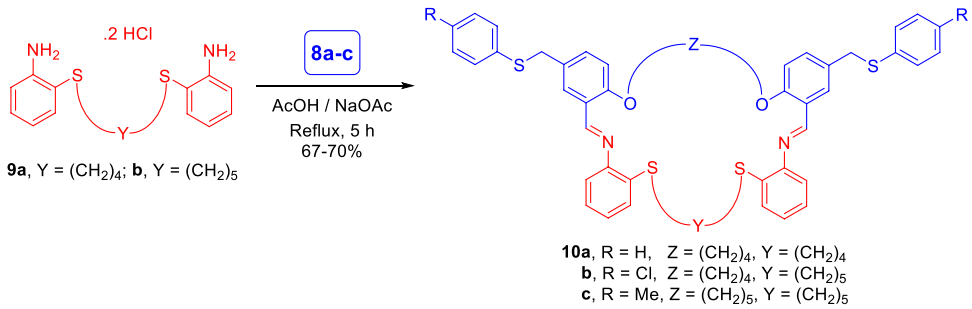
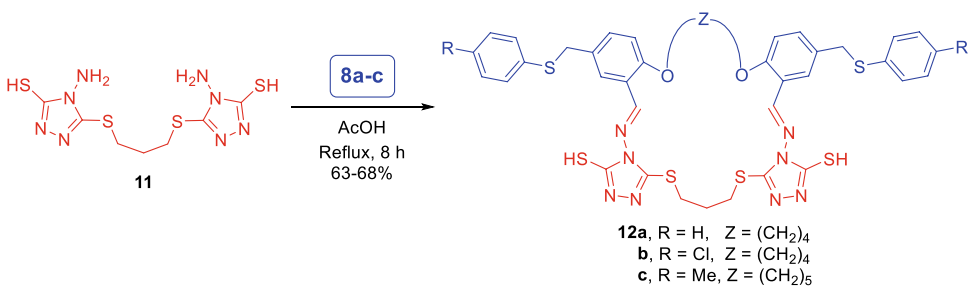


Fig. 2 Structure of (*E*)-bis(Schiff bases) 5 and (*E*)-macrocyclic bis(Schiff bases) 7

Scheme 5 Synthesis of thiamacrocyclic bis(Schiff bases) 10



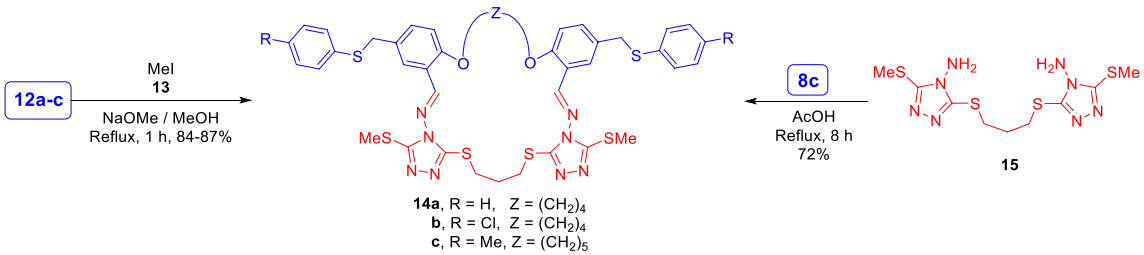
Scheme 6 Synthesis of *S*-triazole-fused thiamacrocyclic bis(Schiff bases) 12



the absence of methine-H protons as well as the SCH_2 attached to the thienothiophene linker. Instead, the spectra showed a singlet signal at δ 9.32 owing to NH protons (see Experimental section). Based on the aforementioned findings, the formation of *S*-triazole-fused macrocyclic bis(Schiff bases) 17 was excluded and instead, the structure thieno[2,3-*b*]thiophene-linked macrocycle 18a, with fused [1,2 4]triazolo[3,4-*b*][1,3,4]thiadiazine units, was assigned for the products (Scheme 8).

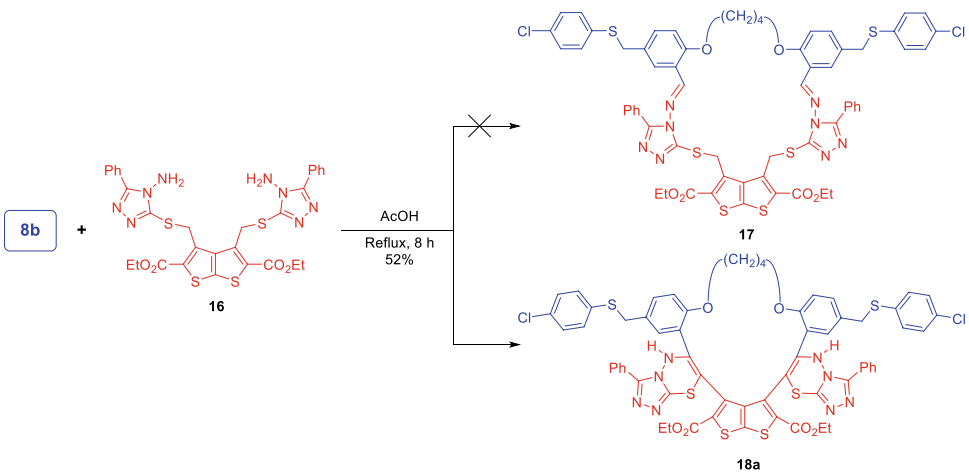
Using the same reaction conditions, bis(aldehyde) 8c reacted with bis(4-amino-3-phenyl-4*H*-1,2,4-triazole) 16 to afford the corresponding [1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine-fused macrocycle 18b as a sole product (see Scheme 9 and Experimental section).

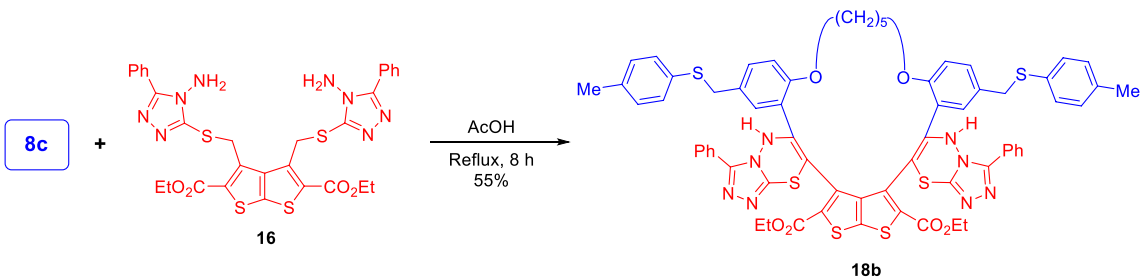
The reaction may proceed via an initial formation of the macrocyclic bis(Schiff base) 17. Next, glacial acetic acid catalyzes the formation of a small amount of the tautomeric form 17A and so, facilitate the reaction between the nucleophilic methylene-C, attached to thienothiophene linker, with the electrophilic methine-C in Schiff base to give [19], followed by autooxidation under the prior reaction conditions to afford [1, 2, 4]triazolo[3,4-b][1,3,4]thiadiazine-fused macrocycles 18 (Scheme 10) [70]. The development of the [1, 3, 4]thiadiazine ring is the driving force for the formation of 18a,b. Moreover, we anticipate that the restricted rotational freedom in the macrocyclic bis(Schiff base) 17, induced by the rigidity provided by the heterocyclic and aromatic units, as well as the presence of the two reacting



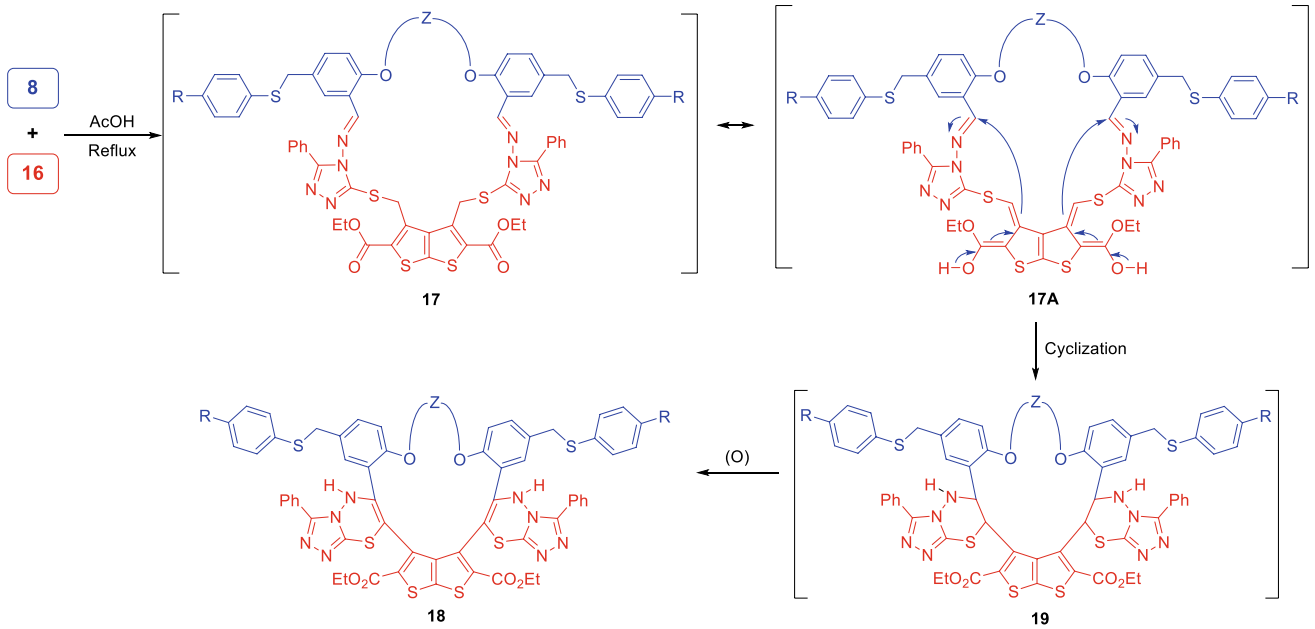
Scheme 7 Synthesis of thiamacrocyclic bis(methylthio) derivatives 14

Scheme 8 Synthesis of thieno[2,3-*b*]thiophene-linked macrocycle 18a, with fused [1, 2, 4]triazolo[3,4-*b*][1,3,4] thiadiazine units





Scheme 9 Synthesis of [1, 2, 4]triazolo[3,4-*b*][1,3,4]thiadiazine-fused macrocycle 18b



Scheme 10 Proposed mechanism for the formation of [1, 2, 4]triazolo[3,4-*b*][1,3,4]thiadiazine-fused macrocycles 18

species in close proximity in the same macrocycle, will aid in intramolecular ring closure.

Conclusion

In this study, the precursors bis(aldehydes), linked to aliphatic spacers via phenoxy linkage, were prepared and then reacted with the appropriate bis(amines) to afford a new series of macrocyclic as well as thiamacrocyclic bis(Schiff bases). Next, the utility of *S*-triazole-fused bis(amine) linked to a propane spacer as synthons was investigated in order to provide new heteromacrocyclic bis(amines) (Schiff bases). Unexpectedly, the reaction of *S*-triazole-fused bis(amine) linked to a thieno[2,3-*b*]thiophene spacer with the appropriate bis(aldehydes) afforded new [1,2,4]triazolo[3,4-*b*][1,3,4] thiadiazine-fused macrocycles.

Experimental

All solvents were acquired from commercial sources and used as received unless otherwise stated. All other chemicals were acquired from Merck or Aldrich. These chemicals were used without further purification. The melting points were measured on a Stuart melting point apparatus and are uncorrected. IR spectra were recorded on a Smart iTR, which is an ultra-high-performance, versatile attenuated total reflectance (ATR) sampling accessory on the Nicolet iS10 FT-IR spectrometer manufactured. NMR spectra were recorded on a Bruker Avance III 400 spectrometer (400 MHz for ^{1}H-NMR and 100 MHz for ^{13}C-NMR) using TMS as an internal standard and DMSO-d_6 as solvent and chemical shifts 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 carried out on a EuroVector instrument C, H, N analyzer EA3000 Series.

General procedure for the synthesis of bis(Schiff bases) 5a,b

A mixture of the appropriate 3b or 3c (10 mmol) and alkane-1,ω-diamine 4a,b (5 mmol) in glacial acetic acid (25 mL) was heated at reflux for 3 h. The mixture was cooled, filtered off, washed with ethanol, and then recrystallized from the suitable solvent.

2,2'-((1*E*,1'*E*)-(Propane-1,3-diylbis(azaneylylidene)) bis(methaneylylidene))bis(4-(((4-chlorophenyl)thio)methyl) phenol) (5a)

Yellow solid (dioxane/ethanol mixture, 85%); m.p. 130 °C; IR (υ cm^{-1}): 1640 (C = N); ^{1}H-NMR (DMSO-d_6): δ 1.99 (quint, J = 6.8 Hz, 2H, NCH_2CH_2), 3.65 (t, J = 6.8 Hz, 4H, 2 NCH_2), 4.18 (s, 4H, 2 SCH_2), 6.81 (d, J = 8.8 Hz, 2H, ArH), 7.30–7.32 (m, 10H, ArH), 7.38 (s, 2H, ArH), 8.51 (s, 2H, 2 CH = N), 13.44 (br s, 2H, 2 OH); ^{13}C-NMR (DMSO-d_6): δ 31.4, 36.1, 55.8, 116.7, 118.3, 126.8, 128.8, 130.0, 130.7, 131.7, 132.9, 135.7, 160.0, 165.8; Anal. for

$C_{31}H_{28}Cl_2N_2O_2S_2$ (595.6): C, 62.52; H, 4.74; N, 4.70; found: C, 62.58; H, 4.97; N, 4.91%.

2,2'-((1*E*,1'*E*)-(Butane-1,4-diylbis(azaneylylidene)) bis(methaneylylidene))bis(4-((*p*-tolylthio)methyl)phenol) (5b).

Yellow solid (dioxane/ethanol mixture, 88%); m.p. 142 °C; IR (υ cm^{-1}): 1641 (C = N); ^{1}H-NMR (DMSO-d_6): δ 1.68 (br s, 4H, 2 NCH_2CH_2), 2.23 (s, 6H, 2 *p*-CH_3), 3.61 (br s, 4H, 2 NCH_2), 4.11 (s, 4H, 2 SCH_2), 6.78 (d, J = 8.4 Hz, 2H, ArH), 7.09 (d, J = 8.0 Hz, 4H, ArH), 7.21 (d, J = 8.0 Hz, 4H, ArH), 7.26 (d, J = 8.4 Hz, 2H, ArH), 7.35 (s, 2H, ArH), 8.49 (s, 2H, 2 CH = N), 13.52 (br s, 2H, 2 OH); ^{13}C-NMR (DMSO-d_6): δ 20.5, 28.2, 36.0, 54.2, 116.6, 118.5, 126.9, 128.7, 130.4, 130.6, 130.7, 134.8, 135.6, 159.7, 165.9; MS *m/z* (%): 568 (M^+, 52.3); Anal. for $C_{34}H_{36}N_2O_2S_2$: C, 71.80; H, 6.38; N, 4.93; found: C, 72.05; H, 6.38; N, 4.76%.

General procedure for the synthesis of macrocyclic bis(Schiff bases) 7a–d

A solution of the appropriate bis(aldehydes) 8a-8d (5 mmol) in glacial acetic acid (150 mL) was added to a solution of the appropriate alkane-1,ω-diamine 4a,b (5 mmol) in glacial acetic acid (150 mL) and heated at reflux for 5 h. The solution was evaporated until only 25 mL remained, then cooled, filtered off, washed with ethanol, and recrystallized from the appropriate solvent.

Macrocycle 7a

Colorless solid (dioxane/ethanol mixture, 75%); m.p. 194–195 °C; IR (υ cm^{-1}): 1640 (C = N); ^{1}H-NMR (DMSO-d_6): δ 1.94 (br s, 4H, 2 OCH_2CH_2), 2.04 (br s, 2H, NCH_2CH_2), 3.66 (br s, 4H, 2 NCH_2), 4.10 (br s, 4H, 2 OCH_2), 4.23 (s, 4H, 2 SCH_2), 6.98 (d, J = 8.8 Hz, 2H, ArH), 7.17 (t, J = 7.6 Hz, 2H, ArH), 7.25–7.33 (m, 8H, ArH), 7.37 (d, J = 8.8 Hz, 2H, ArH), 7.83 (s, 2H, ArH), 8.65 (s, 2H, 2 CH = N); ^{13}C-NMR (DMSO-d_6): δ 25.2, 31.3, 36.0, 55.9, 68.0, 116.5, 118.6, 125.8, 126.5, 128.4, 128.9, 130.6, 135.6, 135.8, 159.9, 165.8; MS *m/z* (%): 580 (M^+, 44.2); Anal. for $C_{35}H_{36}N_2O_2S_2$: C, 72.38; H, 6.25; N, 4.82; found: C, 72.13; H, 5.99; N, 5.06%.

Macrocycle 7b

Colorless solid (dioxane/ethanol mixture, 74%); m.p. 188 °C; IR (υ cm^{-1}): 1644 (C = N); ^{1}H-NMR (DMSO-d_6): δ 1.68 (br s, 4H, 2 NCH_2CH_2), 1.94 (br s, 4H, 2 OCH_2CH_2), 3.60 (br s, 4H, 2 NCH_2), 4.09 (br s, 4H, 2 OCH_2), 4.24 (s, 4H, 2 SCH_2), 6.99 (d, J = 8.8 Hz, 2H, ArH), 7.32 (s, 8H, ArH), 7.37 (d, J = 8.8 Hz, 2H, ArH), 7.83 (s, 2H, ArH), 8.68 (s, 2H, 2 CH = N); ^{13}C-NMR (DMSO-d_6): δ 25.1, 28.2, 36.0, 54.2, 68.0, 116.3, 118.7, 126.5, 128.8, 130.1, 130.4, 130.8, 131.8, 135.5, 159.8, 165.7; Anal. for $C_{36}H_{36}Cl_2N_2O_2S_2$ (663.7): C, 65.15; H, 5.47; N, 4.22; found: C, 64.89; H, 5.75; N, 4.00%.

Macrocycle 7c

Colorless solid (dioxane/ethanol mixture, 72%); m.p. 180–183 °C; IR (υ cm^{-1}): 1642 (C = N); ^{1}H-NMR (DMSO-d_6): δ 1.62 (br s, 2H, $OCH_2CH_2CH_2$), 1.82 (br s, 4H, 2 OCH_2CH_2), 2.03 (br s, 2H, NCH_2CH_2), 2.24 (s, 6H, 2 *p*-CH_3), 3.65 (br s, 4H, 2 NCH_2), 4.04 (br s, 4H, 2 OCH_2), 4.16 (s, 4H, 2 SCH_2), 6.95 (d, J = 8.4 Hz, 2H, ArH), 7.09 (d, J = 8.0 Hz, 4H, ArH), 7.21 (d, J = 8.0 Hz, 4H, ArH), 7.34 (d, J = 8.8 Hz, 2H, ArH), 7.78 (s, 2H, ArH), 8.60 (s, 2H, 2 CH = N); ^{13}C-NMR (DMSO-d_6): δ 20.5, 22.1, 28.2, 31.5, 36.1, 55.7, 68.2, 116.6, 118.4, 126.9, 128.8, 130.3, 130.7, 130.8, 134.7, 135.8, 159.9, 165.9; MS *m/z* (%): 622 (M^+, 27.7); Anal. for $C_{38}H_{42}N_2O_2S_2$: C, 73.27; H, 6.80; N, 4.50; found: C, 73.01; H, 6.98; N, 4.72%.

Macrocycle 7d

Colorless solid (dioxane/ethanol mixture, 76%); m.p. 174–176 °C; IR (υ cm^{-1}): 1639 (C = N); ^{1}H-NMR (DMSO-d_6): δ 1.62 (br s, 6H, $OCH_2CH_2CH_2$ and 2 NCH_2CH_2), 1.82 (br s, 4H, 2 OCH_2CH_2), 2.23 (s, 6H, 2 *p*-CH_3), 3.60 (br s, 4H, 2 NCH_2), 4.04 (br s, 4H, 2 OCH_2), 4.16 (s, 4H, 2 SCH_2), 6.96 (d, J = 8.4 Hz, 2H, ArH), 7.08 (d, J = 8.0 Hz, 4H, ArH), 7.21 (d, J = 8.0 Hz, 4H, ArH), 7.33 (d, J = 8.8 Hz, 2H, ArH), 7.80 (s, 2H, ArH), 8.62 (s, 2H, 2 CH = N); ^{13}C-NMR (DMSO-d_6): δ 20.5, 22.0, 28.1, 28.2, 36.1, 54.2, 68.2, 116.8, 118.4, 126.9, 128.9, 130.5, 130.8, 131.0, 134.9, 135.8, 159.8, 165.7; Anal. for $C_{39}H_{44}N_2O_2S_2$ (636.9): C, 73.55; H, 6.96; N, 4.40; found: C, 73.31; H, 6.72; N, 4.59%.

General procedure for the synthesis of alkane-linked bis(aldehydes) 8a–c

A mixture of the appropriate benzaldehydes 3a–c (10 mmol), 1,ω-dibromoalkanes 6 (5 mmol) and anhydrous potassium carbonate (20 mmol) in DMF (30 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.

6,6'-(Butane-1,4-diylbis(oxy))bis(3-((phenylthio)methyl) benzaldehyde) (8a)

Colorless solid (dioxane/ethanol mixture, 83%); m.p. 158–160 °C; IR (υ cm^{-1}): 1667 (CO); ^{1}H-NMR (DMSO-d_6): δ 1.95 (t, J = 6.4 Hz, 4H, 2 OCH_2CH_2), 4.15 (t, J = 6.4 Hz,

4H, 2 OCH_2), 4.23 (s, 4H, 2 SCH_2), 7.14 (d, J = 8.8 Hz, 2H, ArH), 7.19 (t, J = 7.6 Hz, 2H, ArH), 7.25–7.33 (m, 8H, ArH), 7.59 (d, J = 8.8 Hz, 2H, ArH), 7.64 (s, 2H, ArH), 10.31 (s, 2H, 2 CHO); ^{13}C-NMR (DMSO-d_6): δ 25.1, 35.4, 68.0, 113.5, 123.8, 125.9, 127.6, 128.4, 128.9, 129.7, 135.6, 136.6, 160.0, 188.9; MS *m/z* (%): 542 (M^+, 36.9); Anal. for $C_{32}H_{30}O_4S_2$: C, 70.82; H, 5.57; found: C, 71.06; H, 5.31%.

6,6'-(Butane-1,4-diylbis(oxy))bis(3-(((4-chlorophenyl)thio) methyl)benzaldehyde) (8b)

Colorless solid (dioxane/ethanol mixture, 85%); m.p. 164–166 °C; IR (υ cm^{-1}): 1668 (CO); ^{1}H-NMR (DMSO-d_6): δ 1.95 (t, J = 6.4 Hz, 4H, 2 OCH$_2$CH_2), 4.17 (t, J = 6.4 Hz, 4H, 2 OCH_2), 4.24 (s, 4H, 2 SCH_2), 7.15 (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), 10.31 (s, 2H, 2 CHO); ^{13}C-NMR (DMSO-d_6): δ 25.2, 35.5, 68.0, 113.6, 123.8, 127.7, 128.8, 129.2, 130.2, 130.6, 134.7, 136.6, 160.0, 188.9; Anal. for $C_{32}H_{28}Cl_2O_4S_2$ (611.5): C, 62.84; H, 4.61; found: C, 62.58; H, 4.86%.

6,6'-(Pentane-1,5-diylbis(oxy))bis(3-((*p*-tolylthio)methyl) benzaldehyde) (8c)

Colorless solid (dioxane/ethanol mixture, 89%); m.p. 112 °C; IR (υ cm^{-1}): 1662 (CO); ^{1}H-NMR (DMSO-d_6): δ 1.62 (br s, 2H, OCH$_2$CH$_2$CH_2), 1.83 (br s, 4H, 2 OCH$_2$CH_2), 2.23 (s, 6H, 2 p-CH$_3$), 4.11 (br s, 4H, 2 OCH_2), 4.16 (s, 4H, 2 SCH_2), 7.08 (d, J = 8.0 Hz, 4H, ArH), 7.12 (d, J = 8.8 Hz, 2H, ArH), 7.21 (d, J = 8.0 Hz, 4H, ArH), 7.55 (d, J = 8.8 Hz, 2H, ArH), 7.61 (s, 2H, ArH), 10.32 (s, 2H, 2 CHO); ^{13}C-NMR (DMSO-d_6): δ 20.5, 22.0, 28.1, 36.1, 68.2, 113.5, 123.8, 127.5, 129.2, 129.5, 129.9, 131.6, 135.6, 136.6, 160.0, 188.8; Anal. for $C_{35}H_{36}O_4S_2$ (584.7): C, 71.89; H, 6.21; found: C, 72.04; H, 6.09%.

General procedure for the synthesis of thiamacrocyclic bis(Schiff bases) 10a–c

A solution of the appropriate bis(aldehydes) 8a–d (5 mmol) in glacial acetic acid (150 mL) was added to a solution of the appropriate 2,2'-(alkane-1,ω-diylbis(sulfanediyl))dianiline dihydrochloride 9a,b (5 mmol) and anhydrous sodium acetate (12 mmol) in glacial acetic acid (150 mL) and heated at reflux for 5 h. The solution was evaporated until only 25 mL remained, then cooled, filtered off, washed with water, and recrystallized from the appropriate solvent.

Macrocycle 10a

Colorless solid (dioxane, 68%); m.p. 194 °C; IR (υ cm^{-1}): 1593 (C = N); ^{1}H-NMR (DMSO-d_6): δ 1.68 (br s, 4H, 2 SCH$_2$CH_2), 1.94 (br s, 4H, 2 OCH$_2$CH_2), 2.97 (br s, 4H, 2 SCH_2CH$_2$), 4.10 (br s, 4H, 2 OCH_2), 4.24 (s, 4H, 2 SCH_2), 6.99 (d, J = 8.8 Hz, 2H, ArH), 7.15–7.21 (m, 4H, Ar–H), 7.23 (t, J = 8.0 Hz, 2H, ArH), 7.27–7.44 (m, 14H, ArH), 7.83 (s, 2H, ArH), 8.67 (s, 2H, 2 CH = N); ^{13}C-NMR (DMSO-d_6): δ 25.2, 27.5, 31.2, 36.0, 68.0, 116.6, 118.4, 121.5, 125.7, 126.7, 127.1, 127.3, 128.1, 128.4, 128.8, 130.5, 130.6, 135.5, 135.8, 146.8, 159.8, 162.4; Anal. for $C_{48}H_{46}N_2O_2S_4$ (811.1): C, 71.08; H, 5.72; N, 3.45; found: C, 70.89; H, 5.99; N, 3.18%.

Macrocycle 10b

Colorless solid (dioxane, 70%); m.p. 200–203 °C; IR (υ cm^{-1}): 1591 (C = N); ^{1}H-NMR (DMSO-d_6): δ 1.55 (br s, 6H, SCH$_2$CH$_2$CH_2 and 2 SCH$_2$CH_2), 1.95 (br s, 4H, 2 OCH$_2$CH_2), 2.94 (br s, 4H, 2 SCH_2CH$_2$), 4.08 (br s, 4H, 2 OCH_2), 4.23 (s, 4H, 2 SCH_2), 6.97 (d, J = 8.8 Hz, 2H, ArH), 7.17 (d, J = 8.0 Hz, 2H, ArH), 7.22 (t, J = 8.0 Hz, 2H, ArH), 7.32 (s, 8H, ArH), 7.35–7.38 (m, 4H, ArH), 7.42 (t, J = 8.0 Hz, 2H, ArH), 7.84 (s, 2H, ArH), 8.71 (s, 2H, 2 CH = N); ^{13}C-NMR (DMSO-d_6): δ 25.2, 27.2, 27.9, 31.8, 35.9, 68.1, 116.9, 118.2, 121.5, 126.6, 126.9, 127.2, 128.2, 128.8, 130.2, 130.7, 130.8, 131.6, 132.9, 135.5, 147.0, 159.7, 162.0; Anal. for $C_{49}H_{46}Cl_2N_2O_2S_4$ (894.0): C, 65.83; H, 5.19; N, 3.13; found: C, 66.07; H, 4.95; N, 2.87%.

Macrocycle 10c

Colorless solid (dioxane, 67%); m.p. 192 °C; IR (υ cm^{-1}): 1594 (C = N); ^{1}H-NMR (DMSO-d_6): δ 1.55 (br s, 6H, SCH$_2$CH$_2$CH_2 and 2 SCH$_2$CH_2), 1.61 (br s, 2H, OCH$_2$CH$_2$CH_2), 1.82 (br s, 4H, 2 OCH$_2$CH_2), 2.23 (s, 6H, 2 p-CH$_3$), 2.93 (br s, 4H, 2 SCH_2CH$_2$), 4.02 (br s, 4H, 2 OCH_2), 4.15 (s, 4H, 2 SCH$_2$), 6.95 (d, J = 8.4 Hz, 2H, ArH), 7.07 (d, J = 8.0 Hz, 4H, ArH), 7.15 (d, J = 8.0 Hz, 2H, ArH), 7.20–7.24 (m, 6H, ArH), 7.33–7.36 (m, 4H, ArH), 7.40 (t, J = 8.0 Hz, 2H, ArH), 7.79 (s, 2H, ArH), 8.67 (s, 2H, 2 CH = N); ^{13}C-NMR (DMSO-d_6): δ 20.4, 22.1, 27.1, 27.8, 28.2, 31.7, 36.0, 68.1, 116.7, 118.2, 121.7, 126.9, 127.0, 127.2, 128.0, 128.6, 130.4, 130.6, 130.7, 130.8, 135.0, 136.6, 147.2, 159.8, 162.3; Anal. for $C_{52}H_{54}N_2O_2S_4$ (867.2): C, 72.02; H, 6.28; N, 3.23; found: C, 72.26; H, 6.04; N, 2.99%.

General procedure for the synthesis of *S*-triazole-fused thiamacrocyclic bis(Schiff bases) 12a–c

A solution of the bis(aldehydes) 8a–c (5 mmol) in glacial acetic acid (150 mL) was added to a solution of bis(4-amino-4*H*-1,2,4-triazole-3-thiol) 11 (5 mmol) in glacial acetic acid (150 mL) and heated at reflux for 8 h. The solution was evaporated until only 25 mL remained, then cooled, filtered off,

washed with ethanol, and recrystallized from the appropriate solvent.

Macrocycle 12a

Colorless solid (dioxane, 68%); m.p. 226–228 °C; IR (υ cm^{-1}): 1628 (C=N); ^{1}H-NMR (DMSO-d_6): δ 1.92 (br s, 4H, 2 OCH_2CH_2), 2.04 (br s, 2H, SCH_2CH_2), 3.23 (br s, 4H, 2 SCH_2CH_2), 4.12 (br s, 4H, 2 OCH_2), 4.25 (s, 4H, 2 SCH_2), 6.96 (d, J=8.8 Hz, 2H, ArH), 7.15 (t, J=7.6 Hz, 2H, ArH), 7.27–7.33 (m, 8H, ArH), 7.35 (d, J=8.8 Hz, 2H, ArH), 7.79 (s, 2H, ArH), 10.49 (s, 2H, 2 CH=N), 13.94 (s, 2H, 2 SH); ^{13}C-NMR (DMSO-d_6): δ 25.4, 27.7, 31.5, 36.2, 68.2, 113.9, 125.7, 127.0, 127.5, 128.3, 128.8, 130.4, 135.6, 135.9, 149.7, 154.5, 157.2, 162.3; Anal. for $C_{39}H_{38}N_8O_2S_6$ (843.1): C, 55.56; H, 4.54; N, 13.29; found: C, 55.31; H, 4.78; N, 13.03%.

Macrocycle 12b

Colorless solid (dioxane, 63%); m.p. 230–233 °C; IR (υ cm^{-1}): 1630 (C=N); ^{1}H-NMR (DMSO-d_6): δ 1.93 (br s, 4H, 2 OCH_2CH_2), 2.03 (br s, 2H, SCH_2CH_2), 3.21 (br s, 4H, 2 SCH_2CH_2), 4.12 (br s, 4H, 2 OCH_2), 4.25 (s, 4H, 2 SCH_2), 6.96 (d, J=8.8 Hz, 2H, ArH), 7.32 (s, 8H, ArH), 7.36 (d, J=8.8 Hz, 2H, ArH), 7.79 (s, 2H, ArH), 10.47 (s, 2H, 2 CH=N), 13.88 (s, 2H, 2 SH); ^{13}C-NMR (DMSO-d_6): δ 25.3, 27.6, 31.5, 36.1, 68.3, 113.7, 126.8, 127.4, 128.7, 130.1, 130.4, 130.5, 131.8, 135.9, 149.3, 154.2, 157.7, 162.0; Anal. for $C_{39}H_{36}Cl_2N_8O_2S_6$ (912.0): C, 51.36; H, 3.98; N, 12.29; found: C, 51.12; H, 4.22; N, 12.05%.

Macrocycle 12c

Colorless solid (dioxane, 65%); m.p. 226 °C; IR (υ cm^{-1}): 1631 (C=N); ^{1}H-NMR (DMSO-d_6): δ 1.64 (br s, 2H, $OCH_2CH_2CH_2$), 1.83 (br s, 4H, 2 OCH_2CH_2), 2.05 (br s, 2H, SCH_2CH_2), 2.24 (s, 6H, 2 p-CH_3), 3.24 (br s, 4H, 2 SCH_2CH_2), 4.08 (br s, 4H, 2 OCH_2), 4.18 (s, 4H, 2 SCH_2), 6.95 (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), 7.33 (d, J=8.8 Hz, 2H, ArH), 7.75 (s, 2H, ArH), 10.54 (s, 2H, 2 CH=N), 13.97 (s, 2H, 2 SH); ^{13}C-NMR (DMSO-d_6): δ 20.4, 22.2, 27.5, 28.3, 31.6, 36.2, 68.1, 113.8, 126.9, 127.6, 128.7, 130.2, 130.5, 130.7, 134.6, 135.5, 149.0, 153.8, 158.4, 161.7; Anal. for $C_{42}H_{44}N_8O_2S_6$ (885.2): C, 56.99; H, 5.01; N, 12.66; found: C, 57.25; H, 4.83; N, 12.90%.

General procedure for the synthesis of thiamacrocyclic bis(methylthio) derivatives 14a–c

Method 'A'

A mixture of macrocycles 12a–c (5 mmol) and iodomethane **13** (10 mmol) in methanolic sodium methoxide solution (prepared from the reaction of 10 mmol sodium metal in 25 mL of methanol) was heated at reflux for 1 h. The mixture was cooled, filtered off, washed with ethanol, and recrystallized from the appropriate solvent.

Method 'B'

A solution of the bis(aldehyde) 8c (5 mmol) in glacial acetic acid (150 mL) was added to a solution of bis(4-amino-3-methylthio-4*H*-1,2,4-triazole) 15 (5 mmol) in glacial acetic acid (150 mL) and heated at reflux for 8 h. The solution was evaporated until only 25 mL remained, then cooled, filtered off, washed with ethanol, and recrystallized from the appropriate solvent.

Macrocycle 14a Colorless solid (dioxane/ethanol mixture, 84%); m.p. 172 °C; IR (υ cm^{-1}): 1628 (C=N); ^{1}H-NMR (DMSO-d_6): δ 1.90 (br s, 4H, 2 OCH_2CH_2), 2.02 (br s, 2H, SCH_2CH_2), 2.67 (s, 6H, 2 SCH_3), 3.19 (br s, 4H, 2 SCH_2CH_2), 4.11 (br s, 4H, 2 OCH_2), 4.23 (s, 4H, 2 SCH_2), 6.99 (d, J=8.8 Hz, 2H, ArH), 7.18 (t, J=7.6 Hz, 2H, ArH), 7.26–7.33 (m, 8H, ArH), 7.37 (d, J=8.8 Hz, 2H, ArH), 7.81 (s, 2H, ArH), 8.97 (s, 2H, 2 CH=N); ^{13}C-NMR (DMSO-d_6): δ 13.5, 25.4, 27.8, 31.5, 36.1, 68.2, 113.8, 125.7, 127.0, 127.6, 128.3, 128.9, 130.4, 135.7, 135.9, 149.8, 154.4, 157.2, 162.2; Anal. for $C_{41}H_{42}N_8O_2S_6$ (871.2): C, 56.53; H, 4.86; N, 12.86; found: C, 56.29; H, 5.09; N, 13.13%.

Macrocycle 14b Colorless solid (dioxane/ethanol mixture, 87%); m.p. 184 °C; IR (υ cm^{-1}): 1630 (C=N); ^{1}H-NMR (DMSO-d_6): δ 1.91 (br s, 4H, 2 OCH_2CH_2), 2.01 (br s, 2H, SCH_2CH_2), 2.66 (s, 6H, 2 SCH_3), 3.20 (br s, 4H, 2 SCH_2CH_2), 4.11 (br s, 4H, 2 OCH_2), 4.22 (s, 4H, 2 SCH_2), 6.98 (d, J=8.8 Hz, 2H, ArH), 7.33 (s, 8H, ArH), 7.37 (d, J=8.8 Hz, 2H, ArH), 7.82 (s, 2H, ArH), 8.95 (s, 2H, 2 CH=N); ^{13}C-NMR (DMSO-d_6): δ 13.6, 25.4, 27.7, 31.6, 36.2, 68.2, 113.9, 126.7, 127.3, 128.8, 130.2, 130.4, 130.7, 131.9, 135.7, 149.6, 154.5, 158.2, 162.4; Anal. for $C_{41}H_{40}Cl_2N_8O_2S_6$ (940.0): C, 52.38; H, 4.29; N, 11.92; found: C, 52.65; H, 4.04; N, 11.84%.

Macrocycle 14c Colorless solid (dioxane/ethanol mixture, 86% using 'A'; 72% using 'B'); m.p. 164–166 °C; IR (υ cm^{-1}): 1631 (C=N); ^{1}H-NMR (DMSO-d_6): δ 1.61 (br s, 2H, $OCH_2CH_2CH_2$), 1.82 (br s, 4H, 2 OCH_2CH_2), 2.01 (br s, 2H, SCH_2CH_2), 2.22 (s, 6H, 2 p-CH_3), 2.65 (s, 6H,

2 SCH_3), 3.20 (br s, 4H, 2 SCH_2CH_2), 4.06 (br s, 4H, 2 OCH_2), 4.15 (s, 4H, 2 SCH_2), 6.94 (d, J = 8.8 Hz, 2H, ArH), 7.09 (d, J = 8.0 Hz, 4H, ArH), 7.21 (d, J = 8.0 Hz, 4H, ArH), 7.32 (d, J = 8.8 Hz, 2H, ArH), 7.78 (s, 2H, ArH), 8.91 (s, 2H, 2 CH=N); ^{13}C-NMR (DMSO-d_6): δ 13.5, 20.3, 22.2, 27.6, 28.2, 31.5, 36.1, 68.2, 113.7, 126.7, 127.5, 128.8, 130.2, 130.5, 130.8, 134.4, 135.8, 148.8, 154.0, 158.2, 161.9; Anal. for $C_{44}H_{48}N_8O_2S_6$ (913.2): C, 57.87; H, 5.30; N, 12.27; found: C, 58.14; H, 5.52; N, 12.04%.

General procedure for the synthesis of [1, 2, 4] triazolo[3,4-*b*][1,3,4]thiadiazine-fused macrocycles 18a,b

A solution of the bis(aldehydes) 8a,b (5 mmol) in glacial acetic acid (150 mL) was added to a solution of bis(4-amino-3-phenyl-4*H*-1,2,4-triazole) 16 (5 mmol) in glacial acetic acid (150 mL) and heated at reflux for 5 h. The solution was evaporated until only 25 mL remained, then cooled, filtered off, washed with ethanol, and recrystallized from the appropriate solvent.

Macrocycle 18a

Colorless solid (dioxane, 52%); m.p. 230–233 °C; IR (υ cm^{-1}): 3413 (NH), 1702 (CO); ^{1}H-NMR (DMSO-d_6): δ 1.07 (t, J = 7.2 Hz, 6H, 2 OCH_2CH_3), 1.87 (br s, 4H, 2 OCH_2CH_2), 3.91 (q, J = 7.2 Hz, 4H, 2 OCH_2CH_3), 4.04 (br s, 4H, 2 OCH_2), 4.26 (s, 4H, 2 SCH_2), 6.90 (d, J = 8.4 Hz, 2H, ArH), 7.25 (d, J = 8.4 Hz, 2H, ArH), 7.31 (s, 8H, ArH), 7.36–7.44 (m, 8H, ArH), 7.88 (d, J = 7.6 Hz, 4H, ArH), 9.32 (s, 2H, 2 NH); ^{13}C-NMR (DMSO-d_6): δ 14.0, 25.3, 36.2, 61.4, 68.2, 118.2, 121.0, 124.0, 126.8, 127.4, 127.8, 128.4, 128.7, 130.1, 130.4, 131.8, 133.0, 133.1, 136.2, 137.2, 138.9, 143.5, 145.8, 149.8, 151.2, 154.3, 155.7, 161.1; Anal. for $C_{62}H_{48}Cl_2N_8O_6S_6$ (1264.3): C, 58.90; H, 3.83; N, 8.86; found: C, 59.14; H, 4.06; N, 8.63%.

Macrocycle 18b

Colorless solid (dioxane, 55%); m.p. 264–266 °C; IR (υ cm^{-1}): 3416 (NH), 1703 (CO); ^{1}H-NMR (DMSO-d_6): δ 1.08 (t, J = 7.2 Hz, 6H, 2 OCH_2CH_3), 1.59 (br s, 2H, $OCH_2CH_2CH_2$), 1.79 (br s, 4H, 2 OCH_2CH_2), 2.23 (s, 6H, 2 *p*-CH_3), 3.92 (q, J = 7.2 Hz, 4H, 2 OCH_2CH_3), 4.02 (br s, 4H, 2 OCH_2), 4.22 (s, 4H, 2 SCH_2), 6.88 (d, J = 8.4 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 = 8.4 Hz, 2H, ArH), 7.35 (s, 2H, ArH), 7.39–7.45 (m, 6H, ArH), 7.86 (d, J = 7.6 Hz, 4H, ArH), 9.29 (s, 2H, 2 NH); ^{13}C-NMR (DMSO-d_6): δ 13.9, 20.4, 22.1, 28.2, 36.2, 61.3, 68.2, 118.1, 121.2, 124.3, 126.7, 127.2, 127.8, 128.2, 128.6, 130.4, 130.5, 130.8, 133.0, 134.9, 136.3, 137.0, 138.7, 143.2, 145.6, 149.6, 151.1, 154.2, 155.9, 161.2; Anal. for $C_{65}H_{56}N_8O_6S_6$ (1237.5): C, 63.08; H, 4.56; N, 9.05; found: C, 62.85; H, 4.34; N, 8.84%.

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