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ARTICLE

Synthesis, antimicrobial activity, and ion transportation investigation of four new [1 + 1] condensed furan and thiophene-based cycloheterophane amides

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Abstract

Four new macrocyclic compounds with thiophene (**L1** and **L2**) and furan (**L3** and **L4**) rings were synthesized and characterized by IR, ^{1}H NMR, ^{13}C NMR, and Q-TOF spectral data. Macrocyclic amides (**L1**, **L2**, **L3**, and **L4**) were tested for ion transportation with Na^{+} and K^{+} ions, and also, antimicrobial activities were investigated against the Gram-negative *Escherichia coli* ATCC 25922, Gram-positive *Staphylococcus aureus* ATCC 25923, Gram-negative *Listeria monocytogenes* ATCC 19115, Gram-negative *Salmonella typhimurium* ATCC 14028, *Bacillus cereus* bacteria, and *Candida albicans* ATCC 10231 for all amides.

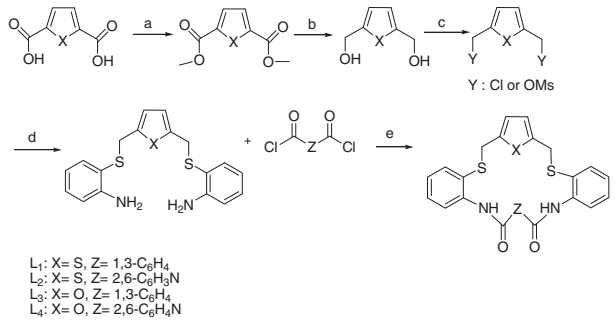
1 | INTRODUCTION

Macrocyclic compounds having heteroatoms like S,O,N are common synthetic targets in drug chemistry,[1–4] coordination chemistry,[5–7] material applications,[8–10] and nanotechnology.[11] The importance of these cyclic and macrocyclic structures is realized early in the development of different areas.[12–15] Especially macrocyclic compounds are advantageous over acyclic macro-compounds as they have cavity with varying size.[16–18] One of these classes of compounds, cyclophane peptides, which are known as cyclic peptides, has been found extensively in natural products and marine environment.[19–21] For example, plitidepsin isolated from Aplidium albicans affects the shrinkage of tumors in pancreas, stomach, bladder, and prostate cancers.[22] Other popular macrocyclic peptide drug vancomycin is made by the soil bacterium *Amycolatopsis orientalis* and used to treat a number of bacterial infections as an antibiotic.[23] Gramicidin S is also a cyclic peptide and an antibiotic that is used for some Gram-positive and Gram-negative bacteria as well as some fungi.[24] As seen in these examples, there are lots of macrocyclic compounds derived from natural products that then are used as commercial drugs, and as a result, the interest of exploring these types of macrocyclic compounds is increasing day by day.[25,26] In medicinal chemistry, we encounter the biomimetic synthesis of cyclic peptide analogues[27] and marvelous new macrocyclic derivatives that are selective antimicrobials,[28–31] new therapeutic,[25] and more resistant agents to proteolytic degradation[32,33] and fluorescent.[34] Another important aspect of these macrocyclic compounds is that these compounds are carrier for biologically important ions, neutral molecules, or catalysts.[35–39]

In our recent studies, we have achieved the synthesis of macrocyclic tetra-amides bearing nitrogen, sulphur, and oxygen and investigated pharmacological and ion-transporting properties of these compounds.[37,40–42] As a continuation of our previous work, the macrocyclic amides that have furan or thiophene ring were synthesized by following the same experimental procedure, and also, antimicrobial activities of these compounds were explored. These compounds have been named according to the IUPAC Phane Nomenclature System.[43,44]

2 | RESULTS AND DISCUSSION

All the macrocyclic amides were prepared with the route that was shown in Scheme 1, predicated on the condensation of diacid chlorides with diamines at low temperature in dry dichloromethane. The synthetic procedure to



SCHEME 1 Reagents and conditions: a, CH_3OH, $SOCl_2$, 24 hours, 58% and 84%; b, THF, $LiAlH_4$, 2 hours, 54% and 93%; c, MsCl, Et_3N, CH_2Cl_2, 38% and $SOCl_2$, CH_2Cl_2, pyridine, 58%; d, K_2CO_3, DMF, 2-aminothiophenol 84% and 83%; e, CH_2Cl_2, Et_3N, 0 °C, 5 hours, room temperature overnight 34%, 48%, 31%, and 28% yields

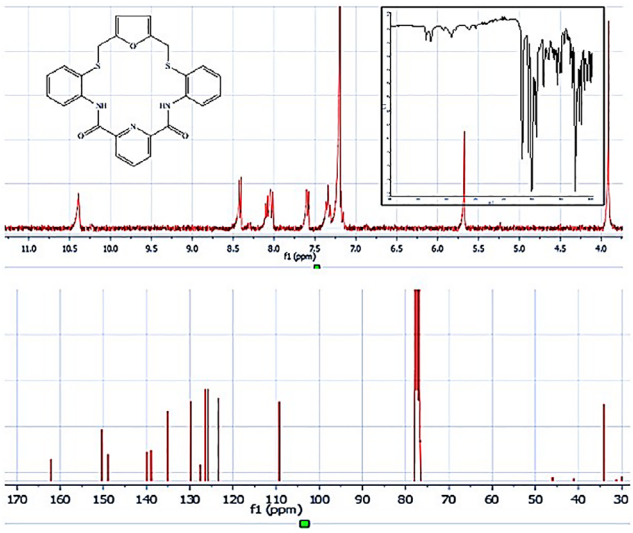


FIGURE 1 1,7(1,2)-dibenzena-4(2,6)-pyridina-2,6-diaza-3,5-dioxo-8,12-dithia-10(2,5)-furanacyclododecafan (**L4**) ^{1}H NMR, ^{13}C NMR spectra in $CDCl_3$-*d* and IR spectra [Color figure can be viewed at wileyonlinelibrary.com]

obtain pyridine-2,6-dicarbonyl dichloride and benzene-2,-6-dicarbonyl dichloride was concerted from the literature.[45] For the synthesis of 2,5-dihydroxymethylfuran and 2,5-dihydroxymethylthiophene, 2,5-dicarboxylic acids of the compounds were selected, and they were converted to the ester forms by known procedure.[46] The diols were prepared from related esters by reduction with $LiAlH_4$ and used without any purification.[47] The synthetic procedure to obtain the mesylate and chloride was adapted with some modifications.[48,49] Then, they were reacted with 2-aminothiophenol to generate diamines. The full procedure for the preparation of the compounds is given in Section 4. The spectroscopic data from the Q-TOF, FTIR, ^{1}H NMR, and ^{13}C NMR spectroscopy provide useful information about their formation and structural characterization. In Figure 1, ^{1}H NMR, ^{13}C NMR, and FTIR spectra of compound **L4** are illustrated.

2.1 | Q-TOF spectra

The Q-TOF spectra of the macrocyclic compounds give important structural information about the nature of the compounds. The mass spectra show a molecular positive ion peaks $[M + H]^+$ for each corresponding molecule. The Q-TOF values are compatible with the calculated ones.

2.2 | Vibrational spectra

The characteristic wave regions for macrocyclic amides are as follows: 3300 to 3200 cm^{-1} corresponding to *ν* (H—O—H) lattice water, *ν*(N—H) amides, and *ν*(C—H) aliphatic; and aromatic characteristic modes are follows: 1670 to 800 cm^{-1} belonging to *ν*(CONH—) amides, *ν* (C—N), and *ν*(C═C) aromatic vibration modes. The bands corresponding to free aniline —NH_2 *ν*(N—H) (3410 cm^{-1}) were not observed in the IR spectra of the products, which suggests complete condensation of the reactions and possible formation of amide linkages. Another signal carbonyl of acid chloride COCl *ν*(CO) (1750 cm^{-1}) disappeared in the IR spectra possibly because of the amide formation.

2.3 | Magnetic resonance spectra

The ^{1}H NMR spectra of the (**L1**-**L4**) molecules in $CDCl_3$ do not give any signal corresponding to 2-aminothiophenol —NH_2 (at 6.8 ppm); instead, they show broad bands in the region of 8.30 to 10.40 ppm corresponding to amide protons. When we compare the methylene proton chemical shifts with the starting material diamines, no significant changes were observed as expected, and sharp singlets around 4 ppm were observed belonging to the macrocyclic products. In the ^{13}C NMR spectra of the cyclic products, peaks related to the acid chlorides COCl (C═O) (~173 ppm) disappeared; instead, (CONH) signals were observed between 166 and 171 ppm.

2.4 | Ion transport

Macrocycles with cavities are useful transport vehicles for biologically important ions.[35] As an easy application, we tried Na^+ and K^+ selectivities of macrocycles **L1**, **L2**, **L3**, and **L4.** To examine the ion transportation, we used a U tube. First, macrocyclic compound (**L1**) (124 mg,

0.20 mmol) was dissolved in dichloromethane and transferred to glass vessel as shown in Figure 2. Then, one arm of the U tube was filled with distilled water (6 mL), and the other arm was filled with distilled water (6 mL) containing metal cations (NaCl, 0.585 g, 10 mmol; KCl, 0.740 g 10 mmol).

Dichloromethane layer was stirred gently for 72 hours, and elemental analysis was performed in AES for water phases. Results were given at Table 1. For **L1** and **L2**, the experiments proved that K^+ and Na^+ ions were transported by both cyclophane amides from one arm to the other over with a very low rate, and there was no observed selectivity of this process at all. But for **L3** and **L4**, the observation shows that K^+ ion selectivity was better than Na^+. According to these results, thiophene ring had no effect on Na^+ or K^+ ion selectivity; on the other hand, furan ring increases K^+ ion selectivity. The cavities and the coordination may not be appropriate for the selected ions with thiophene; however, using furan instead of thiophene in the macrocycle has increased the selectivity of K^+. These results support that both the cavity and the ring components of the macrocycles were important in the studies of ion selectivity.[35,37,42] Additionally, to prove the ion-carrying properties of macrocyclic compounds, a single crystal of a coordination compound of macrocycles with Na^+ or K^+ ion was also tried, but there was no success in those attempts.

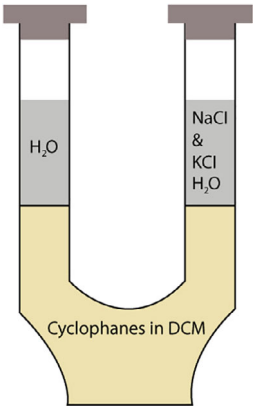


FIGURE 2 Apparatus used for ion transport study [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 1 Metal ion rate (mg, %) transport of macrocycles (**L1**, **L2**, **L3**, and **L4**)

Macrocycle	Na^+	K^+
L1	% 1,73	% 1.62
L2	% 1,46	% 1,26
L3	% 1,31	% 4,72
L4	% 3,49	% 6,68

In order to show ion coordination of macrocyclic compounds, especially **L4**, which carries relatively the highest amount of ion, was examined by ^1H NMR. Afterwards, the methylene chloride phase in U tube was evaporated; ^1H NMR spectrum of residue showed slight chemical shifts for SCH_2 and the CONH signals towards downfield from 3.91 to 3.98 and from 10.39 to 10.46 ppm, respectively.

2.5 | Microbial activity

The results concerning in vitro antimicrobial activities of the macrocycles and minimal inhibitory concentration (MIC) values of associated antibiotic and antifungal reagents are listed in Table 2.[50] Five different concentrations were studied, and percentage of alive values was related to the macrocyclic compounds that affect the

TABLE 2 Antimicrobial activity (MIC, μmol/mL) of the (**L1**-**L4**) compounds

MICs, μmol/mL						
	Gram positive			Gram negative		Yeast
Compounds	*Staphylococcus aureus*	*Bacillus cereus*	*Escherichia coli*	*Listeria monocytogenes*	*Salmonella typhimurium*	*Candida albicans*
L1	>0.204	>0.204	0.204	>0.204	>0.204	>0.204
L2	>0.204	0.204	>0.204	>0.204	>0.204	0.102
L3	>0.211	0.013	0.211	0.105	>0.211	>0.211
L4	>0.211	0.007	0.211	0.105	>0.211	>0.211
GEN	-	0.001	-	-	-	-
AMP	0.046 -	-	0.046	0.046	0.046	-
Ab	-	-	-	-	-	0.002

Note: In each case, dual tests were performed, and the average was taken as the final reading.
Abbreviation: MIC, minimal inhibitory concentration.

microorganisms by different ways. Experimental results indicated that compounds **L3** and **L4** show good activities against Gram-positive pathogen *Bacillus cereus*, moderate activity against *Listeria*, and low activity against *Escherichia coli*. Compound **L2** shows moderate activity against *Candida albicans* and low activity against *B cereus* and *Listeria*. Compound **L1** shows low activity to *E coli*. None of the compounds were effective on *Salmonella typhimurium* and *Staphylococcus aureus*.

3 | CONCLUSIONS

As a result, four new [1 + 1] condensed furan and thiophene-based cycloheterophane amides were synthesized and characterized by IR, NMR, and Q-TOF. These compounds were tested against Gram-positive (*S aureus* ATCC 25923 and *B cereus* ATCC 11778), Gram-negative (*E coli* ATCC 25922 and *Listeria monocytogenes* ATCC 19115, and *Salmonella typhimurium* ATCC 14028) bacteria, yeast culture (*C albicans* ATCC 10231), and especially **L3** and **L4** were effective against *B cereus*. For ion transportation, there was not any significant selectivity between Na^+ and K^+ ions with **L1** and **L2**, while the selectivity for **L3** and **L4** was higher only for K^+ ions.

4 | EXPERIMENTAL SECTION

4.1 | General

All chemicals including pyridine-2,6-dicarboxylic acid, benzene-1,3-dicarboxylic acid, and solvents were reagent grade, and they were used as purchased without further purification except dichloromethane (molecular sieve under Ar) and THF (Na/benzophenone under Ar). ^{1}H NMR and ^{13}C NMR spectra were recorded in deuteriochloroform solution or deuterioacetone with a Varian Mercury Plus 300 MHz spectrometer.

Infrared spectra were obtained on Perkin Elmer FTIR Spectrophotometer Frontier as solid or liquid phase. Q-TOF spectra were recorded on UPLC-UHR-Q/TOF ABSCIEX Triple TOF 4600. TLC analysis was performed on silica-gel plates (Merck, 60 F-254). Chemical shifts (δ) are expressed in units of parts per million relatives to TMS. The analytical data, mass, FTIR, NMR, and physical properties are summarized for each experiment.

4.1.1 | Pyridine-2,6-dicarbonyl dichloride

According to the procedure,[45] pyridine-2,6-dicarboxylic acid (1.25 g, 7.5 mmol) was dissolved in methylene chloride (25 mL) and cooled to 0 °C. Then, thionyl chloride (1.2 mL, 16.5 mmol) was added to reaction flask. The mixture was heated to reflux under argon for 5 hours. The product dried in vacuo (1.31 g, 86%).

4.1.2 | Benzene-1,3-dicarbonyl dichloride

According to the procedure,[45] benzene-1,3-dicarboxylic acid was dissolved in methylene chloride (25 mL) and reacted with thionyl chloride (1.2 mL, 16.5 mmol). The product was obtained 90%.

4.1.3 | Thiophene-2,5-dicarboxylic acid dimethyl ester

According to procedure,[46] thiophene-2,5-dicarboxylic acid (4.87 g, 28.3 mmol) was dissolved in methanol (150 mL) and cooled to 0 °C in ice bath. Then, thionyl chloride ($SOCl_2$) (5 mL) was slowly added dropwise to the reaction flask. The mixture was warmed to room temperature and refluxed for 3 hours. The reaction was monitored by TLC, and methanol was removed under reduced pressure. Residue was washed with cold methanol. White crystalline solid was obtained (5.16 g, yield 92%). mp: 145 °C ^{1}H NMR (300 MHz, $CDCl_3$), δ_H ppm: 7.76 (s, 2H, CH), 3.92 (s, 6H, CH_3).

4.1.4 | 2,5-Bis(hydroxymethyl)thiophene

According to procedure,[47] $LiAlH_4$ (0.8 g, 20 mmol) was added in dry THF (50 mL) in the 250 mL two-necked flask under argon atmosphere. Reaction mixture was cooled to 0 °C, and thiophene-2,5-dicarboxylic acid dimethyl ester (1.65 g, 8.24 mmol) in THF (50 mL) was added dropwise in the flask. The reaction mixture was heated at reflux temperature for 3 h. Then, it was stirred at room temperature for 1 hour. Respectively, water and 15% NaOH solution were added to the flask cautiously. The reaction mixture was filtered, and solvent was evaporated. Residue was extracted with ether (4 × 20 mL). Combined organic phases were dried over $MgSO_4$ and concentrated in rotary evaporator. Yellowish oil was obtained (1.11 g, yield 93%). ^{1}H NMR (300 MHz, D_6-Acetone), δ_H ppm: 6,81 (s, 2H, CH), 4,71 (s, 4H, CH_2).

4.1.5 | 2,5-thiophenedimethylmethanesulfonate

According to procedure[48] 2.21 g, 2,5-bis(hydroxymethyl) thiophene (15,35 mmol) was dissolved in CH_2Cl_2

(75 mL). 6 mL triethylamine ($d = 0.73$ g/mL) was slowly added dropwise at 0 °C over 30 minutes. Methane sulfonyl chloride (2.5 mL, 32.3 mmol, $d = 1.48$ g/mL) was then added dropwise. When the addition was completed, a reflux condenser was fitted, and reaction flask was heated at reflux temperature for 1 hour. The mixture was warmed to room temperature and washed with saturated aqueous $NaHCO_3$ (15 mL). Organic phase was dried over $MgSO_4$, and solvent was evaporated under reduced pressure. After removal of the solvent, brown slurry was obtained. It was dried under vacuum overnight (2.5 g, yield 38%) ^{1}H NMR (300 MHz, $CDCl_3$), δ_H ppm: 3.15 (s, 6H, CH_3), 4.58 (s, 4H, CH_2), 6.34 (s, 2H, CH).

4.1.6 | Synthesis of 2,5-bis (2-aminothiophenoxymethyl)-thiophene

According to procedure,[46] 2-aminothiophenol (3.5 g, 28 mmol) in DMF (50 mL) was charged to two-necked flask, and K_2CO_3 (4.5 g, 32.5 mmol) was added to the mixture. The reaction mixture was stirred for 2 hours. Following, 2,5-bis(chloromethyl)-thiophene (3.09 g, 17 mmol) in DMF (20 mL) was added dropwise to the reaction flask with dropping funnel and then stirred at room temperature for 2 days. Then, DMF was removed under reduced pressure; residue was dissolved in CH_2Cl_2 (5 mL) and added slowly dropwise into 500 mL of ice-cold distilled water vigorous stirring for 2 days. The slurry was decanted and air-dried (4.16 g, 83%). ^{1}H NMR (300 MHz, $CDCl_3$), δ_H ppm: 4.03 (s, $2CH_2$), 4.21 (s, $2NH_2$), 6.40 (s, 2CH), 6.73 (m, 4CH), 7.16 (m, 4CH). ^{13}C NMR (75 MHz, $CDCl_3$) δ_C, ppm: 34.70, 115.56, 117.30, 118.81, 126.15, 130.39, 136.77, 140.97, 149.17, IR (katı, cm^{-1}): 3464, 3352 ν(N—H), 2928 ν(C—H), 1497 ν(C═C), 783 ν(C—H).

4.1.7 | Synthesis of 2,5-bis (chloromethyl)-furan

According to procedure,[49] 2,5-bis(hydroxymethyl)-furan (2.20 g, 17.2 mmol) was dissolved in 20 mL CH_2Cl_2. Then, pyridine (3 mL, 37.09 mmol, $d = 0.978$ g/mL) and thionyl chloride (5 mL, 68.5 mmol, $d = 1.631$ g/mL) were added to flask at 0 °C. Reaction mixture was stirred for a night under N_2 and washed with saturated aqueous $NaHCO_3$ (15 mL). Organic phase was dried over $MgSO_4$, and solvent was evaporated under reduced pressure. It was dried under vacuum overnight and used without any purification. Brown slurry was obtained (1.65 g 58%). ^{1}H NMR (300 MHz, $CDCl_3$), δ_H ppm: 4.51 (s, $2CH_2$), 6.27 (s, 2CH).

4.1.8 | Synthesis of 2,5-bis (2-aminothiophenoxymethyl)-furan

Same procedure with 2,5-bis(2-aminothiophenoxymethyl)-thiophene was carried out. Brown slurry was obtained (2.62 g, 84%). ^{1}H NMR (300 MHz, $CDCl_3$), δ_H ppm: 3.85 (s, $2CH_2$), 4.33 (s, $2NH_2$), 5.78 (s, 2CH), 6.57, 6.72 (m, 4CH), 7.12, 7.21 (m, 4CH). ^{13}C NMR (300 MHz, $CDCl_3$) δ_C, ppm: 38.90, 109.08, 115.47, 118.45, 130.55, 131.84, 137.06, 148.87, 151.07. IR (katı, cm^{-1}): 747, 1019, 1229, 1285, 1486, 2963, 3087, 3261, 3317.

4.2 | General procedure for [1 + 1] condensed macrocyclic amide synthesis

A 500-mL, two-necked, round-bottomed flask fitted with two dropping funnels was charged with dry CH_2Cl_2 (100 mL) and Et_3N (3 mL) at 0 °C under the argon atmosphere. A solution of diacid chloride (0.5 mmol) in dry methylene chloride (50 mL) and a solution of diamine (0.5 mmol) in dry methylene chloride (50 mL) were simultaneously added dropwise to a well stirred solution at the same rate under dry argon atmosphere in a day while maintaining the temperature at 0 °C. After the addition was completed, reaction mixture was left for stirring at room temperature overnight. Solvent was evaporated in a rotary evaporator under vacuum, and the residue was added very slowly into 1 L of ice-cold distilled water with vigorous stirring for 3 days. Solid product was decanted, washed several times with cold water, and dried under vacuum.[37]

4.2.1 | 1,7(1,2),4(1,3)-Tribenzena-2,6-diaza-3,5-dioxo-8,12-dithia-10(2,5)-thiophenacyclododecafan (L1)

3 mL triethylamine in CH_2Cl_2 (100 mL), benzene 1,3-dicarbonyl chloride (100 mg, 0.5 mmol) in CH_2Cl_2 (50 mL), and 2,6-bis(2-aminothiophenoxymethyl) thiophene (180 mg, 0.5 mmol) in CH_2Cl_2 (50 mL) were reacted, and light yellow solid product was obtained (250 mg, 34%). Thermal decomposition temperature (TDT): 186 °C. HRMS (ESI-MS): calcd for $C_{26}H_{20}N_2O_2S_3$: 489.0765 $[M + H]^+$; found: 489.0740. FTIR (solid, cm^{-1}): 3377, 3360 ν(N—H), 1672 ν(C═O), 1501 ν(C═C), 760 ν(C—H). ^{1}H NMR ($CDCl_3$-*d*), δ_H ppm: 4.07 (s, 2CH2), 6.17 (s, 2CH), 7.15 (t, 2CH, J = 7.43 Hz), 7.42 (t, 2CH, $J = 7.82$ Hz), 7.61 (m, 4CH), 8.09 (d, 2CH, $J = 10.16$ Hz), 8.44 (d, 2CH, $J = 8.31$ Hz), 9.08 (s, NH). ^{13}C NMR ($CDCl_3$-*d*), δ_C ppm: 36.1, 119.4, 121.4, 122.2, 125.0, 125.23, 129.2, 131.1, 134.1, 134.8, 139.1, 139.7, 163.9.

4.2.2 | 1,7(1,2)-Dibenzena-4(2,6)-pyridina-2,6-diaza-3,5-dioxo-8,12-dithia-10(2,5)-thiophenacyclododecafan (L2)

3 mL triethylamine in CH_2Cl_2 (100 mL), pyridine-2,6-dicarbonyl chloride (100 mg, 0.5 mmol) in CH_2Cl_2 (50 mL), and 2,6-bis(2-aminothiophenoxymethyl) thiophene (180 mg, 0.5 mmol) in CH_2Cl_2 (50 mL) were reacted, and light yellow solid product was obtained (350 mg, 48%). TDT: 166 °C. HRMS (ESI-MS): calcd for $C_{25}H_{19}N_3O_2S_3$:490.0718 $[M + H]^+$; found: 490.0716. FTIR (solid, cm^{-1}): 3367, 3290 ν(N—H), 2924 ν(C—H), 1687 ν(C═O), 1515 ν(C═C), 750 ν(C—H). ^{1}H NMR ($CDCl_3$-*d*), δ_H ppm: 4.05 (s, CH2), 6.14 (s, 2CH), 7.20 (d, 2CH, J = 7.19 Hz), 7.30 (t, 2CH, J = 7.69 Hz), 7.62 (d, 2CH, J = 8.00 Hz), 8.06 (m, 3CH), 8.42 (d, 2CH, J = 7.79 Hz), 10.09 (s, 2NH). ^{13}C NMR ($CDCl_3$-*d*), δ_C ppm: 37.4, 123.6, 125.5, 126.0, 126.3, 126.9, 129.9, 135.4, 139.4, 139.6, 141.6, 149.6, 162.3.

4.2.3 | 1,7(1,2),4(1,3)-Tribenzena-2,6-diaza-3,5-dioxo-8,12-dithia-10(2,5)-furanacyclododecafan (L3)

3 mL triethylamine in CH_2Cl_2 (100 mL), benzene 1,3-dicarbonyl chloride (100 mg, 0.5 mmol) in CH_2Cl_2 (50 mL), and 2,6-bis(2-aminothiophenoxymethyl) furan (180 mg, 0.5 mmol) in CH_2Cl_2 (50 mL) were reacted, and light brown solid product was obtained (212 mg, 31%). TDT: 168 °C. HRMS (ESI-MS): calcd for $C_{26}H_{20}N_2O_3S_2$: 473.0994 $[M + H]^+$; found: 473.0996. FTIR (solid, cm^{-1}): 3357, 3337 ν(N—H), 2923 ν(C—H), 1675 ν(C═O), 1578 (C═C), 751 ν(C—H). ^{1}H NMR ($CDCl_3$-*d*), δ_H ppm: 4.06 (s, $2CH_2$), 5.85 (s, 2CH), 7.21 (t, 2CH, J = 7.43 Hz), 7.42 (t, 2CH, J = 7.42 Hz), 7.62 (d, 2CH, J = 7.74 Hz), 7.70 (d, CH, J = 7.91 Hz), 7.96 (s, 2NH), 8.24 (d, 2CH, J = 7.92 Hz), 8.37 (d, 2CH, J = 7.76 Hz), 9.00 (s, CH). ^{13}C NMR ($CDCl_3$-*d*), δ_C ppm: 34.05, 109.53, 121.84, 122.05, 124.39, 125.38, 130.00, 130.49, 132.85, 134.36, 135.68, 139.21, 149.87, 165.18.

4.2.4 | 1,7(1,2)-Dibenzena-4(2,6)-pyridina-2,6-diaza-3,5-diokso-8,12-ditiya-10(2,5)-furanasiklododekafan (L4)

3 mL triethylamine in CH_2Cl_2 (100 mL), pyridine-2,-6-dicarbonyl chloride (100 mg, 0.5 mmol) in CH_2Cl_2 (50 mL), and 2,6-bis(2-aminothiophenoxymethyl) furan (180 mg, 0.5 mmol) in CH_2Cl_2 (50 mL) were reacted, and light brown solid product was obtained (195 mg, 28%). TDT: 170 °C. HRMS (ESI-MS): calcd for $C_{25}H_{19}N_3O_3S_2$: 474.0946 $[M + H]^+$; found: 474.0965. FTIR (solid, cm^{-1}): 3376, 3265 ν(N—H), 1684 ν(C═O), 1525 ν(C═C), 747 ν(C—H). ^{1}H NMR ($CDCl_3$-*d*), δ_H ppm: 3.91 (s, $2CH_2$), 5.67 (s, 2CH), 7.15 (t, 2CH, J = 7.69 Hz), 7.34 (t, 2CH, J = 7.44 Hz), 7.59 (d, 2CH, J = 7.69 Hz), 8.03 (d, 2CH, J = 7.99 Hz), 8.08 (t, CH, J = 7.44 Hz), 8.41(d, 2CH, J = 7.74 Hz), 10.39 (s, 2NH). ^{13}C NMR ($CDCl_3$-*d*), δ_C ppm: 39.01, 109.9, 123.4, 125.8, 126.3, 127.7, 129.8, 135.3, 138.8, 139.8, 149.0, 150.30, 162.22.

4.3 | Pharmacology microorganisms

For the biological assay, broth microdilution method, which is recommended by Clinical Laboratory Standards Institute (CLSI), was used.[51] Selected bacteria were Gram-negative *E coli* ATCC 25922, Gram-positive *S aureus* ATCC 25923, Gram-negative *L monocytogenes* ATCC 19115, Gram-negative *Salmonella typhimurium* ATCC 14028, *B cereus* bacteria, and *C albicans* ATCC 10231, which were studied as a yeast. Ampicillin and gentamicin were used in bacterial cultures as antibiotic control, and amphotericin B was used in yeast culture.

4.4 | Antimicrobial screening

4.4.1 | Dilution method

Screening of the antibacterial and antifungal activities was carried out by preparing a broth microdilution, following the procedure outlined in Manual of Clinical Microbiology.[51] DMSO was used as a solvent. All the bacteria were incubated and activated into nutrient broth at 30 °C for 24 hours, and the yeasts were incubated in malt extract broth for 48 hours in tryptic soy broth. For comparing antimicrobial activity, ampicillin, gentamycin, and amphotericin B were used. The extracts, sterilized by 0.45-μm Millipore filters, were added to MH broth medium. Serial dilutions were made that furnished a concentration range from 6.25 to 100 μg/mL. Absorbance values were determined at 600 nm, and percentage of alive values was calculated.

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