

Synthesis, extraction and antibacterial studies of some new bis-1,2,4-triazole derivatives part II

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Abstract The treatment of 4-amino-3,5-diphenyl-4*H*-1,2,4-triazole **3** with various bis-aldehydes resulted in the formation of bis-4-arylidenamino-3,5-diphenyl-4*H*-1,2,4-triazoles (**4a–d**) derivatives. NaBH₄ reduction of 4-arylidenamino derivatives of 1,2,4-triazoles afforded 4-arylamino-3,5-diphenyl-4*H*-1,2,4-triazoles (**5a–d**). The synthesized all new triazole derivatives of the Schiff base and corresponding bis amino compounds **4a,d–5a,d** were characterized by IR, ¹H-NMR, ¹³C-NMR spectral data. In order to investigate the relative effects of the differences between the structures of the synthesized triazole derivatives on their extraction-abilities and—selectivities for different metal cations, constants of overall extraction (log*K*_{ex}) of 1:1 (M:L) complexes, the extractions (log*K*_{ex}) for CHCl₃/H₂O systems have been determined with ICP-AES spectroscopy at 25 ± 0.1 °C. Remarkable complexation properties are found towards some transition metal cations. The stability sequences of the

triazole derivatives in CHCl₃ for the metal cations generally found in order: Fe(III) > Cu(II) > Pb(II) > Co(II) > Zn(II) > Mn(II) > Ni(II) > Mg(II) > Ca(II). The synthesized all compounds were tested for antimicrobial activity against 11 bacteria.

Keywords Bis-aldehydes · 1,2,4-Triazole · Bis-Schiff bases · Complexation · Antibacterial studies

Introduction

Triazole derivatives have been reported to have pharmacological, insecticidal, fungicidal, and herbicidal activities [1–6]. In addition, it was reported that compounds having triazole moieties, such as Vorozole, Letrozole and Anastrozole, have been used as nonsteroidal aromatase inhibitors in medicine for treating breast cancer [7–9]. Moreover, 1,2,4-triazoles are a new class of antimicrobial and antiradical agents [10–12]. For instance, fluconazole and itraconazole are used as antimicrobial drugs in medicine [13, 14]. However, in the last decades, the increasing drug resistance to the commonly used antibiotics has become a serious health problem. Therefore, for the effective treatment of infectious diseases, the synthesis of a new class of antibiotics having different structures from those commonly used is crucial.

In addition, diaryl heterocycles such as celecoxib, valdecoxib, rofecoxib and etoricoxib have been extensively used as anti-inflammatory drugs to treat acute or chronic inflammation by providing symptomatic pain relief. All these tricyclic molecules possess 1,2-diaryls substitution on a central 5- or 6-membered ring system such as pyrazole, furanone isoxazole, and pyridine [15].

Schiff bases comprise a group of both cyclic and acyclic chemical compounds containing –C=N– moieties. They

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are made from the condensation of an amine and a molecule bearing an active carbonyl function. The presence of potentially donating atoms in their structure makes these molecules an important class of ionophore, which are widely used in metal ion complexation studies [16–21].

Solvent extraction is one of the most widely applied technique to separate metals from a mixture. The development of selective extraction techniques including selective extractants has expanded its use to metal recovery and purification, among which Schiff bases are one of the widely used extractants [22, 23]. Determination of ion-pair formation constants of organic ligands-metal ion complexes in water can be examined by different methods through the extraction of metals to various organic solvents with organic ligands. The solvent extraction of metal cations containing ligands is generally preferred for its easy determination by spectrophotometric methods [24–26].

In this paper the synthesis of a new Schiff base-amino ligands (**4a**, **4b**, **4c**, **4d**, **5a**, **5b**, **5c**, **5d**), (Scheme 2), were synthesized and characterized by IR, ¹H-NMR, ¹³C-NMR spectral data. The ion-binding properties of the synthesized ligand were examined by using it in solvent extraction for Cu²⁺, Ni²⁺, Co²⁺, Pb²⁺, Mn²⁺, Fe³⁺, Cd²⁺, Ca²⁺, Mg²⁺ and Zn²⁺ ions from aqueous solutions into the organic phase. The synthesized compounds were tested for antimicrobial activity using the agar diffusion technique against 11 bacteria. The structure details of synthesized compounds are given in Table 1.

Experimental

General

Melting points were determined on a Barnstead Electrothermal melting point apparatus and are uncorrected. ¹H-NMR and ¹³C-NMR spectra (δ , ppm) were recorded on a

Table 1 Formulas of synthesized compounds

	Y	X
1a	CH ₂ CH ₂ OCH ₂ CH ₂	OCH ₃
1b	CH ₂ CH ₂ OCH ₂ CH ₂ OCH ₂ CH ₂	OCH ₃
1c	CH ₂ CH ₂ OCH ₂ CH ₂	H
1d	CH ₂ CH ₂ OCH ₂ CH ₂ OCH ₂ CH ₂	H
4a	CH ₂ CH ₂ OCH ₂ CH ₂	OCH ₃
4b	CH ₂ CH ₂ OCH ₂ CH ₂ OCH ₂ CH ₂	OCH ₃
4c	CH ₂ CH ₂ OCH ₂ CH ₂	H
4d	CH ₂ CH ₂ OCH ₂ CH ₂ OCH ₂ CH ₂	H
5a	CH ₂ CH ₂ OCH ₂ CH ₂	OCH ₃
5b	CH ₂ CH ₂ OCH ₂ CH ₂ OCH ₂ CH ₂	OCH ₃
5c	CH ₂ CH ₂ OCH ₂ CH ₂	H
5d	CH ₂ CH ₂ OCH ₂ CH ₂ OCH ₂ CH ₂	H

Varian-Mercury 200 MHz spectrophotometer using tetramethylsilane as the internal reference. The IR spectra (ν , cm⁻¹) were obtained with a Perkin-Elmer 1600 FTIR spectrometer in KBr pellets, Extraction ability measured in ICP-AES-Inductively Coupled Plasma-Atomic Emission Spectroscopy: Perkin Elmer Optima 2100 DV. The necessary chemicals were purchased from Merck and Fluka.

Synthesis of bis-aldehydes **1a–d**

Starting dialdehyde compounds, **1a–1d** were synthesized according to literature [27].

Synthesis of ethyl benzoate benzoylhydrazone (**2**)

A solution of an benz hydrazide (0.01 mol) in absolute ethanol (25 mL) was added to solution of iminoester hydrochloride (0.01 mol) in absolute ethanol (25 mL). The mixture was stirred for 6 h at 0–5 °C and subsequently for 2 h at room temperature. The reaction mixture was then poured into a beaker containing cold water (40 mL) and ice (10 g). The precipitate formed was washed with ice-water (50 mL), dried and the product was recrystallized from 2:1 benzene-petroleum ether to give compounds **2**. Yield 83%; m.p. 120–121 °C (lit [28], m.p. 121 °C).

Synthesis of 4-amino-3,5-diphenyl-4H-1,2,4-triazole (**3**)

Compound **2** (0.005 mol) was added to a solution of hydrazine hydrate (0.01 mol) in 1-propanol (50 mL) and the mixture was refluxed for 24 h. On cooling, a precipitate was formed. This product was filtered and, after drying, was washed with benzene (20 mL). The product was then recrystallized from an appropriate solvent to give compound **3**. Yield 80%; m.p. 264–265 °C (lit [29], m.p. 265 °C).

Synthesis of bis-Schiff bases **4a–d**

The corresponding bis-aldehyde (0.01 mol) was added to a solution of compound **3** (0.005 mol) in glacial acetic acid (20 mL) and the mixture was refluxed for 16 h. After cooling, the mixture was poured into a beaker containing ice-water (100 mL). The precipitate formed was filtered. After drying *in vacuo*, the product was recrystallized from 1:2 benzene-petroleum ether to give the desired compound.

N,N'-(2,2'-(2,2'-oxybis(ethane-2,1-diyl)bis(oxy))bis(3-methoxy-2,1-phenylene))bis(methan-1-yl-1-ylidene)bis(3,5-diphenyl-4H-1,2,4-triazol-4-amine) (**4a**)

Yield (1.5 g, 67,00%); m.p. 194–195 °C; IR: 1596 (C=N), 1271 (C–O), 769, 697 cm⁻¹ (aromatic ring); ¹H-NMR (DMSO-*d*₆) δ (ppm): 3.90 (s, 6H, OCH₃), 3.95–4.12 (m,

4H, O–C–CH₂), 4.20–4.35 (m, 4H, OCH₂), Ar–H: [6.80–6.90 (m, 2H), 7.00–7.12 (m, 2H), 7.27 (s, 4H), 7.40–7.60 (m, 8H), 7.90–7.95 (m, 8H)], 7.97–8.05 (m, 2H)], 8.08 (s, 2H, CH); ¹³C-NMR (DMSO-*d*₆) δ (ppm): 171.36 (2C, N=CH), 150.85 (4C, triazole C₃, C₅), Ar–C: [150.04 (C), 130.41 (4C), 129.52 (8C), 128.86 (8C), 127.21 (2C), 126.56 (C), 125.40 (2C), 124.79 (2C), 113.50 (2C), 113.03 (2C), 110.85 (2C), 110.58 (2C)], 69.54 (2C, OCH₂), 68.84 (2C, O–C–CH₂), 56.34 (2C, OCH₃).

N,N'-(2,2'-(2,2'-(ethane-1,2-diylbis(oxy))bis(ethane-2,1-diyl))bis(oxy)bis(3-methoxy-2,1-phenylene)) bis(methan-1-yl-1-ylidene)bis(3,5-diphenyl-4H-1,2,4-triazol-4-amine) (**4b**)

Yield (2.20 g, 61.62%); m.p. 114–115 °C; IR: 1597 (C=N), 1271 (C–O), 768, 697 cm⁻¹ (aromatic ring); ¹H-NMR (DMSO-*d*₆) δ (ppm): 3.75 (s, 6H, OCH₃), 3.80–4.00 (m, 8H, O–C–CH₂), 4.20–4.30 (m, 4H, OCH₂), Ar–H: [6.90 (d, 2H), 7.08 (d, 2H), 7.30 (s, 2H), 7.40–7.60 (m, 12H)], 7.85–8.00 (m, 8H)], 8.05 (s, 2H, CH); ¹³C-NMR (DMSO-*d*₆) δ (ppm): 171.33 (2C, N = CH), 150.85 (4C, triazole C₃, C₅), Ar–C: [150.03 (C), 130.41 (4C), 129.52 (8C), 129.13(C), 128.86 (8C), 127.21 (2C), 126.85 (C), 126.56 (C), 125.41 (2C), 124.75 (2C), 113.44 (2C), 112.97 (2C), 110.56 (2C)], 70.65 (2C, OCH₂), 69.40 (2C, O–C–CH₂), 68.79 (2C, O–C–CH₂), 56.34 (2C, OCH₃).

N,N'-(2,2'-(2,2'-oxybis(ethane-2,1-diyl)bis(oxy))bis(2,1-phenylene))bis(methan-1-yl-1-ylidene) bis(3,5-diphenyl-4H-1,2,4-triazol-4-amine) (**4c**)

Yield (1.50 g, 69.12%); m.p. 185–186 °C; IR: 1597 (C=N), 1255 (C–O), 768, 696, 746 cm⁻¹ (aromatic ring); ¹H-NMR (DMSO-*d*₆) δ (ppm): 3.60–3.72 (m, 4H, O–C–CH₂), 3.73–3.90 (m, 4H, OCH₂), Ar–H: [6.00 (t, 2H), 6.42 (d, 2H), 6.60 (d, 2H), 6.70 (t, 2H), 7.08 (t, 2H)], 7.28 (s, 2H), 7.30–7.55 (m, 10H), 7.75–7.90 (m, 6H)], 7.94 (s, 2H, CH); ¹³C-NMR (DMSO-*d*₆) δ (ppm): 165.56 (2C, N=CH), 150.81 (4C, triazole C₃, C₅), Ar–C: [150.81 (2C), 135.76 (2C), 130.41 (4C), 129.50 (8C), 129.03 (8C), 128.03 (2C), 127.82 (2C), 127.25 (2C), 122.09 (2C), 120.46 (2C), 114.49 (2C)], 70.65 (2C, OCH₂), 69.40 (2C, O–C–CH₂), 68.79 (2C, O–C–CH₂), 56.34 (2C, OCH₃).

N,N'-(2,2'-(2,2'-(ethane-1,2-diylbis(oxy)) bis(ethane-2,1-diyl))bis(oxy) bis (2,1-phenylene))bis (methan-1-yl-1-ylidene) bis (3,5-diphenyl-4H-1,2,4-triazol-4-amine) (**4d**)

Yield (0.7 g, 59.8%); m.p. 149–150 °C; IR: 1592 (C=N), 1220 (C–O), 766, 692, 752 cm⁻¹ (aromatic ring); ¹H-NMR (DMSO-*d*₆) δ (ppm): 3.22 (s, 4H, O–C–CH₂), 3.39 (t, 4H, O–C–CH₂), 3.90 (t, 4H, OCH₂), Ar–H: [7.00–7.20 (m, 5H),

7.43–7.51 (m, 12H), 7.80 (d, 6H), 7.96 (d, 5H)], 8.65 (s, 2H, CH); ¹³C-NMR (DMSO-*d*₆) δ (ppm): 165.80 (2C, N=CH), 150.84 (4C, triazole C₃, C₅), Ar–C: [159.43 (2C), 135.80 (2C), 130.45 (4C), 129.51 (8C), 129.13 (2C), 129.03 (8C), 127.79 (2C), 127.23 (2C), 122.09 (2C), 120.47 (2C), 114.52 (2C)], 69.12 (2C, OCH₂), 68.99 (4C, O–C–CH₂).

Synthesis of reduced compounds **5a–d**

The corresponding compound **4a–d** (0.005 mol) was dissolved in dried methanol (50 mL) and NaBH₄ (0.01 mol) was added in small portions to this solution. The mixture was refluxed for 20 min and then allowed to cool. After evaporation at 30–35 °C under reduced pressure, the solid residue was washed with cold water. After drying in vacuo, the solid product was recrystallized from an appropriate solvent (1:1 ethanol-water, unless otherwise noted) to afford the desired compound.

N,N'-(2,2'-(2,2'-oxybis(ethane-2,1-diyl) bis(oxy)) bis(3-methoxy-2,1-phenylene)) bis(methylene)bis(3,5-diphenyl-4H-1,2,4-triazol-4-amine) (**5a**)

Yield (0.50 g, 71.42%); m.p. 170–171 °C; IR: 3245 (NH), 1592 (C=N), 1265 (C–O), 767, 693 cm⁻¹ (aromatic ring); ¹H-NMR (DMSO-*d*₆) δ (ppm): 3.21 (s, 4H, O–C–CH₂), 3.63 (d, 4H, NH–CH₂), 3.77 (s, 6H, OCH₃), 4.00 (t, 4H, OCH₂), 6.21 (d, 2H, NH), Ar–H: [6.35 (s, 2H), 6.65 (d, 2H), 6.77–6.91 (m, 2H), 7.10 (s, 2H), 7.53 (s, 10H), 7.95 (t, 8H)]; ¹³C-NMR (DMSO-*d*₆) δ (ppm): 149.44 (4C, triazole C₃, C₅), Ar–C: [154.63 (2C), 130.45 (4C), 129.25 (8C), 128.65 (8C), 128.07 (2C), 121.53 (2C), 119.27 (2C), 114.13 (2C), 113.69 (2C), 113.12 (2C), 111.64 (2C)], 69.85 (2C, OCH₂), 68.84 (2C, NH–CH₂), 55.58 (2C, O–C–CH₂), 54.39 (2C, OCH₃).

N,N'-(2,2'-(2,2'-(ethane-1,2-diylbis(oxy)) bis(ethane-2,1-diyl)) bis(oxy)bis(3-methoxy-2,1-phenylene)) bis(methylene) bis(3,5-diphenyl-4H-1,2,4-triazol-4-amine) (**5b**)

Yield (0.65 g, 59.08%); m.p. 186–187 °C; IR: 3230 (NH), 1593 (C=N), 1263 (C–O), 775, 688 cm⁻¹ (aromatic ring); ¹H-NMR (DMSO-*d*₆) δ (ppm): 3.25 (s, 8H, O–C–CH₂), 3.63 (d, 4H, NH–CH₂), 3.67 (s, 6H, OCH₃), 3.94 (d, 4H, OCH₂), 6.19 (d, 2H, NH), Ar–H: [6.34 (d, 2H), 6.64 (d, 2H), 7.10 (s, 2H), 7.53 (d, 12H), 7.93 (d, 8H)]; ¹³C-NMR (DMSO-*d*₆) δ (ppm): 149.41 (4C, triazole C₃, C₅), Ar–C: [154.63 (2C), 148.18 (2C), 130.45 (4C), 129.25 (8C), 128.65 (8C), 128.08 (4C), 121.52 (2C), 121.00 (2C), 113.56 (2C), 113.10 (2C)], 70.59 (2C, OCH₂), 69.61 (2C,

NH-CH₂), 68.65 (2C, O-C-CH₂), 55.57 (2C, O-C-CH₂), 54.38 (2C, OCH₃).

N,N'-(2,2'-(2,2'-oxybis(ethane-2,1-diyl) bis(oxy)) bis(2,1-phenylene)) bis(methylene) bis(3,5-diphenyl-4H-1,2,4-triazol-4-amine) (**5c**)

Yield (0.27 g, 67.5%); m.p. 143–144 °C; IR: 3233 (NH), 1602 (C=N), 1248 (C-O), 771, 753, 695 cm⁻¹ (aromatic ring); ¹H-NMR (DMSO-*d*₆) δ (ppm): 3.30–3.45 (m, 4H, O-C-CH₂), 3.80–3.87 (m, 4H, NH-CH₂), 3.88–4.00 (m, 4H, OCH₂), 6.80 (d, 2H, NH), Ar-H: [7.10 (t, 2H), 7.35–7.55 (m, 14H), 7.80–8.00 (m, 8H), 8.10 (d, 2H), 8.55 (s, 2H)]; ¹³C-NMR (DMSO-*d*₆) δ (ppm): 154.33 (4C, triazole C₃, C₅), Ar-C: [130.78 (2C), 130.28 (4C), 129.83 (2C), 129.14 (8C), 128.56 (8C), 127.87 (2C), 124.33 (2C), 122.49 (2C), 121.16 (2C), 120.84 (2C), 112.43 (2C)], 69.54 (2C, OCH₂), 67.91 (2C, NH-CH₂), 49.85 (2C, O-C-CH₂).

N,N'-(2,2'-(2,2'-(ethane-1,2-diylbis(oxy))bis(ethane-2,1-diyl)) bis(oxy)bis(2,1-phenylene)) bis(methylene) bis(3,5-diphenyl-4H-1,2,4-triazol-4-amine) (**5d**)

Yield (0.18 g, 72.00%); m.p. 164–165 °C; IR: 3316 (NH), 1602 (C=N), 1249 (C-O), 770, 754, 695 cm⁻¹ (aromatic ring); ¹H-NMR (DMSO-*d*₆) δ (ppm): 2.65 (s, 8H, O-C-CH₂), 3.50 (s, 4H, NH-CH₂), 3.74–3.80 (m, 4H, OCH₂), 6.22 (s, 2H, NH), Ar-H: [6.66 (t, 4H), 6.90 (s, 2H), 7.06 (t, 2H), 7.46–7.54 (m, 12H), 7.95 (s, 4H), 8.05 (d, 4H)]; ¹³C-NMR (DMSO-*d*₆) δ (ppm): 154.54 (4C, triazole C₃, C₅), Ar-C: [130.63 (4C), 130.46 (4C), 129.50 (8C), 129.23 (8C), 128.86 (2C), 128.68 (2C), 128.02 (2C), 127.97 (2C), 114.85 (4C)], 70.61 (2C, OCH₂), 69.59 (2C, O-C-CH₂), 67.82 (2C, NH-CH₂), 54.18 (2C, O-C-CH₂).

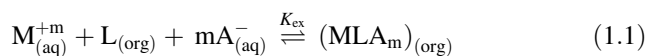
Antibacterial activity assay

Antibacterial activity was measured using the standard method of diffusion disc plates on agar [30, 31]. In order to test antibacterial activity, synthesized compounds were dissolved in DMSO and diluted in Tween 20 (5%). A preliminary assay with aqueous solutions of Tween 20 up to 5% was performed to assure that no micro-organism growth inhibition occurred. Twenty millilitres of Mueller Hinton Agar medium (Merck) was poured into each 12 cm Petri dish. All bacterial strains were grown in Mueller Hinton Broth medium (Merck) for 24 h at 37 °C. Growth was adjusted to OD (600 nm) of 0.1 by dilution with Mueller Hinton Broth medium (Merck). One hundred microlitres of suspension with approximately 10⁸ bacteria per mL was placed in Petri dishes and dispersed over agar. Then sterile paper discs (6 mm diameter) were placed on the agar to load 20 μl of each sample (10, 4, 2, 1 and

0.5 mg/mL). For bacteria, as a positive control, ampicillin (10 mg), streptomycin (10 mg) and kanamycin (30 mg) were used, and as negative control DMSO was used. Inhibition diameters were determined after incubation for 24 h at 37 °C. All tests were performed in triplicate.

Extraction studies

We studied in the present work with a common formalism of equations [32–35], K_{ex} is extraction equilibrium constant; $[M^{+m}]$ and $[MLA_m]$ are the concentrations of metal cation in aqueous phase and organic phase, respectively. K_{DL} denotes a distribution constant of ligand between organic solvent and water. Equilibrium constants of synthesized all ligands collected in Table 2.



$$K_{\text{ex}} = \frac{[MLA_m]_{(\text{org})}}{[M^{+m}]_{(\text{aq})} [L]_{(\text{org})} [A^{-}]_{(\text{aq})}^m} \quad (1.2)$$

$$K_{\text{dL}} = \frac{[L]_{(\text{org})}}{[L]_{(\text{w})}} \quad (1.3)$$

From selective extractions performed for ten different transition metal cations under identical conditions (i.e., the same ligand and ten metals the same concentrations), the selectivity factor, S_f , for M_1 over M_2 is determined as a ratio of $K_{\text{D,L}} M_1$ and $K_{\text{D,L}} M_2$, as described by equation Eq. 1.4:

$$S_f = K_{\text{dLM1}} / K_{\text{dLM2}} \quad (1.4)$$

Extraction and selectivity factor values, complexation and distribution constants of synthesized all ligands collected in Tables 3 and 4.

Extraction procedure

The overall extraction equilibrium constants for the 1:1 complexes of the synthesized ligands with metal ions, between the organic solvent and water, have been determined at 25 °C ± 0.1. They were conducted in CHCl₃–water systems maintaining an identical initial cation concentration in water, $[M_0^+]_{\text{w}}$, and an organic ligand concentration in the organic phase, $[L_0]_{\text{org}}$, so that in all extractions $[M_0^+]_{\text{w}} : [L_0]_{\text{org}}$ ratios were 1:1. An ion association complex formed between the metal-organic ligand complex ion and a metal anion was extracted into the CHCl₃ organic solvent, and then the metal concentration of the separated aqueous phase was measured with an ICP-AES spectrophotometer.

The extraction measurements were done in 100 mL glass thermostated cell compartment with a mechanical stirrer where a 25 mL solution of an aqueous salt (1×10^{-5} M) and ligand in CHCl₃ organic solvent in

Table 2 Equilibrium constants for extractions of the metal cations with synthesized ligands in CHCl₃ at 25 °C ± 0.1^a

Metals	NL ^b	4a	5a	4b	5b	4c	5c	4d	5d
Cu ⁺²	0.22	1.04	1.40	1.15	1.25	1.15	1.11	1.22	1.15
Pb ⁺²	0.45	1.38	0.89	0.88	1.36	0.68	0.98	0.91	0.96
Zn ⁺²	0.01	0.24	0.16	0.22	0.28	0.10	0.09	0.13	0.10
Cd ⁺²	0.01	0.02	0.00	0.00	0.00	0.00	0.00	0.01	0.05
Ni ⁺²	–	0.05	0.11	0.07	0.24	0.19	0.27	0.07	0.22
Ca ⁺²	–	–	–	–	–	–	–	–	–
Mn ⁺²	0.08	0.17	0.14	0.14	0.10	0.12	0.11	0.15	0.14
Co ⁺²	0.09	1.11	1.16	1.08	0.96	1.02	1.07	1.03	1.02
Fe ⁺³	1.12	138.50	78.71	138.50	557.00	138.50	185.00	28.37	30.00
Mg ⁺²	–	0.20	0.00	0.05	–	0.03	0.03	0.04	0.04

Cu⁺²:CuCl₂, Pb⁺²:PbCl₂, Zn⁺²:ZnCl₂, Cd⁺²:CdCl₂, Ni⁺²:NiCl₂, Ca⁺²:CaCl₂, Mn⁺²:MnCl₂, Co⁺²:CoCl₂, Fe⁺³:FeCl₃, Mg⁺²:Mg(NO₃)₂

^a Corr. Coefficient: 0.999, ^b K_{D,L} values for no ligand in solution

appropriate concentration were placed and stirred for 120 min at 25 ± 0.1 °C and subsequently allowed to stand for 60 min to complete the phase separation. The optimum concentrations of the ligands were determined by extracting the metal ions with 10 mL of various concentrations of the ligands (1 × 10⁻⁵ M).

After extraction, complexation abilities of synthesized ligands with metal cation were determined with spectroscopic method. The extracted metal cation in the aqueous phases have been determined spectroscopically: ICP-AES. Each value was the average of three subsequent measurements. Complexation and distribution constants summarized in Table 2.

Results and discussion

The Schiff bases and the ligands were prepared through a four step syntheses, the starting materials of which, bisaldehydes **1** and 3,5-diphenyl-4-amino-4*H*-1,2,4-triazole **3** were synthesized according to the published procedures (Scheme 1), [27]. Treatment of the aldehyde **A** with potassium hydroxide and then addition of dibromoalkyl reagent into the medium gave the first starting material bisaldehydes **1**. The second starting material triazole **3** was synthesized with the reaction of readily available imine **2** with hydrazine [28]. Finally, the reactions of the compounds **1** and **3** afforded the desired products **4** (Scheme 2).

Although the reduction of imine type compounds have been well defined in the literature [36]. Attempts of reducing the imines **4** we have in our hand could lead to the reduction of the heterocyclic ring. Then, the selective reduction of the imino group was achieved using NaBH₄, the corresponding bisaminotriazoles **5** in good yields (Scheme 2).

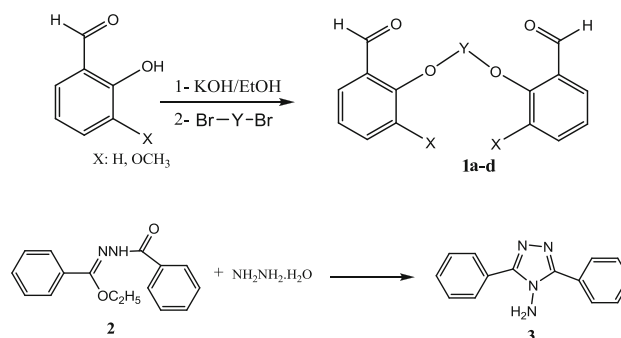
In contrast to compound **3**, the NMR spectra of compounds **4a–d** displayed signals belonging to arylidenamino

groups. When compounds **4a–d** were converted to compounds **5a–d** a new signal appeared at 6.19–6.80 ppm representing –NH– signals in the ¹H-NMR spectra of compounds **5a–d**, and the signals due to (–CH₂) group bearing 4-amino group were recorded at 3.63–3.87 ppm, while the =CH– group of compounds **4a–d** resonated at a lower region, 7.94–8.65 ppm.

Antibacterial activity was measured using the standard method of diffusion disc plates on agar, however only a few ligands did show biological activity against the studied microorganisms. Moderate activity was observed only in **4a** and **5a** molecules against *Staphylococcus epidermidis* bacteria. The **5a** molecule is reduced derivative of **4a** molecule. When we look at the results of activity values, we can say that ethylene oxide groups size and presence of methoxy group is important in the activity. Antibacterial activity results of synthesized ligands are listed in Table 5.

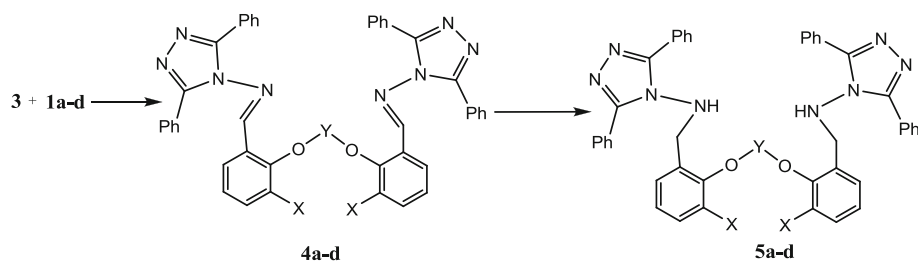
Extraction ability of the bifunctional schiff base ligands

The bifunctional schiff base ionophores having various binding sites were synthesized to estimate their binding ability toward cations through phase transfer systems. Development of a new selective complexation reagent and



Scheme 1 Synthetic pathway for preparation of compounds **1** and **3**

Scheme 2 Synthetic pathway for preparation of compounds **4** and **5**



investigation of ion extraction selectivity are very important the mutual separation [28]. The ion binding role of polyglycols with specific end groups (so called podands) has been recognized. Flexible podands like polyethylene chains are relatively faster metal–ligand exchange of the complex [37–40].

The selective transport of metal ions across lipid membranes is a fundamental process in biology. The synthesized ligands exhibit the extraordinary property of dissolving/extracting metal ions into non-aqueous as well as in nonpolar solvents and are very effective as well as very much selective for the separation of various metal ions having a tremendous impact in separation science and technology. This remarkable range of specific selectivity for binding various metal ions depending on the size of the ligands and type of the donor atoms makes ligands a very useful extracting agent for separating metal ions. The metal ion–organic ligand binding strength is primarily controlled by the number of available electron donor sites within the ligand, donor atom basicity, the distance separating the metal ion and the oxygen, nitrogen and the alignment of the dipoles [41, 42].

Two-phase solvent extraction studies were performed in order to examine the extraction behaviour of CuCl_2 , PbCl_2 , ZnCl_2 , CdCl_4 , NiCl_2 , CaCl_2 , MnCl_2 , CoCl_2 , FeCl_3 , and $\text{Mg}(\text{NO}_3)_2$ metal salts from the aqueous phase into the organic phase (CHCl_3) by using triazole derivatives of the novel Schiff base and corresponding bisamino compounds. The results of various metal extraction studies with the ligands in chloroform solvent media are summarized in Table 2. In this study, assuming that the formation of 1:1 complexes of the metal cations have been extracted at the natural pH of the aqueous metal salt solutions.

The $\log K_{\text{ex}}$ values for complexation behaviour of all synthesized ligands with the metal cations in chloroform have decreased almost in the parallel order, $\text{Fe(III)} > \text{Cu(II)} > \text{Pb(II)} > \text{Co(II)} > \text{Zn(II)} > \text{Mn(II)} > \text{Ni(II)} > \text{Mg(II)} > \text{Ca(II)}$. From the data given in Table 3, it was observed that most of the metal cations were highly extracted by the synthesized ligands whereas for the alkaline earth metal ions found no extraction abilities.

The selective stability constants of various metal complexes of the ligands as the interactions of the ligands with the metal ions in chloroform are listed in Table 4. For

selective extraction, a modified extraction technique was applied, considering S_f values of the metal cations. An aqueous solution of the metals (1×10^{-5} M) and a separate organic solution of the each ligand (1×10^{-5} M) were used. Competitive metal salt extractions were conducted with a 10.00 cm^3 of an aqueous solution containing the metal cations (Fe(III) , Cu(II) , Pb(II) , Co(II) , Zn(II) , Mn(II) , Ni(II) , Mg(II) , Ca(II)) and 10.00 cm^3 of an organic solution of the ligand.

One of the most important findings was the increase Fe(III) selectivity in mixture over the other transition metal cations for the examined ligands. The highest selectivity factors of Fe(III) in mixture were achieved again with all ligands. For the Fe(III) cation in mixture the S_f values, determined by competitive extraction, were approximately ca. 23,25–55,70,000 take times greater than those calculated from the results of selective extraction experiments of other transition metal cations.

Heavy metal removal is an important task for health. Therefore selective extraction power of organic ligands is extremely important. In this study, selective extraction abilities of the synthesized ligands were investigated. A graph of selectivity values was depicted in Fig. 1. The results indicated that among all the studied metals such as Fe(III) , Cd(II) , Ni(II) , Ca(II) and Mg(II) , Fe(III) showed selective complexation toward the all the ligands (in Table 4). A graph of very high selectivity values of iron was depict in Fig. 2. On the other hand, selectivity values of each other metals was depict in Fig. 3, 4, 5, 6, 7, 8, 9, 10 and 11. In copper results in Fig. 3; **4b**, **4c**, **5a**, **5b** and **5c** ligands were showed very high selectivity against Cd(II) , Mg(II) and Ca(II) , on the other hand **4a**, **4d** and **5d** ligands were only showed very high selectivity against Ca(II) . Ca(II) and Mg(II) atoms has the lowest complexation values in all transition metals. Podand compounds are open chain molecules, structures have the ability to move freely to hold metal ion during complexation.

Conclusions

The stability constants of metal complexes of the non-cyclic and cyclic ligands as N-pivot side-armed podands and lariat ethers, i.e., **4a–d** and **5a–d**, are listed in Table 2,

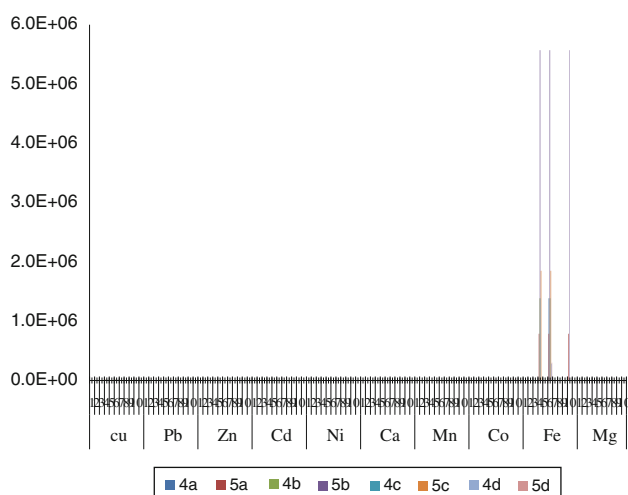


Fig. 1 Selectivity factor graphic of all metals for **4a–d** and **5a–d** ligands. 1 M/Cu, 2 M/Pb, 3 M/Zn, 4 M/Cd, 5 M/Ni, 6 M/Ca, 7 M/Mn, 8 M/Co, 9 M/Fe, 10 M/Mg

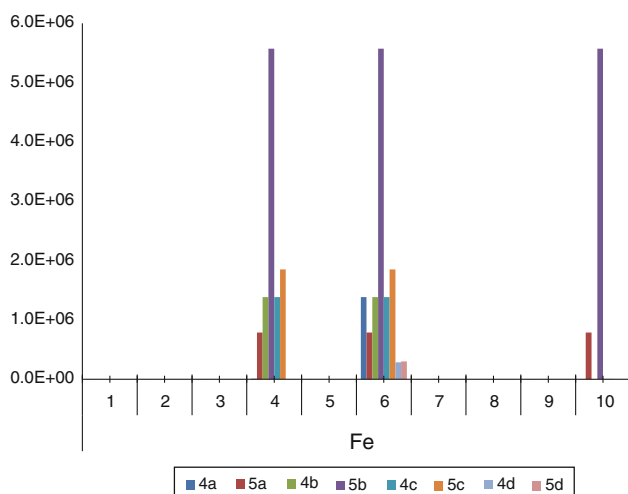


Fig. 2 Selectivity factor graphic of iron for **4a–d** and **5a–d** ligands. 1 Fe/Cu, 2 Fe/Pb, 3 Fe/Zn, 4 Fe/Cd, 5 Fe/Ni, 6 Fe/Ca, 7 Fe/Mn, 8 Fe/Co, 9 Fe/Fe, 10 Fe/Mg

as the interactions of these ligands with the alkali metal ions in CHCl_3 media. Assuming that formation of 1:1 complexes the alkali metal cations between our ligands extracted at the natural pH of the aqueous metal salt solutions. The $\log K_{\text{ex}}$ values of the ligands have been decreased with $\text{Fe(III)} > \text{Cu(II)} > \text{Pb(II)} > \text{Co(II)} > \text{Zn(II)} > \text{Mn(II)} > \text{Ni(II)} > \text{Mg(II)} > \text{Ca(II)}$ metal ions respectively. Among the new ligands examined, all podands exhibit low extraction of alkali metals. For Ca(II) and Mg(II) ions, relatively high extraction percentage are observed with all schiff base and amine forms of podands for transition metals. The $\log K_{\text{ex}}$ values well display to extraction selectivity of the ligands for Fe(III) -organic salt over for other metals organic salt. Fe(III) -Organic

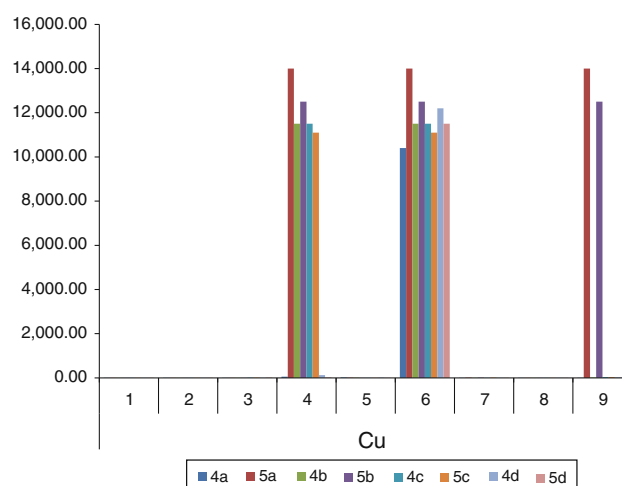


Fig. 3 Selectivity factor graphic of copper for **4a–d** and **5a–d** ligands. 1 Cu/Cu, 2 Cu/Pb, 3 Cu/Zn, 4 Cu/Cd, 5 Cu/Ni, 6 Cu/Ca, 7 Cu/Mn, 8 Cu/Co, 9 Cu/Mg

ligands is more strongly complexed with both imin and amine forms of the podands in the order of **5b** > **5c** > **4a** = **4b** = **4c** > **5a** > **5d** > **4d**.

In the supramolecular chemistry, some conformationally rigid cavitands are relatively slow in exchanging their metal–ligand solutions [37–40, 43]. The lipophilicity and functionality of specific terminal groups having various polyethylene frameworks could be useful in enhancing the cation transport and detection [40, 44, 45]. The polyethylene glycol chains and their podands binding the cation by chelation have been well known because of the use of pure polyethylene glycols–glymes for the salt solvating. The end groups may play a specific role for the chelation depending on their polarity [46]. Sometimes, surprisingly podands shows high complexation values compared to cyclic similar compounds [47].

The results concerning the study of the transition metal cations with these ligands are very important in respect. First, in all cases of extraction studies, Fe(III) is found to be the best extracted metal cation for all synthesized ligands. Fe(III) cation in mixture, have been found to be the best selective extracted for the extraction solvent and the given all ligands as shown in Tables 3 and 4.

In this study, a convenient method was established for the synthesis in good yields of new bis triazole Schiff bases **4a–d** and corresponding bis amino triazole compounds **5a–d**. The eight new bis-(4H-1,2,4-triazole) derivatives synthesized in the study are exhibit some biological activities and these results are reported. And the using method for complexation behaviour of the examined metal cations is simple, rapid, highly selective and sensitive.

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