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A series of new hetero-macrocyclic diamide-ester compounds (**4a - 4z, 6a - 6b**) were synthesized using 4-(dimethylamino)pyridine as catalyst and characterization by infrared spectra, nuclear magnetic resonance spectra, mass spectra and elemental analyses. The structures of **4e** and *meso* **4b** were determined by X-ray crystallography. The association constants of the compounds with various metal ions were determined by UV-visible spectroscopic titration, and showed a selective recognition for certain metal ions.

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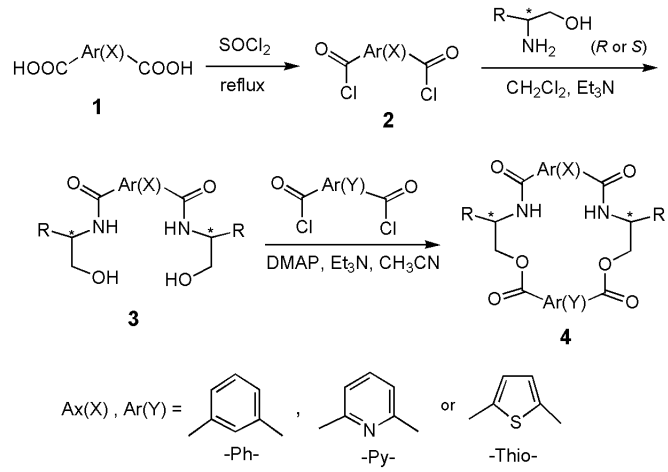
1. Introduction

Large-ring lactones or macrolides such as the erythromycins and cytochalasins have been shown to display antibiotic and anticancer activities [1-3]. Incorporation of geometrical rigidity by inserting an amide group in the ring of macrocyclic crown ether affects the binding properties and selectivity of macrocyclic compounds with metal cations [4,6] and organic molecules [5,7,8]. This effect is due to the dual ligating behavior of the amide O and N atoms [3-4], in addition to the greater negative character displayed by oxygen of amides than of ether and ester functionalities. Gokel and coworkers have reported that crown ethers with amide groups in their side chains exhibited an extraordinary Ca^{2+} binding ability [9]. Gunnlaugsson also found that triamide cyclens could be used as sensors for lanthanide ions [10]. Recently, Kumar and co-workers have reported that diamide-ester macrocyclic compounds showed extraordinary Ag^{+} binding strength with a remarkable selectivity for Ag^{+} over other metal ions [11-13]. Moreover, some diamide-containing

Scheme 1



R = Et (*R*), iso-Pr (*S*), Ph (*R*) or Benzyl (*S*).

	Ar(x)	R		Ar(x)	Ar(y)	R		Ar(x)	Ar(y)	R
3a	-Ph-	Et	**4a**	-Ph-	-Ph-	Et	**4n**	-Py-	-Ph-	iso-Pr
3b	-Ph-	iso-Pr	**4b**	-Ph-	-Py-	Et	**4o**	-Py-	-Py-	iso-Pr
3c	-Ph-	Ph	**4c**	-Ph-	-Thio-	Et	**4p**	-Py-	-Thio-	iso-Pr
3d	-Ph-	Benzyl	**4d**	-Ph-	-Ph-	iso-Pr	**4q**	-Py-	-Ph-	Benzyl
3e	-Py-	Et	**4e**	-Ph-	-Py-	iso-Pr	**4r**	-Py-	-Py-	Benzyl
3f	-Py-	iso-Pr	**4f**	-Ph-	-Thio-	iso-Pr	**4s**	-Py-	-Thio-	Benzyl
3g	-Py-	Benzyl	**4g**	-Ph-	-Ph-	Ph	**4t**	-Thio-	-Ph-	Et
3h	-Thio-	Et	**4h**	-Ph-	-Py-	Ph	**4u**	-Thio-	-Py-	Et
3i	-Thio-	iso-Pr	**4i**	-Ph-	-Thio-	Ph	**4v**	-Thio-	-Thio-	Et
3j	-Thio-	Ph	**4j**	-Ph-	-Ph-	Benzyl	**4w**	-Thio-	-Py-	iso-Pr
3k	-Thio-	Benzyl	**4k**	-Py-	-Ph-	Et	**4x**	-Thio-	-Thio-	iso-Pr
			4l	-Py-	-Py-	Et	**4y**	-Thio-	-Thio-	Ph
			4m	-Py-	-Thio-	Et	**4z**	-Thio-	-Thio-	Benzyl

macrocycles have been utilized as new catalysts [14]. Development of an efficient method for their syntheses has been a subject of keen interest. Previously, we reported on a series of new chiral macrolides and their antifungal activity [15]. Until now, relatively little was reported with respect to the chiral macrocyclic diamide-ester compounds. Herein we report the syntheses of some new diamide-ester macrocycles including their complexation properties with metal ions. The X-ray crystal structures of two of these macrocycles are also reported.

2. Results and discussion

The synthesis of macrolides involves a three-step approach: formation of the diacid chloride, amidation with an aminoethanol, and cyclodiesterification with appropriate diacid chlorides. The synthetic route is shown in Scheme 1.

It is normally difficult to obtain subject macrocycles in high yields during the last step of the intermolecular cyclization for the following reasons: 1) the intermolecular cyclization procedure, 2) the inclusion of two geometrical rigid aromatic moieties and two amide bond units, 3) an unfavorable decrease in the entropy of reaction and 4) the facile formation of chain and polymeric by-products. For the purpose of minimizing these problems, the effect of solvent on ease of cyclization was first investigated. Acetonitrile was found to be the most satisfactory medium. Subsequently, various bases were studied. The inorganic bases, potassium carbonate and sodium hydroxide were found to have little effect on cyclization. Triethylamine (Et_3N) and pyridine were better bases, but gave relativity low yields. The adoption of phase transfer catalyses (PTC) [11-13] also afforded low yields. Alternatively, the combination of a base and a catalyst was investigated for the purpose of promoting the cyclization. It was found that in the presence of pyridine or triethylamine and 4-(dimethylamino)pyridine (DMAP, *highly toxic and corrosive*, care should be exercised) as catalysts, higher yields were achieved. In the synthesis of macrocycle **4a**, a comparison of the effect of catalysts and bases on the reaction is shown in Table 1. Good overall yields of up to 65% for **4a** were obtained. By employing the new base-catalyst combination, high dilution conditions were found to be unnecessary in the cyclization step. In addition, the reaction rate was also found to increase significantly.

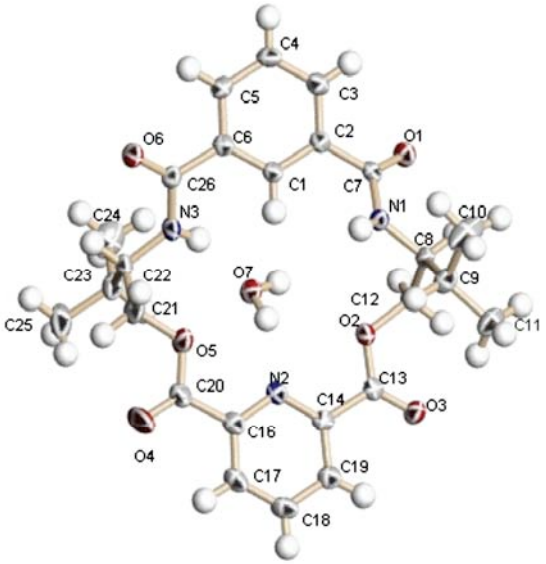


Figure 1. Perspective view of the molecular structure of chiral **4e** (acetone molecule was omitted for clarity). The selected bond distances (Å) and angles (deg): O(4)-C(20) 1.191(3), O(5)-C(20) 1.306(3), O(6)-C(26) 1.236(3), N(3)-C(26) 1.327(3), N(3)-C(22) 1.458(3), C(6)-C(26) 1.501(3), C(16)-C(20) 1.512(4), C(21)-C(22) 1.515(4), C(22)-C(23) 1.531(4); C(20)-O(5)-C(21) 117.53(18), C(26)-N(3)-C(22) 124.08(19), O(4)-C(20)-O(5) 124.0(3), O(4)-C(20)-C(16) 122.1(2), O(5)-C(20)-C(16) 113.89(18), O(5)-C(21)-C(22) 108.76(18), N(3)-C(22)-C(21) 108.4(2), N(3)-C(22)-C(23) 109.68(18), C(21)-C(22)-C(23) 114.7(2), O(6)-C(26)-N(3) 123.61(19), O(6)-C(26)-C(6) 121.03(18), N(3)-C(26)-C(6) 115.37(19).

In order to obtain an in depth understanding of stereochemical properties of the new chiral macrocycles, crystallographic investigations were conducted. An air-stable, colorless single crystal of **4e** was obtained by slow evaporation from an acetone-hexane (v/v 1:1) solution and its X-ray crystal structure was successfully determined as illustrated in Figure 1.

The single crystal structure of **4e** is the first reported for a chiral diamide-ester macrocycle. Each macrocycle incorporates rigid amide and aromatic building blocks, this results in overall molecular rigidity. These structures display some differences from the structures of similar racemic compounds previously reported [16]. In **4e**, the two aromatic units and two ester units are approximately coplanar, while the two carbonyl units of the amide groups and two isopropyl substituent groups are out of the plane and occupy position on the opposite sides of the plane. The two NH(C=O)-CH(R)-CH_2-O(C=O) bonds are twisted

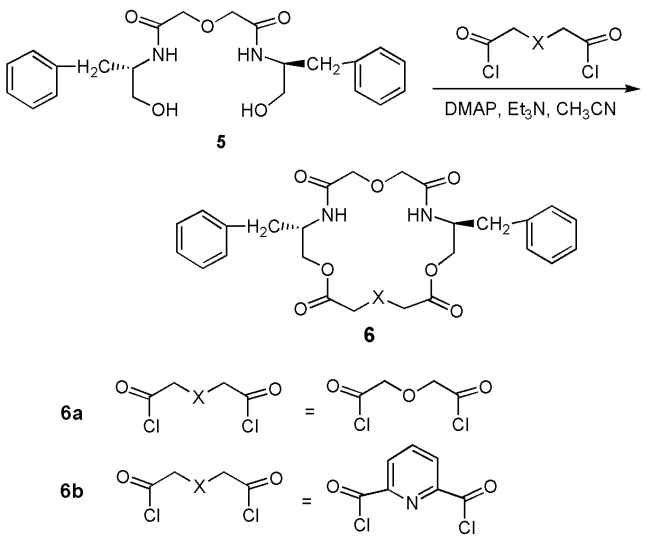
Table 1

Influence of Catalyst and Base on the Product Yield for Macrocycle **4a**

Catalyst	K_2CO_3	Et_3N	Pyridine	DMAP	Et_3N+DMAP	Pyridine+DMAP	PTC [a]
Yield%	2	10	25	28	58	65	27

[a] PTC is: TBA HSO_4+K_2CO_3.

Scheme 2



with respect to the aromatic moieties. This creates a molecular structure with a crystallographic two-fold symmetry axis of rotation at its center.

We have also successfully utilized the base-catalyst combination system to synthesize similar macrocycles containing, for example, the ether (CH_2-O-CH_2) linkage in the main chain instead of an aromatic unit for the preparation of macrocycles **6a** and **6b**. The synthetic route is shown in Scheme 2.

After changing the starting chiral amino alcohol to a racemic amino alcohol in the amidation procedure, racemic macrocycles were obtained. For example, when racemic amino butanol was used as the starting material, *meso* **4b** was obtained. It is interesting to note that two single crystals of *meso* **4b** were separately obtained from acetonitrile (m1-**4b**) (Figure 2) and acetone (m2-**4b**) in the presence of less water. The structure was established by X-ray analysis (Figure 2). This molecule possesses a chair-like structure with the benzene and pyridine moieties occupying opposite positions. The two ethyl groups are located on either sides of the molecule. The amide groups are twisted with respect to the phenyl unit, while the carboxylate groups are almost coplanar with the plane of the pyridine. Water molecules play an important role in crystal structures because they can form hydrogen bonds with the heteroatoms from both the amide and pyridine species. Different solvent molecules can give rise to different crystal systems. For example, molecules from acetonitrile solution form orthorhombic crystals in contrast to molecules from acetone solution, which form monoclinic crystals. There exist some structural differences between **4e** and *meso* **4b**. The two side ethyl groups of *meso* **4b** lie on the same side of the macrocyclic molecule, while in **4e**, the two side iso-propyl groups lie on opposite sides.

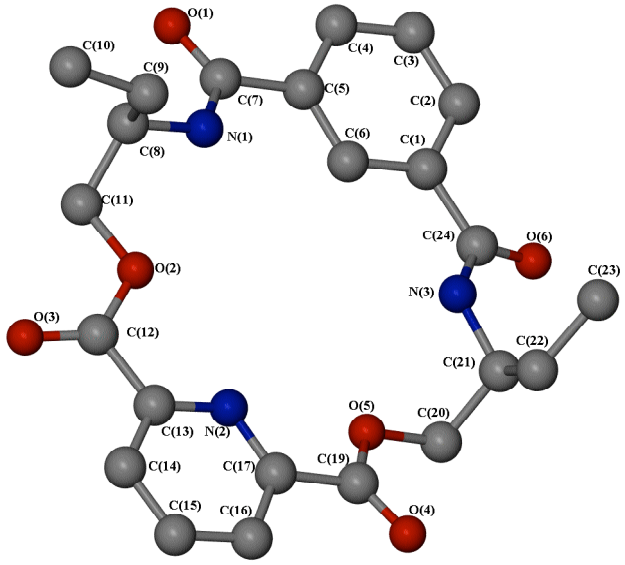


Figure 2. Perspective view of the molecular structure of racemic **4b** obtained from acetonitrile (H atoms, water and acetonitrile solvents were omitted for clarity). The selected bond distances (Å) and angles (deg): C(5)-C(7) 1.506(3), C(7)-O(1) 1.229(3), C(7)-N(1) 1.340(3), C(8)-N(1) 1.464(3), C(8)-C(11) 1.511(4), C(11)-O(2) 1.460(3), C(12)-O(3) 1.208(3), C(12)-O(2) 1.339(3), C(12)-C(13) 1.496(4); O(1)-C(7)-N(1) 123.0(2), O(1)-C(7)-C(5) 121.3(2), N(1)-C(7)-C(5) 115.7(2), N(1)-C(8)-C(11) 110.6(2), N(1)-C(8)-C(9) 109.7(2), C(11)-C(8)-C(9) 113.7(2), C(10)-C(9)-C(8) 112.4(2), O(2)-C(11)-C(8) 109.2(2), O(3)-C(12)-O(2) 124.8(2), O(3)-C(12)-C(13) 121.6(2), O(2)-C(12)-C(13) 113.6(2), C(7)-N(1)-C(8) 122.7(2), C(12)-O(2)-C(11) 115.9(2).

Among the various methods used to characterize the host-guest interaction, the UV-visible spectroscopic titration method has been widely used because of its high sensitivity [17-18]. In this paper, the association constants, K, of the several macrolides with the following metal ions: Cu^{2+}, Co^{2+}, Pb^{2+}, Ni^{2+}, Ag^{+}, Hg^{2+} were determined using this method. The results are shown in Table 2. From these data, it is observed that these macrolides display selective complexation with different metal ions. They can associate with Cu^{2+}, Co^{2+}, Pb^{2+}, Ag^{+}, Hg^{2+} and Ni^{2+}, but the binding ability with different metal ions is quite variable. The value of K varies from 45.3 x 10^3 to 0.03 x 10^3 M^{-1}. An increase in the association constant, K, was observed for ligands **4g**, **4h** and **4i** indicating that nitrogen and sulfur atoms on the macrocycle serve to increase the tendency to coordinate metal ions. Besides, macrocycles **4i** and **4s**, which contain the sulfur-containing thiophene moiety, show remarkably strong affinity for Co^{2+}. The macrocycles tend to complex more strongly with Ag^{+} than any other metal ion.

3. EXPERIMENTAL

All melting points were determined on a Thiele apparatus and are uncorrected; ^1H and ^{13}C NMR spectra were measured on

Table 2

The Association Constants (K) for Selected Macrolides with Metal ions [a] (10^3 M^{-1})

	Cu^{2+}	Pb^{2+}	Co^{2+}	Ag^{+}	Hg^{2+}	Ni^{2+} [b]
4b	3.22	2.11	1.52	9.68	2.62	<0.03
4g	0.71	1.89	1.08	2.05	0.96	<0.03
4h	18.2	5.72	1.71	36.5	6.54	<0.03
4i	7.15	3.34	22.5	7.61	3.42	<0.03
4q	1.90	3.51	1.87	4.16	1.48	<0.03
4r	3.40	1.22	1.84	16.4	7.02	<0.03
4s	21.1	3.07	45.3	35.9	20.9	<0.03

[a] Titration is carried out at rt in methanol and all metal salts are $M^{n+}(ClO_4)^-_n$; [b] Less change of UV- absorption of above macrolides with Ni^{2+}.

Table 3

Crystal Data Collection and Structure Refinement Details for **4e** and *meso* **4b**

	m1-**4b**	m2-**4b**	**4e**
Structural formula	$C_{28.57}H_{34.29}N_{4.57}O_8$	$C_{49}H_{60}N_6O_{15}$	$C_{26.50}H_{34}N_3O_{7.50}$
Formula weight	569.75	973.03	514.57
Temperature	110(2) K	110(2) K	110(2) K
Wavelength	0.71073 Å	0.71073 Å	0.71073 Å
Crystal system	Orthorhombic	Monoclinic	Monoclinic
Space group	P2(1)2(1)2(1)	P2(1)/n	C2
a (Å)	11.5847(9)	11.6729(11)	22.583(14)
b (Å)	15.1972(12)	15.0192(14)	9.505(6)
c (Å)	28.369(2)	27.323(3)	12.450(8)
α	90°	89.98°	90°
β	90°	93.26°	93.869(10)°
γ	90°	90.005°	90°
Volume	4994.5(7) $Å^3$	4782.5(8) $Å^3$	2666(3) $Å^3$
Z	8	4	4
D (calc.): mg/m^3	1.326	1.351	1.282
Absorpt. coefficient	0.098 mm^{-1}	0.101 mm^{-1}	0.094 mm^{-1}
F (000)	2112	2064	1096
Crystal size: mm^3	0.50 x 0.36 x 0.32	0.30 x 0.20 x 0.20	0.30 x 0.10 x 0.10
θ collection range	1.44 to 27.57°	1.49 to 25°	2.33 to 25.00°
Reflections collected	47761	24734	6340
Indepdt. reflections	11311 [R(int) = 0.0338]	8383 [R(int) = 0.0536]	4186 [R(int)=0.0370]
Completeness to theta	99.0 %	99.6 %	92.7%
Absorption correction	None	None	Semi-empirical from quivalents
Max. and min. transm.	0.9693 and 0.9526	0.9801 and 0.9704	0.9906 and 0.9723
Refine method on F^2	Full-matrix least-squares	Full-matrix least-squares	Full-matrix least-squares
Data / restraints / parameters	11311 / 0 / 671	8383 / 0 / 635	4186 / 1 / 341
Goodness-of-fit on F^2	1.073	1.084	1.019
Final R indices [I>2sigma(I)]	R1 = 0.0585, wR2 = 0.1412	R1 = 0.0644, wR2 = 0.1537	R1 = 0.0444, wR2 = 0.1161
R indices (all data)	R1 = 0.0829, wR2 = 0.1651	R1 = 0.1250, wR2 = 0.2172	R1 = 0.0466, wR2 = 0.1182
Largest diff. peak and hole: $e.Å^{-3}$	0.618 and -0.302	0.521 and -0.416	0.216 and -0.204

Varian Innova 300, 500 MHz NMR spectrometer using acetone-d_6 (unless specified otherwise) as the solvent and tetramethylsilane as the internal standard; optical rotation values were measured with a Perkin-Elmer 241 polarimeter at sodium D line 589 nm. Elemental analyses were carried out on an elemental Vario EL elemental analyzer; infrared spectra were recorded on an EQUINOX 55-A590/3F instrument; UV-visible spectra were obtained with a Peking UV-1200 spectrophotometer; mass spectra were measured on a Finnigan Voyager instrument. Dicarboxylic acids **1** were purchased from Aldrich fine chemical company.

3.1 General Procedure for the Preparation of the Diacid Chloride **2**.

The dicarboxylic acid **1** (0.06 mol) was treated with thionyl chloride (30 ml) and two drops of *N*,*N*-dimethylformamide and then heated at reflux for 6 - 10 hours. The excess thionyl chloride was removed by evaporation under reduced pressure. Residual thionyl chloride was removed by co-evaporation with 30 ml of

anhydrous benzene to afford the corresponding diacid chloride **2**.

3.2 General Procedure for the Preparation of **3a** - **3k**.

To a cold (-5 – 0 ºC) solution of a chiral ethanolamine (20 - 24 mmol) and 5 ml of triethylamine in 30 ml of dichloromethane was added a solution of diacid chloride **2** (10 mmol) in 10 ml of dichloromethane over a period of two hours. The reaction mixture was stirred at 0 ºC for four hours and then at 25 ºC for additional four hours. The product precipitated from the solution and was collected by filtration then washed with 30 ml of H_2O. The crude product was either purified by recrystallization from acetone-petroleum (8:2) or by column chromatography with silica gel as adsorbent and acetone-hexanes (2:1) as the eluent. Intermediate **3a** was isolated as a liquid, while intermediate **3b** - **3k** were obtained as white solids.

N,*N*'-Bis-[(1*R*)-1-(hydroxymethyl)propyl]-isophthalamide (**3a**).

This compound was obtained as yellow liquid 2.43 g, yield 79%; $[\alpha]_D^{25}$ = +13.3° (c = 1, acetone); IR, ν_{max}: 3318, 3071, 2966, 2875, 1644, 1539, 1461, 1300, 1053 cm^{-1}; ^{1}H-NMR, δ_H: 0.90 (6H, t, *J*=7.5 Hz, CH_3), 1.63-1.65 (4H, m, CH_2Me), 3.06-3.36 (2H, m, CH), 3.65 (2H, d, *J*=7.0Hz, OH), 3.80-4.42 (4H, m, CH_2O), 7.4-8.4 (4H, m, ArH), 8.0 (2H, d, *J*=7.5Hz, CONH).

Anal. Calcd. for $C_{16}H_{24}N_2O_4$: C, 63.32; H, 7.84; N, 9.08. Found: C, 63.54; H, 7.91; N, 9.02.

N,*N*-Bis-[(1*S*)-1-(hydroxymethyl)-2-methylpropyl]-isophthalamide (**3b**).

This compound was obtained as white solid 2.32 g, yield 69%; mp: 172-174 ºC; $[\alpha]_D^{25}$ = -85.7° (c = 0.15, acetone); IR, ν_{max}: 3440, 3292, 3083, 2958, 2875, 1644, 1582, 1545, 1473, 1409, 1333, 1283, 1072, 1021, 981, 717 cm^{-1}; ^{1}H-NMR, δ_H: 0.98 (12H, 2d, *J*=11.0Hz, CH_3), 2.02-2.05 (2H, m, CH), 3.71 (4H, dd, *J*=8.5, 1.0Hz, CH_2), 3.91-3.94 (4H, m), 7.50-8.36 (4H, m, ArH), 7.60 (2H, d, *J*=7.5Hz, CONH; MS(FAB): 337 (M+1, 100%), 305, 234, 207, 120, 104, 77, 57.

Anal. Calcd. for $C_{18}H_{28}N_2O_4$: C, 64.26; H, 8.39; N, 8.33. Found: C, 64.21; H, 8.28; N, 8.40.

N,*N*'-Bis-[(1*R*)-2-hydroxy-1-phenylethyl]-isophthalamide (**3c**).

This compound was obtained as white solid 2.75 g, yield 68%; mp: 175-178 ºC; $[\alpha]_D^{25}$ = +33.2° (c = 2.0, acetone); IR, ν_{max}: 3304, 3060, 2931, 2877, 1644, 1532, 1580, 1532, 1454, 1293, 1189, 1070, 1033, 915, 757, 700 cm^{-1}; ^{1}H NMR, δ_H: 3.32 (2H, d, *J*=7.3Hz, OH), 3.61-3.74 (4H, m, CH_2O), 5.04-5.11 (2H, m, CH), 7.20-8.37 (14H, m, ArH), 8.86 (2H, d, *J*=8.0Hz, CONH); MS(FAB): 405 (M+1, 25%), 373, 279, 268, 149, 102(100%), 77.

Anal. Calcd. for $C_{24}H_{24}N_2O_4$: C, 71.27; H, 5.98; N, 6.93. Found: C, 71.36; H, 6.02; N, 6.89.

N,*N*'-Bis-[(1*S*)-1-(hydroxymethyl)-2-phenylethyl]-isophthalamide (**3d**).

This compound was obtained as white solid 3.02 g, yield 70%; mp: 152-154 ºC; $[\alpha]_D^{25}$ = -207.0° (c = 0.15, acetone); IR, ν_{max}: 3412, 3342, 3078, 3029, 2958, 2924, 2880, 1632, 1578, 1548, 1492, 1453, 1407, 1331, 1295, 1255, 1184, 1051, 1030, 924, 819, 730, 703, 562 cm^{-1}; ^{1}H NMR, δ_H: 2.91-3.09 (4H, m, CH_2), 3.67 (4H, dd, *J*=8.5, 1.0Hz, CH_2O), 4.10 (2H, t, *J*=9.5Hz, OH), 4.33-4.38 (2H, m, CH), 7.67 (2H, d, *J*=13.5 Hz, CONH), 7.17-8.23 (14H, m, ArH); MS(FAB): 433 (M+1, 100%), 341, 282, 255, 219, 154, 91, 77.

Anal. Calcd. for $C_{26}H_{28}N_2O_4$: C, 72.20; H, 6.53; N, 6.48. Found: C, 72.36; H, 6.50; N, 6.55.

N,*N*-Bis-[(1*R*)-1-(hydroxymethyl)propyl]-2,6-pyridinedicarboxamide (**3e**).

This compound was obtained as white solid 2.35 g. yield 76%; mp: 116-118 ºC; $[\alpha]_D^{25}$ = -37.98° (c = 1.0, MeOH); IR, ν_{max}: 3303, 3191, 2959 , 2851, 1679, 1644, 1546, 1519, 1060 cm^{-1}; ^{1}H NMR, δ_H: 0.92 (6H, t, *J*=7.6Hz, CH_3), 1.54-1.78 (4H, m, CH_2Me), 3.52-3.69 (4H, m, CH_2O), 3.81-4.08 (4H, m, CHN and OH), 8.20-8.28 (3H, m, py-H), 8.76 (2H, d, *J*=7.3 Hz CONH); ^{13}C NMR, δ_C, 10.84, 23.72, 53.43, 64.77, 124.44, 139.26, 149.22, 163.27; MS(FAB): 310 (M+1, 75%).

Anal. Calcd. for $C_{15}H_{23}N_3O_4$: C, 58.24; H, 7.49; N, 13.58. Found: C, 57.96; H, 7.61; N, 13.32.

N,*N*'-Bis-[(1*S*)-1-(hydroxymethyl)-2-methylpropyl]-2,6-pyridinedicarboxamide (**3f**).

This compound was obtained as [19] white solid 2.22 g, yield 66%; mp: 103-105 ºC; $[\alpha]_D^{25}$ = -82.3° (c = 0.15, acetone); IR, ν_{max}: 3422, 3292, 2964, 2888, 1658, 1549, 1460, 1387, 1325, 1221, 1171, 1126, 1056, 996, 929, 850, 809, 753, 696, 643, 623, 553 cm^{-1}; ^{1}H NMR, δ_H: 0.98 (12H, 2d, *J*=11.5Hz, CH_3), 1.98-2.09 (2H, m, CH), 3.64-3.78 (4H, m, CH_2O), 3.80-3.89 (2H, m, CH), 4.03 (2H, t, *J*=8.5Hz, OH), 8.19-8.29 (5H, m, CONH and ArH); MS(FAB): 337 (M+1, 20%), 306 (100%), 294, 276, 220, 191, 149, 134, 106, 86, 55.

Anal. Calcd. for $C_{17}H_{27}N_3O_4$: C, 60.51; H, 8.07; N, 12.45. Found: C, 60.43; H, 8.12; N, 12.36.

N,*N*'-Bis-[(1*S*)-1-(hydroxymethyl)-2-phenylethyl]-2,6-pyridinedicarboxamide (**3g**).

This compound was obtained as colorless solid 3.07 g, yield 71%; mp: 85-87 ºC; $[\alpha]_D^{25}$ = –136.6° (c = 0.2, MeOH); IR, ν_{max}: 3330, 3026, 2937, 2875, 1661, 1530, 1446, 1033, 749, 700 cm^{-1}; ^{1}H NMR, δ_H: 2.90-3.08 (8H, m, $PhCH_2$ and CH_2O), 3.66-3.75 (2H, d, *J*=5.0Hz, OH), 4.22-4.39 (2H, m, CH), 7.11-7.28 (10H, m, PhH), 8.00-8.31 (3H, m, PyH), 8.47-8.55 (2H, d, *J*=8.5Hz, CONH); MS(FAB): 433 (M, 7%), 401, 341, 323, 300, 191, 168, 134, 117, 91 (100%), 65.

Anal. Calcd. for $C_{25}H_{27}N_3O_4$: C, 69.27; H, 6.28; N, 9.69. Found: C, 69.13; H, 6.35; N, 9.72.

N,*N*'-Bis-[(1*R*)-1-(hydroxymethyl)propyl]-2,5-thiophenedicarboxamide (**3h**).

This compound was obtained as white solid 2.29 g, yield 73%; mp: 200-202 ºC; $[\alpha]_D^{20}$ = -52.53° (c = 1.0, MeOH); IR, ν_{max}: 3395, 3303, 2966, 2931, 2875, 1679, 1644, 1539, 842 cm^{-1}; ^{1}H NMR, δ_H: 0.85 (6H, t, *J*=7.4Hz, CH_3), 1.40-1.70 (4H, m, CH_2Me), 3.30-3.46 (2H, m, CHN), 3.66-3.96 (4H, m, CH_2O), 4.66 (2H, s, OH), 7.76 (2H, s, thiophene-H), 8.14 (2H, d, *J*=7.5Hz, CONH,); MS(FAB): 314 (M+1, 100%), 283, 226, 90.

Anal. Calcd. for $C_{14}H_{22}N_4O_2S$: C, 53.48; H, 7.06; N, 8.92. Found: C, 53.05; H, 6.88; N, 9.26.

N,*N*'-Bis-[(1*S*)-1-(hydroxymethyl)-2-methylpropyl]-2,5-thiophenedicarboxamide (**3i**).

This compound was obtained as white solid 2.43 g, yield 71%; mp: 195-197 ºC; $[\alpha]_D^{20}$ = -24.94° (c = 0.28, MeOH); IR, ν_{max}: 3296, 3254, 3075, 2959, 2931, 1987, 1616, 1553, 1518, 1461, 1321, 1025, 744 cm^{-1}; ^{1}H NMR (CD_3OD): δ_H 0.89-1.01 (12H,

m, CH_3), 1.91-2.00 (2H, m, CHMe), 3.67-3.75 (4H, m, CH_2O), 3.83-3.89 (2H, m, CHN), 4.89 (2H, s, OH), 7.72 (2H, s, thiophene-H), 8.08 (2H, d, *J*=7.5Hz, CONH); MS(FAB): 343 (M+1, 100%), 325, 279, 240, 213, 165, 111.

Anal. Calcd. for $C_{16}H_{26}N_2O_4S$: C, 56.12; H, 7.65; N, 8.18. Found: C, 55.78; H, 7.72; N, 8.06.

N,*N*-Bis-[(1*R*)-2-hydroxy-1-phenylethyl]-2,5-thiophenedicarboxamide (**3j**).

This compound was obtained as white solid 2.87 g, yield 70%; mp: 201-204 ºC; $[\alpha]_D^{20}$ = +42.25° (c = 0.14, MeOH); IR, ν_{max}: 3332, 3083, 3029, 2952, 2875, 1630, 1539, 1518, 1454, 1285, 1039, 744 cm^{-1}; ^1H NMR, δ_H: 3.71 (2H, s, OH), 3.86 (4H, d, *J*=6.5Hz, CH_2O), 5.19-5.21 (2H, dd, *J*=6.5, 7.5Hz, CH), 7.22-7.45 (10H, m, PhH), 7.76 (2H, s, thiophene-H), 7.98 (2H, d, *J*=7.0Hz, CONH); MS(FAB): 411 (M+1, 3%), 341, 274, 219.

Anal. Calcd. for: $C_{22}H_{22}N_2O_4S$: C, 64.37; H, 5.40; N, 6.82. Found: C, 64.16; H, 5.28; N, 6.95.

N,*N*'-Bis-[(1*S*)-1-(hydroxymethyl)-2-phenylethyl]-2,5-thiophenedicarboxamide (**3k**).

This compound was obtained as white solid 3.06 g, yield 74%; mp: 188-191 ºC; $[\alpha]_D^{20}$ = -144.7° (c = 0.14, acetone); IR, ν_{max}: 3332, 3083, 3664, 3029, 2938, 2889, 1630, 1545, 1510, 1454, 1293, 1138, 1032, 751 cm^{-1}; ^1H NMR, δ_H: 2.89-3.03 (4H, m, CH_2Ph), 3.63 (4H, d, *J*=5.0Hz, CH_2O), 3.72 (2H, s, OH), 4.27-4.30 (2H, m, CH), 7.15-7.30 (10H, m, PhH), 7.49 (2H, d, *J*=8.0Hz, CONH), 7.59 (2H, s, thiophene-H); MS(FAB): 439 (M+1, 70%), 347, 288, 219, 194, 91.

Anal. Cacld. for: $C_{24}H_{26}N_2O_4S$: C, 65.73; H, 7.98; N, 6.39. Found: C, 65.44; H, 7.82; N, 6.55.

Preparation of Compound **5** [20].

3.3 General Procedure for the Preparation of the Macrocycle **4a** - **4z** and **6a** - **6b**.

To a hot (50 – 70 ºC) solution of compounds **3** or **5** (1.2 mmol) in 40 ml of acetonitrile was added 4-(dimethylamino)pyridine (20-30 mg), followed by the addition of a solution of 0.5 g of compound **2** in 20 ml of acetonitrile over a period of about 40 minutes. Triethylamine (2 ml) was added to the reaction mixture over a period of 1 – 2 hours and then the reaction mixture was stirred for another 10 hours. A white precipitate, triethylamine hydrochloride formed, and was removed by filtration. The filtrate was evaporated under reduced pressure to afford a residue, which was purified by column chromatography (silica gel, acetone-petroleum ether) to provide the title compounds **4**.

(5*R*,15*R*)-5,15-Diethyl-3,17-dioxa-6,14-diazatricyclo[17.3.1.$1^{8,12}$]-tetracosa-1(22),8,10,12(24),19(23),20-hexaene-2,7,13,18-tetraone (**4a**).

This compound was obtained as white solid 0.31 g, yield 58%; mp: 272-274 ºC; $[\alpha]_D^{25}$ = -105.8° (c = 0.2, acetone); IR, ν_{max}: 3320, 3071, 2960, 2875, 1721, 1644, 1539, 1461, 1307, 1236, 1096, 730 cm^{-1}. ^1H NMR, δ_H: 0.94-0.99 (6H, t, *J*=12.5Hz, CH_3), 1.67-1.72 (4H, q, *J*=12.5Hz, CH_2Me), 4.28-4.39 (4H, m, CH and CH_2O), 4.81-4.86 (2H, dd, *J*=6.0, 17.5Hz, CH_2O), 7.53-8.94 (8H, m, ArH), 7.90 (2H, d, *J*=8.0Hz, CONH); ^{13}C NMR, _c: 10.99, 24.48, 51.57, 66.65, 126.82-136.25 (m), 166.40, 167.70; MS(FAB): 439 (M+1, 5%), 368, 277, 149.

Anal. Calcd. for $C_{24}H_{26}N_2O_6$: C, 65.74; H, 5.98; N, 6.39. Found: C, 65.65; H, 6.10; N, 6.32.

(5*R*,15*R*)-5,15-Diethyl-3,17-dioxa-6,14,23-triaza-tricyclo-[17.3.1.$1^{8,12}$]tetracosa-1(22),8,10,12(24),19(23),20-hexaene-2,7,13,18-tetraone (**4b**).

This compound was obtained as white solid 0.15 g, yield 28%; mp: 239-241 ºC; $[\alpha]_D^{25}$ = +260.2° (c = 0.2, acetone); IR, ν_{max}: 3310, 3071, 2966, 2875, 1728, 1651, 1581, 1539, 1461, 1124, 1082 cm^{-1}; ^1H NMR, δ_H: 1.00 (6H, t, *J*=7.5Hz, CH_3), 1.69-1.73 (4H, m, CH_2Me), 4.36- 4.37 (2H, m, CH), 4.43-4.87 (4H, m, CH_2O), 7.58-8.27 (7H, m, ArH), 8.37 (2H, d, *J*=8.0Hz, CONH). MS(FAB): 440 (M+1, 14%), 322, 273, 202, 72 (100%).

Anal. Calcd. for $C_{23}H_{25}N_3O_6$: C, 62.86; H, 5.73; N, 9.56. Found: C, 63.07; H, 5.78; N, 9.45.

(4*R*,15*R*)-4,15-Diethyl-6,13-dioxa-23-thia-3,16-diaza-tricyclo[16.3.1.$1^{8,11}$]tricosa-1(21),8,10,18(22),19-pentaene-2,7,12,17-tetraone (**4c**).

This compound was obtained as white solid 0.19 g, yield 36%; mp: 233-235 ºC; $[\alpha]_D^{25}$ = -61.6° (c = 0.1, acetone); IR, ν_{max}: 3435, 3311, 3270, 3078, 2965, 2930, 2880, 1724, 1639, 1545, 1458, 1385, 1352, 1305, 1244, 1207, 1142, 1089, 965, 783, 745, 704 cm^{-1}. ^1H NMR, δ_H: 1.08 (6H, t, *J*=7.5Hz, CH_3), 1.67-1.77 (4H, m, CH_2), 4.35-4.42 (2H, m, CH), 4.16 (2H, dd, *J*=9.0, 11Hz, CH_2O), 4.68 (2H, dd, *J*=4.5, 11.0Hz, CH_2O), 7.78 (2H, s, thiophene-H), 7.74-7.75 (2H, d, *J*=9.0Hz, CONH), 7.50-7.87 (4H, m, ArH); MS (FAB): 445 (M+1, 16%), 399, 355, 281, 202, 149, 95, 57, 55(100%).

Anal. Calcd. for $C_{22}H_{24}N_2O_6S$: C, 59.45; H, 5.44; N, 6.30; S, 7.21. Found: C, 59.61; H, 5.52; N, 6.24; S, 7.13.

(5*S*,15*S*)-5,15-Diisoproyl-3,17-dioxa-6,14-diaza-tricyclo-[17.3.1.$1^{8,12}$]tetracosa-1(22),8,10,12(24),19(23),20-hexaene-2,7,13,18-tetraone (**4d**).

This compound was obtained as white solid 0.28 g, yield 50%; mp: >300ºC; $[\alpha]_D^{25}$= -272.0° (c = 0.1, acetone); IR, $\nu_{max.}$ 3401, 3311, 3069, 2963, 2926, 2875, 1724, 1647, 1533, 1464, 1378, 1343, 1301, 1260, 1157, 1260, 1135, 1077, 1041, 926, 734, 751 cm^{-1}; ^1H NMR, δ_H: 0.99, 1.08 (12H, 2d, *J*=6.5Hz, CH_3), 1.89-1.94 (2H, m, CH), 4.18-4.22 (2H, m, CH), 4.31-4.34 (2H, dd, *J*=3.0, 11.2Hz, CH_2O), 4.93-4.96 (2H, dd, *J*=5.0, 11.5Hz, CH_2O), 7.80-7.82 (2H, d, *J*=8.0Hz, CONH), 7.53-8.88 (8H, m, ArH); ^{13}C NMR, δ_C: 19.89, 20.03, 55.71, 65.32, 6.16, 126.62, 129.39, 129.71, 130.91, 131.63, 131.74, 132.48, 134.74, 136.55, 166.39, 167.57; MS(FAB): 467 (M+1, 50%), 413, 234, 216, 171, 149 (100%), 105, 69, 57.

Anal. Calcd. for $C_{26}H_{30}N_2O_6$: C, 66.94; H, 6.48; N, 6.00. Found: C, 66.82; H, 6.51; N, 6.14.

(5*S*,15*S*)-5,15-Diisopropyl-3,17-dioxa-6,14,23-triaza-tricyclo-[17.3.1.$1^{8,12}$]tetracosa-1(22),8,10,12(24),19(23),20-hexaene-2,7,13,18-tetraone (**4e**).

This compound was obtained as white solid 0.16 g, yield 28%; mp: 262-264 ºC; $[\alpha]_D^{25}$ = -252.4° (c = 0.5, acetone); IR, $\nu_{max.}$ 3595, 3433, 3297, 3071, 2966, 2930, 2875, 1722, 1648, 1612, 1542, 1462, 1423, 1382, 1319, 1272, 1243, 1151, 1086, 1043, 997, 918, 821, 757, 732, 703, 652, 533 cm^{-1}; ^1H NMR, δ_H: 1.00-1.10 (12H, 2d, *J*=7.0Hz, CH_3), 2.04-2.09 (2H, m, CH), 4.13-4.19 (2H, m, CH), 4.60-4.63 (2H, dd, *J*=3.5, 11.2Hz, CH_2O), 4.72-4.75 (2H, dd, *J*=4.5, 11.2Hz, CH_2O), 7.76-7.78 (2H, d, *J*=9.0Hz, CONH),7.50-8.34 (7H, m, ArH); MS(FAB): 468 (M+1, 100%), 301, 154, 104, 77.

Anal. Calcd. for $C_{25}H_{29}N_3O_6$: C, 64.23; H, 6.25; N, 8.99. Found: C, 64.27; H, 6.28; N, 8.94.

(4*S*,15*S*)-4,15-Diisopropyl-6,13-dioxa-23-thia-3,16-diaza-tricyclo-[16.3.1.1^{8,11}]tricosa-1(21),8,10,18(22),19-pentaene-2,7,12,17-tetraone (**4f**).

This compound was obtained as white solid 0.21 g, yield 37%; mp: >280 ºC; $[\alpha]_D^{25}$ = -85.9° (c = 0.1, acetone); IR, $\nu_{max:}$ 3303, 3074, 2964, 2930, 2875, 1732, 1642, 1537, 1463, 1487, 1348, 1299, 1256, 1156, 1099, 1030, 965, 743, 704 cm^{-1}; ^{1}H NMR, δ_H: 0.94-1.03 (12H, m, CH_3), 1.83-1.99 (2H, m, CH), 4.00-4.67 (6H, m, CH_2O and CH), 7.49-8.39 (6H, m, ArH), 8.30 (2H, d, *J*=8,5Hz, CONH); MS(FAB): 473 (M+1, 100%), 429, 234, 216, 154, 111, 69, 55.

Anal. Calcd. for $C_{24}H_{28}N_2O_6S$: C, 61.00; H, 5.97; N, 5.93; S, 6.79. Found: C, 61.12; H, 5.99; N, 5.86; S, 6.68.

(5*R*,15*R*)-5,15-Diphenyl-3,17-dioxa-6,14-diaza-tricyclo-[17.3.1.1^{8,12}]tetracosa-1(22),8,10,12(24),19(23),20-hexaene-2,7,13,18-tetraone (**4g**)**.**

This compound was obtained as white solid 0.21 g, yield 30%; mp: 245-247 ºC; $[\alpha]_D^{25}$ = +161.5° (c = 0.1, MeOH); IR, $\nu_{max:}$ 3293, 3259, 3063, 2925, 2854, 1710, 1663, 1642, 1607, 1539, 1455, 1350, 1242, 1085, 745, 699 cm^{-1}; ^{1}H NMR, δ_H: 4.56-4.59 (2H, dd, *J*=3.5, 11.0Hz, CH_2O), 4.99-5.02 (2H, dd, *J*=7.0, 12.0Hz, CH_2O), 5.66-5.70 (2H, m, CH), 8.41 (2H, d, *J*=8.0Hz, CONH), 7.27-9.04 (18H, m, phenyl-H); MS(FAB): 535 (M+1, 15%), 277, 251, 204, 149, 57 (100%).

Anal. Calcd. for $C_{32}H_{26}N_2O_6$: C, 71.90; H, 4.90; N, 5.24. Found: C, 71.96; H, 4.81; N, 5.18.

(5*R*,15*R*)-5,15-Diphenyl-3,17-dioxa-6,14,23-triaza-tricyclo[17.3.1.1^{8,12}]tetracosa-1(22),8,10,12(24),19(23),20-hexaene-2,7,13,18-tetraone (**4h**).

This compound was obtained as white solid 0.17 g, yield 26%; mp: 142-144 ºC; $[\alpha]_D^{25}$ = +340.9° (c = 0.1, MeOH); IR, $\nu_{max:}$ 3289, 3254, 3064, 3029, 2952, 1707, 1644, 1539, 1545, 1349, 1243, 1089, 1032, 976, 744, 702 cm^{-1}; ^{1}H NMR, δ_H: 4,70-5.01 (4H, m, CH_2O), 5.57-5.66 (2H, m, CH), 7.26-8.48 (17H, m, ArH), 8.66 (2H, d, *J*=8.0Hz, CONH); MS(FAB): 536 (M+1, 10%), 369, 267, 123, 83, 57 (100%).

Anal. Calcd. for $C_{31}H_{25}N_3O_6$: C, 69.52; H, 4.71; N, 7.85. Found: C, 69.44; H, 4.82; N, 7.81.

(4*R*,15*R*)-4,15-Diphenyl-6,13-dioxa-23-thia-3,16-diaza-tricyclo-[16.3.1.1^{8,11}]tricosa-1(21),8,10,18(22),19-pentaene-2,7,12,17-tetraone (**4i**).

This compound was obtained as white solid 0.19 g, yield 29%; mp: 195-197 ºC; $[\alpha]_D^{25}$ = +255.8° (c = 0.1, MeOH); IR, $\nu_{max:}$ 3297, 3266, 3060, 3040, 2875, 2937, 1719, 1642, 1542, 1493, 1455, 1381, 1301, 235, 1136, 1098, 1077, 995, 922, 759, 773, 698 cm^{-1}; ^{1}H NMR, δ_H: 4.18 (2H, t, *J*=1.0Hz, CH_2O), 4.75-4.77 (2H, dd, *J*=4.5, 11.0Hz, CH_2O), 5.40-5.52 (2H, m, CH), 7.33-8.49 (14H, m, Ar-H), 7.87 (2H, s, thiophene-H), 9.21 (2H, d, *J*=8.5Hz, CONH); MS(FAB): 542 (M+2, 5%), 514, 391, 343, 167, 109, 69, 57 (100%).

Anal. Calcd. for $C_{30}H_{24}N_2O_6S$: C, 66.65; H, 4.47; N, 5.18; S, 5.93. Found: C, 66.78; H, 4.61; N, 5.11; S, 5.88.

(5*S*,15*S*)-5,15-Dibenzyl-3,17-dioxa-6,14-diaza-tricyclo-[17.3.1.1^{8,12}]tetracosa-1(22),8,10,12(24),19(23),20-hexaene-2,7,13,18-tetraone (**4j**).

This compound was obtained as white solid 0.45 g, yield 67%; mp: 280 ºC; $[\alpha]_D^{25}$ = -205.1° (c = 0.05, CH_3OH); IR, ν_{max}: 3359, 3001, 2880, 2831, 2665, 1693, 1610, 1580, 1529, 1454, 1419, 1282, 1162, 1076, 933, 730, 691 cm^{-1}; ^{1}H NMR, δ_H: 2.90-2.94 (4H, m, CH_2), 4.43-4.54 (6H, m, CH_2O and CH), 7.19-8.73 (18H, m, ArH), 8.65-8.68 (2H, d, *J*=7.8Hz, CONH). MS(FAB): 563 (M+1, 18%), 391, 341, 239, 181.

Anal. Calcd. for $C_{34}H_{30}N_2O_6$: C, 72.58; H, 5.37; N, 4.98. Found: C, 72.49; H, 5.52; N, 5.06.

(4*R*,16*R*)-4,16-Diethyl-6,14-dioxa-3,17,23-triaza-tricyclo-[17.3.1.1^{8,12}]tetracosa-1(22),8,10,12(24),19(23),20-hexaene-2,7,13,18-tetraone (**4k**).

This compound was obtained as white solid 0.25 g, yield 47%; mp: 219-221 ºC; $[\alpha]_D^{25}$ = +354.6° (c = 0.15, acetone); IR, ν_{max}: 3346, 3086, 2966, 2875, 1728, 1679, 1651, 1518, 1454, 1307, 1075, 723 cm^{-1}. ^{1}H NMR, δ_H: 0.95 (6H, t, *J*=7.5Hz, CH_3), 1.65–1.82 (4H, m, CH_2), 4.31-4.36 (2H, m, CH), 4.16-5.09 (4H, 2dd, *J*=3.0, 11.5Hz, CH_2O), 7.7-9.15 (7H, m, ArH), 8.66 (2H, d, *J*=9.0Hz, CONH); MS(FAB): 440 (M+1, 5%), 299, 277, 207, 185, 93 (100%).

Anal. Calcd. for $C_{23}H_{25}N_3O_6$: C, 62.86; H, 5.73; N, 9.56. Found: C, 62.98; H, 5.81; N, 9.47.

(5*R*,15*R*)-5,15-Diethyl-3,17-dioxa-6,14,23,24-tetraaza-tricyclo-[17.3.1.1^{8,12}]tetracosa-1(22),8,10,12(24),19(23),20-hexaene-2,7,13,18-tetraone (**4l**).

This compound was obtained as white solid 0.22 g, yield 42%; mp: 244-246 ºC; $[\alpha]_D^{25}$ = +260.2° (c = 0.15, acetone); IR, ν_{max}: 3416, 3085, 2973, 2938, 2882, 1721, 1672, 1518, 1321, 1131, 1082, 751 cm^{-1}. ^{1}H NMR, δ_H: 0.95-1.00 (6H, 2t, *J*=7.0Hz, CH_3), 1.65-1.76 (4H, m, CH_2Me), 4.43-4.46 (2H, m, CH), 4.22-5.21 (4H, 2dd, *J*=2.0, 11.5Hz, CH_2O), 8.23 –8.40 (6H, m, pyridine-H), 8.43 (2H, d, *J*=8.0Hz, CONH); MS(FAB): 441 (M+1, 4%), 300, 278, 185, 149, 93 (100%).

Anal. Calcd. for $C_{22}H_{24}N_4O_6$: C, 59.99; H, 5.49; N, 12.72. Found: C, 60.14; H, 5.43; N, 12.60.

(4*R*,15*R*)-4,15-Diethyl-6,13-dioxa-23-thia-3,16,22-triaza-tricyclo[16.3.1.1^{8,11}]tricosa-1(21),8,10,18(22),19-pentaene-2,7,12,17-tetraone (**4m**).

This compound was obtained as white solid 0.33 g, yield 62%; mp: 215-217 ºC; $[\alpha]_D^{25}$= -96.3° (c = 0.10, acetone); IR, $\nu_{max:}$ 3332, 3279, 3084, 2968, 2932, 2877, 1727, 1656, 1531, 1450, 1367, 1346, 1305, 11248, 1203, 1144, 1101, 1028, 997, 962, 842, 744, 664 cm^{-1}; ^{1}H NMR, δ_H: 1.00 (6H, t, *J*=7.0Hz, CH_3), 1.71-1.93 (4H, m, CH_2), 4.12-4.17 (2H, m, CH), 4.35-4.38 (2H, dd, *J*=4.0, 10.5Hz, CH_2O), 4.58-4.61 (2H, dd, *J*=5.5, 11.0Hz, CH_2O), 7.76 (2H, s, thiophene-H), 8.14-8.17 (1H, dd, *J*=7.0, 8.0Hz, py-H), 8.25 (2H, d, *J*=7.5Hz, py-H), 8.32 (2H, d, *J*=8.5Hz, CONH); ^{13}C NMR, δ_C: 11.15, 24.53, 52.60, 66.08, 125.47, 133,25, 139.41, 139.62, 151.43, 160.72, 164.55; MS(FAB): 446 (M+1, 100%), 155, 111, 77, 55.

Anal. Calcd. for $C_{21}H_{23}N_3O_6S$: C, 56.62; H, 5.20; N, 9.43; S, 7.20. Found: C, 56.91; H, 5.23; N, 9.35; S, 7.13.

(4*S*,16*S*)-4,16-Diisopropyl-6,14-dioxa-3,17,23-triaza-tricyclo[17.3.1.1^{8,12}]tetracosa-1(22),8,10,12(24),19(23),20-hexaene-2,7,13,18-tetraone (**4n**).

This compound was obtained as white solid 0.23 g, yield 41%; mp: 258-260 ºC; $[\alpha]_D^{25}$ = -278.6° (c = 0.10, acetone); IR, $\nu_{max:}$ 3517, 3392, 3072, 2964, 2874, 1722, 1668, 1522, 1448, 1378, 1302, 1229, 1129, 1077, 998, 961, 924, 841, 732, 646, 601 cm^{-1}; ^{1}H NMR,

δ_H: 0.93, 1.03 (12H, 2d, *J*=7.0Hz, CH_3), 2.01-2.08 (2H, m, CH), 4.09-4.16 (4H, m, CH_2O and CH), 5.22-5.25 (2H, dd, *J*=3.0, 11.2Hz, CH_2O), 8.58-8.60 (2H, d, *J*=8.5Hz, CONH), 7.73-9.09 (7H, m, ArH); ^{13}C NMR, δ_C: 19.98, 20.34, 55.95, 65.32, 125.95, 130.09, 131.36, 135.06, 139.97, 150.65, 164.04, 165.55, 175.13; MS(FAB): 468 (M+1, 95%), 424, 277, 234, 190, 149 (100%), 105, 55.

Anal. Calcd. for $C_{25}H_{29}N_3O_6$: C, 64.23; H, 6.25; N, 8.99. Found: C, 64.02; H, 6.21; N, 9.06.

(5*S*,15*S*)-5,15-Diisopropyl-3,17-dioxa-6,14,23,24-tetraazatricyclo[17.3.1.1^{8,12}]tetracosa-1(22),8,10,12(24),19(23),20-hexaene-2,7,13,18-tetraone (**4o**).

This compound was obtained as colorless solid 0.22 g, yield 40%; mp: 263-265 ºC; $[\alpha]_D^{25}$ = -342.7° (c = 0.30, acetone); IR, $\nu_{max:}$ 3415, 3097, 3012, 2962, 2935, 2882, 1725, 1675, 1590, 1515, 1462, 1443, 1380, 1319, 1266, 1235, 1151, 1128, 1084, 1054, 997, 844, 751,692, 646, 567 cm^{-1}; ^1H NMR, δ_H: 0.94-1.04 (12H, 2d, *J*=7.0Hz, CH_3), 1.92-1.98 (2H, m, CH), 4.16-4.19 (2H, dd, *J*=2.7, 11.7Hz, CH_2O), 4.24-4.29 (2H, m, CH), 5.34-5.36 (2H, dd, *J*=2.0, 11.5Hz, CH_2O), 8.34-8.36 (2H, d, *J*=8.5Hz, CONH), 8.24-8.43 (6H, m, ArH); MS(FAB): 469 (M+1, 100%), 425, 234, 216, 154, 69, 55.

Anal. Calcd. for $C_{24}H_{28}N_4O_6$: C, 61.53; H, 6.02; N, 11.96. Found: C, 61.47; H, 6.08; N, 11.87.

(4*S*,15*S*)-4,15-Diisopropyl-6,13-dioxa-23-thia-3,16,22-triazatricyclo[16.3.1.1^{8,11}]tricosa-1(21),8,10,18(22),19-pentaene-2,7,12,17-tetraone (**4p**).

This compound was obtained as white solid 0.10 g, yield 18%; mp: 175-178 ºC; $[\alpha]_D^{25}$ = -82.9° (c = 0.1, dmso); IR, $\nu_{max:}$ 3379, 3319, 3083, 2964, 2935, 2880, 1726, 1669, 1585, 1536, 1449, 1371, 1344, 1300, 1244, 1161, 1133, 1097, 98, 973, 839, 789, 747, 646 cm^{-1}; ^1H NMR, δ_H: 0.91-1.03 (12H, m, CH_3), 1.92-2.04 (2H, m, CH), 3.91-4.73 (6H, m, CH_2O and CH), 7.44-8.66 (7H, m, ArH and CONH); MS(FAB): 474 (M+1, 100%), 240, 154, 77, 57.

Anal. Calcd. for $C_{23}H_{27}N_3O_6S$: C, 58.34; H, 5.75; N, 8.87; S, 6.27. Found: C, 58.61; H, 5.80; N, 8.65; S, 6.04.

(4*S*,16*S*)-4,16-Dibenzyl-6,14-dioxa-3,17,23-triazatricyclo[17.3.1.1^{8,12}]tetracosa-1(22),8,10,12(24),19(23),20-hexaene-2,7,13,18-tetraone (**4q**).

This compound was obtained as white solid 0.34 g, yield 50%; mp: 239-242 ºC; $[\alpha]_D^{25}$ = -125.8° (c = 0.1, acetone); IR, ν_{max}: 3426, 3079, 2952, 2929, 1727, 1668, 1502, 1314, 1119, 751, 697 cm^{-1}; ^1H NMR, δ_H: 2.92-3.18 (4H, m, $PhCH_2$), 4.60 (2H, m, CH), 4.25-4.87 (4H, m, CH_2O), 7.15-7.35 (11H, m, phenyl-H), 7.77-8.25 (2H, m, phenyl-H), 8.32-8.37 (3H, m, pyridyl-H), 8.88 (2H, d, *J* = 7.8Hz, CONH), 9.10 (1H, d, *J* = 1.8Hz, phenyl-H); MS(FAB): 564 (M+1, 13%), 239, 191, 165, 149, 121, 95, 69 (100%), 57, 55.

Anal. Calcd. for $C_{33}H_{29}N_3O_6$: C, 70.33; H, 5.19; N, 7.46. Found: C, 70.21; H, 5.22; N, 7.56.

(5*S*,15*S*)-5,15-Dibenzyl-3,17-dioxa-6,14,23,24-tetraazatricyclo[17.3.1.1^{8,12}]tetracosa-1(22),8,10,12(24),19(23),20-hexaene-2,7,13,18-tetraone (**4r**).

This compound was obtained as white solid 0.19 g, yield 28%; mp: 272-275 ºC; $[\alpha]_D^{25}$ = –118.8° (c = 0.1, MeOH); IR, ν_{max}: 3428, 3080, 2952, 2931, 1727, 1669, 1503, 1315, 1120, 751, 698 cm^{-1}; ^1H NMR, δ_H: 2.94-2.99 (4H, m, $PhCH_2$), 4.75 (2H, m, CH), 4.25-4.98 (4H, m, CH_2O), 7.18-7.27 (10H, m, phenyl-H), 8.21-8.45 (6H, m, pyridyl-H), 8.60 (2H, d, *J* = 7.8Hz, CONH); MS(FAB): 565 (M+1, 24%), 239, 57, 55.

Anal. Calcd. for $C_{32}H_{28}N_4O_6$: C, 68.07; H, 5.00; N, 9.92. Found: C, 68.38; H, 5.12; N, 9.75.

(4*S*,15*S*)-4,15-Dibenzyl-6,13-dioxa-23-thia-3,16,22-triazatricyclo[16.3.1.1^{8,11}]tricosa-1(21),8,10,18(22),19-pentaene-2,7,12,17-tetraone (**4s**).

This compound was obtained as white solid 0.15 g, yield 22%; mp: 220-222 ºC; $[\alpha]_D^{25}$ = –94.5° (c = 0.1, acetone); IR, ν_{max}: 3400, 3083, 2957, 2926, 1735, 1700, 1676, 1517, 1234, 1093, 745, 701 cm^{-1}; ^1H NMR, δ_H: 3.00-3.40 (4H, m, $PhCH_2$), 4.45 (2H, m, CH), 4.38-4.60 (4H, m, CH_2O), 7.18-7.31 (10H, m, phenyl-H), 7.80 (2H, d, *J* = 2.0Hz, thiophene-H), 8.13-8.28 (3H, m, pyridyl-H), 8.44 (2H, d, *J* = 7.5Hz, CONH); MS(FAB): 570 (M+1, 60%), 478, 237, 91, 57, 55.

Anal. Calcd. for $C_{31}H_{27}N_3O_6S$: C, 65.36; H, 4.78; N, 7.38; S, 5.63. Found: C, 65.21; H, 4.89; N, 7.65; S, 5.57.

(5*R*,14*R*)-5,14-Diethyl-3,16-dioxa-23-thia-6,13-diazatricyclo[16.3.1.1^{8,11}]tricosa-1(21),8,10,18(22),19-pentaene-2,7,12,17-tetraone (**4t**).

This compound was obtained as white solid 0.13 g, yield 24%; mp: >260 ºC; $[\alpha]_D^{25}$ = -144.0° (c = 0.1, dmso); IR, $\nu_{max:}$ 3289, 3083, 2966, 2875, 1729, 1681, 1634, 1544, 1513, 1436, 1387, 1299, 1253, 1192, 1142, 1096, 1077, 928, 822, 728 cm^{-1}; ^1H NMR, δ_H: 0.99-1.05 (6H, t, *J*=7.5Hz, CH_3), 1.74-1.85 (4H, m, CH_2), 4.38-4.40 (4H, m, CH_2O), 4.51-4.53 (2H, m, CH), 7.70-7.71 (2H, d, *J*=7.8Hz, CONH), 7.62-8.65 (6H, m, ArH); ^{13}C NMR, _c: 10.23, 23.37, 52.17, 66.22, 127.94, 129.17, 129.52, 129.68, 130.09, 130.18, 132.98, 133.46, 133.54, 142.87, 160.77, 165.39, 166.23; MS(FAB): 445 (M+1, 4%), 388, 219, 163, 154 (100%), 89, 77; *Anal*. Calcd. for $C_{22}H_{24}N_2O_6S$: C, 59.45; H, 5.44; N, 6.30; S, 7.21. Found: C, 59.56; H, 5.51; N, 6.34; S, 7.10.

(5*R*,14*R*)-5,14-Diethyl-3,16-dioxa-23-thia-6,13,22-triazatricyclo[16.3.1.1^{8,11}]tricosa-1(21),8,10,18(22),19-pentaene-2,7,12,17-tetraone (**4u**).

This compound was obtained as yellow solid 0.11 g, yield 21%; mp: 247-250 ºC; $[\alpha]_D^{25}$ = -88.3° (c = 0.1,dmso); IR, ν_{max}: 3318, 3078, 2966, 2931, 2875, 1728, 1633, 1546, 1454, 1319, 1243, 1138, 1075, 1039, 991, 835, 751 cm^{-1}; ^1H NMR, δ_H: 0.89-0.94 (6H, m, CH_3), 1.62-1.71 (4H, m, CH_2), 4.19-4.24 (2H, m, CH), 4.32-4.36 (2H, dd, *J*=8.0, 11Hz, CH_2O), 4.46-4.49 (2H, dd, *J*=3.7, 11.2Hz, CH_2O), 7.64 (2H, s, thiophene-H), 8.08-8.19 (3H, m, pyH), 8.38-8.40 (2H, d, *J*= 8.5Hz, CONH).

Anal. Calcd. for $C_{21}H_{23}N_3O_6S$: C, 56.62; H, 5.20; N, 9.43; S, 9.70. Found: C, 56.48; H, 5.27; N, 9.47; S, 9.79.

(5*R*,14*R*)-5,14-Diethyl-3,16-dioxa-21,22-dithia-6,13-diazatricyclo[16.2.1.1^{8,11}]docosa-1(20),8,10,18-tetraene-2,7,12,17-tetraone (**4v**).

This compound was obtained as yellow solid 0.097 g, 18%; mp: 163-166 ºC; $[\alpha]_D^{25}$ = -76.7° (c = 0.1, dmso); IR, ν_{max}: 3418, 34293, 3090, 2966, 2935, 2880, 1713, 1634, 1542, 1458, 1382, 1349, 1253, 1093, 1030, 964, 831, 778, 748, 676 cm^{-1}; ^1H NMR, δ_H: 0.80-0.945 (6H, m, CH_3), 1.50-1.70 (4H, m, CH_2), 4.17-4.43 (6H, m, CH and CH_2O), 7.60-7.79 (4H, m, ArH), 8.34-8.40 (2H, d, *J*=8.5Hz, CONH); MS(FAB): 451 (M+1, 5%), 226, 178, 154 (100%), 71, 55.

Anal. Calcd. for $C_{20}H_{22}N_2O_6S_2$: C, 53.32; H, 4.92; N, 6.22; S, 14.23. Found: C, 53.45; H, 4.96; N, 6.17; S, 14.12.

(5*S*,14*S*)-5,14-Diisopropyl-3,16-dioxa-23-thia-6,13,22-triaza-tricyclo[16.3.1.1^{8,11}]tricosa-1(21),8,10,18(22),19-pentaene-2,7,12,17-tetraone (**4w**).

This compound was obtained as white solid 0.097 g, yield 17%; mp: 158-161 ºC; $[\alpha]_D^{25}$ = -324.3° (c = 0.1, dmso); IR, ν_{max}: 3324, 2945, 2853, 1724, 1634, 1544, 1515,1463, 1375, 1323, 1266, 1146, 1080, 1030, 998, 907, 827, 749 cm^{-1}; ^{1}H NMR, δ_H: 0.87-0.99 (12H, m, CH_3), 1.88-1.99 (2H, m, CH), 3.50-4.53 (6H, m, CH_2O and CH), 7.63-8.51 (7H, m, ArH and CONH); MS(FAB): 474 (M+1, 5%), 375, 343, 325, 240, 222, 196, 149, 111 (100%), 69, 55.

Anal. Calcd. for $C_{23}H_{27}N_3O_6S$: C, 58.34; H, 5.75; N, 8.87; S, 6.77. Found: C, 58.16; H, 5.83; N, 8.90; S, 6.68.

(5*S*,14*S*)-5,14-Diisopropyl-3,16-dioxa-21,22-dithia-6,13-diaza-tricyclo[16.2.1.1^{8,11}]docosa-1(20),8,10,18-tetraene-2,7,12,17-tetraone (**4x**).

This compound was obtained as white solid 0.16 g, yield 28%; mp: 254-257 ºC; $[\alpha]_D^{25}$ = -102.4° (c = 0.1, dmso); IR, ν_{max}: 3342, 3089, 2960, 2925, 1710, 1646, 1538, 1461, 1350, 1304, 1248, 1209, 1157, 1099, 952, 821, 747, 706, 673 cm^{-1}; ^{1}H NMR, δ_H: 0.93-0.99 (12H, 2d, *J*=7.0Hz, CH_3), 1.93-1.98 (2H, m, CH), 3.97-4.03 (2H, m, CH), 4.32-4.35 (2H, dd, *J*=8.0, 11.0Hz, CH_2O), 4.47-4.50 (2H, dd, *J*=3.0, 11.5Hz, CH_2O), 7.64, 7.69 (4H, 2s, thiophene-H), 8.31 (2H, d, *J*=8.5Hz, CONH); MS(FAB): 479 (M+1, 20%), 284, 256, 219, 154, 95, 55 (100%).

Anal. Calcd. for $C_{22}H_{26}N_2O_6S_2$: C, 55.21; H, 5.48; N, 5.85; S, 13.40. Found: C, 55.32; H, 5.53; N, 5.79; S, 13.31.

(5*R*,14*R*)-5,14-Diphenyl-3,16-dioxa-21,22-dithia-6,13-diaza-tricyclo[16.2.1.1^{8,11}]docosa-1(20),8,10,18-tetraene-2,7,12,17-tetraone (**4y**).

This compound was obtained as white solid 0.098 g, yield 15%; mp: >260 ºC; $[\alpha]_D^{25}$ = -173.3° (c = 0.1, dmso); IR, ν_{max}: 3334, 3094, 3060, 3039, 2952, 1715, 1645, 1534, 1451, 1350, 1294, 1246, 1208, 1094, 1030, 976, 915, 818, 784, 743, 698, 533 cm^{-1}; ^{1}H NMR, δ_H: 4.30-4.42 (2H, m, CH), 4.69-5.43 (4H, m, CH_2O), 7.33-8.53 (14H, m, ArH), 8.69-8.71 (2H, d, *J*=8.0Hz, CONH); MS(FAB): 547 (M+1, 3%), 341, 246, 219, 156, 154 (100%), 77.

Anal. Calcd. for $C_{28}H_{22}N_2O_6S_2$: C, 61.52; H, 4.06; N, 5.12; S, 11.73. Found: C, 61.47; H, 4.14; N, 5.15; S, 11.69.

(5*S*,14*S*)-5,14-Dibenzyl-3,16-dioxa-21,22-dithia-6,13-diaza-tricyclo[16.2.1.1^{8,11}]docosa-1(20),8,10,18-tetraene-2,7,12,17-tetraone (**4z**).

This compound was obtained as yellow solid 0.21 g, yield 30%; mp: 248-251 ºC; $[\alpha]_D^{25}$ = -136.8° (c = 0.1, dmso); IR, ν_{max}: 3298, 3026, 2963, 2858, 2650, 1720, 1687, 1637, 1546, 1454, 1404, 1306, 1253, 1111, 1028, 973, 918, 828, 746, 698, 669 cm^{-1}; ^{1}H NMR, δ_H: 2.92-2.99 (4H, m, CH_2), 4.26-4.29 (2H, dd, *J*=7.0, 11.5Hz, CH_2O), 4.40-4.43 (2H, dd, *J*=4.7, 11.2Hz, CH_2O), 4.56-4.51 (2H, m, CH), 7.16-7.77 (14H, m, Ph-H and thiophene-H), 8.47-8.49 (2H, d, *J*=8.5Hz, CONH); ^{13}C NMR, δ_C: 36.14, 49.83, 66.11, 126.11, 128.04, 128.10, 128.84, 132.87, 133.62, 137.49, 137.82, 140.39, 142.60, 160.42, 160.61, 162.01; MS(FAB): 575 (M+1, 3%), 341, 257, 219, 156, 154 (100%), 77.

Anal. Calcd. for $C_{30}H_{26}N_2O_6S_2$: C, 62.70; H, 4.56; N, 4.87; S, 11.16. Found: C, 62.76; H, 4.61; N, 4.78; S, 11.12.

(9*S*,17*S*)-9,17-Dibenzyl-1,4,7,13-tetraoxa-10,16-diaza-cyclooctadecane-2,6,11,15-tetraone (**6a**).

This compound was obtained as white solid 0.31 g, yield 52%; mp: 233-235 ºC; $[\alpha]_D^{22}$ = -106.2° (c = 0.2, acetone); ^{1}H NMR(dmso-d_6), δ_H: 2.09 (4H, s, CH_2C=O), 2.66-2.74 (2H, dd, *J*=9.0, 13.2Hz, CH_2Bz), 2.81-2.87 (2H, dd, *J*=5.4, 14.1Hz, CH_2Bz), 3.71-3.88 (4H, m), 4.24(2H, d, *J*=3.3Hz), 4.30-4.38 (2H, m, CH), 4.54-4.58 (2H, dd, *J*=3.0, 11.1Hz), 7.16-7.27 (10H, m, ph-H), 8.55 (2H, d, *J*=9.0Hz, CONH); ^{13}C NMR(dmso-d_6), δ_C: 30.77, 36.00, 49.01, 66.25, 66.45, 71.11, 126.39, 128.33, 129.01, 138.00, 169.70, 169.84; HR-MS for $C_{26}H_{31}N_2O_8$ (M+H), Calcd. 499.2081, found 499.2153.

Anal. Calcd. for: $C_{26}H_{30}N_2O_8$: C, 62.64; H, 6.07; N, 5.62. Found: C, 62.83; H, 6.10; N, 5.56.

(5*S*,13*S*)-5,13-Dibenzyl-3,9,15-trioxa-6,12,21-triaza-bicyclo-[15.3.1]heneicosa-1(20),17(21),18-triene-2,7,11,16-tetraone (**6b**).

This compound was obtained as white solid 0.29 g, yield 48%; mp: 190-191 ºC; $[\alpha]_D^{22}$ = -54.7° (c = 0.2, acetone); ^{1}H NMR(dmso-d_6), δ_H: 2.07 (4H, s, CH_2C=O), 2.89-2.97 (4H, m, CH_2Bz), 3.00-3.08 (1H, dd, *J*=7.5, 13.2Hz, 3.88-4.06 (2H, dd, *J*=14.7, 38.7Hz), 4.26-4.30 (1H, dd, *J*=3.0, 8.4Hz), 4.53-4.62 (1H, m), 4.64-4.69 (1H, dd, *J*=3.9, 14.1Hz), 7.17-7.28 (10H, m, Ar-H), 8.19 (2H, d, *J*=8.1Hz, CONH), 8.25-8.30 (1H, dd, *J*=6.9, 8.7Hz, Ar-H), 8.37 (1H, d, *J*=0.3Hz, Ar-H), 8.40 (1H, d, *J*=1.5Hz, Ar-H); ^{13}C NMR (dmso-d_6), δ_C: 37.65, 50.46, 50.55, 66.85, 71.42, 127.22, 129.14, 129.21, 130.02, 139.18, 139.89, 148.95, 165.51, 168.92; HR-MS for $C_{29}H_{30}N_3O_7$ (M+H), Calcd. 532.2085, found 532.2189.

Anal. Calcd. for: $C_{29}H_{29}N_3O_7$: C, 65.53; H, 5.50; N, 7.91. Found: C, 65.67; H, 5.56; N, 7.83.

3.4 X-ray Crystallography.

The crystallographic measurements were carried out on a Siemens P4 diffractometer with graphite-monochromated Mo-Kα radiation (λ = 0.71073 Å) and 12 kW rotating generator. The data were collected at 110 K. The structure was solved and refined using the programs SHELXS-97 (Sheldrick, 1997) and SHELXL (Sheldrick, 1997). The program X-Seed (Barbour, 1999) was used as an interface to the SHELX programs. Details about crystal data collection and structure refinement are summarized in Table 3. CCDC-246454 (**4e**), CCDC-210467 (m2-**4b**, crystal from acetone) and CCDC-215986 (m1-**4b**, crystal from acetonitrile) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge *via* www.ccdc.cam.ac.uk/conts/retrieving.html, or from the Cambridge Crystallographic Data Center, 12, Union Road, Cambridge CB21EZ, UK; fax: (+44) 1223-336-033; or deposit@ccdc.cam.ac.uk.

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