Iğdır Üniversitesi Fen Bilimleri Enstitüsü Dergisi, 11(2): 1293-1301, 2021
Journal of the Institute of Science and Technology, 11(2): 1293-1301, 2021

ISSN: 2146-0574, eISSN: 2536-4618

Chemistry **DOI: 10.21597/jist.802116**

Research Article

Received: 03-09-2020 **Accepted: 31-12-2020**

To Cite: Sunkur M, Tiğiz Z, Barış Cebe D, Aral T, 2021. Synthesis and Enantiomeric Recognition Studies of Novel C_2-Symmetrical Chiral Tetra-Amide Compounds. Journal of the Institute of Science and Technology, 11(2): 1293-1301,

Synthesis and Enantiomeric Recognition Studies of Novel C_2-Symmetrical Chiral Tetra-Amide Compounds

Murat SUNKUR[1*], Züleyha TİĞİZ[2], Deniz BARIŞ CEBE[1], Tarık ARAL[1]

ABSTRACT: Two novel C_2-symmetrical chiral tetraamide compounds derived from (S)-isoleucine were synthesised and their enantiomeric recognition abilities towards enantiomers of some amino acid esters and 1-arylethylamins were examined by UV-titration method. These receptor compounds exhibited strong complexation (with Ka up to 5787.23 M^{-1}) and very good enantioselectivity (up to Ka^S/Ka^R= 13.98).

Keywords: Enantiomeric recognition, chiral amide, C2-symmetrical amino acid esters, 1-arylethylamines, molecular recognition.

[1] Murat SUNKUR (**Orcid ID:** 0000-0002-8513-7860), Deniz BARIŞ CEBE (**Orcid ID:** 0000-0001-5860-2133), Tarık ARAL (**Orcid ID:** 0000-0002-6612-2751), Batman Üniversitesi, Fen Edebiyat Fakültesi, Kimya Bölümü, Batman, Türkiye
[2] Züleyha TİĞİZ (**Orcid ID:** 0000-0002-5884-392X), Batman Üniversitesi, Fen Bilimleri Enstitüsü, Kimya ABD, Batman, Türkiye

***Sorumlu Yazar/Corresponding Author:** Murat SUNKUR, e-mail: murat.sunkur@batman.edu.tr

Bu çalışma Züleyha TİĞİZ'in Yüksek Lisans tezinden üretilmiştir.

INTRODUCTION

Enantiomeric recognition is a special type of molecular recognition and is based on the principle that the molecular receptor form complexes with enantiomers of a chiral molecule with different ability (Marchi-Artzner et al., 1998; Bohanon et al., 1999; Pu, 2004; Hembury et al., 2008). Enantiomeric recognition study of new model systems is essential in our understanding the selectivity of complex biological processes. Therefore, the design and synthesis of new chiral systems for small chiral molecules could contribute to offer new perspectives for the development of pharmaceuticals, enantioselective sensors, catalysts and other molecular devices (Izatt et al., 1994; Horvath et al., 2000; Tang et al., 2006; Qing et al., 2009; Demirtas et al., 2009; Su et al., 2009).

Chiral amines, protonated amines, and amino acids are the basic building blocks of a wide variety of biological processes. And also, these chiral compounds play an important role in the design and synthesis of pharmaceuticals and other chiral molecules. Therefore the enantiomeric recognition study of these compounds is of very important. The design of receptors with a chiral recognition ability for chiral amino acids and amines is still receiving considerable attention, although much work on enantiomeric recognition of amino compounds by chiral macrocyclic ligands has been reported (Chadwick et al., 1984; Diederich, 1988; Fitzmaurice et al., 2002; Karakaplan and Aral, 2005; Aydın et al., 2009; Köylü et al., 2011). Especially C_2-symmetric ligands have been widely used in chiral recognition (Kizirian et al., 2003; Turgut et al., 2009). Amide units are often used as binding cites of these receptor molecules because of their high affinity towards both anions and cations due to the bearing both hydrogen bonding donor and acceptor atoms (Zhang et al., 2014).

Since the pioneering research on the application of chiral recognition reported by Cram and co-workers, great number of chiral macrocyclic and complex structured ligands have been synthesized and studied for enantiomeric recognition of racemic compounds (Nakashima et al., 2000; Lu et al., 2010; Lee et al., 2010; Deniz et al., 2011; Park et al., 2012; Sipos et al., 2012; Bako et al., 2012; Howard et al., 2013; Yi et al., 2013; Tsioupi et al., 2013; Paik et al., 2013; Guo et al., 2013; Liu et al., 2014; Şeker et al., 2014) However, in recent years non-cyclic ligands have begun to be used in enantiomeric recognition studies (Peri et al., 1998; Liu et al., 2001; Wang et al., 2007; Ballistreri et al., 2010; Aral et al., 2013; Kormos et al., 2013; Ulatowski and Jurczak, 2014; Pal et al., 2015; Forte et al., 2015; Pal et al., 2016). Still there are limited papers have been reported on the using non-cyclic ligands as chiral receptor for enantiomeric recognition of the racemic compounds.

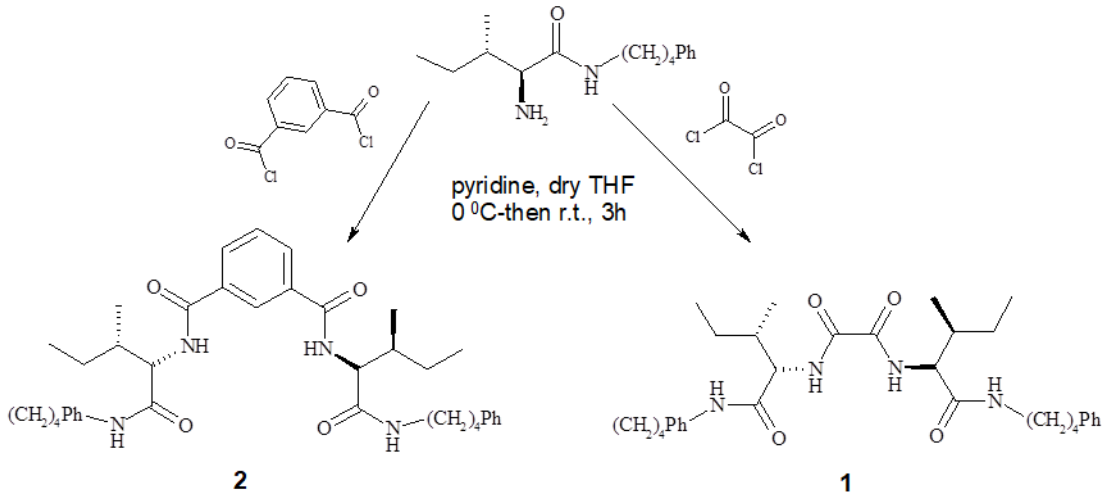

Figure 1. Synthesis of C_2-symmetrical chiral tetraamides.

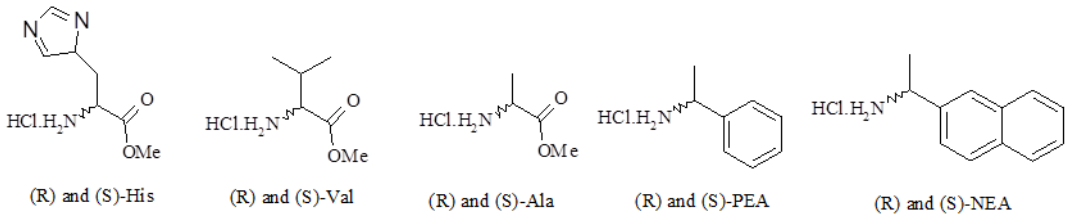

Figure 2. Chiral compounds used as guests for enantiomeric recognition of receptor **1** and **2**.

We report herein a practical synthesis of two novel C_2-symmetrical chiral tetra-amide ligands (**1** and **2**) starting from (*S*)-isoleucine (Figure 1) and evaluation of enantiomeric recognition properties of these ligands toward amino acid esters and 1-arylethylamines (Figure 2) by UV-Vis titration method.

MATERIALS AND METHODS

General

All chemicals were reagent grade unless otherwise specified. *R/S* 1-phenylethylamine and 1-(1-naphthyl)ethylamine, *R/S*-amino acid methyl ester hydrochlorides, oxalyl chloride and isophtaloyl chloride were purchased from the Sigma-Aldrich or Merck chemical company. Silica gel / TLC-cards (F_{254}) used for thin layer chromatography (TLC) were purchased from the Merck chemical company. Melting points were determined by a Gallenkamp Model apparatus with open capillaries. Infrared Spectra were recorded on a Mattson 1000 FTIR model spectrometer. Optical rotations were taken on a Perkin Elmer 341 model polarimeter. ^{1}H (400 MHz) and ^{13}C (100 MHz) NMR spectra were recorded on a Bruker DPX-400 High Performance Digital FT-NMR Spectrometer. The chemical shifts (d) and coupling constants (J) are expressed in parts per million and hertz.

Syntheses

Receptor 1 (N^1,N^2-bis((1*S*,2*S*)-1-(4-phenylbutylcarbamoyl)-2-methylbutyl)oxalamide)

The oxalyl chloride solution (0.98 g, 7.75 mmol) in dry THF was added drop wise to the solution of amine (2 g, 15.5 mmol) in dry THF at 0 °C under argon atmosphere. Then, the reaction was continued to be stirred for three hours at room temperature. After the completion of reaction the mixture was extracted with 1 N HCl (2×100 mL), 10% $NaHCO_3$ (2×100 mL) and distilled water (2×100 mL). Organic layer was dried over $MgSO_4$, filtered, and THF was evaporated by rotary evaporator under reduced pressure to obtain white solids as a pure product. Mp: 212-214 °C decomposed. $[\alpha]_D^{25}$ = -38.5 (c= 0.7, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 0.82-0.95 (m, 6H), 1.55-1.73 (m, 12H), 2.09-2.18 (m, 2H), 2.58-2.63 (m, 4H), 2.99-3.11 (m, 2H), 3.31-3.40 (m, 2H), 4.28 (t, *J*=12 Hz, 2H), 6.91 (bs, 2H, amide HN-), 7.10-7.35 (m, 10H), 8.60 (bs, 2H, amide HN-). ^{13}C NMR ($CDCl_3$, 400 MHz) δ (ppm): 10.99, 15.47, 25.06, 28.31, 28.61, 35.45, 36.18, 39.41, 58.66, 125.80, 128.38, 141.99, 159.54, 170.18. ; IR (cm^{-1}): 3308, 3257, 3082, 2960, 2934, 2858, 1663, 1644, 1218, 1171. CHN Anal. calcd. for $C_{34}H_{50}N_4O_4$ (%): C, 70.56%; H, 8.71%; N, 9.68%. Found: C, 70.62%; H, 8.82%; N, 9.65%.

Receptor 2 (N^1,N^2-bis((1*S*,2*S*)-1-(4-phenylbutylcarbamoyl)-2-methylbutyl)phthalamide)

The isophtalolyl chloride solution (1.57 g, 7.75 mmol) in dry THF was added drop wise to the solution of amine (2 g, 15.5 mmol) in dry THF at 0 °C under argon atmosphere. Then, the reaction was continued to be stirred for three hours at room temperature. After the completion of reaction the mixture was extracted with 1 N HCl (2×100 mL), 10% $NaHCO_3$ (2×100 mL) and distilled water (2×100 mL) respectively. Organic layer was dried over $MgSO_4$, filtered, and THF was evaporated by rotary evaporator under reduced pressure to obtain white solids as a pure product. Mp: 228-234 °C decomposed.

$[\alpha]_D^{25}$ = -14.9 (c=0.8, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 0.88-0.98 (m, 12H), 1.54-1.67 (m, 12H), 1.82-2.14 (m, 2H), 2.57-2.61 (m, 4H), 3.10-3.40 (m, 2H+2H), 4.34 (4, J=12, 2H), 6.53 (bs, 2H, amide HN-), 7.11-7.38 (m, 13H), 7.86 (d, 2H, amide HN), 8.18 (s, 1H). ^{13}C NMR ($CDCl_3$, 400 MHz) δ (ppm): 11.14, 15.50, 25.26, 28.68, 29.04, 35.43, 37.32, 39.38, 58.64, 125.81, 126.24, 128.33, 128.35, 130.14, 134.51, 142.00, 166.68, 171.26. IR (cm^{-1}): 3285, 1267, 3074, 2954, 2927, 2853, 1651, 1636, 1252. CHN Anal. calcd. for $C_{40}H_{54}N_4O_4$: C, 73.36%; H, 8.31%; N, 8.56%; O, 9.77%. Found: C, 73.45%; H, 8.41%; N, 8.51%.

RESULTS AND DISCUSSION

Synthesis

In the first stage of this study, two novel C_2-symmetrical chiral tetra-amide ligands (**1, 2**) having four stereogenic centers were synthesized starting from (*S*)-isoleucine (Figure 1). Starting amine compound was re-synthesized according to the procedure described in the related reference (Aral et al., 2017). This compound bearing amide group was reacted with oxalyldichloryde and isophtaloyl chloride to give the C_2-symmetrical chiral tetra-amide compounds **1** and **2** respectively with quantitative yields. The synthesis procedure is quite simple and no further purification is performed except for the work-up process. Pure products were obtained after the extraction process. The structure proposed for these chiral tetraamides (**1, 2**) were confirmed by ^{1}H NMR, ^{13}C NMR and FTIR spectroscopic analyses.

Enantiomeric Recognition Studies By UV-Vis Titration Method

UV-Vis spectroscopy is a commonly used method for calculating binding constants. Standard UV-Vis titration experiments were applied for calculating association constant (Ka) of complex formed between receptor and guest molecules (Figure 2) according to Benesi–Hildebrand equation basis of UV-Vis spectrum of complexes in $CHCl_3$ at 25 ºC (Bennesi and Hildebrand, 1949). Examples of experimental data for UV titration of (*S*)- and (*R*)-Histidine-OMe hydrochloride ((S)-His and (R)-His) with receptor **1** and **2** are shown in Table 1.

Table 1. Experimental data for UV titration of L- and D-Histidine with receptor **1** and **2**.

Receptor Conc.	**Guests Conc.**	**Receptor 1**				**Receptor 2**			
$[H]_o$ ($\times 10^{-3}$) M	**$[G]_o$** ($\times 10^{-3}$) M	**(*S*)-Histidine**		**(*R*)-Histidine**		**(*S*)-Histidine**		**(*R*)-Histidine**	
		A	**ΔA**	**A**	**ΔA**	**A**	**ΔA**	**A**	**ΔA**
1.00	0	0.401		0.401		0.420		0.420	
1.00	0.20	0.602	0.202	0.488	0.088	0.618	0.198	0.469	0.049
1.00	0.50	0.693	0.293	0.568	0.168	0.680	0.260	0.512	0.092
1.00	0.80	0.726	0.326	0.645	0.245	0.730	0.310	0.586	0.166
1.00	1.00	0.737	0.337	0.695	0.295	0.741	0.321	0.610	0.190
1.00	1.50	0.750	0.350	0.725	0.325	0.755	0.335	0.701	0.281
1.00	2.00	0.759	0.359	0.759	0.359	0.759	0.339	0.759	0.339
1.00	3.00	0.764	0.364	0.772	0.372	0.764	0.344	0.784	0.364
1.00	4.50	0.777	0.377	0.788	0.388	0.771	0.351	0.790	0.370
1.00	6.00	0.784	0.384	0.790	0.390	0.774	0.354	0.800	0.380

$[H]_o$: Concentration of the host, **$[G]_o$**: Concentration of the guest in each UV tube, **A**: UV absorbance at λmax

Plots of calculated 1/ΔA values as a function of 1/ΔG_0 values gave excellent linear relationships for all guest molecules examined, supporting 1:1 complexation between receptor molecules and guests. To confirm 1:1 stoichiometry, Job plots for the complexes were studied. The typical UV spectral changes upon addition of (*S*)-His to receptor **2** are shown in Figure 3.

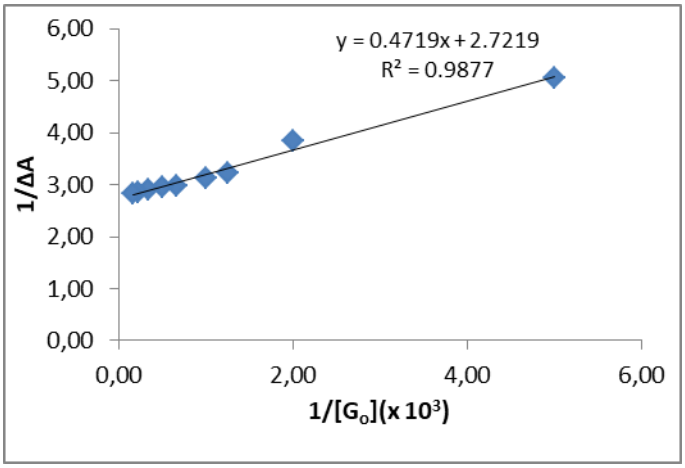

Figure 3. Typical plot of 1/ΔA versus 1/[G_0] for host-guest complexation of receptor **2** with (*S*)-His.

Table 2. Association constants (K_a) and enantioselectivities K_S/K_R (or K_R/K_S) for the complexation of L-/D-guests with the receptor **1** and **2** in $CDCl_3$ at 25 ºC

Receptor	Guest	$K_a(M^{-1})$	$-\Delta G_0$ (kj.mol^{-1})[a]	$\Delta\Delta G_0$ (kj.mol^{-1})[b]	K_a^R/K_a^S
1	(*S*)-Val	412.40	14.9	**5.10**	**7.85**
	(*R*)-Val	3236.75	20.00		
	(*S*)-Ala	710.70	16.29	2.56	2.84
	(*R*)-Ala	2015.83	18.85		
	(S)-His	1048.13	17.23	4.00	5.03
	(R)-His	**5270.83**	**21.23**		
	(*S*)-PEA	157.94	12.54	2.34	2.57
	(*R*)-PEA	406.45	14.88		
	(*S*)-NEA	96.68	11.32	4.64	6.49
	(*R*)-NEA	627.57	15.96		
Receptor	**Guest**	**K_a (M^{-1})**	**$-\Delta G_0$ (kj.mol^{-1})[a]**	**$\Delta\Delta G_0$ (kj.mol^{-1})[c]**	**K_a^S/K_a^R**
2	(*S*)-Val	780.37	16.50	4.39	5.88
	(*R*)-Val	132.83	12.11		
	(*S*)-Ala	509.98	15.44	3.82	4.54
	(*R*)-Ala	111.93	11.68		
	(S)-His	**5787.23**	**21.46**	**6.53**	**13.98**
	(R)-His	414.06	14.93		
	(*S*)-PEA	1225.35	17.62	4.85	7.06
	(*R*)-PEA	173.49	12.77		
	(*S*)-NEA	1896.10	18.70	5.55	9.37
	(*R*)-NEA	202.32	13.15		

[a] $\Delta G^o = -2.303RTLogK$

[b] $\Delta\Delta G^o = -(\Delta G^o_R - \Delta G^o_S)$

[c] $\Delta\Delta G^o = -(\Delta G^o_S - \Delta G^o_R$

It has been shown that receptor **1** and **2** show weak, strong and very strong complexations with guest enantiomers. The weakest complexation occurred between receptor **1** and (*R*)-NEA (Ka = 202.32 M^{-1}), while the strongest complexation occurred between receptor **2** and (*S*)-His (Ka = 5787.23 M^{-1}). In general, the receptor **1** forms a stronger complexation with Val and Ala enantiomers which are bearing aliphatic alkyl groups, while the receptor **2** forms a stronger complexation with the PEA and NEA enantiomers which are containing aromatic rings. Presumably, while phenyl ring of PEA and NEA enantiomers provide strong interaction with receptor **2** containing phenyl ring attached to the carbonyl groups, leads to steric repulsion with receptor **1** that does not contain any atoms between carbonyl groups. Therefore, receptor **1** exhibited stronger complexation with valine and alanine than PEA, NEA enantiomers. However, His is show strong complexation with both of receptor **1** and **2**. It may be due to

the nitrogen atom of imidazole ring of His. These hetero atoms provide stronger hydrogen bonding and ion-dipole interaction with amide groups of receptor molecules. The binding constant (Ka), free energy change ($-\Delta G_0$ and $-\Delta\Delta G_0$) and enantioselectivity (Ka^R/Ka^S) for complexes formed between receptors (**1**, **2**) and guest enantiomers are given in Table 2.

It was found that receptor **1** recognise (*R*)- enantiomers of all guest while receptor **2** recognise (*S*)-enantiomers of all guests. Receptor **1** forms strongest complexation with (*R*)-His, but highest enantioselectivity with Val (Ka^R/Ka^S = 7.85, $\Delta\Delta G_0$ = 5.10 kj.mol^{-1}). Receptor **1** provides the weakest complexation with the NEA enantiomers, while exhibiting a very high enantioselectivity (Ka^R/Ka^S = 6.49, $\Delta\Delta G_0$ = 4.64 kj.mol^{-1}). Compared with NEA, PEA showed lower enantioselectivity due to lower steric repulsion of phenyl ring towards receptor **1** (Ka^R/Ka^S = 2.57, $\Delta\Delta G_0$ = 2.34 kj.mol^{-1}), and receptor **2** (Ka^R/Ka^S = 7.06, $\Delta\Delta G_0$ = 4.85 kj.mol^{-1}). Similarly, valine with a more bulky alkyl group provided higher selectivity than alanine towards both receptor **1** and **2**.

Receptor **2** shows stronger complexation and higher enantioselectivity with NEA, PEA and His guests containing aromatic ring, than Val and Ala. The strongest complexation and highest enantioselectivity were occurred between receptor **2** and (*S*)-His (Ka^S = 5787.23 M^{-1}, Ka^S/Ka^R = 13.98, $\Delta\Delta G_0$ = 21.46 kj.mol^{-1}), while lowest complexation and enantioselectivity occurred between Ala (Ka^S/Ka^R = 4.54, $\Delta\Delta G_0$ = 3.82 kj.mol^{-1}).

CONCLUSION

Two new C_2-symmetrical chiral tetraamide compounds as potential enantioselective receptors have been synthesized, and their enantiomeric recognition ability towards three amino acid methyl ester hydrochloride and two 1-arylethylamines were studied. Both Receptor **1** and **2** show strongest complexation with His, while receptor **1** shows highest enantioselectivity toward Val, and receptor **2** shows highest enantioselectivity toward His. These results show that hydrogen bonding, ion-dipole interaction, π- π interaction and van der Waals interactions play a role in complexation. Bulky groups on the guest molecule lead to weaker complexation, higher enantioselectivity. Extra heteroatoms in the guest molecules give stronger hydrogen bonding and ion dipole interaction and leading to stronger complexation. As a result, two synthesized receptors (**1**, **2**) showed high or very high enantioselectivity towards the all guest molecules used.

ACKNOWLEDGEMENTS

We would like to acknowledge the Batman University Scientific Research Projects Coordination Unit for the financial support provided by BTUBAP-2018-FED-2.

Conflict of Interest

The article authors declare that there is no conflict of interest between them.

Author's Contiıbutions

The authors declare that they have contributed equally to the article.

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