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SYNTHESIS AND SPECTROSCOPIC INVESTIGATIONS OF A NEW γ-*L*-GLUTAMYL AMIDE AS POTENTIAL LIGAND FOR TRANSITION METAL COMPLEXES

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ABSTRACT. Considering the important chemical and biochemical application of L-glutamyl amides, this research reports a new compound namely (*S*)-2-amino-5-((4-(octyloxy)phenyl)amino)-5-oxopentanoic acid, as a potential ligand for transition metal complexes or for biological tests. This derivative was synthesized by a regioselective acylation of 4-(octyloxy)aniline using *N*-phthaloyl-L-glutamic anhydride, followed by hydrolysis of phthaloyl group with hydrazine hydrate. The mild conditions under which the reactions took place prevented the final synthetic product from being racemized. The identity of the glutamyl amide as well as the synthesis intermediates have been confirmed by spectral analyses such as ^{1}H-NMR, ^{13}C-NMR, HRMS and FT-IR in the solid state.

Keywords: *L-glutamic acid, L-glutamyl-amides, 4-(octyloxy)aniline derivatives, spectroscopic studies*

INTRODUCTION

Due to the great importance of L-glutamic acid in a lot of biochemical reaction such as the biosynthesis of other amino acids through a transamination process, or as a key excitatory neurotransmitter in the central nervous

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system, playing a vital role in nerve signaling, learning, and memory, can be considered a vital amino acid with far-reaching effects on brain function, energy metabolism, and overall health. An excellent substrate for determination of γ-glutamyl transpeptidase (GGT) proved to be γ-L-glutamyl-*p*-nitroanilide which has been used successfully in the diagnosis of liver, pancreas, kidney diseases and recently as a prognostic tool for heart failures [1,2].

For this reason, other glutamyl amide derivatives have also been successfully tested as substrate for GGT with satisfactory results [3,4].

Another application for L-glutamide derivatives was reported as organogelator. A new organogelator was created by attaching L-glutamide derivatives to a cyclotriphosphazene core, resulting in an improved gelation ability, chirality, and thixotropic properties compared to a similar organogelator without the core. This new organogel sensor was developed using a cyclotriphosphazene core and L-glutamide derivatives, showing improved self-assembly and thixotropic properties [5].

The results of a recent study show that some of the L-γ-methyleneglutamic acid amides exhibit selective anticancer activity against various breast cancer cell lines, with some compounds showing potency comparable to Tamoxifen or Olaparib, drugs currently used to treat breast cancer [6]. Ethyl or *tert*-butyl esters of L-γ-methyleneglutamic acid amides have potential as novel therapeutics for the treatment of multiple subtypes of breast cancer, glioblastoma, head and neck cancer [7].

On the other hand, 4-(octyloxy)aniline has proven to be a compound with multiple applications in chemistry and material science. Many compounds based on 4-(octyloxy)aniline fragments have found applications in the development of polarizing liquid crystal-based films with good polarization and light absorption characteristics. These materials are used in optical display devices that control the amount of light passing through them. Thus, derivatives of 4-(octyloxy)aniline based on biphenyl, biphenyltetracarboxydiimde, methylthioether or Schiff base moiety reveals promising results for the optoelectronic devices industry [8-13].

Azobenzene-based compounds are synthesized for their photoresponsivity properties, enabling applications in optical storage devices, light shutters, and remote-controllable devices [14].

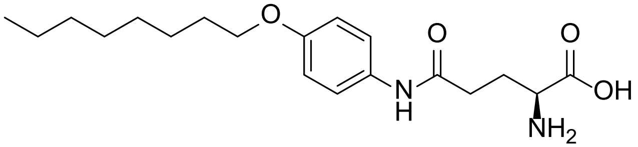
Pyrazine-2,5-dicarboxylic acid derivatives with different *p*-alkoxy anilines were found to be efficient organogelators, readily forming stable gels in various organic solvents, contributing to advancement in material science [15].

Recently, dyes laterally substituted with *p*-alkoxy-aniline moieties, including 4-(octyloxy)aniline, have been studied for their mesomorphic properties, gelling ability or applications in dyeing [16,17].

Compounds, like *N,N'*-diarylthiourea or thiobenzenanilide derivatives and some chlorinated plastoquinone analogs, are synthesized for their potential anticancer properties, targeting breast cancer cells, leukemia and difficult-to-treat melanomas [18-20]. Other chlorinated plastoquinone analogs, were evaluated for their ability to inhibit microbial growth, including bacteria and fungi [21]. Derivatives containing glutamic acid fragments and 4-(octyloxy)aniline have demonstrated substantial lymphopenic activity *in vivo* in mouse and rat tests [22].

A novel series of gemini surfactants bearing 4-alkoxyphenyl hydrophobic tails with superior surface properties and good antibacterial activity might be good candidates for wastewater and surface treatments [23]. Another research direction where 4-(octyloxy)aniline was successfully employed was in dendrimer chemistry [24-26].

Taking into account the multiple applications of L-glutamic acid and 4-(octyloxy)aniline in a multitude of domains, in this work we aimed to synthesize and analyse by physico-chemical methods the amide resulting from the condensation of these two reactants as a potential ligand in complexation with transition metal ions or as a good compound for the biological studies. In this context, we report a new amide which was prepared following the protocol used for peptide synthesis, i.e. regioselective acylation of the aromatic amine with the anhydride of the *N*-protected amino acid. This new glutamyl amide namely (*S*)-2-amino-5-((4-(octyloxy)phenyl)amino)-5-oxopentanoic acid (**4**) was synthesized in four steps with an overall yield of 42%, in mild condition, which facilitated the preservation of the optical purity both of the intermediates and the final synthesis product.



(**4**)

Figure 1. (*S*)-2-amino-5-((4-(octyloxy)phenyl)amino)-5-oxopentanoic acid

RESULTS AND DISCUSSION

A proper method that does not affect the chiral center of the amino acid, consists of the use a mild phthaloylation at the amino group in the first synthesis step. A common compound often used for this purpose is phthalic anhydride, but this produces partial racemization, which cannot be avoided [27,28].

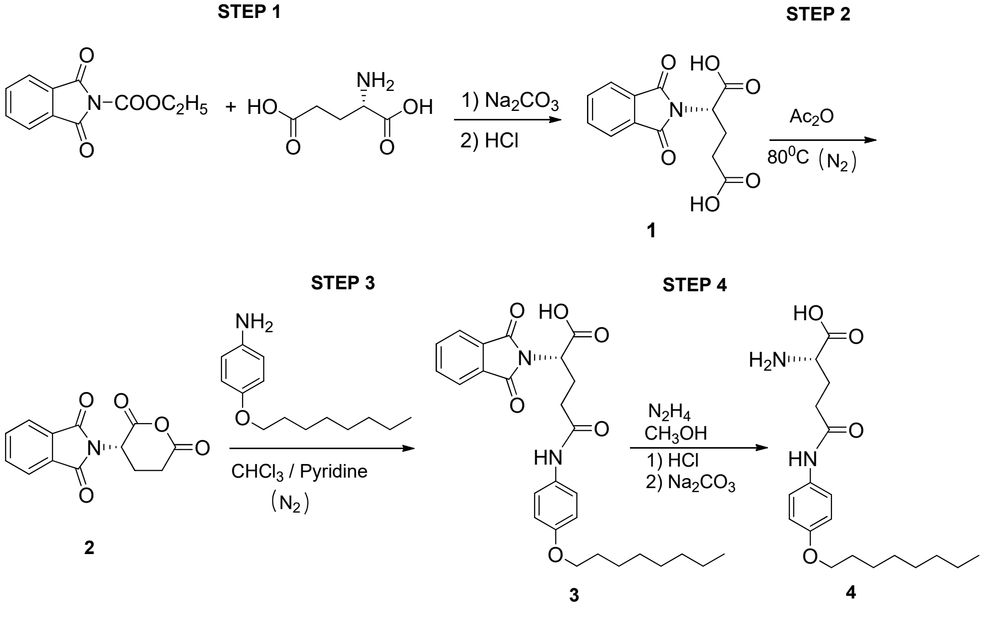
In our earlier work, we identified *N*-ethoxycarbonylphthalimide as being a commercial and easy-to-use reagent, with satisfactory yield in the protection stage, which reacts in mild condition, without racemization at the chiral center [29-31].

Then, the *N*-protected glutamic acid was treated with acetic anhydride, by heating at 80^0C, for a short time under nitrogen atmosphere, and the *N*-phtaloyl-γ-L-glutamic anhydride (**2**) was obtained as an activation form for the carboxylic group, in the second stage of the synthesis. This step occurs with high yield, no racemization.

A regioselective acylation of 4-(octyloxy)aniline with the *N*-protected anhydride in chloroform and catalytic quantity of pyridine under nitrogen atmosphere led to obtaining the *N*-phthaloyl-γ-L-glutamyl amide (**3**), also optically active (see Experimental Section).

After this, we have easily removed the phthaloyl group with hydrazine hydrate in methanol under reflux and the free amide (**4**) was obtained until pH 6-6.5, as a pale grey-blue solid, in the last synthesis step.

The first three steps were monitored by TLC in ethanol:acetone=3:1 (v/v) and visualization in UV at λ=245nm, but for the last step it was necessary to change the system with 1-propanol:acetic acid:water=8:1:1 (v/v/v) and visualization in ninhydrin or I_2 vapor, like in the other cases of amides derived from amino acids, synthesized by us [29-31].



Scheme 1. Synthesis of (*S*)-2-amino-5-((4-(octyloxy)phenyl)amino)-5-oxopentanoic acid

The identitys of the all-synthesized compounds were confirmed by routine analysis such as ^{1}H-NMR, ^{13}C-NMR, HRMS and FT-IR spectra.

The ^{1}H-NMR spectrum for the compound (**4**) was recorded in DMSO+DCl$_{aq}$ at 400MHz. A low-intensity signal at 10.13 ppm was observed, which corresponds to the free carboxylic acid proton of the amino acid residue. This attenuated signal is likely a result of deuterium exchange with the solvent. A multiple signal appears at chemical shift range at 8.65-8.59 ppm due to the NH group, while the aromatic protons of the amine are found at 7.46 ppm and 6.79 ppm, respectively, through distinct doublets and increased coupling constants, which are also found in other cases of 4-(octyloxy)aniline derivatives [12,18,26]. The multisignals within 3.92-3.83 ppm range are assigned to the NH$_2$ group overlapping with the proton H$_2$ belonging to the amino acid rest. The aliphatic side chain protons reveal overlapped signals within 2.15-0.79, specific fact for compounds with this aniline derivative (Figure 2a).

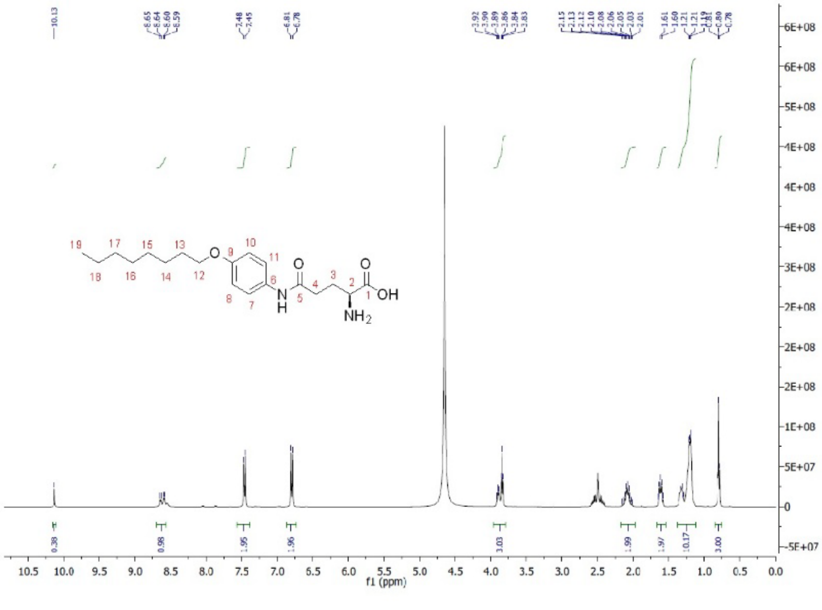


Figure 2a. ^{1}H-NMR spectrum of γ-L-glutamyl amide (**4**)

Regarding the ^{13}C-NMR spectrum, the presence of the signals of the compound and of the solvent can be both identified (see Experimental Section and Figure 2b). On the ^{13}C-NMR were noticed 17 signals. The aromatic part has 6 carbons, but because of symmetry there are 4, carbon C$_8$ and C$_{10}$ also C$_7$ and C$_{11}$ are equivalent, respectively (Figure 2b).

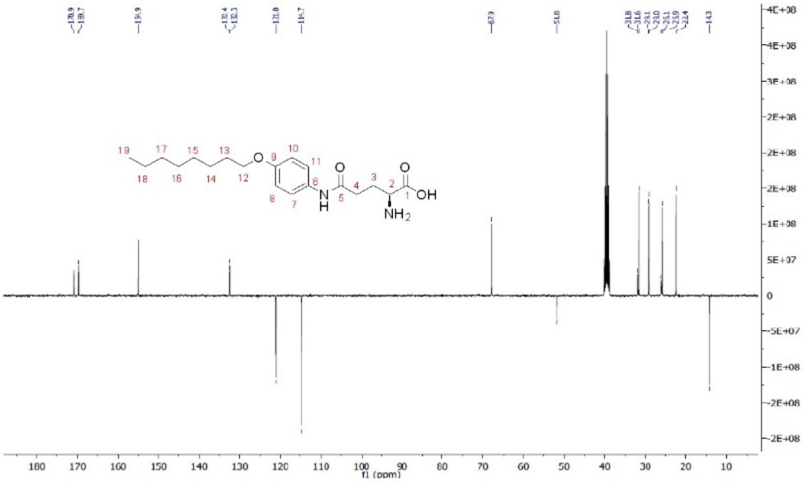


Figure 2b. ^{13}C-NMR spectrum of γ-L-glutamyl amide (**4**)

HRMS spectrum (ESI+) of γ-glutamyl amide (**4**) confirms the presence of the [M+Na], as a molecular peak, at 373.2112 value and [M+H] at 351.2292 value, respectively (Figure 3).

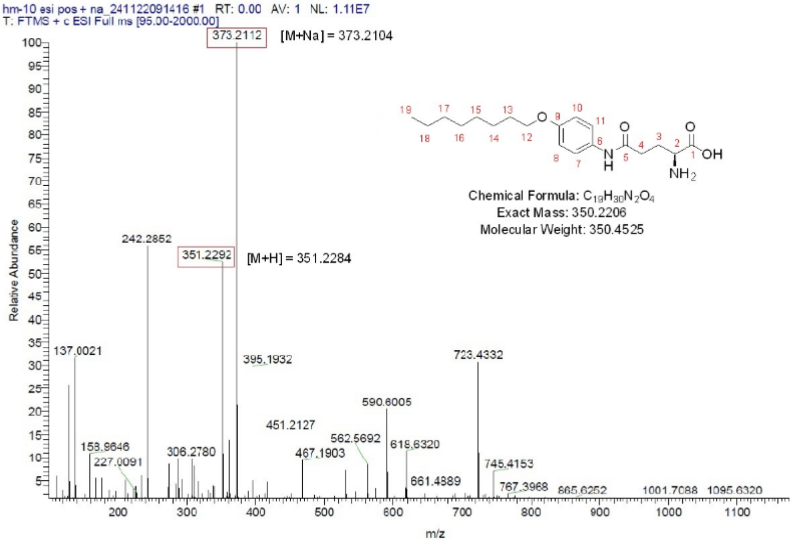


Figure 3. HRMS spectrum (ESI) of γ-L-glutamyl amide (**4**)

FT-IR spectroscopy provided complementary data that confirmed the structural assignment of the synthesized glutamyl amide.

In the spectral region of 3100-2500 cm^{-1} a wide band formed by some overlapped bands is observed, that may be assigned to $\nu_{O\text{-}H}$ vibration due to intra- and intermolecular hydrogen bonding in the crystalline state [32]. Also, in this area, probably the stretching frequencies from aliphatic and aromatic fragments overlap as well.

Two very sharp bands at 1655 cm^{-1} and 1582 cm^{-1}, could be attributed to the $\nu(COO^{-}as)$ and $\nu(COO^{-}sym)$ respectively, specific to solid state amide I and II bands [33]. The stretching vibration $\nu(NH_2)$ appears at a strong signal at 3277 cm^{-1} while the $\nu(NH)$ and $\delta(NH)$ frequencies can be found at 1248 cm^{-1} and 1628 cm^{-1} respectively.

On the other hand, the stretching frequencies $\nu(CH_2as)$ and $\nu(CH_2sym)$ corresponding to the aliphatic residue are very well highlighted at 2932 cm^{-1} and 2852 cm^{-1} respectively [33,34]. Other stretching, bending and combination bands which appear in the "fingerprint" region down to 1500 cm^{-1}, cannot be ascribed with certainty (Figure 4).

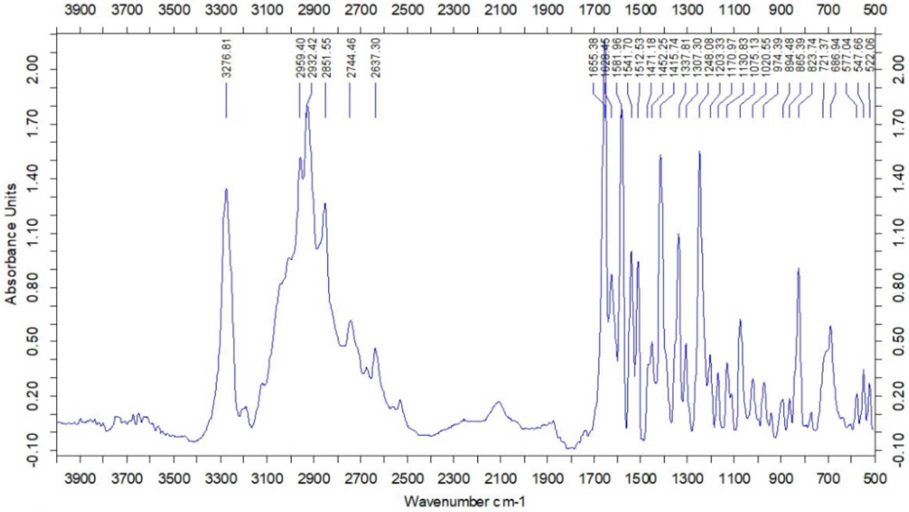


Figure 4. IR spectrum of γ-L-glutamyl amide (**4**)

CONCLUSIONS

The objective of this study was to synthesize a novel γ-L-glutamyl amide from two compounds with extensive application: an important amino acid, L-glutamic acid, and an amine 4-(octyloxy)aniline that has recently been widely used in chemistry and material science.

The amide bond formation process was applied for this purpose, from peptide synthesis starting with an *N*-terminal amino acid, in four steps. In the protection stage, we used *N*-ethoxycarbonylphthalimide, as a proper acylating agent, in order to introduce the phthaloyl group in mild condition, to avoid racemization.

It was established that by maintaining mild conditions throughout all synthesis stages, the compounds in question were able to retain their optical activity and were obtained in relatively good yields.

The compound's identity was confirmed by spectral analysis like NMR, HRMS and FT-IR data.

Finally γ-L-glutamyl amide (**4**), namely (*S*)-2-amino-5-((4-(octyloxy)phenyl)amino)-5-oxopentanoic acid, can be used as a potential ligand to form novel complexes with different metal ions and also for the purpose of conducting biological tests.

EXPERIMENTAL SECTION

Materials and instrumentation

All reagents and chemicals were purchased from commercial sources and used as received. TLC monitoring was performed by using aluminum sheets with silica gel 60 F_{254} (Merck® visualization in UV at λ=254 nm; I_2 vapor or ninhydrin). NMR spectra were recorded on BRUKER® AM 400 instruments operating at 400 and 100 MHz for ^1H and ^{13}C nuclei, respectively. All chemical shifts (δ value) are given in ppm without TMS added. The chemical shifts were measured against the solvent residual peak. Elemental analyses were determined on Thermo Scientific Flash EA 1112 Elemental Analyzer. Melting points were measured on an ELECTROTHERMAL® instrument and were not corrected. Specific rotations were estimated on a Polamat A Karl Zeiss Jena photopolarimeter. Mass spectra were carried out on a LTQ ORBITRAP® XL (Thermo Scientific) instrument which was externally calibrated using the manufacturer's ESI(+) calibration mix. The samples were introduced into the spectrometer by direct infusion. FT-IR spectra were recorded in KBr pellets on a BRUKER® VECTOR 22 Spectrometer which operates with OPUS soft.

Synthesis of N-Phthaloyl-L-Glutamic Acid ***(1)***

To a solution of 6.25g (0.0589 mol) Na_2CO_3 and 25mL distilled water, 3g (0.0204 mol) L-glutamic acid was added at room temperature with vigorous stirring until the amino acid was solved. The solution was cooled at 0-1^0 C and 6.25g (0.0285 mol) of *N*-carbetoxyphthalimide was added gradually, within 1 hour. The mixture was left to stirring overnight at room temperature, then cooling again and filtrating to remove the ethylureatane. The resultant pH solution was found to be between 8.6 and 9. The remaining solution was acidified with HCl to pH = 1-1.5, when an oily product was formed, which crystallized within 12 hours in the refrigerator. The resulted product was filtrated, followed by a thorough wash with the mother solution and acidified water with HCl, dried 2 days in air, then in a desiccator. The product was purified through a process of dissolution and reprecipitation. Initially, it was dissolved in a 1M Na_2CO_3 solution, followed by reprecipitation with 6N HCl. The resultant solid was then dried under the same conditions.

$C_{13}H_{11}NO_6$ (**1**) white solid; MW = 277.2295; mp = 159-160^{0}C; Yield 76%; TLC analysis: R_f = 0.48 (ethanol:acetone = 3:1 (v/v)) visualization in UV at λ = 254 nm; Elemental analysis (%) calcd(found): C: 56.32(56.47); H: 4.00(4.14); N: 5.05(4.89); HRMS (ESI+) [M+Na]: 300.0472; Exact Mass: 277.0586; $[\alpha]_{546}^{25} = -89\ (c = 1,\ DMF)$.

^{1}H-NMR (DMSO, 400MHz, δ(ppm)): 10.97 (2H, s, 2 COOH groups); 7.92-7.85 (4H, overlapped signal, Ar-H); 4.81 (1H, t, $^3J_{H,H}$=12Hz, CH); 2.39-2.22 (4H, m, 2 CH_2 from aliphatic rest); ^{13}C-NMR (DMSO, 100MHz, δ(ppm)): 173.9 (COOH); 170.5 (COOH); 167.6 (CO); 134.9 (C_{arom}); 131.4 (C_{arom}); 123.5 (C_{arom}); 51.2 (CH); 30.5 (CH_2); 23.8 (CH_2); FT-IR (KBr, cm^{-1}): ν_{max}: 3054(bb); 2911(m); 1777(vs); 1728(vs); 1707(vs); 1690(vs); 1429(m); 1387(vs); 1259(vs); 1203(s); 1168(m); 713(s).

*Synthesis of N-Phthaloyl-L-Glutamic Anhydride (**2**)*

A mixture of *N*-Phthaloyl-L-Glutamic Acid **(1)** 3g (0.0108 mol) and acetic anhydride 10mL (98.5% pure, ρ=1.08g/cm^3, 0.1042 mol) was heated at 90^{0}C for 30 minutes under nitrogen atmosphere. An opalescent solution appears in short time. The mixture was subjected to a cooling process in a freezer, with a duration of 3 hours. Thereafter, the precipitate that had formed was filtered, washed with cold ether and dried in a desiccator for a period of 5 days.

$C_{13}H_9NO_5$ (**2**) white solid; MW = 259.2143; mp = 199-200^{0}C; Yield 93%; TLC analysis: R_f = 0.52 (ethanol:acetone = 3:1 (v/v)) visualization in UV at λ = 254 nm; Elemental analysis (%) calcd(found): C: 60.24(60.01); H: 3.50(3.67); N: 5.40(5.23); HRMS (ESI+) [M+Na]: 282.0366; Exact Mass: 259.0481; $[\alpha]_{546}^{25} = -43\ (c = 3,\ dioxane)$.

^{1}H-NMR (DMSO, 400MHz, δ(ppm)): 7.92 (2H, dd, $^2J_{H,H}$=12Hz, Ar-H); 7.86 (2H, dd, $^2J_{H,H}$=12Hz, Ar-H); 4.81 (1H, dd, $^2J_{H,H}$=12Hz, CH from aliphatic rest); 2.40-2.34 (2H, m, from aliphatic rest); 2.32-2.23 (2H, m, from aliphatic rest); ^{13}C-NMR (DMSO, 100MHz, δ(ppm)): 174.2 (CO from aliphatic rest); 170.8 (CO from aliphatic rest); 167.9 (CO from aromatic rest); 135.2 (C_{arom});

131.7 (C_{arom}); 123.8 (C_{arom}); 51.5 (CH); 30.8 (CH_2); 24.1 (CH_2); FT-IR (KBr, cm^{-1}): v_{max}: 1818(m); 1780(s); 1715(vs); 1392(s); 1225(m); 1117(s); 1034(s); 722(m).

*Synthesis of N-Phthaloyl-γ-L-glutamyl-4-(octyloxy)anilide (**3**)*

A suspension of *N*-Phthaloyl-L-Glutamic Anhydride (**2**) 2.59g (0.001 mol) and an equivalent quantity of pyridine as a catalyst in 20 mL chloroform was heated at 50^0C under nitrogen atmosphere. A solution of 4-(octyloxy)aniline 2.21g (0.001 mol) in 10 mL chloroform was added slowly, dropwise, over a period of 1 hour. The solution was then stirred for 3 hours under reflux. After being kept 24 hours at room temperature, the solvent was removed under reduced pressure. The residue was triturated with ether, filtered off, washed with cold ether and dried in a desiccator.

$C_{27}H_{32}N_2O_6$ (**3**) pale blue solid; MW = 480.5528; mp = 139-140^{0}C; Yield 68%; TLC analysis: R_f = 0.65 (ethanol:acetone = 3:1 (v/v)) visualization in UV at λ = 254 nm; Elemental analysis (%) calcd(found): C: 67.48(67.26); H: 6.71(6.84); N: 5.83(5.98); HRMS (ESI+) [M+Na]: 503.2147 Exact Mass: 480.2260; $[\alpha]_{546}^{25} = -76\,(c = 0.25,\ DMSO)$.

^{1}H-NMR (DMSO, 400MHz, δ(ppm)): 9.66 (1H, s, -COOH); 7.98-7.83 (2H, m, Ar-H); 7.32 (2H, d, $^2J_{H,H}$=8Hz, Ar-H); 6.76 (1H, d, $^2J_{H,H}$=8Hz, NH); 6.61 (2H, dt, $^2J_{H,H}$=12Hz, CH from Ar-H); 6.51 (2H, dt, $^2J_{H,H}$=12Hz, CH from Ar-H); 4.79 (1H, m, CH from Glu rest); 3.85 (2H, t, $^3J_{H,H}$=12Hz OCH_2 octyl rest); 3.77 (2H, t, $^3J_{H,H}$=12Hz, $NCOCH_2$); 2.52-2.33 (2H, m, CH_2 from Glu rest); 1.68-1.58 (2H, m, OCH_2CH_2 from octyl rest); 1.36-1.23 (10H, m, $OCH_2(CH_2)_5$ from octyl rest); 0.83 (3H, t, $^3J_{H,H}$=12Hz, CH_3 from octyl rest) ^{13}C-NMR (DMSO, 100MHz, δ(ppm)): 170.5 (-CONH); 169.6 (-COOH); 167.5 (CO from aromatic rest); 154.5 (=C-O-) 150.3 (=CHN); 141.9 (C_{arom}); 134.8 (C_{arom}); 132.2 (C_{arom}); 131.3 (C_{arom}); 123.4 (C_{arom}); 67.9 (-NCH from Glu); 67.6 (CH_2 from Glu); 51.4 (CH_2 from Glu); 31.3 (-OCH_2 from octyl rest); 28.9 ($(CH_2)_4$ from octyl rest); 25.6 (CH_2 from octyl rest); 22.2 (CH_2 from octyl rest); 14.0 (CH_3 from octyl rest) FT-IR (KBr, cm^{-1}): v_{max}:: 3349 (w); 2923(m); 2853(m); 1709(vs); 1511(s); 1392(s); 1257(m); 1113(w); 829(m); 720(m).

*Synthesis of γ-L-glutamyl-4-(octyloxy)anilide (**4**)*

A suspension of phthaloyl amide (**3**) (1.6 g, 0.0027 mol) in 25mL methanol was treated with 0.6 mL (0.0122 mol) hydrazine hydrate (100%) with vigorous stirring, under reflux for 3 hours. Then the mixture set aside at room temperature for 24 hours. The precipitate was filtered, well washed with cold methanol and suspended 15 mL acetone at room temperature. The suspension was stirred for 30 minutes, after which it was filtered once more, washed with cold acetone and ether. The dried material was suspended in

10 mL 6N HCl, filtered after 15 minutes from phthalylhidrazide, and aqueous layer was adjusted to pH 6-6.5 with 6M Na_2CO_3 when the final product precipitate. Following filtration, the glutamyl anilide can be purified through dissolving in a 1M Na_2CO_3 solution, followed by reprecipitation with 6N HCl at the isoelectric point.

$C_{19}H_{30}N_2O_4$ (**4**); pale grey-blue solid; MW = 350.4525; mp = 204-205^{0}C; Yield 88%; TLC analysis: R_f = 0.58 (1-propanole:acetic acid:water = 8:1:1 (v/v/v)) visualization with ninhydrin ethanolic solution or I_2 vapor; Elemental analysis (%) calcd(found): C: 65.12(65.39); H: 8.63(8.51); N: 7.99(8.12); HRMS (ESI+) [M+Na]: 373.2112 (molecular peak); [M+H]: 351.2292; Exact Mass: 350.2206; $[\alpha]_{546}^{25} = +42\ (c = 0.25,\ DMSO + HCl\,0.5N)$.

^{1}H-NMR (DMSO, 400MHz, δ(ppm)): 10.13 (1H, s, -COOH) 8.65-8.59 (1H, bs, NH); 7.46 (2H, d, $^2J_{H,H}$=12Hz, H_7, H_{11}, Ar-H); 6.79 (2H, d, $^2J_{H,H}$=12Hz, H_8, H_{10}, Ar-H); 3.92-3.83 (3H, overlapped signals from NH_2 and H_2); 2.15-2.01 (2H, m, H_3); 1.65-1.58 (6H, m, H_4, H_{12}, H_{13}); 1.31-1.19 (10H, m, H_{14-18}); 0.79 (3H, t, $^3J_{H,H}$=12Hz, H_{19}); ^{13}C-NMR (DMSO, 100MHz, δ(ppm)): 170.9 (C_5); 169.7 (C_1); 145.9 (C_9); 132.4 (C_6); 121.0 (C_8, C_{10}); 114.7 (C_7, C_{11}); 67.9 (C_{12}); 51.8 (C_2); 31.8 (C_{17}); 31.6 (C_4); 29.1, 29.0, 29.0 (C_3, C_{13}, C_{15}); 26.1 (C_{16}); 25.9 (C_{14}); 22.4 (C_{18}); 14.3 (C_{19}); FT-IR(KBr, cm^{-1}): v_{max}: 3277(s); 2959(s); 2932(vs); 2852(s); 1655(vs); 1628(m); 1582(vs); 1542 (m); 1513(m); 1452(s); 1338(s); 1248(s); 1075(m); 865(m); 687(m).

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