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Article

Imidazo[1,2-*a*]quinoxalines Derivatives Grafted with Amino Acids: Synthesis and Evaluation on A375 Melanoma Cells

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Abstract: Imiquinalines (imidazoquinoxaline derivatives) are anticancer compounds with high cytotoxic activities on melanoma cell lines. The first generation of imiquinalines, with two lead compounds (EAPB0203 and EAPB0503), shows remarkable *in vitro* ($IC_{50} = 1570$ nM and $IC_{50} = 200$ nM, respectively, on the A375 melanoma cell line) and *in vivo* activity on melanoma xenografts. The second generation derivatives, EAPB02302 and EAPB02303, are more active, with $IC_{50} = 60$ nM and $IC_{50} = 10$ nM, respectively, on A375 melanoma cell line. The aim of this study was to optimize the bioavailability of imiquinaline derivatives, without losing their intrinsic activity. For that, we achieved chemical modulation on the second generation of imiquinalines by conjugating amino acids on position 4. A new series of twenty-five compounds was efficiently synthesized by using microwave assistance and tested for its activity on the A375 cell line. In the new series, compounds **11a**, **9d** and **11b** show cytotoxic activities less than second generation compounds, but similar to that of the first generation ones ($IC_{50} = 403$ nM, $IC_{50} = 128$ nM and $IC_{50} = 584$ nM, respectively). The presence of an amino acid leads to significant enhancement of the water solubility for improved drugability.

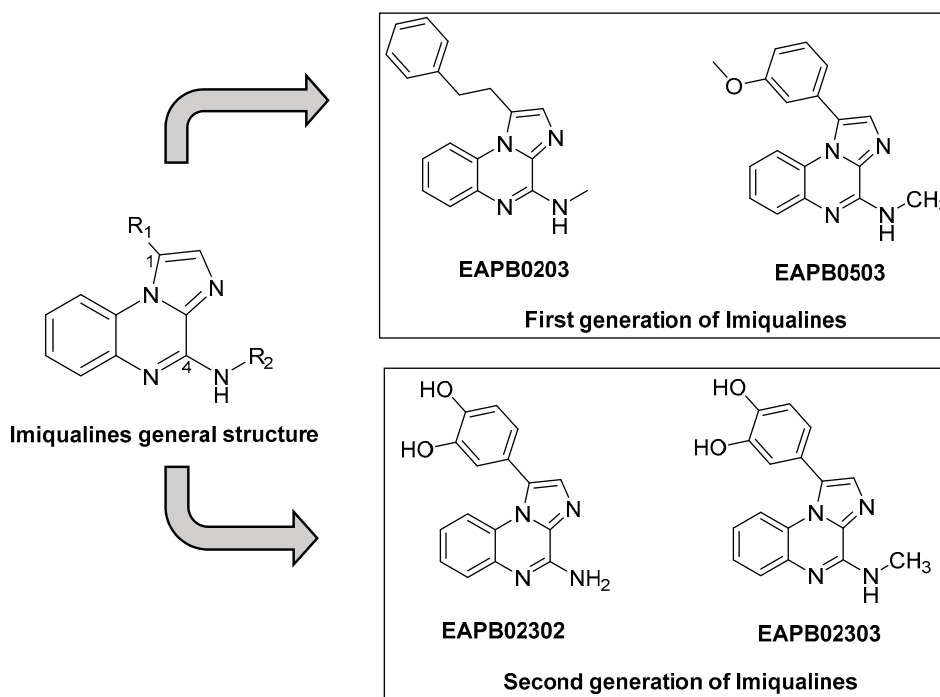
Keywords: imidazo[1,2-*a*]quinoxaline; melanoma; imiquinaline; A375 structure–activity relationship

1. Introduction

Cutaneous melanoma is a malignant tumour of melanocytes located in the basal epidermis. It is the most aggressive and lethal form of skin cancer because of its fast-metastatic development [1,2]. Its incidence has been increasing worldwide for several decades. While in its early stages remarkable outcomes can be achieved with surgery alone, metastatic melanoma requires therapeutic treatment intervention. Thanks to genomic studies, knowledge regarding the molecular biology of melanomas has improved, leading to recent FDA-approved therapies [3–5]. However, all the subtypes of the disease are not equally treated [5] and marked resistance mostly against kinase inhibitors rapidly occurs [6,7]. As the incidence among the worldwide fair-skinned population is increasing, this public health concern remains challenging.

Our group is working on the development of the imidazo[1,2-*a*]quinoxaline derivatives presented in Scheme 1, called imiquinalines, as potential antitumoral agents, particularly for the treatment of melanoma [8,9]. The first generation of imiquinalines was essentially substituted on position 1 by multiple aromatic moieties directly grafted to the main structure or *via* an alkyl linker. The second

generation is characterized by the presence of the 3,4-dihydroxyphenyl moiety on position 1 since the presence of such catechol residue enhances global hydrophilicity. The chemical modulations of the first hits, EAPB0203 and EAPB0503, afforded new leads EAPB02302 and its *N*-demethylated derivative EAPB02303, with impressive *in vitro* activities in the nanomolar range on the A375 human melanoma cancer cell line [10,11].



Scheme 1. General and lead compounds structures of the imiqualines.

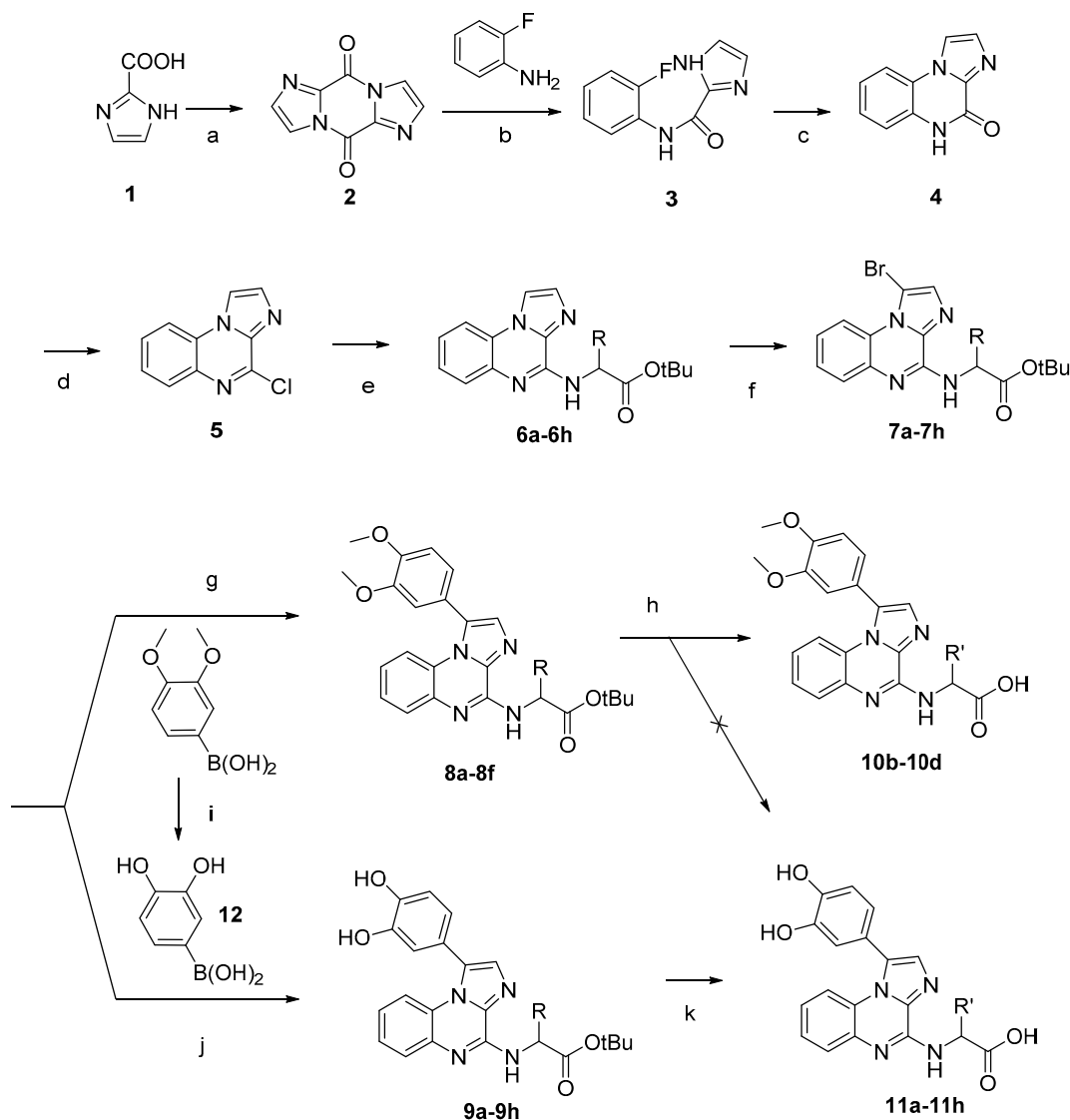
EAPB02302 and EAPB02303 are considered as promising anticancer agents but exhibit high lipophilicity (cLogP values estimated at 2.68 and 3.55, respectively), which might be critical for future preclinical *in vivo* studies. Indeed, their low solubility in water might be a major drawback for further development, especially in the case of intravenous use. In a preliminary study [12], the pharmacokinetic parameters of EAPB02303 were determined in mice after a single intraperitoneal administration. For this, the compound was solubilized in a mixture of DMSO, Tween 80 and sodium chloride solution 0.9% (10/10/80, *v/v/v*). The use of DMSO is recognized as toxic [13], in particular when used repeatedly as would be the case in an efficacy study. In order to optimize the results of efficacy studies, we chose to chemically modulate our lead compounds to obtain more soluble compounds with a moderate impact on the cytotoxic activity. The result of the introduction of various amino acids on position 4 of the heterocycle on both the physicochemical properties and biological activity was studied. Such an approach to increase solubility, which remains a key factor for potential pharmaceutical development, has already been described in the literature [14–17]. The introduction of amino acid moieties has been showed to increase the water solubility as well as selective cytotoxicity [18–20]. We present herein the synthesis of new imidazo[1,2-*a*]quinoxalines decorated with a panel of natural α -amino acids and their *in vitro* preliminary evaluation on A375 cell line.

2. Results and Discussion

2.1. Synthesis of Imidazo[1,2-*a*]quinoxaline Derivatives

The synthetic pathways and the structures of imidazo[1,2-*a*]quinoxalines used in this study are given in Schemes 2 and 3. Intermediates 1 to 5 were synthesized thanks to a route we previously described [9,21]. Briefly, the carbonylimidazole dimer 2 results from the condensation of the

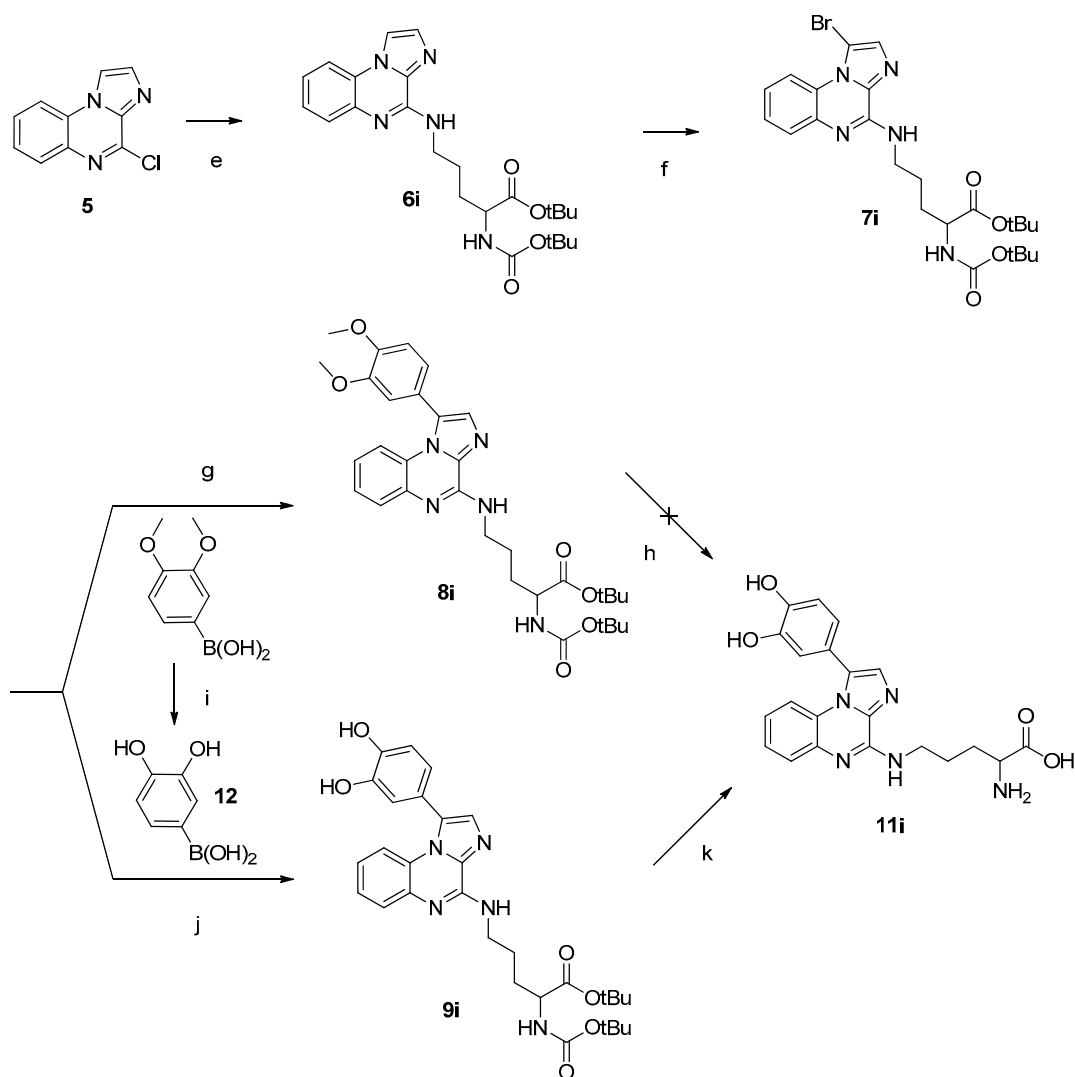
2-imidazole carboxylic acid **1** in presence of thionyl chloride. Addition of *O*-fluoroaniline to the dimer **2** gives the intermediate **3**. Cyclisation is facilitated by using sodium hydride in dimethylacetamide. Treatment of compound **4** with phosphorus oxychloride and *N,N*-diethylaniline gives the chlorinated key intermediate **5**.



Scheme 2. Synthesis of imidazo[1,2-*a*]quinoxaline derivatives grafted with the α -amino group of the amino acid. *Reagents and Conditions:* (a) SOCl_2 , reflux, 18 h; (b) NaHMDS, THF, 0 °C to RT, 5 h; (c) NaH, DMA, reflux, 48 h; (d) DEA, POCl_3 , MW (130 °C, 15 min); (e) H-amino acid (PG)-OtBu, DIEA, DMF, MW (150 °C, 30–60 min); (f) NBS, CHCl_3 , reflux, 2 h; (g) 3,4-dimethoxyphenylboronic acid, $\text{Pd}(\text{PPh}_3)_4$, Na_2CO_3 , DME, MW (140 °C, 20 min); (h) BBr_3 , CH_2Cl_2 , RT, 1h–3h, (i) BBr_3 , CH_2Cl_2 , RT, 1h; (j) 3,4-dihydroxyphenylboronic acid **12**, $\text{Pd}(\text{PPh}_3)_4$, Na_2CO_3 , DME, MW (140 °C, 20 min); (k) TFA/ CH_2Cl_2 (1/1, v/v), RT, 1–2 h.

The chlorine of **5** can be substituted by an amino group in the presence of diisopropylethylamine in DMF under microwave assistance. Among the commercially available amino acids, we chose to study the effect of a short or long, substituted or not, aliphatic or aryl side chain with or without a hydrophilic amino or phenolic group. The amino group could be either the α -amine of an amino acid or the amine of the side chain for the ornithine residue. The introduction of HGlyOtBu, HAlaOtBu, HValOtBu, HLeuOtBu, HLysOtBu, HOrnOtBu, HPheOtBu, HTyrOtBu is described in Scheme 2 and the grafting of BocOrnOtBu is depicted in Scheme 3. The bromination of the intermediates **6** by

N-bromosuccinimide leads to compounds **7**. The 3,4-dimethoxyphenyl group is introduced in position 1 via a Suzuki-Miyaura cross-coupling reaction to furnish compounds **8a–8f** and **8i**. Boron tribromide did not allow the cleavage of all the protections to give the targeted compounds **11a–11i**, even if supplementary equivalents of BBr_3 were added at the beginning or during the reaction, or if the reaction time was extended. Such an approach allows one to obtain compounds **10b–10d** as the main products. These compounds present remaining methoxy groups on the phenyl on position 1 without the protecting groups on the amino acid. The by-products correspond to one remaining methoxy group on the phenyl either at position 3' or 4', but unfortunately, they could not be recovered separately.



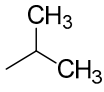
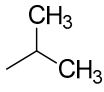
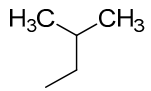
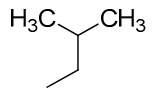
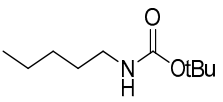
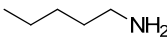
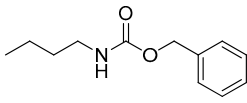
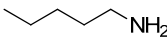
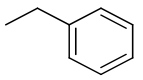
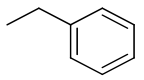
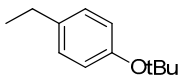
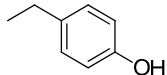
Scheme 3. Synthesis of the ornithine-containing imidazo[1,2-*a*]quinoxaline derivative grafted by the side chain. *Reagents and Conditions:* (e) Boc-Orn-OtBu, HCl, DIEA, DMF, MW (150 °C, 30–60 min); (f) NBS, CHCl_3 , reflux, 2 h; (g) 3,4-dimethoxyphenylboronic acid, $\text{Pd}(\text{PPh}_3)_4$, Na_2CO_3 , DME, MW (140 °C, 20 min); (h) BBr_3 , CH_2Cl_2 , RT, 1 h–3 h; (i) BBr_3 , CH_2Cl_2 , RT, 1 h; (j) 3,4-dihydroxyphenylboronic acid **12**, $\text{Pd}(\text{PPh}_3)_4$, Na_2CO_3 , DME, MW (140 °C, 20 min); (k) TFA/ CH_2Cl_2 (1/1, *v/v*), RT, 1–2 h.

As target compounds **11a–11f** could not be obtained by this way, we decided to deprotect first the 3,4-dimethoxyphenylboronic acid using boron tribromide in order to obtain the 3,4-dihydroxy-phenylboronic acid **12**. This boronic acid readily reacts with intermediates **7** under microwave irradiation to furnish the hydroxylated derivatives **9a–9i**. A final step of deprotection of the amino acid moiety using TFA in CH_2Cl_2 was used to obtain the final compounds **11a–11i**.

2.2. In Vitro Cytotoxic Activity on A375 Cell Line and Calculated ClogP

All new imidazo[1,2-*a*]quinoxaline derivatives **8b–d**, **8f**, **9a–9i**, **10b–d** and **11a–11i** were tested for their in vitro antiproliferative activities on the human melanoma cell line A375. Their IC₅₀ values (concentration of the compound (nM) producing 50% cell growth inhibition after 96 h of drug exposure) were determined using in vitro cytotoxicity assays and are displayed in Tables 1 and 2.

Table 1. Synthesis of imidazo[1,2-*a*]quinoxaline derivatives grafted with the α -amine of the amino acid as described in Scheme 2: cLogP, theoretical water solubility (mg/mL) at pH 7.4 calculated values and IC₅₀ values against A375 (human melanoma cell line).

Amino Acids	-R	-R'	Compounds	ClogP ^a	Theoretical Water Solubility (mg/mL) at pH 7.4 ^b	IC ₅₀ Values ^c (nM)
Gly	—H	—H	8a	5.25	5.88×10^{-4}	ND ^d
			9a	4.99	1.79×10^{-3}	1932
			11a	2.59	47.18	403
Ala	—CH ₃	—CH ₃	8b	5.61	3.80×10^{-4}	>10,000
			9b	5.34	1.15×10^{-3}	6103
			10b	3.21	6.01	5947
Val			11b	2.94	19.92	584
			8c	6.47	1.35×10^{-4}	>10,000
			9c	6.21	4.07×10^{-4}	7180
Leu			10c	4.07	1.91	>10,000
			11c	3.81	6.5	7166
			8d	6.98	7.43×10^{-5}	>10,000
Lys			9d	6.72	2.23×10^{-4}	128
			10d	4.58	0.89	>10,000
			11d	4.32	3.08	838
Orn			8e	7.05	5.70×10^{-5}	ND ^d
			9e	6.79	1.56×10^{-4}	4575
			11e	2.78	4.34×10^{-3}	673
Phe			8f	7.01	3.43×10^{-5}	>10,000
			9f	6.75	9.07×10^{-5}	1111
			11f	2.57	5.82×10^{-3}	3404
Tyr			9g	6.82	1.06×10^{-4}	1999
			11g	3.71	6.47	951
			9h	7.99	3.31×10^{-5}	4117
			11h	3.05	10.17	2174

^{a,b} cLogP and theoretical water solubility (mg/mL) at pH 7.4 values are calculated using the ACDLabs@software; ^c IC₅₀ values, concentration of the compound (nM) producing 50% cell growth inhibition after 96 h of drug exposure, as determined by the MTT assay. Each experiment was performed in triplicate, and the results are presented as average values. Coefficients of variation were less than 10%; ^d ND: Not determined.

Table 2. Synthesis of imidazo[1,2-*a*]quinoxaline derivatives grafted with the side chain amine of ornithine as described in Scheme 3: ClogP, theoretical water solubility (mg/mL) at pH 7.4 calculated values and IC₅₀ values against A375 (human melanoma cell line).

Amino acid	Compounds	ClogP ^a	Theoretical Water Solubility (mg/mL) at pH 7.4 ^b	IC ₅₀ Values ^c (nM)
Orn	8i	6.12	1.62×10^{-4}	>10,000
	9i	5.86	4.50×10^{-4}	>10,000
	11i	2.99	3.05×10^{-3}	5168

^{a,b} ClogP and theoretical water solubility (mg/mL) at pH 7.4 values are calculated using the ACDLabs® software. ^c IC₅₀ values, concentration of the compound (nM) producing 50% cell growth inhibition after 96 h of drug exposure, as determined by the MTT assay. Each experiment was performed in triplicate, and the results are presented as average values. Coefficients of variation were less than 10%.

Lipophilicity, expressed as the logarithm of a compound's octanol/water partition coefficient (ClogP), is a physicochemical property of drugs that affects many biological mechanisms, especially drug absorption and distribution (absorption, plasma protein binding and membrane permeation) [22]. This parameter can also be correlated to solubility, metabolism and toxicity [23,24]. In a drug discovery process, compounds must be sufficiently lipophilic to cross the membrane barriers and at the same time be sufficiently water soluble to reach their targets. Therefore, a poor water solubility is a common cause of rejection during development [25]. This is why we also estimated the lipophilicity and hydrophilicity properties of all new compounds by predicting their ClogP and theoretical water solubility values thanks to fragmentation methods available on the ACDLabs® software. These calculated values are purely theoretical but give a good estimate of what might be the solubility of the compounds in blood circulation (pH 7.4). This approach is used in pharmaceutical industry for the screening of new compounds [26,27]. Results of our new imidazo[1,2-*a*]quinoxaline derivatives were compared each other as well as with the first and second generation imiquinaline leads as shown in Table 3.

Table 3. First and second generation imiquinalines leads: ClogP, theoretical water solubility (mg/mL) at pH 7.4 calculated values and IC₅₀ values against A375 (human melanoma cell line).

Compounds	ClogP ^a	Theoretical Water Solubility (mg/mL) at pH 7.4 ^b	IC ₅₀ Values ^c (nM)
EAPB0203	4.6	3.46×10^{-3}	1570
EAPB0503	4.48	2.60×10^{-3}	200
EAPB02302	2.68	4.28×10^{-2}	60
EAPB02303	3.55	1.74×10^{-2}	10

^{a,b} ClogP and theoretical water solubility (mg/mL) at pH 7.4 values are calculated using the ACDLabs® software. ^c IC₅₀ values, concentration of the compound (nM) producing 50% cell growth inhibition after 96 h of drug exposure, as determined by the MTT assay. Each experiment was performed in triplicate, and the results are presented as average values. Coefficients of variation were less than 10%.

Compounds **8b**, **8c**, **8d** and **8f** have fully protected amino acid residues (side chain and carboxylic function) with 3,4-dimethoxy substitution on the phenyl ring in position 1. They exhibit weak IC₅₀ values higher than 10,000 nM. Compounds belonging to this chemical series are very lipophilic with estimated ClogP values higher than 5 (5.25, 5.61, 6.47, 6.98, 7.05 and 7.01 for compounds **8a**, **8b**, **8c**, **8d**, **8e** and **8f**, respectively). The theoretical water solubility of compounds **8** at pH 7.4 is very low since the order varies from 5.88×10^{-4} to 3.43×10^{-5} mg/mL for compounds **8a** and **8f**, respectively. Therefore, the presence of protective groups on the amino acids and the dimethoxy groups on the phenyl appears not to be valuable, both in terms of water solubility and cytotoxic efficiency.

Compounds **9a–9i** are only protected on the amino acids moieties. These compounds exhibit various cytotoxic activities with IC₅₀ values ranging from 128 to 7180 nM, for **9d** and **9c**, respectively. These compounds show high lipophilicity since their ClogP values range from 4.99 to 7.99 for **9a** and **9h** respectively. Similarly, the theoretical values of water solubility are between 3.31×10^{-5} and

1.79×10^{-3} mg/mL for **9h** and **9a**, respectively. By comparing compounds **8** and **9**, we note that the replacement of the methoxy groups by the hydroxy groups induces, for some residues, an important increase of the biological activities. Nevertheless, such modification, with conservation of the amino acid protection, does not improve the theoretical water solubility of the new synthesized compounds.

Compounds **10b–10d** are deprotected on the amino acid residues but still present dimethoxy groups on the phenyl substitution at position 1. These compounds exhibit IC_{50} values higher than 5000 nM (IC_{50} values at 5947 nM for **10b** and higher than 10,000 nM for **10c** and **10d**). However, ClogP values are below 5 and theoretical water solubilities are higher than 0.8 mg/mL. The transition from compounds **8** to compounds **10** provides a significant decrease of lipophilicity as well as an improvement of theoretical water solubility. The comparison of the compounds according to the grafted residue permits to highlight this improvement. Actually, ClogP values decrease from 5.61 to 3.21, from 6.47 to 4.07 and from 6.98 to 4.58 for compounds **8b** to **10b**, **8c** to **10c** and **8d** to **10d**, respectively. Even more impressive, the theoretical water solubility values increase from 3.8×10^{-4} to 6.01, $1.35 \cdot 10^{-4}$ to 1.91 and 7.43×10^{-5} to 0.89 mg/mL for compounds **8b** to **10b**, **8c** to **10c** and **8d** to **10d**, respectively. The deprotection of the amino acid residues does not improve the cytotoxic activity but clearly improve the theoretical water solubility. The presence of dihydroxy groups on the phenyl substitution at position 1 appears to be necessary for the conservation of the cytotoxic activity.

Compounds **11a–11i** are fully deprotected on the amino acid residues as well as on the catechol group at the position 1. Among these compounds, five have attractive IC_{50} values below 1000 nM: 403, 584, 673, 838 and 951 for **11a**, **11b**, **11e**, **11d** and **11g**, respectively. These compounds show ClogP values ranged from 2.57 to 4.32 for **11f** and **11d**. Several compounds present very interesting theoretical water solubility: compounds **11a**, **11b**, **11c**, **11d**, **11g** and **11h** exhibit values higher than 3 mg/mL. Very high values are obtained for compounds **11a** and **11b** at 47.18 and 19.92 mg/mL, respectively. The presence of an alkyl or aryl moiety on the side chain of the amino acid residue does not decrease the water solubility for these compounds. Nevertheless, the tendency appears to not be the same for compounds **11e**, **11f** and **11i** with theoretical water solubility values less than 1×10^{-2} mg/mL. These compounds possess ornithine (grafted by the α -amine or by the amine of the side chain of the amino acid) or lysine residues. These two residues are therefore not valuable for increasing the water solubility of the compounds at pH 7.4.

Compounds **11a**, **11b**, **11c** and **11d** present an alkyl chain at position 4 while compounds **11g** and **11h** display an aryl chain on this same position. Saturated alkyl groups appear to be most interesting for our compounds. A trend that seems to stand out in these four compounds is that when the carbon number of the alkyl chain increases, the biological activity and the theoretical solubility decrease (except for **11c** which activity does not follow this tendency). Moreover, the presence of a phenyl group causes an increase in lipophilicity and a decrease in biological activities, in particular with the presence of a phenol (compound **11h**) on the side chain of the amino acid moiety. The compounds with lysine or ornithine residues did not show favorable results neither for biological activities or water solubility.

The transition of compounds **9** to compounds **11** is carried out by the cleavage of all the protecting groups of the amino acid moieties. Such a deprotection step forms less lipophilic compounds (lower ClogP) with similar or higher activity for all the amino acids tested, except for compounds **11d** and **11f** with the leucine and ornithine residues grafted by the amine in the α -position, respectively. It should be noted that the presence of an ornithine amino acid residue grafted by the α -amine or the amine of the side chain of the amino acid does not result in any significant differences in the biological activity (IC_{50} values at 3404 nM for **11f** and 5168 nM for **11i**) or to the solubility (theoretical water solubility values at 5.82×10^{-3} and 3.05×10^{-3} mg/mL for **11f** and **11i**, respectively). Surprisingly, compound **11e** which present a butan-1-amine substitution on the lateral chain of the amino acid show an higher biological activity than compound **11f** with a propan-1-amine substitution on its lateral chain (IC_{50} values at 673 nM for **11e** and 3404 nM for **11f**) with equivalent theoretical water solubilities (values of $4.34 \cdot 10^{-3}$ and $5.82 \cdot 10^{-3}$ mg/mL for **11e** and **11f**, respectively).

Consequently, compounds **11a**, **11b**, **11d** and **11g** in particular hold our attention, both in terms of improvement of the solubility and in terms of conservation of the biological activity. The activities of these compounds are in the same potency order as the leads of the first generation of imiquinalines (IC₅₀ values of 200 and 1570 nM for EAPB0503 and EAPB0203, respectively), presented in Table 3. Moreover, these new compounds show highly improved water solubility. Indeed, the values for the first generation compounds were only 2.60×10^{-3} and 3.46×10^{-3} mg/mL for EAPB0203 and EAPB0503, respectively. On the other hand, the second generation imiquinaline compounds exhibit higher activities than the new compounds, with IC₅₀ values at 10 and 60 nM for EAPB02303 and EAPB02302 respectively. However, the solubility values of these compounds are low, with values of 1.74×10^{-2} mg/mL for EAPB02303 and 4.28×10^{-2} mg/mL for EAPB02302.

All of these data and results allow us to put forward a preferential amino acid with a small alkyl side chain in order to get a good compromise between maintaining the activity and increasing water solubility. From the close analysis of Tables 1 and 2, it can be observed that compounds **11a**, **11b**, **9d**, **11d**, **11e** and **11g** are the most active members of this series against the tested melanoma A375 cell line (IC₅₀ values less than 1000 nM). Surprisingly, compound **9d** shows the lowest IC₅₀ value among these new synthesized compounds. Among these six attractive compounds, only **11a**, **11b**, **11d**, **11e** and **11g** show a marked and considerable improvement of the theoretical water solubility.

3. Experimental Section

3.1. Chemistry

3.1.1. General Information

All solvents and reagents were obtained from Sigma Aldrich Chemical Co. (Saint Louis, MO, USA), Iris Biotech GmbH (Marktredwitz, Germany), Alfa Aesar Co. (Karlsruhe, Germany), VWR (Radnor, PA, USA) and FluoroChem UK (Hadfield, UK) and used without further purification unless indicated otherwise. Silica gel chromatography was conducted with 230–400 mesh 60 Å silica gel (Sigma Aldrich Chemical Co.). The progress of reaction was monitored by TLC exposure to UV light (254 nm and 366 nm). Thin layer chromatography plates (Kieselgel 60 F254) were purchased from Merck (Darmstadt, Germany). Microwave assisted organic syntheses were performed on a Biotage Initiator 2.0 microwave system (Uppsala, Sweden). ¹H (400 MHz) and ¹³C-NMR (100 MHz) spectra were obtained on a Brüker AC-400 spectrometer (Billerica, MA, USA). Chemical shifts are given as parts per million (ppm) using residual dimethylsulfoxide signal for protons ($\delta_{\text{DMSO}} = 2.46$ ppm) and carbons ($\delta_{\text{DMSO}} = 40.00$ ppm). Coupling constants are reported in Hertz (Hz). Spectral splitting partners are designed as follow: singlet (s); doublet (d); triplet (t); quartet (q); multiplet (m). Mass spectral data were obtained on a Waters Micromass Q-ToF (Milford, MA, USA) spectrometer equipped with ESI source (Laboratoires de Mesures Physiques, Plateau technique de l'Institut des Biomolécules Max Mousseron, Université de Montpellier, Montpellier, France). Mass spectra were recorded in positive mode between 50 and 1500 Da, capillary and cone tension were 3000 and 20 V, respectively. The High Resolution Mass Spectroscopy (HRMS) analyses are carried out by direct introduction on a Synapt G2-S mass spectrometer (Waters, SN: UEB205) equipped with ESI source. The mass spectra were recorded in positive mode, between 100 and 1500 Da. The capillary tension is 1000 V and the cone tension is 30 V. The source and desolvation temperature are 120 °C and 250 °C, respectively. NMR ¹H and ¹³C spectra of all compounds are in Supplementary Materials.

3.1.2. Amino Acids Grafted on 4-Chloroimidazo[1,2-*a*]quinoxaline

Tert-butyl 2-(imidazo[1,2-*a*]quinoxalin-4-ylamino)acetate (**6a**): Glycine *tert*-butyl ester hydrochloride (0.824 g, 4.9 mmol), *N,N*-diisopropylethylamine (1.6 mL, 9.8 mmol) and 4-chloroimidazo[1,2-*a*]quinoxaline **5** (0.5 g, 2.5 mmol) were dissolved in dimethyl-formamide (10 mL) in a microwave adapted vial and sealed. The reaction mixture was irradiated at 150 °C for 30 min. The solvent was removed under reduced

pressure. The crude mixture was dissolved in ethyl acetate (100 mL) and successively washed with saturated aqueous ammonium chloride, distilled water and finally brine. The organic phase was dried on sodium sulfate, filtered and concentrated under reduced pressure. The product was purified by flash chromatography eluted with cyclohexane/ethyl acetate 80/20 to 50/50. The compound is obtained as a beige solid (42% yield). $C_{16}H_{18}N_4O_2$. M_W : 298.34 g/mol. 1H -NMR δ (ppm, DMSO- d_6): 1.42 (s, 9H, 3 \times CH₃ OtBu), 4.13 (d, 2H, J = 8 Hz, CH₂ α), 7.31–7.35 (m, 1H, CH 7), 7.40–7.44 (m, 1H, CH 8), 7.56 (dd, 1H, J = 4 Hz, J = 8 Hz, CH 9), 7.66 (d, 1H, J = 4 Hz, CH 2), 7.96 (t, 1H, J = 8 Hz, NH), 8.13 (dd, 1H, J = 4 Hz, J = 8 Hz, CH 6), 8.64 (d, 1H, J = 4 Hz, CH 1). ^{13}C -NMR δ (ppm, DMSO- d_6): 28.23 (CH₃ tBu), 43.30 (CH₂ α), 80.85 (Cq tBu), 115.14 (CH 1), 115.91 (CH 6), 123.57 (CH 7), 124.93 (Cq 5a), 126.74 (CH 9), 126.88 (CH 8), 132.52 (CH 2), 132.71 (Cq 3a), 136.81 (Cq 9a), 147.49 (Cq 4), 169.79 (C=O). MS (ESI +, QTof, m/z): 299.0 [M + H]⁺.

Tert-butyl 2-(imidazo[1,2-*a*]quinoxalin-4-ylamino)propanoate (6b): Same procedure used for the synthesis of **6a** was employed. L-Alanine *tert*-butyl ester hydrochloride (1.339 g, 7.4 mmol), *N,N*-diisopropylethylamine (2.4 mL, 14.7 mmol) and 4-chloroimidazo[1,2-*a*]quinoxaline **5** (0.5 g, 2.5 mmol) were dissolved and reacted in dimethyl-formamide (10 mL). The product was purified by flash chromatography eluted with cyclohexane/ethyl acetate 80/20 to 50/50. The compound is obtained as a beige solid (48% yield). $C_{17}H_{20}N_4O_2$. M_W : 312.37 g/mol. 1H -NMR δ (ppm, DMSO- d_6): 1.41 (s, 9H, 3 \times CH₃ OtBu), 1.51 (d, 3H, J = 8 Hz, CH₃ β), 4.56–4.63 (m, 1H, CH α), 7.33–7.36 (m, 1H, CH 7), 7.41–7.43 (m, 1H, CH 8), 7.56 (dd, 1H, J = 4 Hz, J = 8 Hz, CH 9), 7.66 (d, 1H, J = 4 Hz, CH 2), 7.75 (d, 1H, J = 4 Hz, NH), 8.13 (dd, 1H, J = 4 Hz, J = 8 Hz, CH 6), 8.64 (d, 1H, J = 4 Hz, CH 1). ^{13}C -NMR δ (ppm, DMSO- d_6): 17.46 (CH₃ β), 28.14 (CH₃ tBu), 50.22 (CH α), 80.59 (Cq tBu), 115.18 (CH 1), 115.91 (CH 6), 123.64 (CH 7), 124.93 (Cq 5a), 126.73 (CH 9), 126.88 (CH 8), 132.42 (CH 2), 132.58 (Cq 3a), 136.72 (Cq 9a), 147.03 (Cq 4), 172.84 (C=O). MS (ESI +, QTof, m/z): 313.2 [M + H]⁺.

Tert-Butyl 2-(imidazo[1,2-*a*]quinoxalin-10-ylamino)-3-methylbutanoate (6c): Using the same procedure as for the synthesis of **6a**, L-valine *tert*-butyl ester hydrochloride (2.060 g, 9.8 mmol), *N,N*-diisopropylethylamine (2.4 mL, 14.7 mmol) and 4-chloroimidazo[1,2-*a*]quinoxaline **5** (0.5 g, 2.5 mmol) were mixed in dimethylformamide (10 mL). The product was purified by flash chromatography eluted with cyclohexane/ethyl acetate 80/20 to 50/50. The compound is obtained as a beige solid (51% yield). $C_{19}H_{24}N_4O_2$. M_W : 340.42 g/mol. 1H -NMR δ (ppm, DMSO- d_6): 1.03 (d, 3H, J = 8 Hz, CH₃ γ), 1.06 (d, 3H, J = 8 Hz, CH₃ γ'), 1.43 (s, 9H, 3 \times CH₃ OtBu), 2.29–2.37 (m, 1H, CH β), 4.52 (t, 1H, J = 16 Hz, CH α), 7.15 (d, 1H, J = 8 Hz, NH), 7.33–7.37 (m, 1H, CH 7), 7.42–7.44 (m, 1H, CH 8), 7.59 (dd, 1H J = 4 Hz, J = 8 Hz, CH 9), 7.68 (d, 1H, J = 4 Hz, CH 2), 8.14 (dd, 1H, J = 4 Hz, J = 8 Hz, CH 6), 8.66 (d, 1H, J = 4 Hz, CH 1). ^{13}C -NMR δ (ppm, DMSO- d_6): 19.42 (CH₃ γ , CH₃ γ'), 28.17 (CH₃ tBu), 30.41 (CH β), 59.76 (CH α), 81.15 (Cq tBu), 115.37 (CH 1), 115.95 (CH 6), 123.88 (CH 7), 125.00 (Cq 5a), 126.84 (CH 9), 126.95 (CH 8), 132.48 (CH 2), 132.58 (Cq 3a), 136.59 (Cq 9a), 147.29 (Cq 4), 171.59 (C=O). MS (ESI +, QTof, m/z): 341.0 [M + H]⁺.

Tert-butyl 2-(imidazo[1,2-*a*]quinoxalin-4-ylamino)-4-methylpentanoate (6d): The same as for the synthesis of **6a** was used, employing L-leucine *tert*-butyl ester hydrochloride (2.198 g, 9.8 mmol), *N,N*-diisopropylethylamine (2.4 mL, 14.7 mmol) and 4-chloro-imidazo[1,2-*a*]quinoxaline **5** (0.5 g, 2.5 mmol) in dimethylformamide (10 mL). The product was purified by flash chromatography eluted with cyclohexane/ethyl acetate 80/20 to 50/50. The compound is obtained as a beige solid (60% yield). $C_{20}H_{26}N_4O_2$. M_W : 354.45 g/mol. 1H -NMR δ (ppm, DMSO- d_6): 0.93 (d, 3H, J = 8 Hz, CH₃ δ), 0.96 (d, 3H, J = 8 Hz, CH₃ δ'), 1.40 (s, 9H, 3 \times CH₃ OtBu), 1.60–1.67 (m, 1H, CH₂ β), 1.77–1.79 (m, 1H, CH γ), 1.93–1.95 (m, 1H, CH₂ β), 4.63 (t, 1H, J = 4 Hz, CH α), 7.26–7.33 (m, 1H, CH 7), 7.40–7.44 (m, 1H, CH 8), 7.57 (dd, 1H, J = 4 Hz, J = 8 Hz, CH 9), 7.64 (d, 1H, J = 4 Hz, NH), 7.66 (d, 1H, J = 4 Hz, CH 2), 8.13 (dd, 1H, J = 4 Hz, J = 8 Hz, CH 6), 8.64 (d, 1H, J = 4 Hz, CH 1). ^{13}C -NMR δ (ppm, DMSO- d_6): 22.06 (CH₃ δ), 23.31 (CH₃ δ'), 25.14 (CH γ), 28.15 (CH₃ tBu), 40.01 (CH₂ β), 52.93 (CH α), 80.67 (Cq tBu), 115.21 (CH 1), 115.90 (CH 6), 123.64 (CH 7), 124.93 (Cq 5a), 126.76 (CH 8), 126.89 (CH 9), 132.41 (CH 2), 132.58 (Cq 3a), 136.74 (Cq 9a), 147.40 (Cq 4), 172.75 (C=O). MS (ESI +, QTof, m/z): 355.0 [M + H]⁺.

Tert-butyl 6-((tert-butoxycarbonyl)amino)-2-(imidazo[1,2-a]quinoxalin-4-ylamino)hexanoate (6e): The same procedure used for the synthesis of **6a** was employed with *N*- ϵ -tert-butylloxycarbonyl-L-lysine *tert*-butyl ester hydrochloride (2.565 g, 7.6 mmol), *N,N*-diisopropyl-ethylamine (2.4 mL, 14.7 mmol) and 4-chloroimidazo[1,2-*a*]quinoxaline **5** (0.5 g, 2.5 mmol) in dimethylformamide (10 mL). The product was purified by flash chromatography eluted with cyclohexane/ethyl acetate 80/20 to 50/50. The compound is obtained as a beige solid (32% yield). C₂₅H₃₅N₅O₄. M_W: 469.58 g/mol. ¹H-NMR δ (ppm, DMSO-*d*₆): 1.35 (s, 9H, 3 \times CH₃ OtBu), 1.41 (s, 9H, 3 \times CH₃ OtBu), 1.43–1.49 (m, 4H, CH₂ γ , CH₂ δ), 1.86–1.92 (m, 2H, CH₂ β), 2.91–2.93 (m, 2H, CH₂ ϵ), 4.52–4.56 (m, 1H, CH α), 6.79 (t, 1H, *J* = 4 Hz, NH-CH₂ ϵ), 7.26–7.35 (m, 1H, CH 7), 7.39–7.42 (m, 1H, CH 8), 7.52 (dd, 1H, *J* = 4 Hz, *J* = 8 Hz, CH 9), 7.64 (d, 1H, *J* = 4 Hz, NH-CH α), 7.66 (d, 1H, *J* = 4 Hz, CH 2), 8.12 (dd, 1H, *J* = 4 Hz, *J* = 8 Hz, CH 6), 8.64 (d, 1H, *J* = 4 Hz, CH 1). ¹³C-NMR δ (ppm, DMSO-*d*₆): 23.52 (CH₂ γ), 28.19 (CH₃ tBu), 28.74 (CH₃ tBu), 29.67 (CH₂ δ), 30.92 (CH₂ β), 40.35 (CH₂ ϵ), 54.64 (CH α), 79.68 (Cq tBu), 80.80 (Cq tBu), 115.25 (CH 1), 115.93 (CH 6), 123.70 (CH 7), 124.98 (Cq 5a), 126.81 (CH 9), 126.92 (CH 8), 132.44 (CH 2), 132.60 (Cq 3a), 136.75 (Cq 9a), 147.35 (Cq 4), 172.41 (C=O). MS (ESI +, QTof, *m/z*): 470.0 [M + H]⁺.

Tert-butyl 5-(((benzyloxy)carbonyl)amino)-2-(imidazo[1,2-a]quinoxalin-4-ylamino)-pentanoate (6f): Using the same procedure used for the synthesis of **6a** with *N*- δ -carbobenzyloxy-L-ornithine α -*tert*-butyl ester hydrochloride (3.702 g, 10.3 mmol), *N,N*-diisopropylethylamine (2.4 mL, 14.7 mmol) and 4-chloroimidazo[1,2-*a*]quinoxaline **5** (0.5 g, 2.5 mmol) in dimethylformamide (10 mL). The product was purified by flash chromatography eluted with cyclohexane/ethyl acetate 80/20 to 50/50. The compound is obtained as a beige solid (38% yield). C₂₇H₃₁N₅O₄. M_W: 489.57 g/mol. ¹H-NMR δ (ppm, 400 MHz, DMSO-*d*₆): ¹H-NMR δ (ppm, DMSO-*d*₆): 1.29 (s, 9H, 3 \times CH₃ OtBu), 1.46–1.50 (m, 2H, CH₂ γ), 1.79–1.84 (m, 2H, CH₂ β), 2.94–2.98 (m, 2H, CH₂ δ), 4.44–4.46 (m, 1H, CH α), 4.90 (s, 2H, CH₂-Phenyl), 7.17–7.21 (m, 1H, CH 7), 7.23 (s, 1H, NH-CH₂ δ), 7.24–7.27 (m, 5H, CH Phenyl), 7.29–7.33 (m, 1H, CH 8), 7.46 (dd, 1H, *J* = 4 Hz, *J* = 8 Hz, CH 9), 7.52 (d, 1H, *J* = 4 Hz, NH-CH α), 7.56 (d, 1H, *J* = 4 Hz, CH 2), 8.02 (dd, 1H, *J* = 4 Hz, *J* = 8 Hz, CH 6), 8.53 (d, 1H, *J* = 4 Hz, CH 1). ¹³C-NMR δ (ppm, DMSO-*d*₆): 26.63 (CH₂ γ), 28.13 (CH₃ tBu), 28.66 (CH₂ β), 40.71 (CH₂ δ), 54.50 (CH α), 65.67 (CH₂-Phenyl), 80.91 (Cq tBu), 115.30 (CH 1), 115.99 (CH 6), 123.77 (CH 7), 125.03 (Cq 5a), 126.84 (CH 9), 126.97 (CH 8), 128.86 (CH Phenyl), 132.50 (CH 2), 132.65 (Cq 3a), 136.77 (Cq 9a), 147.36 (Cq 4), 156.65 (Cq Phenyl), 172.28 (C=O). MS (ESI +, QTof, *m/z*): 490.0 [M + H]⁺.

Tert-Butyl 2-(imidazo[1,2-a]quinoxalin-4-ylamino)-3-phenylpropanoate (6g): The same procedure as for the synthesis of **6a** was used with L-phenylalanine *tert*-butyl ester hydrochloride (1.9 g, 7.4 mmol), *N,N*-diisopropylethylamine (2.4 mL, 14.7 mmol) and 4-chloroimidazo[1,2-*a*]quinoxaline **5** (0.5 g, 2.5 mmol) in dimethylformamide (10 mL). The product was purified by flash chromatography eluted with cyclohexane/ethyl acetate 80/20 to 50/50. The compound is obtained as a beige solid (37% yield). C₂₃H₂₄N₄O₂. M_W: 388.46 g/mol. ¹H-NMR δ (ppm, DMSO-*d*₆): 1.33 (s, 9H, 3 \times CH₃ OtBu), 3.19–3.23 (m, 1H, CH₂ β), 3.32–3.36 (m, 1H, CH₂ β), 4.82–4.84 (m, 1H, CH α), 7.21 (t, 1H, *J* = 8 Hz, CH Phenyl), 7.29 (t, 2H, *J* = 8 Hz, 2 \times CH Phenyl), 7.32–7.34 (m, 3H, CH 7, 2 \times CH Phenyl), 7.41–7.44 (m, 1H, CH 8), 7.57 (dd, 1H, *J* = 4 Hz, *J* = 8 Hz, CH 9), 7.61 (d, 1H, *J* = 8 Hz, NH), 7.66 (d, 1H, *J* = 4 Hz, CH 2), 8.13 (dd, 1H, *J* = 8, 4 Hz, CH 6), 8.64 (d, 1H, *J* = 4 Hz, CH 1). ¹³C-NMR δ (ppm, DMSO-*d*₆): 26.97 (CH₃ tBu), 35.91 (CH₂ β), 54.93 (CH α), 79.88 (Cq tBu), 114.18 (CH 1), 114.85 (CH 6), 122.74 (CH 7), 123.89 (Cq 5a), 125.74 (CH 9), 125.84 (CH Phenyl), 125.86 (CH 8), 127.59 (CH Phenyl), 128.69 (CH Phenyl), 131.41 (CH 2), 135.54 (Cq 3a), 137.05 (Cq 9a), 146.02 (Cq 4), 170.53 (C=O). MS (ESI +, QTof, *m/z*): 389.0 [M + H]⁺.

Tert-butyl 3-(4-(tert-butoxy)phenyl)-2-(imidazo[1,2-a]quinoxalin-4-ylamino)propanoate (6h): The same procedure as for the synthesis of **6a** was used with *O*-*tert*-butyl-L-tyrosine *tert*-butyl ester hydrochloride (1.6 g, 4.9 mmol), *N,N*-diisopropylethylamine (2.4 mL, 14.7 mmol) and 4-chloroimidazo[1,2-*a*]quinoxaline **5** (0.5 g, 2.5 mmol) in dimethylformamide (10 mL). The product was purified by flash chromatography eluted with cyclohexane/ethyl acetate 80/20 to 50/50. The compound is obtained as a beige solid (26% yield). C₂₇H₃₂N₄O₃. M_W: 460.57 g/mol. ¹H-NMR δ (ppm, DMSO-*d*₆): 1.23 (s, 9H, 3 \times CH₃ OtBu), 1.31 (s, 9H, 3 \times CH₃ OtBu), 3.11–3.17 (m, 1H, CH₂ β), 3.25–3.31

(m, 1H, CH₂ β), 4.78–4.83 (m, 1H, CH α), 6.86 (dd, 2H, *J* = 4 Hz, *J* = 8 Hz, CH Phenyl), 7.22 (dd, 2H, *J* = 4 Hz, *J* = 8 Hz, CH Phenyl), 7.32–7.36 (m, 1H, CH 7), 7.40–7.44 (m, 1H, CH 8), 7.57 (dd, 1H, *J* = 4 Hz, *J* = 8 Hz, CH 9), 7.61 (d, 1H, *J* = 4 Hz, NH), 7.66 (d, 1H, *J* = 4 Hz, CH 2), 8.13 (dd, 1H, *J* = 4 Hz, *J* = 8 Hz, CH 6), 8.64 (d, 1H, *J* = 4 Hz, CH 1). ¹³C-NMR δ (ppm, DMSO-*d*₆): 28.02 (CH₃ tBu), 28.93 (CH₃ tBu), 36.63 (CH₂ β), 56.09 (CH α), 78.11 (Cq tBu), 80.87 (Cq tBu), 115.22 (CH 1), 115.90 (CH 6), 123.80 (CH 7), 123.98 (2 × CH Phenyl), 124.96 (Cq 5a), 126.79 (CH 9), 126.90 (CH 8), 130.31 (2 × CH Phenyl), 132.47 (CH 2), 132.61 (Cq 3a), 136.60 (Cq 9a), 147.04 (Cq 4), 154.03 (2 × Cq Phenyl), 171.72 (C=O). MS (ESI +, QTof, *m/z*): 461.2 [M + H]⁺.

*Tert-butyl 6-((tert-butoxycarbonyl)amino)-2-(imidazo[1,2-*a*]quinoxalin-4-ylamino)hexanoate (6i)*: Same procedure used for the synthesis of **6a** was employed with *N*-α-*tert*-butyloxycarbonyl-L-ornithine *tert*-butyl ester hydrochloride (1.596 g, 4.9 mmol), *N,N*-diisopropyl-ethylamine (1.6 mL, 9.8 mmol) and 4-chloroimidazo[1,2-*a*]quinoxaline **5** (0.5 g, 2.5 mmol) in dimethylformamide (10 mL). The product was purified by flash chromatography eluted with cyclohexane/ethyl acetate 80/20 to 50/50. The compound is obtained as a beige solid (48% yield). C₂₄H₃₃N₅O₄. M_W: 455.56 g/mol. ¹H-NMR δ (ppm, DMSO-*d*₆): 1.35 (s, 9H, CH-CO₂tBu), 1.41 (s, 9H, NH-CO₂tBu), 1.85–1.96 (m, 2H, CH₂ β), 2.91–2.95 (m, 2H, CH₂ γ), 3.35–3.39 (m, 2H, CH₂ δ), 4.51–4.56 (m, 1H, CH α), 6.79 (d, 1H, *J* = 4 Hz, NH-CH α), 7.32–7.35 (m, 1H, CH 7), 7.39–7.42 (m, 1H, CH 8), 7.56 (dd, 1H, *J* = 4 Hz, *J* = 8 Hz, CH 9), 7.60 (d, 1H, *J* = 4 Hz, NH-CH₂ δ), 7.66 (s, 1H, CH 2), 8.13 (dd, 1H, *J* = 4 Hz, *J* = 8 Hz, CH 6), 8.64 (d, 1H, CH 1). ¹³C-NMR δ (ppm, DMSO-*d*₆): 25.87 (CH₂ β), 28.04 (CH₃ tBu), 28.67 (CH₃ tBu), 28.43 (CH₂ γ), 39.79 (CH₂ δ), 54.75 (CH α), 78.45 (Cq tBu), 80.53 (Cq tBu), 115.02 (CH 1), 115.79 (CH 6), 122.99 (CH 7), 124.65 (Cq 5a), 126.50 (CH 9), 126.73 (CH 8), 132.20 (CH 2), 132.87 (Cq 3a), 147.78 (Cq 4), 156.00 (Cq 9a), 172.33 (C=O). MS (ESI +, QTof, *m/z*): 456.01 [M + H]⁺.

3.1.3. Bromination

*Tert-butyl 2-((1-bromoimidazo[1,2-*a*]quinoxalin-4-yl)amino)acetate (7a)*: A solution of **6a** (0.26 g, 0.87 mmol) and *N*-bromosuccinimide (0.19 g, 1.0 mmol) in CHCl₃ (50 mL) was heated under reflux for 2 h. The solvent was removed under reduced pressure. The crude mixture was dissolved in ethyl acetate (50 mL) and successively washed with saturated aqueous ammonium chloride, saturated aqueous sodium bicarbonate, distilled water and finally brine (50 mL). The organic phase was dried on sodium sulfate, filtered and concentrated under reduced pressure. The compound was obtained as a beige oil (97% yield) and used without purification. C₁₆H₁₇BrN₄O₂. M_W: 377.24 g/mol. ¹H-NMR δ (ppm, DMSO-*d*₆): 1.42 (s, 9H, 3 × CH₃ OtBu), 4.12 (d, 2H, *J* = 8 Hz, CH₂ α), 7.34–7.37 (m, 1H, CH 7), 7.45–7.50 (m, 1H, CH 8), 7.59 (dd, 1H, *J* = 4 Hz, *J* = 8 Hz, CH 9), 7.76 (s, 1H, CH 2), 8.02 (t, 1H, *J* = 8 Hz, NH), 8.96 (dd, 1H, *J* = 4 Hz, *J* = 8 Hz, CH 6). ¹³C-NMR δ (ppm, DMSO-*d*₆): 28.22 (CH₃ tBu), 43.26 (CH₂ α), 80.93 (Cq tBu), 99.61 (Cq 1), 115.12 (CH 6), 123.08 (CH 7), 126.08 (Cq 5a), 127.35 (CH 9), 127.78 (CH 8), 134.01 (Cq 3a), 134.79 (CH 2), 137.63 (Cq 9a), 147.05 (Cq 4), 169.64 (C=O). MS (ESI +, QTof, *m/z*): 377.0 [M + H]⁺.

*Tert-butyl 2-((1-bromoimidazo[1,2-*a*]quinoxalin-4-yl)amino)propanoate (7b)*: A solution of **6b** (0.3 g, 0.96 mmol) and *N*-bromosuccinimide (0.2 g, 1.1 mmol) in CHCl₃ (50 mL) was heated under reflux for 2 h. The solvent was removed under reduced pressure. The crude mixture was dissolved in ethyl acetate (50 mL) and successively washed with saturated aqueous ammonium chloride, saturated aqueous sodium bicarbonate, distilled water and finally brine. The organic phase was dried on sodium sulfate, filtered and concentrated under reduced pressure. The compound was obtained as a beige oil (98% yield) and used without purification. C₁₇H₁₉BrN₄O₂. M_W: 391.26 g/mol. ¹H-NMR δ (ppm, DMSO-*d*₆): 1.41 (s, 9H, 3 × CH₃ OtBu), 1.51 (d, 3H, *J* = 8 Hz, CH₃ β), 4.55–4.59 (m, 1H, CH α), 7.34–7.38 (m, 1H, CH 7), 7.46–7.48 (m, 1H, CH 8), 7.60 (dd, 1H, *J* = 4 Hz, *J* = 8 Hz, CH 9), 7.76 (s, 1H, CH 2), 7.82 (d, 1H, *J* = 4 Hz, NH), 8.97 (dd, 1H, *J* = 4 Hz, *J* = 8 Hz, CH 6). ¹³C-NMR δ (ppm, DMSO-*d*₆): 17.40 (CH₃ β), 28.03 (CH₃ tBu), 50.24 (CH α), 80.70 (Cq tBu), 99.68 (CH 1), 115.06 (CH 6), 123.17 (CH 7), 126.06 (Cq 5a), 127.30 (CH 9), 127.45 (CH 8), 133.87 (Cq 3a), 134.73 (CH 2), 137.47 (Cq 9a), 146.58 (Cq 4), 172.66 (C=O). MS (ESI +, QTof, *m/z*): 391.1 [M + H]⁺.

Tert-butyl 2-((1-bromoimidazo[1,2-a]quinoxalin-4-yl)amino)-3-methylbutanoate (7c): A solution of **6c** (0.38 g, 1.1 mmol) and *N*-bromosuccinimide (0.24 g, 1.4 mmol) in CHCl₃ (50 mL) was heated under reflux for 2 h. The solvent was removed under reduced pressure. The crude mixture was dissolved in ethyl acetate (50 mL) and successively washed with saturated aqueous ammonium chloride, saturated aqueous sodium bicarbonate, distilled water and finally brine. The organic phase was dried on sodium sulfate, filtered and concentrated under reduced pressure. The compound was obtained as a beige oil (96% yield) and used without purification. C₁₉H₂₃BrN₄O₂. M_W: 419.31 g/mol. ¹H-NMR δ (ppm, DMSO-*d*₆): 1.02 (d, 3H, *J* = 8 Hz, CH₃ γ), 1.05 (d, 3H, *J* = 8 Hz, CH₃ γ'), 1.43 (s, 9H, 3 × CH₃ OtBu), 2.31–2.36 (m, 1H, CH β), 4.49 (t, 1H, *J* = 16 Hz, CH α), 7.20 (d, 1H, *J* = 8 Hz, NH), 7.35–7.40 (m, 1H, CH 7), 7.47–7.49 (m, 1H, CH 8), 7.62 (dd, 1H, *J* = 4 Hz, *J* = 8 Hz, CH 9), 7.76 (s, 1H, CH 2), 8.97 (dd, 1H, *J* = 4 Hz, *J* = 8 Hz, CH 6). ¹³C-NMR δ (ppm, DMSO-*d*₆): 19.42 (CH₃ γ, CH₃ γ'), 28.17 (CH₃ tBu), 30.40 (CH β), 59.76 (CH α), 81.25 (Cq tBu), 99.86 (Cq 1), 115.08 (CH 6), 123.38 (CH 7), 126.16 (Cq 5a), 127.44 (CH 9), 127.47 (CH 8), 133.81 (Cq 3a), 134.74 (CH 2), 137.40 (Cq 9a), 146.84 (Cq 4), 171.44 (C=O). MS (ESI +, QTof, *m/z*): 419.1 [M + H]⁺.

Tert-butyl 2-((1-bromoimidazo[1,2-a]quinoxalin-4-yl)amino)-4-methylpentanoate (7d): A solution of **6d** (0.35 g, 1.0 mmol) and *N*-bromosuccinimide (0.2 g, 1.2 mmol) in CHCl₃ (50 mL) was heated under reflux for 2 h. The solvent was removed under reduced pressure. The crude mixture was dissolved in ethyl acetate (50 mL) and successively washed with saturated aqueous ammonium chloride, saturated aqueous sodium bicarbonate, distilled water and finally brine. The organic phase was dried on sodium sulfate, filtered and concentrated under reduced pressure. The compound was obtained as a beige oil (95% yield) and used without purification. C₂₀H₂₅BrN₄O₂. M_W: 433.34 g/mol. ¹H-NMR δ (ppm, DMSO-*d*₆): 0.91 (d, 3H, *J* = 8 Hz, CH₃ δ), 0.95 (d, 3H, *J* = 8 Hz, CH₃ δ'), 1.40 (s, 9H, 3 × CH₃ OtBu), 1.60–1.62 (m, 1H, CH₂ β), 1.77–1.79 (m, 1H, CH γ), 1.94–1.96 (m, 1H, CH₂ β), 4.60 (t, 1H, *J* = 4 Hz, CH α), 7.35–7.38 (m, 1H, CH 7), 7.46–7.50 (m, 1H, CH 8), 7.60 (dd, 1H, *J* = 4 Hz, *J* = 8 Hz, CH 9), 7.71 (d, 1H, *J* = 4 Hz, NH), 7.76 (s, 1H, CH 2), 8.97 (dd, 1H, *J* = 4 Hz, *J* = 8 Hz, CH 6). ¹³C-NMR δ (ppm, DMSO-*d*₆): 22.03 (CH₃ δ), 23.31 (CH₃ δ'), 25.12 (CH γ), 28.14 (CH₃ tBu), 40.10 (CH₂ β), 52.95 (CH α), 80.76 (Cq tBu), 99.21 (Cq 1), 115.07 (CH 6), 123.17 (CH 7), 126.08 (Cq 5a), 127.37 (CH 9), 127.46 (CH 8), 133.88 (Cq 3a), 134.71 (CH 2), 137.55 (Cq 9a), 146.97 (Cq 4), 172.59 (C=O). MS (ESI +, QTof, *m/z*): 433.1 [M + H]⁺.

Tert-butyl 2-((1-bromoimidazo[1,2-a]quinoxalin-4-yl)amino)-6-((Tert-butoxycarbonyl)amino)-hexanoate (7e): A solution of **6e** (1.2 g, 2.5 mmol) and *N*-bromosuccinimide (0.54 g, 3.1 mmol) in CHCl₃ (50 mL) was heated under reflux for 2 h. The solvent was removed under reduced pressure. The crude mixture was dissolved in ethyl acetate (50 mL) and successively washed with saturated aqueous ammonium chloride, saturated aqueous sodium bicarbonate, distilled water and finally brine. The organic phase was dried on sodium sulfate, filtered and concentrated under reduced pressure. The compound was obtained as a beige oil (78% yield) and used without purification. C₂₅H₃₄BrN₅O₄. M_W: 548.47 g/mol. ¹H-NMR δ (ppm, DMSO-*d*₆): 1.22–1.24 (m, 2H, CH₂ γ), 1.34 (s, 9H, 3 × CH₃ OtBu), 1.40 (s, 9H, 3 × CH₃ OtBu), 1.54–1.56 (m, 2H, CH₂ β), 1.89–1.91 (m, 2H, CH₂ δ), 2.83–2.89 (m, 2H, CH₂ ε), 4.13–4.19 (m, 1H, CH α), 6.78 (t, 1H, *J* = 4 Hz, NH-CH₂ ε), 7.34–7.39 (m, 1H, CH 7), 7.46–7.48 (m, 1H, CH 8), 7.65 (dd, 1H, *J* = 4 Hz, *J* = 8 Hz, CH 9), 8.03 (s, 1H, CH 2), 8.34 (d, 1H, *J* = 4 Hz, NH-CH α), 8.97 (dd, 1H, *J* = 4 Hz, *J* = 8 Hz, CH 6). ¹³C-NMR δ (ppm, DMSO-*d*₆): 22.90 (CH₂ γ), 28.15 (CH₃ tBu), 28.73 (CH₃ tBu), 29.46 (CH₂ δ), 31.34 (CH₂ β), 39.36 (CH₂ ε), 54.61 (CH α), 80.85 (Cq tBu), 81.14 (Cq tBu), 99.70 (Cq 1), 115.06 (CH 6), 123.19 (CH 7), 126.09 (Cq 5a), 127.39 (CH 9), 127.46 (CH 8), 133.87 (CH 2), 134.70 (Cq 3a), 137.54 (Cq 9a), 146.88 (Cq 4), 171.39 (C=O), 172.21 (C=O). MS (ESI +, QTof, *m/z*): 548.1 [M + H]⁺.

Tert-butyl 5-((benzyloxy)carbonyl)amino)-2-((1-bromoimidazo[1,2-a]quinoxalin-4-yl)amino)pentanoate (7f): A solution of **6f** (0.45 g, 0.9 mmol) and *N*-bromosuccinimide (0.20 g, 1.1 mmol) in CHCl₃ (50 mL) was heated under reflux for 2 h. The solvent was removed under reduced pressure. The crude mixture was dissolved in ethyl acetate (50 mL) and successively washed with saturated aqueous ammonium chloride, saturated aqueous sodium bicarbonate, distilled water and finally brine. The organic phase was dried on sodium sulfate, filtered and concentrated under reduced pressure. The compound was

obtained as a beige oil (94% yield) and used without purification. $C_{27}H_{30}BrN_5O_4$. M_W : 568.46 g/mol. 1H -NMR δ (ppm, DMSO- d_6): 1.40 (s, 9H, 3 \times CH₃ OtBu), 1.51–1.59 (m, 2H, CH₂ γ), 1.89–1.92 (m, 2H, CH₂ β), 3.03–3.08 (m, 2H, CH₂ δ), 4.52–4.54 (m, 1H, CH α), 5.00 (s, 2H, CH₂-Phenyl), 7.26 (s, 1H, NH-CH₂ δ), 7.31–7.35 (m, 5H, CH Phenyl), 7.36–7.39 (m, 1H, CH 7), 7.46–7.50 (m, 1H, CH 8), 7.59 (dd, 1H, J = 4 Hz, J = 8 Hz, CH 9), 7.67 (d, 1H, J = 4 Hz, NH-CH α), 7.76 (s, 1H, CH 2), 8.99 (dd, 1H, J = 4 Hz, J = 8 Hz, CH 6). ^{13}C -NMR δ (ppm, DMSO- d_6): 26.53 (CH₂ γ), 28.13 (CH₃ tBu), 28.50 (CH₂ β), 40.42 (CH₂ δ), 54.43 (CH α), 65.59 (CH₂-Phenyl), 80.92 (Cq tBu), 99.69 (Cq 1), 115.07 (CH 6), 123.20 (CH 7), 126.10 (Cq 5a), 127.39 (CH 9), 127.45 (CH 8), 128.18 (CH Phenyl), 128.78 (CH Phenyl), 133.87 (Cq 3a), 134.70 (CH 2), 137.72 (Cq 9a), 146.85 (Cq 4), 156.56 (Cq Phenyl), 172.05 (C=O). MS (ESI +, QTof, m/z): 568.3 [M + H]⁺.

Tert-butyl 2-((1-bromoimidazo[1,2-a]quinoxalin-4-yl)amino)-3-phenylpropanoate (7g): A solution of **6g** (0.34 g, 0.9 mmol) and *N*-bromosuccinimide (0.18 g, 1.1 mmol) in CHCl₃ (50 mL) was heated under reflux for 2 h. The solvent was removed under reduced pressure. The crude mixture was dissolved in ethyl acetate (50 mL) and successively washed with saturated aqueous ammonium chloride, saturated aqueous sodium bicarbonate, distilled water and finally brine. The organic phase was dried on sodium sulfate, filtered and concentrated under reduced pressure. The compound was obtained as a beige oil (83% yield) and used without purification. $C_{23}H_{23}BrN_4O_2$. M_W : 467.36 g/mol. 1H -NMR δ (ppm, DMSO- d_6): 1.33 (s, 9H, 3 \times CH₃ OtBu), 3.18–3.22 (m, 1H, CH₂ β), 3.31–3.34 (m, 1H, CH₂ β), 4.79–4.81 (m, 1H, CH α), 7.21 (t, 1H, J = 8 Hz, CH Phenyl), 7.27–7.30 (m, 2H, 2 \times CH Phenyl), 7.32–7.34 (m, 2H, 2 \times CH Phenyl), 7.35–7.38 (m, 1H, CH 7), 7.46–7.49 (m, 1H, CH 8), 7.60 (dd, 1H, J = 4 Hz, J = 8 Hz, CH 9), 7.65 (d, 1H, J = 8 Hz, NH), 7.75 (s, 1H, CH 2), 8.97 (dd, 1H, J = 2 Hz, J = 8 Hz, CH 6). ^{13}C -NMR δ (ppm, DMSO- d_6): 28.04 (CH₃ tBu), 36.91 (CH₂ β), 56.01 (CH α), 81.06 (Cq tBu), 99.76 (Cq 1), 115.07 (CH 6), 123.33 (CH 7), 126.13 (Cq 5a), 126.96 (CH Phenyl), 127.45 (CH 9), 127.47 (CH 8), 128.68 (CH Phenyl), 129.77 (CH Phenyl), 133.80 (Cq Phenyl), 134.76 (CH 2), 137.45 (Cq 3a), 138.05 (Cq 9a), 146.66 (Cq 4), 171.45 (C=O). MS (ESI +, QTof, m/z): 467.1 [M + H]⁺.

Tert-butyl 2-((1-bromoimidazo[1,2-a]quinoxalin-4-yl)amino)-3-(4-(Tert-butoxy)phenyl)propanoate (7h): A solution of **6h** (0.34 g, 0.9 mmol) and *N*-bromosuccinimide (0.18 g, 1.1 mmol) in CHCl₃ (50 mL) was heated under reflux for 2 h. The solvent was removed under reduced pressure. The crude mixture was dissolved in ethyl acetate (50 mL) and successively washed with saturated aqueous ammonium chloride, saturated aqueous sodium bicarbonate, distilled water and finally brine. The organic phase was dried on sodium sulfate, filtered and concentrated under reduced pressure. The compound was obtained as a beige oil (91% yield) and used without purification. $C_{23}H_{23}BrN_4O_2$. M_W : 467.36 g/mol. 1H -NMR δ (ppm, DMSO- d_6): 1.22 (s, 9H, 3 \times CH₃ OtBu), 1.31 (s, 9H, 3 \times CH₃ OtBu), 3.11–3.16 (m, 1H, CH₂ β), 3.24–3.26 (m, 1H, CH₂ β), 4.76–4.81 (m, 1H, CH α), 6.85 (dd, 2H, J = 4 Hz, J = 8 Hz, CH Phenyl), 7.20 (dd, 2H, J = 4 Hz, J = 8 Hz, CH Phenyl), 7.34–7.38 (m, 1H, CH 7), 7.46–7.50 (m, 1H, CH 8), 7.59 (dd, 1H, J = 4 Hz, J = 8 Hz, CH 9), 7.65 (d, 1H, J = 8 Hz, NH), 7.75 (d, 1H, J = 4 Hz, CH 2), 8.98 (dd, 1H, J = 4 Hz, J = 8 Hz, CH 6). ^{13}C -NMR δ (ppm, DMSO- d_6): 28.04 (CH₃ tBu), 28.93 (CH₃ tBu), 36.61 (CH₂ β), 56.03 (CH α), 78.10 (Cq tBu), 81.01 (Cq tBu), 99.71 (Cq 1), 115.08 (CH 6), 123.32 (CH 7), 123.96 (2 \times CH Phenyl), 126.13 (Cq 5a), 127.42 (CH 9), 127.47 (CH 8), 130.33 (2 \times CH Phenyl), 132.54 (Cq 3a), 134.78 (CH 2), 137.43 (Cq 9a), 146.61 (Cq 4), 154.06 (2 \times Cq Phenyl), 171.53 (C=O). MS (ESI +, QTof, m/z): 467.1 [M + H]⁺.

Tert-butyl 5-((1-bromoimidazo[1,2-a]quinoxalin-4-yl)amino)-2-((Tert-butoxycarbonyl)amino)pentanoate (7i): A solution of **6i** (0.49 g, 1.1 mmol) and *N*-bromosuccinimide (0.23 g, 1.3 mmol) in CHCl₃ (50 mL) was heated under reflux for 2 h. The solvent was removed under reduced pressure. The crude mixture was dissolved in ethyl acetate (50 mL) and successively washed with saturated aqueous ammonium chloride, saturated aqueous sodium bicarbonate, distilled water and finally brine. The organic phase was dried on sodium sulfate, filtered and concentrated under reduced pressure. The compound was obtained as a beige oil (92% yield) and used without purification. $C_{24}H_{32}BrN_5O_4$. M_W : 534.45 g/mol. 1H -NMR δ (ppm, DMSO- d_6): 1.44 (s, 9H, CH-CO₂tBu), 1.46 (s, 9H, NH-CO₂tBu), 1.79–1.83 (m, 2H,

CH₂ β), 1.91–1.94 (m, 2H, CH₂ γ), 3.73–3.78 (m, 2H, CH₂ δ), 4.25–4.29 (m, 1H, CH α), 5.39 (d, 1H, *J* = 4 Hz, NH-CH α), 6.33 (d, 1H, *J* = 4 Hz, NH-CH₂ δ), 7.27–7.31 (m, 1H, CH 7), 7.41–7.45 (m, 1H, CH 8), 7.48 (s, 1H, CH 2), 7.81 (dd, 1H, *J* = 4 Hz, *J* = 8 Hz, CH 9), 8.98 (dd, 1H, *J* = 4 Hz, *J* = 8 Hz, CH 6). ¹³C-NMR δ (ppm, DMSO-*d*₆): 25.74 (CH₂ β), 28.07 (CH₃ tBu), 28.45 (CH₃ tBu), 30.17 (CH₂ γ), 40.42 (CH₂ δ), 54.00 (CH α), 79.75 (Cq tBu), 81.98 (Cq tBu), 99.05 (Cq 1), 115.02 (CH 6), 122.77 (CH 7), 124.54 (Cq 5a), 127.12 (CH 8), 127.98 (CH 9), 134.22 (CH 2), 135.98 (Cq 3a), 146.86 (Cq 4), 155.59 (Cq 9a), 171.92 (C=O). MS (ESI +, QTof, *m/z*): 534.1 [M + H]⁺.

3.1.4. Suzuki-Miyaura Cross-Coupling Reactions

Tert-butyl 2-((1-(3,4-dimethoxyphenyl)imidazo[1,2-*a*]quinoxalin-4-yl)amino)acetate (**8a**): To a mixture of **7a** (0.270 g, 0.71 mmol) in DME/H₂O (2/1, 15 mL) were added 3,4-dimethoxyphenylboronic acid (0.143 g, 0.79 mmol), tetrakis(triphenylphosphine) palladium (0.042 g, 0.036 mmol) and sodium carbonate (0.152 g, 1.43 mmol) in a microwave-adapted vial. The reaction was submitted to microwave irradiations during 20 min at 150 °C and then filtered on a Celite pad. The filtrate was concentrated under reduced pressure and successively washed with saturated aqueous ammonium chloride, saturated aqueous sodium bicarbonate, distilled water and finally brine. The organic phase was dried on sodium sulfate, filtered and concentrated under reduced pressure. The product was purified by flash chromatography eluted with cyclohexane/ethyl acetate 80/20 to 50/50. The compound is obtained as a white solid (19% yield). C₂₄H₂₆N₄O₄. MW: 434.49 g/mol. ¹H-NMR δ (ppm, DMSO-*d*₆): 1.44 (s, 9H, 3 × CH₃ OtBu), 3.74 (s, 3H, OCH₃ Phenyl), 3.87 (s, 3H, OCH₃ Phenyl), 4.14 (d, 2H, *J* = 8 Hz, CH₂ α), 7.01–7.05 (m, 1H, CH 7), 7.11 (d, 1H, *J* = 4 Hz, CH Phenyl), 7.14 (s, 1H, *J* = 4 Hz, CH Phenyl), 7.18 (d, 1H, *J* = 4 Hz, CH Phenyl), 7.31 (dd, 1H, *J* = 4 Hz, *J* = 8 Hz, CH 6), 7.33–7.35 (m, 1H, CH 8), 7.54 (s, 1H, CH 2), 7.56 (dd, 1H, *J* = 4 Hz, *J* = 8 Hz, CH 9), 7.96 (t, 1H, *J* = 8 Hz, NH). ¹³C-NMR δ (ppm, DMSO-*d*₆): 28.26 (CH₃ tBu), 43.33 (CH₂ α), 80.86 (Cq tBu), 112.31 (CH Phenyl), 114.25 (CH Phenyl), 115.93 (CH 6), 122.75 (CH 7), 123.30 (CH Phenyl), 126.03 (Cq 5a), 126.58 (CH 8), 127.20 (CH 9), 132.66 (CH 2), 133.141 (Cq 3a), 130.93 (Cq 1), 137.71 (Cq 9a), 149.27 (Cq Phenyl), 150.14 (Cq Phenyl), 147.74 (Cq 4), 169.85 (C=O). MS (ESI +, QTof, *m/z*): 435.1 [M + H]⁺.

Tert-butyl 2-((1-(3,4-dimethoxyphenyl)imidazo[1,2-*a*]quinoxalin-4-yl)amino)propanoate (**8b**): Following the same procedure used for the synthesis of **8a**, to a mixture of **7b** (0.440 g, 1.12 mmol) in DME/H₂O (2/1, 15 mL) were added 3,4-dimethoxyphenylboronic acid (0.225 g, 1.24 mmol), tetrakis(triphenylphosphine) palladium (0.065 g, 0.056 mmol) and sodium carbonate (0.237 g, 2.24 mmol) in a microwave-adapted vial. The product was purified by flash chromatography eluted with cyclohexane/ethyl acetate 80/20 to 50/50. The compound is obtained as a white solid (42% yield). C₂₅H₂₈N₄O₄. MW: 448.51 g/mol. ¹H-NMR δ (ppm, DMSO-*d*₆): 1.32 (s, 9H, 3 × CH₃ OtBu), 1.42 (d, 3H, *J* = 8 Hz, CH₃ β), 3.64 (s, 3H, OCH₃ Phenyl), 3.76 (s, 3H, OCH₃ Phenyl), 4.48–4.52 (m, 1H, CH α), 6.90–6.95 (m, 1H, CH 7), 7.01 (d, 1H, *J* = 4 Hz, CH Phenyl), 7.03 (s, 1H, CH Phenyl), 7.08 (d, 1H, *J* = 4 Hz, CH Phenyl), 7.20 (dd, 1H, *J* = 4 Hz, *J* = 8 Hz, CH 6), 7.22–7.25 (m, 1H, CH 8), 7.42 (s, 1H, CH 2), 7.46 (dd, 1H, *J* = 4 Hz, *J* = 8 Hz, CH 9), 7.82 (d, 1H, *J* = 4 Hz, NH). ¹³C-NMR δ (ppm, DMSO-*d*₆): 17.59 (CH₃ β), 28.25 (CH₃ tBu), 50.30 (CH α), 80.72 (Cq tBu), 112.40 (CH Phenyl), 114.33 (CH Phenyl), 116.00 (CH 6), 122.77 (CH 7), 122.90 (Cq 1), 123.37 (CH Phenyl), 126.10 (CH 8), 126.65 (Cq 5a), 127.28 (CH 9), 131.05 (Cq 3a), 132.63 (CH 2), 137.68 (Cq 9a), 147.33 (Cq 4), 149.36 (Cq Phenyl), 150.22 (Cq Phenyl), 172.96 (C=O). MS (ESI +, QTof, *m/z*): 449.2 [M + H]⁺. HRMS calculated for C₂₅H₂₉N₄O₄ 449.2189, found 449.2186.

Tert-butyl 2-((1-(3,4-dimethoxyphenyl)imidazo[1,2-*a*]quinoxalin-4-yl)amino)-3-methylbutanoate (**8c**): Following the same procedure used for the synthesis of **8a**, to a mixture of **7c** (0.370 g, 0.88 mmol) in DME/H₂O (2/1, 15 mL) were added 3,4-dimethoxyphenylboronic acid (0.176 g, 0.97 mmol), tetrakis(triphenylphosphine) palladium (0.051 g, 0.044 mmol) and sodium carbonate (0.186 g, 1.76 mmol) in a microwave-adapted vial. The product was purified by flash chromatography eluted with cyclohexane/ethyl acetate 80/20 to 50/50. The compound is obtained as a white solid (69%

yield). $C_{27}H_{32}N_4O_4$. MW: 476.57 g/mol. 1H -NMR δ (ppm, DMSO- d_6): 0.95 (d, 3H, $J = 8$ Hz, $CH_3 \gamma$), 0.98 (d, 3H, $J = 8$ Hz, $CH_3 \gamma'$), 1.34 (s, 9H, $3 \times CH_3$ OtBu), 2.20–2.28 (m, 1H, CH β), 3.63 (s, 3H, OCH₃ Phenyl), 3.77 (s, 3H, OCH₃ Phenyl), 4.44 (t, 1H, $J = 16$ Hz, CH α), 6.92–6.97 (m, 1H, CH 7), 7.00 (s, 1H, CH Phenyl), 7.02 (d, 1H, $J = 4$ Hz, NH), 7.06 (d, 1H, $J = 4$ Hz, CH Phenyl), 7.08 (d, 1H, $J = 4$ Hz, CH Phenyl), 7.22 (dd, 1H, $J = 4$ Hz, $J = 8$ Hz, CH 6), 7.23–7.26 (m, 1H, CH 8), 7.42 (s, 1H, CH 2), 7.49 (dd, 1H, $J = 4$ Hz, $J = 8$ Hz, CH 9). ^{13}C -NMR δ (ppm, DMSO- d_6): 19.43 ($CH_3 \gamma'$), 19.56 ($CH_3 \gamma$), 28.28 (CH_3 tBu), 30.57 (CH β), 56.15 (OCH₃ Phenyl), 56.24 (OCH₃ Phenyl), 59.73 (CH α), 81.31 (Cq tBu), 112.41 (CH Phenyl), 114.35 (CH Phenyl), 116.02 (CH 6), 122.67 (Cq 1), 123.14 (CH 7), 123.39 (CH Phenyl), 126.19 (Cq 5a), 126.71 (CH 8), 127.39 (CH 9), 131.25 (Cq Phenyl), 132.68 (CH 2), 133.00 (Cq 3a), 137.55 (Cq 9a), 147.56 (Cq 4), 149.36 (Cq Phenyl), 150.26 (Cq Phenyl), 171.70 (C=O). MS (ESI +, QTof, m/z): 477.1 [M + H]⁺. HRMS calculated for $C_{27}H_{33}N_4O_4$ 477.2502, found 477.2505.

Tert-butyl 2-((1-(3,4-dimethoxyphenyl)imidazo[1,2-a]quinoxalin-4-yl)amino)-4-methyl-pentanoate: (**8d**): Following the same procedure used for the synthesis of **8a**, to a mixture of **7d** (0.360 g, 0.83 mmol) in DME/H₂O (2/1, 15 mL) were added 3,4-dimethoxyphenylboronic acid (0.166 g, 0.91 mmol), tetrakis(triphenylphosphine) palladium (0.048 g, 0.041 mmol) and sodium carbonate (0.176 g, 1.66 mmol) in a microwave-adapted vial. The product was purified by flash chromatography eluted with cyclohexane/ethyl acetate 80/20 to 50/50. The compound is obtained as a white solid (61% yield). $C_{28}H_{34}N_4O_4$. MW: 490.59 g/mol. 1H -NMR δ (ppm, DMSO- d_6): 0.83 (d, 3H, $J = 8$ Hz, $CH_3 \delta$), 0.86 (d, 3H, $J = 8$ Hz, $CH_3 \delta'$), 1.31 (s, 9H, $3 \times CH_3$ OtBu), 1.55–1.58 (m, 1H, CH₂ β), 1.67–1.70 (m, 1H, CH γ), 1.84–1.88 (m, 1H, CH₂ β), 3.63 (s, 3H, OCH₃ Phenyl), 3.76 (s, 3H, OCH₃ Phenyl), 4.55 (t, 1H, $J = 4$ Hz, CH α), 6.90–6.94 (m, 1H, CH 7), 7.01 (d, 1H, $J = 4$ Hz, CH Phenyl), 7.05 (s, 1H, CH Phenyl), 7.08 (d, 1H, $J = 4$ Hz, CH Phenyl), 7.20 (dd, 1H, $J = 4$ Hz, $J = 8$ Hz, CH 6), 7.22–7.24 (m, 1H, CH 8), 7.41 (s, 1H, CH 2), 7.45 (dd, 1H, $J = 4$ Hz, $J = 8$ Hz, CH 9), 7.50 (d, 1H, $J = 4$ Hz, NH). ^{13}C -NMR δ (ppm, DMSO- d_6): 22.14 ($CH_3 \delta$), 23.41 ($CH_3 \delta'$), 25.25 (CH γ), 28.25 (CH_3 tBu), 40.29 (CH₂ β), 52.96 (CH α), 56.14 (OCH₃ Phenyl), 56.23 (OCH₃ Phenyl), 80.79 (Cq tBu), 112.40 (CH Phenyl), 114.34 (CH Phenyl), 115.99 (CH 6), 122.78 (Cq 1), 122.88 (CH 7), 123.36 (CH Phenyl), 126.11 (Cq 5a), 126.69 (CH 8), 127.29 (CH 9), 131.09 (Cq 3a), 132.61 (CH 2), 137.70 (Cq 9a), 147.66 (Cq 4), 149.36 (Cq Phenyl), 150.23 (Cq Phenyl), 172.86 (C=O). MS (ESI +, QTof, m/z): 491.0 [M + H]⁺. HRMS calculated for $C_{28}H_{35}N_4O_4$ 491.2658, found 491.2654.

Tert-butyl 6-((Tert-butoxycarbonyl)amino)-2-((1-(3,4-dimethoxyphenyl)imidazo[1,2-a]quinoxalin-4-yl)amino)hexanoate (**8e**): Following the same procedure used for the synthesis of **8a**, to a mixture of **7e** (1.090 g, 1.99 mmol) in DME/H₂O (2/1, 15 mL) were added 3,4-dimethoxyphenylboronic acid (0.397 g, 2.18 mmol), tetrakis(triphenylphosphine) palladium (0.114 g, 0.099 mmol) and sodium carbonate (0.421 g, 3.97 mmol) in a microwave-adapted vial. The product was purified by flash chromatography eluted with cyclohexane/ethyl acetate 80/20 to 50/50. The compound is obtained as a white solid (7% yield). $C_{33}H_{43}N_5O_6$. MW: 605.72 g/mol. 1H -NMR δ (ppm, DMSO- d_6): 1.36 (s, 9H, $3 \times CH_3$ OtBu), 1.41–1.46 (m, 13H, CH₂ γ , $3 \times CH_3$ OtBu, CH₂ δ), 1.88–1.91 (m, 2H, CH₂ β), 2.93–2.95 (m, 2H, CH₂ ϵ), 3.73 (s, 3H, OCH₃ Phenyl), 3.87 (s, 3H, OCH₃ Phenyl), 4.54–4.58 (m, 1H, CH α), 6.80 (t, 1H, $J = 4$ Hz, NH-CH₂ ϵ), 7.01–7.05 (m, 1H, CH 7), 7.11 (d, 1H, $J = 4$ Hz, CH Phenyl), 7.15 (s, 1H, CH Phenyl), 7.18 (d, 1H, $J = 4$ Hz, CH Phenyl), 7.31 (dd, 1H, $J = 4$ Hz, $J = 8$ Hz, CH 6), 7.31–7.35 (m, 1H, CH 8), 7.52 (s, 1H, CH 2), 7.55 (dd, 1H, $J = 4$ Hz, $J = 8$ Hz, CH 9), 7.59 (d, 1H, $J = 4$ Hz, NH-CH α). ^{13}C -NMR δ (ppm, DMSO- d_6): 23.49 (CH₂ γ), 28.18 (CH_3 tBu), 28.72 (CH_3 tBu), 29.64 (CH₂ δ), 30.94 (CH₂ β), 40.40 (CH₂ ϵ), 54.56 (CH α), 56.05 (OCH₃ Phenyl), 56.14 (OCH₃ Phenyl), 77.78 (Cq tBu), 80.80 (Cq tBu), 112.30 (CH Phenyl), 114.22 (CH Phenyl), 115.91 (CH 6), 122.67 (CH 7), 123.28 (CH Phenyl), 126.03 (Cq 5a), 126.56 (CH 8), 127.23 (CH 9), 131.01 (Cq 1), 132.53 (CH 2), 132.98 (Cq 3a), 137.61 (Cq 9a), 147.51 (Cq 4), 149.27 (Cq Phenyl), 150.14 (Cq Phenyl), 156.04 (Cq Phenyl), 172.41 (C=O). MS (ESI +, QTof, m/z): 606.2 [M + H]⁺. HRMS calculated for $C_{33}H_{44}N_5O_6$ 606.3292, found 606.3291.

Tert-butyl 5-(((benzyloxy)carbonyl)amino)-2-((1-(3,4-dimethoxyphenyl)imidazo[1,2-a]quinoxalin-4-yl)amino)pentanoate (**8f**): Following the same procedure used for the synthesis of **8a**, to a mixture of **7f** (0.470 g, 0.89 mmol) in DME/H₂O (2/1, 15 mL) were added 3,4-dimethoxyphenylboronic acid (0.165 g,

0.91 mmol), tetrakis(triphenylphosphine) palladium (0.048 g, 0.041 mmol) and sodium carbonate (0.175 g, 1.65 mmol) in a microwave-adapted vial. The product was purified by flash chromatography eluted with cyclohexane/ethyl acetate 80/20 to 50/50. The compound is obtained as a white solid (42% yield). $C_{35}H_{39}N_5O_6$. MW: 625.71 g/mol. 1H -NMR δ (ppm, DMSO- d_6): 1H -NMR δ (ppm, 400 MHz, DMSO- d_6): 1.52 (s, 9H, 3 \times CH₃ OtBu), 1.77–1.81 (m, 2H, CH₂ γ), 1.99–2.03 (m, 1H, CH₂ δ), 2.10–2.13 (m, 1H, CH₂ δ), 3.34–3.39 (m, 2H, CH₂ β), 3.88 (s, 3H, OCH₃ Phenyl), 4.02 (s, 3H, OCH₃ Phenyl), 5.12 (s, 2H, CH₂-Phenyl), 5.37–5.39 (m, 1H, CH α), 6.99 (d, 2H, J = 4 Hz, CH Phenyl), 7.03 (s, 1H, CH Phenyl), 7.10–7.12 (m, 1H, CH 7), 7.28 (dd, 1H, J = 4 Hz, J = 8 Hz, CH 6), 7.32–7.35 (m, 7H, CH 8, CH₂, CH Phenyl), 7.36 (dd, 1H, J = 4 Hz, J = 8 Hz, CH 9), 7.47 (d, 1H, J = 4 Hz, NH-CH₂ δ), 7.76 (dd, 1H, J = 4 Hz, J = 8 Hz, NH-CH α). ^{13}C -NMR δ (ppm, DMSO- d_6): 25.62 (CH₂ γ), 28.09 (CH₃ tBu), 30.04 (CH₂ β), 40.61 (CH₂ δ), 54.42 (CH α), 66.58 (CH₂-Phenyl), 82.42 (Cq tBu), 111.30 (CH Phenyl), 113.24 (CH Phenyl), 114.69 (Cq 1), 115.99 (CH 6), 123.16 (CH 7), 126.40 (Cq 5a), 126.82 (CH 9), 126.87 (CH 8), 128.01 (CH Phenyl), 128.08 (CH Phenyl), 129.49 (CH Phenyl), 131.85 (CH 2), 132.87 (Cq 3a), 136.68 (Cq 9a), 149.16 (Cq 4), 150.12 (Cq Phenyl), 152.37 (Cq Phenyl), 156.51 (Cq Phenyl), 171.59 (C=O). MS (ESI +, QTof, m/z): 626.0 [M + H]⁺. HRMS calculated for $C_{35}H_{40}N_5O_6$ 626.2979, found 626.2982.

Tert-butyl 2-((Tert-butoxycarbonyl)amino)-5-((1-(3,4-dimethoxyphenyl)imidazo[1,2-a]quinoxalin-4-yl)amino)pentanoate (8i): Following the same procedure used for the synthesis of **8a**, to a mixture of **7i** (0.515 g, 0.96 mmol) in DME/H₂O (2/1, 15 mL) were added 3,4-dimethoxyphenylboronic acid (0.193 g, 1.06 mmol), tetrakis(triphenylphosphine) palladium (0.056 g, 0.048 mmol) and sodium carbonate (0.204 g, 1.93 mmol) in a microwave-adapted vial. The product was purified by flash chromatography eluted with cyclohexane/ethyl acetate 80/20 to 50/50. The compound is obtained as a white solid (45% yield). $C_{32}H_{41}N_5O_6$. MW: 591.70 g/mol. 1H -NMR δ (ppm, DMSO- d_6): 1.34 (s, 9H, CH-CO₂tBu), 1.39 (s, 9H, NH-CO₂tBu), 1.73–1.74 (m, 2H, CH₂ β), 1.77–1.78 (m, 2H, CH₂ γ), 3.56–3.59 (m, 2H, CH₂ δ), 3.74 (s, 3H, OCH₃ Phenyl), 3.87 (s, 3H, OCH₃ Phenyl), 3.89–3.92 (m, 1H, CH α), 6.95–7.00 (m, 1H, CH 7), 7.09 (dd, 1H, J = 4 Hz, J = 8 Hz, CH Phenyl), 7.14 (s, 1H, CH Phenyl), 7.15 (dd, 1H, J = 4 Hz, J = 8 Hz, CH Phenyl), 7.19 (d, 1H, J = 4 Hz, NH-CH α), 7.28 (dd, 1H, J = 4 Hz, J = 8 Hz, CH 6), 7.30–7.32 (m, 1H, CH 8), 7.47 (s, 1H, CH 2), 7.58 (dd, 1H, J = 4 Hz, J = 8 Hz, CH 9), 7.72 (t, 1H, J = 4 Hz, NH-CH₂ δ). ^{13}C -NMR δ (ppm, DMSO- d_6): 25.97 (CH₂ β), 28.06 (CH₃ tBu), 28.25 (CH₃ tBu), 28.67 (CH₂ γ), 39.79 (CH₂ δ), 54.77 (CH α), 56.05 (OCH₃ Phenyl), 56.15 (OCH₃ Phenyl), 78.46 (Cq tBu), 80.54 (Cq tBu), 112.32 (CH Phenyl), 114.22 (CH Phenyl), 115.83 (CH 6), 122.12 (CH 7), 122.82 (CH Phenyl), 123.26 (Cq 1), 125.75 (Cq 5a), 126.41 (CH 8), 127.07 (CH 9), 132.32 (CH 2), 138.24 (Cq 3a), 148.04 (Cq 4), 149.26 (Cq Phenyl), 150.10 (Cq Phenyl), 156.01 (Cq 9a), 172.36 (C=O). MS (ESI +, QTof, m/z): 592.1 [M + H]⁺. HRMS calculated for $C_{32}H_{42}N_5O_6$ 592.3135, found 592.3137.

Tert-butyl 2-((1-(3,4-dihydroxyphenyl)imidazo[1,2-a]quinoxalin-4-yl)amino)acetate (9a): To a mixture of **7a** (0.320 g, 0.85 mmol) in DME/H₂O (2/1, 15 mL) were added compound **12** (0.392 g, 2.54 mmol), tetrakis(triphenylphosphine) palladium (0.049 g, 0.040 mmol) and sodium carbonate (0.179 g, 1.70 mmol) in a microwave-adapted vial. The reaction was submitted to microwave irradiations during 20 min at 150 °C and then filtered on a Celite pad. The filtrate was concentrated under reduced pressure and successively washed with saturated aqueous ammonium chloride, saturated aqueous sodium bicarbonate, distilled water and finally brine. The organic phase was dried on sodium sulfate, filtered and concentrated under reduced pressure. The product was purified by flash chromatography eluted with cyclohexane/ethyl acetate 80/20 to 50/50. The compound is obtained as a white solid (16% yield). $C_{22}H_{22}N_4O_4$. MW: 406.43 g/mol. 1H -NMR δ (ppm, DMSO- d_6): 1H -NMR δ (ppm, DMSO- d_6): 1.42 (s, 9H, 3 \times CH₃ OtBu), 4.15 (d, 2H, J = 8 Hz, CH₂ α), 6.82 (dd, 1H, J = 4 Hz, J = 8 Hz, CH Phenyl), 6.89 (dd, 1H, J = 4 Hz, J = 8 Hz, CH Phenyl), 6.93 (s, 1H, CH Phenyl), 7.02–7.06 (m, 1H, CH 7), 7.33 (dd, 1H, J = 4 Hz, J = 8 Hz, CH 6), 7.35–7.38 (m, 1H, CH 8), 7.46 (s, 1H, CH 2), 7.54 (dd, 1H, J = 4 Hz, J = 8 Hz, CH 9), 7.96–8.00 (m, 1H, NH), 9.32 (s, 1H, C-OH Phenyl), 9.41 (s, 1H, C-OH Phenyl). ^{13}C -NMR δ (ppm, DMSO- d_6): 28.23 (CH₃ tBu), 43.30 (CH₂ α), 80.85 (Cq tBu), 115.37 (Cq 1), 115.92 (CH 6), 116.48 (CH 7), 117.89 (CH Phenyl), 121.13 (CH Phenyl), 122.06 (CH 8), 122.81 (CH Phenyl), 125.98 (Cq 5a), 126.54

(CH 9), 127.77 (Cq Phenyl), 131.43 (Cq 3a), 132.36 (CH 2), 132.89 (Cq 9a), 146.04 (Cq Phenyl), 147.13 (Cq Phenyl), 147.65 (Cq 4), 169.76 (C=O). MS (ESI +, QToF, m/z): 407.2 [M + H]⁺. HRMS calculated for C₂₂H₂₃N₄O₄ 407.1706, found 407.1710.

Tert-butyl 2-((1-(3,4-dihydroxyphenyl)imidazo[1,2-a]quinoxalin-4-yl)amino)propanoate (9b): Following the same procedure used for the synthesis of **9a** (see 4.1.4.8.), to a mixture of **7b** (0.290 g, 0.74 mmol) in DME/H₂O (2/1, 15 mL) were added compound **12** (0.342 g, 2.22 mmol), tetrakis-(triphenylphosphine) palladium (0.043 g, 0.037 mmol) and sodium carbonate (0.157 g, 1.48 mmol) in a microwave-adapted vial. The product was purified by flash chromatography eluted with cyclohexane/ethyl acetate 80/20 to 50/50. The compound is obtained as a white solid (6% yield). C₂₃H₂₄N₄O₄. MW: 420.46 g/mol. ¹H-NMR δ (ppm, DMSO-*d*₆): 1.42 (s, 9H, 3 × CH₃ OtBu), 1.51 (d, 3H, *J* = 8 Hz, CH₃ β), 4.59–4.63 (m, 1H, CH α), 6.81 (d, 1H, *J* = 4 Hz, CH Phenyl), 6.90 (d, 1H, *J* = 4 Hz, CH Phenyl), 6.93 (s, 1H, CH Phenyl), 7.01–7.05 (m, 1H, CH 7), 7.30 (dd, 1H, *J* = 4 Hz, *J* = 8 Hz, CH 6), 7.33–7.37 (m, 1H, CH 8), 7.45 (s, 1H, CH 2), 7.53 (dd, 1H, *J* = 4 Hz, *J* = 8 Hz, CH 9), 7.66 (d, 1H, *J* = 4 Hz, NH), 9.36 (s, 2H, C-OH Phenyl). ¹³C-NMR δ (ppm, DMSO-*d*₆): 17.57 (CH₃ β), 28.16 (CH₃ tBu), 50.17 (CH α), 80.66 (Cq tBu), 115.87 (CH 8), 116.47 (CH Phenyl), 117.88 (CH Phenyl), 121.16 (Cq 1), 122.05 (CH Phenyl), 122.78 (CH 7), 126.02 (Cq 5a), 127.16 (CH 9), 131.35 (Cq 3a), 132.19 (CH 2), 132.80 (Cq 9a), 137.57 (Cq 4), 146.03 (Cq Phenyl), 147.10 (Cq Phenyl), 147.23 (Cq Phenyl), 172.87 (C=O). MS (ESI +, QToF, m/z): 421.2 [M + H]⁺. HRMS calculated for C₂₃H₂₅N₄O₄ 421.1876, found 421.1875.

Tert-butyl 2-((1-(3,4-dihydroxyphenyl)imidazo[1,2-a]quinoxalin-4-yl)amino)-3-methyl-butanoate (9c): Following the same procedure used for the synthesis of **9a** (see 4.1.4.8.), to a mixture of **7c** (0.380 g, 0.91 mmol) in DME/H₂O (2/1, 15 mL) were added compound **12** (0.340 g, 2.72 mmol), tetrakis-(triphenylphosphine) palladium (0.052 g, 0.045 mmol) and sodium carbonate (0.192 g, 1.81 mmol) in a microwave-adapted vial. The product was purified by flash chromatography eluted with cyclohexane/ethyl acetate 80/20 to 50/50. The compound is obtained as a white solid (32% yield). C₂₅H₂₈N₄O₄. MW: 448.51 g/mol. ¹H-NMR δ (ppm, DMSO-*d*₆): 1.03 (d, 3H, *J* = 8 Hz, CH₃ γ), 1.06 (d, 3H, *J* = 8 Hz, CH₃ γ'), 1.44 (s, 9H, 3 × CH₃ OtBu), 2.31–2.35 (m, 1H, CH β), 4.53 (t, 1H, *J* = 8 Hz, CH α), 6.81 (dd, 1H, *J* = 4 Hz, *J* = 8 Hz, CH Phenyl), 6.90 (d, 1H, *J* = 4 Hz, *J* = 8 Hz, CH Phenyl), 6.93 (d, 1H, *J* = 4 Hz, *J* = 8 Hz, CH Phenyl), 7.03–7.05 (m, 1H, CH 7), 7.07 (d, 1H, *J* = 4 Hz, NH), 7.34–7.35 (m, 1H, CH 8), 7.37 (dd, 1H, *J* = 4 Hz, *J* = 8 Hz, CH 6), 7.46 (s, 1H, CH 2), 7.56 (dd, 1H, *J* = 4 Hz, *J* = 8 Hz, CH 9), 9.32 (s, 1H, C-OH Phenyl), 9.41 (s, 1H, C-OH Phenyl). ¹³C-NMR δ (ppm, DMSO-*d*₆): 19.30 (CH₃ γ'), 19.47 (CH₃ γ), 28.19 (CH₃ tBu), 30.54 (CH β), 59.60 (CH α), 81.25 (Cq tBu), 115.90 (CH 6), 116.47 (CH Phenyl), 117.89 (CH Phenyl), 121.05 (Cq 1), 122.07 (CH Phenyl), 123.07 (CH 7), 126.11 (Cq 5a), 126.56 (CH 8), 127.28 (CH 9), 131.55 (Cq Phenyl), 132.24 (CH 2), 132.72 (Cq 3a), 137.43 (Cq 9a), 146.03 (Cq 4), 147.14 (Cq Phenyl), 147.47 (Cq Phenyl), 171.62 (C=O). MS (ESI +, QToF, m/z): 449.3 [M + H]⁺. HRMS calculated for C₂₅H₂₉N₄O₄ 449.2189, found 449.2188.

Tert-butyl 2-((1-(3,4-dihydroxyphenyl)imidazo[1,2-a]quinoxalin-4-yl)amino)-4-methyl-pentanoate (9d): Following the same procedure used for the synthesis of **9a** (see 4.1.4.8.), to a mixture of **7d** (0.460 g, 1.06 mmol) in DME/H₂O (2/1, 15 mL) were added compound **12** (0.400 g, 2.6 mmol), tetrakis-(triphenylphosphine) palladium (0.062 g, 0.053 mmol) and sodium carbonate (0.224 g, 2.11 mmol) in a microwave-adapted vial. The product was purified by flash chromatography eluted with cyclohexane/ethyl acetate 80/20 to 50/50. The compound is obtained as a white solid (16% yield). C₂₆H₃₀N₄O₄. MW: 462.54 g/mol. ¹H-NMR δ (ppm, DMSO-*d*₆): 0.93 (d, 3H, *J* = 8 Hz, CH₃ δ), 0.97 (d, 3H, *J* = 8 Hz, CH₃ δ'), 1.42 (s, 9H, 3 × CH₃ OtBu), 1.56–1.60 (m, 1H, CH₂ β), 1.79–1.83 (m, 1H, CH γ), 1.91–1.95 (m, 1H, CH₂ β), 4.65 (t, 1H, *J* = 4 Hz, CH α), 6.81 (d, 1H, *J* = 4 Hz, CH Phenyl), 6.86 (s, 1H, CH Phenyl), 6.90 (d, 1H, *J* = 4 Hz, CH Phenyl), 7.01–7.05 (m, 1H, CH 7), 7.28–7.32 (m, 1H, CH 8), 7.34 (dd, 1H, *J* = 4 Hz, *J* = 8 Hz, CH 6), 7.46 (s, 1H, CH 2), 7.55 (dd, 1H, *J* = 4 Hz, *J* = 8 Hz, CH 9), 7.59 (d, 1H, *J* = 4 Hz, NH), 9.38 (s, 2H, C-OH Phenyl). ¹³C-NMR δ (ppm, DMSO-*d*₆): 22.09 (CH₃ δ), 23.32 (CH₃ δ'), 25.17 (CH γ), 28.18 (CH₃ tBu), 39.60 (CH₂ β), 52.88 (CH α), 80.76 (Cq tBu), 115.87 (CH 6), 116.48 (CH Phenyl), 117.90 (CH Phenyl), 121.15 (Cq 1), 122.18 (CH Phenyl), 122.79 (CH 7), 126.11 (Cq 5a),

125.80 (CH 8), 126.04 (CH 9), 131.42 (Cq 3a), 132.18 (CH 2), 137.58 (Cq 9a), 146.06 (Cq 4), 147.14 (Cq Phenyl), 147.57 (Cq Phenyl), 172.77 (C=O). MS (ESI +, QToF, m/z): 463.2 [M + H]⁺. HRMS calculated for C₂₆H₃₁N₄O₄ 463.2345, found 463.2343.

Tert-butyl 6-((Tert-butoxycarbonyl)amino)-2-((1-(3,4-dihydroxyphenyl)imidazo[1,2-a]quinoxalin-4-yl)amino)hexanoate (9e): Following the same procedure used for the synthesis of **9a** (see 4.1.4.8.), to a mixture of **7e** (0.242 g, 0.44 mmol) in DME/H₂O (2/1, 15 mL) were added compound **12** (0.170 g, 1.10 mmol), tetrakis- (triphenylphosphine) palladium (0.025 g, 0.022 mmol) and sodium carbonate (0.093 g, 0.88 mmol) in a microwave-adapted vial. The product was purified by flash chromatography eluted with cyclohexane/ethyl acetate 80/20 to 50/50. The compound is obtained as a white solid (40% yield). C₃₁H₃₉N₅O₆. MW: 577.67 g/mol. ¹H-NMR δ (ppm, DMSO-*d*₆): 1.35 (s, 9H, 3 × CH₃ OtBu), 1.40–1.42 (m, 2H, CH₂ γ), 1.43 (s, 9H, 3 × CH₃ OtBu), 1.45–1.47 (m, 2H, CH₂ δ), 1.88–2.00 (m, 2H, CH₂ β), 2.92–2.94 (m, 2H, CH₂ ε), 4.55–4.56 (m, 1H, CH α), 6.79 (t, 1H, *J* = 4 Hz, NH-CH₂ ε), 6.83 (d, 1H, *J* = 4 Hz, CH Phenyl), 6.89 (s, 1H, CH Phenyl), 6.93 (d, 1H, *J* = 4 Hz, CH Phenyl), 7.02–7.05 (m, 1H, CH 7), 7.31–7.33 (m, 1H, CH 8), 7.36 (dd, 1H, *J* = 4 Hz, *J* = 8 Hz, CH 6), 7.45 (s, 1H, CH 2), 7.54 (dd, 1H, *J* = 4 Hz, *J* = 8 Hz, CH 9), 7.57 (d, 1H, *J* = 4 Hz, NH-CH α), 9.33 (s, 1H, C-OH Phenyl), 9.41 (s, 1H, C-OH Phenyl). ¹³C-NMR δ (ppm, DMSO-*d*₆): 22.40 (CH₂ γ), 27.11 (CH₃ tBu), 27.65 (CH₃ tBu), 28.56 (CH₂ δ), 29.91 (CH₂ β), 39.25 (CH₂ ε), 53.44 (CH α), 76.70 (Cq tBu), 79.75 (Cq tBu), 114.79 (CH 6), 115.40 (CH Phenyl), 116.80 (CH Phenyl), 120.07 (CH Phenyl), 121.73 (CH 7), 124.97 (Cq 5a), 125.42 (CH 8), 126.12 (CH 9), 130.32 (Cq 1), 131.09 (CH 2), 131.70 (Cq 3a), 136.49 (Cq 9a), 144.96 (Cq 4), 146.04 (Cq Phenyl), 146.43 (Cq Phenyl), 154.96 (Cq Phenyl), 172.41 (C=O). MS (ESI +, QToF, m/z): 578.3 [M + H]⁺. HRMS calculated for C₃₁H₄₀N₅O₆ 578.2979, found 578.2980.

Tert-butyl 5-((benzyloxy)carbonyl)amino)-2-((1-(3,4-dihydroxyphenyl)imidazo[1,2-a]quinoxalin-4-yl)amino)pentanoate (9f): Following the same procedure used for the synthesis of **9a** (see 4.1.4.8.), to a mixture of **7f** (0.260 g, 0.46 mmol) in DME/H₂O (2/1, 15 mL) were added compound **12** (0.211 g, 1.37 mmol), tetrakis- (triphenylphosphine) palladium (0.026 g, 0.023 mmol) and sodium carbonate (0.097 g, 0.91 mmol) in a microwave-adapted vial. The product was purified by flash chromatography eluted with cyclohexane/ethyl acetate 80/20 to 50/50. The compound is obtained as a white solid (26% yield). C₃₃H₃₅N₅O₆. MW: 597.66 g/mol. ¹H-NMR δ (ppm, DMSO-*d*₆): 1.40 (s, 9H, 3 × CH₃ OtBu), 1.58–1.60 (m, 2H, CH₂ γ), 1.91–1.95 (m, 2H, CH₂ β), 3.05–3.08 (m, 2H, CH₂ δ), 4.55–4.59 (m, 1H, CH α), 5.01 (s, 2H, CH₂-Phenyl), 6.81 (d, 1H, *J* = 4 Hz, CH Phenyl), 6.89 (s, 1H, CH Phenyl), 6.93 (d, 1H, *J* = 4 Hz, CH Phenyl), 7.01–7.06 (m, 1H, CH 7), 7.27 (d, 1H, *J* = 4 Hz, NH-CH₂ δ), 7.31–7.34 (m, 5H, CH Phenyl), 7.37 (dd, 1H, *J* = 4 Hz, *J* = 8 Hz, CH 6), 7.45 (s, 1H, CH 2), 7.54 (d, 1H, *J* = 4 Hz, NH-CH α), 7.56–7.60 (m, 1H, CH 8), 7.63 (dd, 1H, *J* = 4 Hz, *J* = 8 Hz, CH 9). ¹³C-NMR δ (ppm, DMSO-*d*₆): 26.54 (CH₂ γ), 28.09 (CH₂ β), 28.17 (CH₃ tBu), 40.45 (CH₂ δ), 54.34 (CH α), 65.60 (CH₂-Phenyl), 80.92 (Cq tBu), 115.88 (CH 6), 116.48 (CH Phenyl), 117.90 (CH Phenyl), 121.16 (Cq 1), 122.84 (CH 7), 126.06 (Cq 5a), 126.50 (CH 9), 127.20 (CH 8), 128.18 (CH Phenyl), 128.79 (CH Phenyl), 129.16 (CH Phenyl), 131.90 (CH 2), 132.79 (Cq 3a), 137.55 (Cq 9a), 146.04 (Cq 4), 147.12 (Cq Phenyl), 147.47 (Cq Phenyl), 156.59 (Cq Phenyl), 172.23 (C=O). MS (ESI +, QToF, m/z): 598.3 [M + H]⁺. HRMS calculated for C₃₃H₃₆N₅O₆ 598.2666, found 598.2670.

Tert-butyl 2-((1-(3,4-dihydroxyphenyl)imidazo[1,2-a]quinoxalin-4-yl)amino)-3-phenyl-propanoate (9g): Following the same procedure used for the synthesis of **9a** (see 4.1.4.8.), to a mixture of **7g** (0.360 g, 0.77 mmol) in DME/H₂O (2/1, 15 mL) were added compound **12** (0.356 g, 2.31 mmol), tetrakis- (triphenylphosphine) palladium (0.044 g, 0.038 mmol) and sodium carbonate (0.163 g, 1.54 mmol) in a microwave-adapted vial. The product was purified by flash chromatography eluted with cyclohexane/ethyl acetate 80/20 to 50/50. The compound is obtained as a white solid (16% yield). C₂₉H₂₈N₄O₄. MW: 496.56 g/mol. ¹H-NMR δ (ppm, DMSO-*d*₆): 1.36 (s, 9H, 3 × CH₃ OtBu), 3.23–3.27 (m, 1H, CH₂ β), 3.33–3.38 (m, 1H, CH₂ β), 4.91–4.93 (m, 1H, CH α), 6.81 (dd, 1H, *J* = 4 Hz, *J* = 8 Hz, CH Phenyl), 6.89 (d, 1H, *J* = 4 Hz, CH Phenyl), 6.92 (d, 1H, *J* = 8 Hz, CH Phenyl), 7.08 (t, 1H, *J* = 8 Hz, CH Phenyl), 7.20 (t, 1H, *J* = 8 Hz, CH Phenyl), 7.29 (t, 2H, *J* = 8 Hz, CH Phenyl), 7.34 (d, 2H, *J* = 8 Hz, CH 6,

CH Phenyl), 7.34–7.37 (m, 1H, CH 7), 7.38–7.40 (m, 1H, CH 8), 7.52 (s, 1H, CH 2), 7.60 (d, 1H, $J = 8$ Hz, CH 9), 7.92–7.93 (m, 1H, NH), 9.38 (s, 2H, C-OH Phenyl). $^{13}\text{C-NMR } \delta$ (ppm, DMSO- d_6): 26.98 (CH₃ tBu), 35.93 (CH₂ β), 55.04 (CH α), 80.23 (Cq tBu), 114.96 (CH 6), 115.42 (CH Phenyl), 116.75 (CH Phenyl), 119.67 (Cq 1), 120.96 (CH Phenyl), 122.32 (CH 7), 124.69 (Cq 5a), 125.73 (CH Phenyl, CH 9), 125.94 (CH Phenyl), 127.90 (CH Phenyl), 128.71 (CH 8), 130.76 (Cq Phenyl), 131.11 (CH 2), 131.21 (Cq Phenyl), 136.87 (Cq 3a), 138.12 (Cq 9a), 146.17 (Cq 4), 170.13 (C=O). MS (ESI +, QToF, m/z): 497.1 [M + H]⁺. HRMS calculated for C₂₉H₂₉N₄O₄ 497.2189, found 497.2198.

Tert-butyl 3-(4-(Tert-butoxy)phenyl)-2-((1-(3,4-dihydroxyphenyl)imidazo[1,2-a]quinoxalin-4-yl)amino)propanoate (9h): Following the same procedure used for the synthesis of **9a** (see 4.1.4.8.), to a mixture of **7h** (0.260 g, 0.57 mmol) in DME/H₂O (2/1, 15 mL) were added compound **12** (0.170 g, 1.72 mmol), tetrakis- (triphenylphosphine) palladium (0.028 g, 0.028 mmol) and sodium carbonate (0.101 g, 1.15 mmol) in a microwave-adapted vial. The product was purified by flash chromatography eluted with cyclohexane/ethyl acetate 80/20 to 50/50. The compound is obtained as a white solid (22% yield). C₃₃H₃₆N₄O₅. MW: 568.66 g/mol. $^1\text{H-NMR } \delta$ (ppm, DMSO- d_6): 1.24 (s, 9H, 3 × CH₃ OtBu), 1.33 (s, 9H, 3 × CH₃ OtBu), 3.12–3.18 (m, 1H, CH₂ β), 3.26–3.32 (m, 1H, CH₂ β), 4.80–4.84 (m, 1H, CH α), 6.80 (d, 1H, $J = 8$ Hz, CH Phenyl), 6.88 (s, 1H, CH Phenyl), 6.90 (dd, 2H, $J = 4$ Hz, $J = 8$ Hz, CH Phenyl), 6.92 (d, 1H, $J = 8$ Hz, CH Phenyl), 7.01–7.05 (m, 1H, CH 7), 7.25 (d, 2H, $J = 8$ Hz, CH Phenyl), 7.30–7.32 (m, 1H, CH 8), 7.34 (dd, 1H, $J = 4$ Hz, $J = 8$ Hz, CH 6), 7.45 (s, 1H, CH 2), 7.54 (dd, 1H, $J = 4$ Hz, $J = 8$ Hz, CH 9), 7.57 (d, 1H, $J = 8$ Hz, NH), 9.31 (s, 1H, C-OH Phenyl), 9.40 (s, 1H, C-OH Phenyl). $^{13}\text{C-NMR } \delta$ (ppm, DMSO- d_6): 28.05 (CH₃ tBu), 28.95 (CH₃ tBu), 36.64 (CH₂ β), 55.87 (CH α), 78.12 (Cq tBu), 80.91 (Cq tBu), 115.90 (CH 6), 116.46 (CH Phenyl), 117.87 (CH Phenyl), 121.08 (Cq 1), 122.05 (CH Phenyl), 122.91 (CH 7), 124.00 (2 × CH Phenyl), 126.07 (Cq 5a), 126.49 (CH 8), 127.21 (CH 9), 130.33 (2 × CH Phenyl), 132.26 (CH 2), 132.62 (Cq 3a), 137.46 (Cq 9a), 146.02 (Cq 4), 147.11 (Cq Phenyl), 147.22 (Cq Phenyl), 154.05 (2 × Cq Phenyl), 171.75 (C=O). MS (ESI +, QToF, m/z): 569.3 [M + H]⁺. HRMS calculated for C₃₃H₃₇N₄O₅ 569.2764, found 569.2773.

Tert-butyl 2-((Tert-butoxycarbonyl)amino)-5-((1-(3,4-dihydroxyphenyl)imidazo[1,2-a]quinoxalin-4-yl)amino)pentanoate (9i): Following the same procedure used for the synthesis of **9a** (see 4.1.4.8.), to a mixture of **7i** (0.460 g, 0.86 mmol) in DME/H₂O (2/1, 15 mL) were added compound **12** (0.330 g, 2.15 mmol), tetrakis- (triphenylphosphine) palladium (0.050 g, 0.043 mmol) and sodium carbonate (0.182 g, 1.72 mmol) in a microwave-adapted vial. The product was purified by flash chromatography eluted with cyclohexane/ethyl acetate 80/20 to 50/50. The compound is obtained as a white solid (30% yield). C₃₀H₃₇N₅O₆. MW: 563.64 g/mol. $^1\text{H-NMR } \delta$ (ppm, DMSO- d_6): 1.33 (s, 9H, CH-CO₂tBu), 1.39 (s, 9H, NH-CO₂tBu), 1.66–1.72 (m, 4H, CH₂ β , CH₂ γ), 3.56–3.57 (m, 2H, CH₂ δ), 3.89–3.93 (m, 1H, CH α), 6.79 (dd, 1H, $J = 4$ Hz, $J = 8$ Hz, CH Phenyl), 6.87 (d, 1H, $J = 4$ Hz, CH Phenyl), 6.90 (d, 1H, $J = 8$ Hz, CH Phenyl), 6.95–7.00 (m, 1H, CH 7), 7.17 (d, 1H, $J = 8$ Hz, NH-CH α), 7.27–7.29 (m, 1H, CH 8), 7.31 (dd, 1H, $J = 4$ Hz, $J = 8$ Hz, CH 6), 7.40 (s, 1H, CH 2), 7.56 (dd, 1H, $J = 4$ Hz, $J = 8$ Hz, CH 9), 7.69 (t, 1H, $J = 4$ Hz, NH-CH₂ δ), 9.35 (s, 2H, C-OH Phenyl). $^{13}\text{C-NMR } \delta$ (ppm, DMSO- d_6): 26.80 (CH₂ β), 28.04 (CH₃ tBu), 28.67 (CH₃ tBu), 30.42 (CH₂ γ), 39.79 (CH₂ δ), 54.78 (CH α), 78.46 (Cq tBu), 80.53 (Cq tBu), 115.79 (CH 6), 116.45 (CH Phenyl), 117.86 (CH Phenyl), 121.29 (Cq 1), 122.01 (CH Phenyl), 122.06 (CH 7), 125.76 (Cq 5a), 126.29 (CH 8), 127.03 (CH 9), 131.91 (CH 2), 138.20 (Cq 3a), 146.02 (Cq 4), 147.05 (Cq Phenyl), 148.03 (Cq Phenyl), 156.02 (Cq 9a), 172.34 (C=O). MS (ESI +, QToF, m/z): 564.3 [M + H]⁺. HRMS calculated for C₃₀H₃₈N₅O₆ 564.2822, found 564.2827.

3.1.5. Cleavage of the Protective Groups

2-((1-(3,4-Dimethoxyphenyl)imidazo[1,2-a]quinoxalin-4-yl)amino)propanoic acid (10b): To a cooled (0 °C) solution of **8b** (0.170 g, 0.36 mmol) in anhydrous CH₂Cl₂ (20 mL) was added boron tribromide (2.1 mL, 2.1 mmol). The resulting solution was allowed to warm to room temperature and stirred until complete consumption of the starting material (1–3 h, monitored by TLC). The solution was neutralized by addition of saturated aqueous sodium bicarbonate (20 mL). The crude mixture was extracted with

CH₂Cl₂ (3 × 20 mL). The organic phase was dried on sodium sulfate, filtered and concentrated under reduced pressure. The product was purified by flash chromatography eluted with cyclohexane/ethyl acetate 90/20 to 40/50. The compound is obtained as a white solid (71% yield). C₂₁H₂₀N₄O₄. MW: 392.41 g/mol. ¹H-NMR δ (ppm, DMSO-*d*₆): 1.24 (s, 1H, COOH), 1.53 (d, 3H, *J* = 8 Hz, CH₃ β), 3.75 (s, 3H, OCH₃ Phenyl), 3.87 (s, 3H, OCH₃ Phenyl), 4.61–4.63 (m, 1H, CH α), 7.00–7.04 (m, 1H, CH 7), 7.11 (d, 1H, *J* = 4 Hz, CH Phenyl), 7.13 (s, 1H, CH Phenyl), 7.17 (d, 1H, *J* = 4 Hz, CH Phenyl), 7.31 (dd, 1H, *J* = 4 Hz, *J* = 8 Hz, CH 6), 7.33–7.35 (m, 1H, CH 8), 7.50 (s, 1H, CH 2), 7.52 (d, 1H, *J* = 4 Hz, NH), 7.60 (dd, 1H, *J* = 4 Hz, *J* = 8 Hz, CH 9). ¹³C-NMR δ (ppm, DMSO-*d*₆): 18.71 (CH₃ β), 50.30 (CH α), 56.07 (OCH₃ Phenyl), 56.16 (OCH₃ Phenyl), 112.31 (CH Phenyl), 114.22 (CH Phenyl), 115.92 (CH 6), 122.54 (CH 7), 122.70 (Cq 1), 123.28 (CH Phenyl), 126.54 (CH 8), 125.90 (Cq 5a), 127.21 (CH 9), 130.95 (Cq 3a), 132.63 (CH 2), 137.99 (Cq 9a), 147.05 (Cq 4), 149.26 (Cq Phenyl), 150.132 (Cq Phenyl), 172.96 (C=O). MS (ESI +, QToF, *m/z*): 393.0 [M + H]⁺. HRMS calculated for C₂₁H₂₁N₄O₄ 393.1563, found 393.1558.

2-((1-(3,4-Dimethoxyphenyl)imidazo[1,2-*a*]quinoxalin-4-yl)amino)-3-methylbutanoic acid (**10c**): Following the same procedure used for the synthesis of **10b**, to a cooled solution of **8c** (0.290 g, 0.61 mmol) in anhydrous CH₂Cl₂ (20 mL) was added boron tribromide (3.6 mL, 3.6 mmol). The product was purified by flash chromatography eluted with cyclohexane/ethyl acetate 90/20 to 40/50. The compound is obtained as a white solid (80% yield). C₂₃H₂₄N₄O₄. MW: 420.46 g/mol. ¹H-NMR δ (ppm, DMSO-*d*₆): 0.99 (d, 3H, *J* = 8 Hz, CH₃ γ), 1.01 (d, 3H, *J* = 8 Hz, CH₃ γ'), 1.23 (s, 1H, COOH), 2.36–2.41 (m, 1H, CH β), 3.74 (s, 3H, OCH₃ Phenyl), 3.87 (s, 3H, OCH₃ Phenyl), 4.55 (t, 1H, *J* = 16 Hz, CH α), 6.97–7.01 (m, 1H, CH 7), 7.10 (dd, 1H, *J* = 4 Hz, *J* = 8 Hz, CH Phenyl), 7.14 (s, 1H, CH Phenyl), 7.16 (dd, 1H, *J* = 4 Hz, *J* = 8 Hz, CH Phenyl), 7.19 (d, 1H, NH-CH α), 7.28 (d, 1H, *J* = 4 Hz, CH 6), 7.29–7.32 (m, 1H, CH 8), 7.48 (s, 1H, CH 2), 7.54 (dd, 1H, *J* = 4 Hz, *J* = 8 Hz, CH 9). ¹³C-NMR δ (ppm, DMSO-*d*₆): 19.02 (CH₃ γ'), 19.96 (CH₃ γ), 31.19 (CH β), 56.06 (OCH₃ Phenyl), 56.16 (OCH₃ Phenyl), 59.54 (CH α), 112.31 (CH Phenyl), 114.26 (CH Phenyl), 115.87 (CH 6), 122.35 (CH 7), 122.75 (Cq 1), 123.29 (CH Phenyl), 125.89 (Cq 5a), 126.49 (CH 8), 127.18 (CH 9), 130.95 (Cq Phenyl), 132.44 (CH 2), 133.40 (Cq 3a), 138.10 (Cq 9a), 147.60 (Cq 4), 149.25 (Cq Phenyl), 150.12 (Cq Phenyl), 170.00 (C=O). MS (ESI +, QToF, *m/z*): 420.9 [M + H]⁺. HRMS calculated for C₂₃H₂₅N₄O₄ 421.1876, found 421.1873.

2-((1-(3,4-Dimethoxyphenyl)imidazo[1,2-*a*]quinoxalin-4-yl)amino)-4-methylpentanoic acid (**10d**): Following the same procedure used for the synthesis of **10b**, to a cooled solution of **8d** (0.210 g, 0.43 mmol) in anhydrous CH₂Cl₂ (20 mL) was added boron tribromide (2.5 mL, 2.536 mmol). The product was purified by flash chromatography eluted with cyclohexane/ethyl acetate 90/20 to 40/50. The compound is obtained as a white solid (76% yield). C₂₄H₂₆N₄O₄. MW: 434.49 g/mol. ¹H-NMR δ (ppm, DMSO-*d*₆): 0.95 (d, 3H, *J* = 8 Hz, CH₃ δ), 0.98 (d, 3H, *J* = 8 Hz, CH₃ δ'), 1.76–1.80 (m, 3H, CH₂ β, CH γ), 3.74 (s, 3H, OCH₃ Phenyl), 3.87 (s, 3H, OCH₃ Phenyl), 4.66 (t, 1H, *J* = 4 Hz, CH α), 6.98–7.02 (m, 1H, CH 7), 7.11 (d, 1H, *J* = 4 Hz, CH Phenyl), 7.13 (s, 1H, CH Phenyl), 7.17 (d, 1H, *J* = 4 Hz, CH Phenyl), 7.29 (dd, 1H, *J* = 4 Hz, *J* = 8 Hz, CH 6), 7.31–7.33 (m, 1H, CH 8), 7.44 (d, 1H, *J* = 4 Hz, NH), 7.49 (s, 1H, CH 2), 7.56 (dd, 1H, *J* = 4 Hz, *J* = 8 Hz, CH 9). ¹³C-NMR δ (ppm, DMSO-*d*₆): 22.68 (CH₃ δ), 23.69 (CH₃ δ'), 25.24 (CH γ), 40.42 (CH₂ β), 53.00 (CH α), 56.05 (OCH₃ Phenyl), 56.15 (OCH₃ Phenyl), 112.30 (CH Phenyl), 114.24 (CH Phenyl), 115.88 (CH 6), 122.29 (CH 7), 122.77 (Cq 1), 123.27 (CH Phenyl), 125.86 (Cq 5a), 126.49 (CH 8), 127.13 (CH 9), 130.90 (Cq 3a), 132.42 (CH 2), 138.12 (Cq 9a), 147.44 (Cq 4), 149.25 (Cq Phenyl), 150.10 (Cq Phenyl), 172.31 (C=O). MS (ESI +, QToF, *m/z*): 434.9 [M + H]⁺. HRMS calculated for C₂₄H₂₇N₄O₄ 435.2032, found 435.2032.

2-((1-(3,4-Dihydroxyphenyl)imidazo[1,2-*a*]quinoxalin-4-yl)amino)acetic acid (**11a**): To a cooled (0 °C) solution of **9a** (0.055, 0.14 mmol) in anhydrous CH₂Cl₂ (10 mL) was added TFA (5 mL). The resulting solution was allowed to warm to room temperature and stirred until complete consumption of the starting material (1–2 h, monitored by TLC). The solvent was removed under reduced pressure. The product was purified by flash chromatography eluted with cyclohexane/ethyl acetate 90/20 to 40/50. The compound is obtained as a white solid (92% yield). C₁₈H₁₄N₄O₄. MW: 350.33 g/mol. ¹H-NMR δ (ppm, DMSO-*d*₆): 1.23 (s, 1H, COOH), 4.24 (d, 2H, *J* = 8 Hz, CH₂ α), 6.82 (dd, 1H, *J* = 4 Hz, *J* = 8 Hz,

CH Phenyl), 6.90 (dd, 1H, $J = 4$ Hz, $J = 8$ Hz, CH Phenyl), 6.93 (s, 1H, CH Phenyl), 7.03–7.07 (m, 1H, CH 7), 7.31–7.34 (m, 1H, CH 8), 7.35 (dd, 1H, $J = 4$ Hz, $J = 8$ Hz, CH 6), 7.48 (s, 1H, CH 2), 7.58 (dd, 1H, $J = 4$ Hz, $J = 8$ Hz, CH 9), 8.02–8.05 (m, 1H, NH), 9.39–9.43 (m, 2H, C-OH Phenyl). $^{13}\text{C-NMR } \delta$ (ppm, DMSO- d_6): 42.37 (CH₂ α), 115.97 (CH 6), 116.49 (CH Phenyl), 117.86 (CH Phenyl), 120.69 (Cq 1), 122.06 (CH Phenyl), 122.96 (CH 7), 126.13 (Cq 5a), 126.51 (CH 8), 126.62 (CH 9), 132.36 (CH 2), 146.01 (Cq 3a), 147.17 (Cq 9a), 147.56 (Cq 4), 152.74 (Cq Phenyl), 172.09 (C=O). MS (ESI +, QTof, m/z): 351.2 [M + H]⁺. HRMS calculated for C₁₈H₁₅N₄O₄ 351.1093, found 351.1093.

2-((1-(3,4-dihydroxyphenyl)imidazo[1,2-a]quinoxalin-4-yl)amino)propanoic acid (11b): Following the same procedure for the synthesis of **11a**, to a cooled (0 °C) solution of **9b** (0.040, 0.09 mmol) in anhydrous CH₂Cl₂ (10 mL) was added TFA (5 mL). The product was purified by flash chromatography eluted with cyclohexane/ethyl acetate 90/20 to 40/50. The compound is obtained as a white solid (88% yield). C₁₉H₁₆N₄O₄. MW: 364.35 g/mol. $^1\text{H-NMR } \delta$ (ppm, DMSO- d_6): 1.23 (s, 1H, COOH), 1.56 (d, 3H, $J = 8$ Hz, CH₃ β), 4.82–4.84 (m, 1H, CH α), 6.82 (d, 1H, $J = 4$ Hz, CH Phenyl), 6.90 (d, 1H, $J = 4$ Hz, CH Phenyl), 6.93 (s, 1H, CH Phenyl), 7.05–7.08 (m, 1H, CH 7), 7.33 (dd, 1H, $J = 4$ Hz, $J = 8$ Hz, CH 6), 7.35–7.37 (m, 1H, CH 8), 7.50 (s, 1H, CH 2), 7.59 (dd, 1H, $J = 4$ Hz, $J = 8$ Hz, CH 9), 7.95 (d, 1H, $J = 4$ Hz, NH), 9.37 (s, 2H, C-OH Phenyl). $^{13}\text{C-NMR } \delta$ (ppm, DMSO- d_6): 17.79 (CH₃ β), 49.27 (CH α), 116.01 (CH 6), 116.51 (CH Phenyl), 117.87 (CH Phenyl), 120.42 (Cq 1), 120.95 (Cq 5a), 122.06 (CH Phenyl), 123.17 (CH 7), 125.80 (CH 9), 126.69 (CH 8), 131.82 (Cq 3a), 132.42 (CH 2), 132.64 (Cq 9a), 137.42 (Cq 4), 146.06 (Cq Phenyl), 146.95 (Cq Phenyl), 147.22 (Cq Phenyl), 174.64 (C=O). MS (ESI +, QTof, m/z): 365.1 [M + H]⁺. HRMS calculated for C₁₉H₁₇N₄O₄ 365.1250, found 365.1240.

2-((1-(3,4-Dihydroxyphenyl)imidazo[1,2-a]quinoxalin-4-yl)amino)-3-methylbutanoic acid (11c): Following the same procedure for the synthesis of **11a**, to a cooled (0 °C) solution of **9c** (0.035, 0.08 mmol) in anhydrous CH₂Cl₂ (10 mL) was added TFA (5 mL). The product was purified by flash chromatography eluted with cyclohexane/ethyl acetate 90/20 to 40/50. The compound is obtained as a white solid (91% yield). C₂₁H₂₀N₄O₄. MW: 392.41 g/mol. $^1\text{H-NMR } \delta$ (ppm, DMSO- d_6): 1.04 (d, 3H, $J = 8$ Hz, CH₃ γ), 1.07 (d, 3H, $J = 8$ Hz, CH₃ γ'), 1.18 (s, 1H, COOH), 2.36–2.41 (m, 1H, CH β), 4.74–4.76 (m, 1H, CH α), 6.82 (dd, 1H, $J = 4$ Hz, $J = 8$ Hz, CH Phenyl), 6.90 (d, 1H, $J = 4$ Hz, $J = 8$ Hz, CH Phenyl), 6.94 (d, 1H, $J = 4$ Hz, $J = 8$ Hz, CH Phenyl), 7.06–7.10 (m, 1H, CH 7), 7.17 (d, 1H, $J = 4$ Hz, NH), 7.33–7.36 (m, 1H, CH 8), 7.38 (dd, 1H, $J = 4$ Hz, $J = 8$ Hz, CH 6), 7.51 (s, 1H, CH 2), 7.60 (dd, 1H, $J = 4$ Hz, $J = 8$ Hz, CH 9), 9.40 (s, 2H, C-OH Phenyl). $^{13}\text{C-NMR } \delta$ (ppm, DMSO- d_6): 18.86 (CH₃ γ'), 19.63 (CH₃ γ), 30.50 (CH β), 58.70 (CH α), 115.98 (CH 6), 116.49 (CH Phenyl), 117.86 (CH Phenyl), 120.83 (Cq 1), 122.07 (CH Phenyl), 123.29 (CH 7), 126.05 (Cq 5a), 126.72 (CH 8), 126.94 (CH 9), 132.12 (CH 2), 132.52 (Cq Phenyl), 132.82 (Cq 3a), 137.42 (Cq 9a), 146.06 (Cq 4), 147.23 (Cq Phenyl), 147.47 (Cq Phenyl), 171.62 (C=O). MS (ESI +, QTof, m/z): 393.2 [M + H]⁺. HRMS calculated for C₂₁H₂₁N₄O₄ 393.1563, found 393.1561.

2-((1-(3,4-Dihydroxyphenyl)imidazo[1,2-a]quinoxalin-4-yl)amino)-4-methylpentanoic acid (11d): Following the same procedure for the synthesis of **11a**, to a cooled (0 °C) solution of **9d** (0.050, 0.11 mmol) in anhydrous CH₂Cl₂ (10 mL) was added TFA (5 mL). The product was purified by flash chromatography eluted with cyclohexane/ethyl acetate 90/20 to 40/50. The compound is obtained as a white solid (78% yield). C₂₂H₂₂N₄O₄. MW: 406.43 g/mol. $^1\text{H-NMR } \delta$ (ppm, DMSO- d_6): 0.93 (d, 3H, $J = 8$ Hz, CH₃ δ), 0.98 (d, 3H, $J = 8$ Hz, CH₃ δ'), 1.42 (s, 1H, COOH), 1.69–1.72 (m, 1H, CH₂ β), 1.76–1.79 (m, 1H, CH γ), 1.99–2.02 (m, 1H, CH₂ β), 4.85 (t, 1H, $J = 4$ Hz, CH α), 6.82 (d, 1H, $J = 4$ Hz, CH Phenyl), 6.90 (s, 1H, CH Phenyl), 6.93 (d, 1H, $J = 4$ Hz, CH Phenyl), 7.05–7.08 (m, 1H, CH 7), 7.32–7.35 (m, 1H, CH 8), 7.36 (dd, 1H, $J = 4$ Hz, $J = 8$ Hz, CH 6), 7.50 (s, 1H, CH 2), 7.59 (dd, 1H, $J = 4$ Hz, $J = 8$ Hz, CH 9), 7.90 (d, 1H, $J = 4$ Hz, NH), 9.38 (s, 2H, C-OH Phenyl). $^{13}\text{C-NMR } \delta$ (ppm, DMSO- d_6): 20.74 (CH₃ δ), 22.28 (CH₃ δ'), 24.07 (CH γ), 39.08 (CH₂ β), 50.92 (CH α), 114.92 (CH 6), 115.42 (CH Phenyl), 116.77 (CH Phenyl), 119.82 (Cq 1), 120.98 (CH Phenyl), 122.10 (CH 7), 124.67 (Cq 5a), 125.64 (CH 8), 125.72 (CH 9), 130.79 (Cq 3a), 131.28 (CH 2), 144.99 (Cq 9a), 146.14 (Cq 4), 146.28 (Cq Phenyl), 157.42 (Cq Phenyl), 173.51 (C=O). MS (ESI +, QTof, m/z): 407.1 [M + H]⁺. HRMS calculated for C₂₂H₂₃N₄O₄ 407.1719, found 407.1712.

6-Amino-2-((1-(3,4-dihydroxyphenyl)imidazo[1,2-a]quinoxalin-4-yl)amino)hexanoic acid (11e): Following the same procedure for the synthesis of **11a**. To a cooled (0 °C) solution of **9e** (0.035, 0.06 mmol) in anhydrous CH₂Cl₂ (10 mL) was added TFA (5 mL). The product was purified by flash chromatography eluted with cyclohexane/ethyl acetate 90/20 to 40/50. The compound is obtained as a white solid (84% yield). C₂₂H₂₃N₅O₄. MW: 421.45 g/mol. ¹H-NMR δ (ppm, DMSO-*d*₆): 1.23 (s, 1H, COOH), 1.47–1.51 (m, 2H, CH₂ γ), 1.58–1.64 (m, 2H, CH₂ δ), 1.98–2.04 (m, 2H, CH₂ β), 2.79–2.83 (m, 2H, CH₂ ε), 4.76–4.78 (m, 1H, CH α), 6.81 (d, 1H, *J* = 4 Hz, CH Phenyl), 6.90 (s, 1H, CH Phenyl), 6.93 (d, 1H, *J* = 4 Hz, CH Phenyl), 7.03–7.07 (m, 1H, CH 7), 7.31–7.35 (m, 1H, CH 8), 7.37 (dd, 1H, *J* = 4 Hz, *J* = 8 Hz, CH 6), 7.47 (s, 1H, CH 2), 7.58 (dd, 1H, *J* = 4 Hz, *J* = 8 Hz, CH 9), 7.64 (d, 1H, *J* = 4 Hz, NH-CH α), 7.68–7.70 (m, 2H, NH₂), 9.40–9.46 (m, 2H, C-OH Phenyl). ¹³C-NMR δ (ppm, DMSO-*d*₆): 22.04 (CH₂ γ), 26.08 (CH₂ δ), 29.65 (CH₂ β), 38.04 (CH₂ ε), 52.17 (CH α), 114.84 (CH 6), 115.40 (CH Phenyl), 116.79 (CH Phenyl), 120.96 (CH Phenyl), 121.87 (CH 7), 124.88 (Cq 5a), 125.49 (CH 8), 126.01 (CH 9), 130.49 (Cq 1), 131.14 (CH 2), 131.69 (Cq 3a), 136.24 (Cq 9a), 145.00 (Cq 4), 146.10 (Cq Phenyl), 146.51 (Cq Phenyl), 157.59 (Cq Phenyl), 173.29 (C=O). MS (ESI +, QTof, *m/z*): 422.1 [M + H]⁺. HRMS calculated for C₂₂H₂₄N₅O₄ 422.1828, found 422.1834.

5-Amino-2-((1-(3,4-dihydroxyphenyl)imidazo[1,2-a]quinoxalin-4-yl)amino)pentanoic acid (11f): Following the same procedure for the synthesis of **11a**, to a cooled (0 °C) solution of **9f** (0.055, 0.09 mmol) in anhydrous CH₂Cl₂ (10 mL) was added TFA (5 mL). The product was purified by flash chromatography eluted with cyclohexane/ethyl acetate 90/20 to 40/50. The compound is obtained as a white solid (10% yield). C₂₁H₂₁N₅O₄. MW: 407.42 g/mol. ¹H-NMR δ (ppm, DMSO-*d*₆): 1.70–1.74 (m, 2H, CH₂ γ), 1.89–1.93 (m, 1H, CH₂ β), 2.07–2.11 (m, 1H, CH₂ β), 2.66–2.70 (m, 1H, CH₂ δ), 2.78–2.82 (m, 1H, CH₂ δ), 4.33–4.34 (m, 1H, CH α), 6.69 (d, 1H, *J* = 8 Hz, CH Phenyl), 6.80 (d, 1H, *J* = 8 Hz, CH Phenyl), 6.89 (d, 1H, *J* = 4 Hz, CH Phenyl), 6.97–7.01 (m, 1H, CH 7), 7.29–7.33 (m, 1H, CH 8), 7.36 (dd, 1H, *J* = 4 Hz, *J* = 8 Hz, CH 6), 7.40 (s, 1H, *J* = 4 Hz, CH 2), 7.46 (d, 1H, *J* = 4 Hz, NH-CH α), 7.57 (dd, 1H, *J* = 4 Hz, *J* = 8 Hz, CH 9), 8.69 (s, 2H, C-OH Phenyl). ¹³C-NMR δ (ppm, DMSO-*d*₆): 23.61 (CH₂ γ), 29.41 (CH₂ β), 40.41 (CH₂ δ), 54.57 (CH α), 115.88 (CH 6), 116.50 (CH Phenyl), 117.95 (CH Phenyl), 121.23 (Cq 1), 122.04 (CH 7), 122.18 (CH Phenyl), 125.85 (Cq 5a), 126.39 (CH 8), 127.17 (CH 9), 132.08 (CH 2), 133.25 (Cq 3a), 138.31 (Cq 9a), 146.07 (Cq 4), 146.84 (Cq Phenyl), 147.12 (Cq Phenyl), 174.19 (C=O). MS (ESI +, QTof, *m/z*): 408.2 [M + H]⁺. HRMS calculated for C₂₁H₂₂N₅O₄ 408.1672, found 408.1668.

2-((1-(3,4-Dihydroxyphenyl)imidazo[1,2-a]quinoxalin-4-yl)amino)-3-phenylpropanoic acid (11g): Following the same procedure for the synthesis of **11a**, to a cooled (0 °C) solution of **9g** (0.045, 0.09 mmol) in anhydrous CH₂Cl₂ (10 mL) was added TFA (5 mL). The product was purified by flash chromatography eluted with cyclohexane/ethyl acetate 90/20 to 40/50. The compound is obtained as a white solid (87% yield). C₂₅H₂₀N₄O₄. MW: 440.45 g/mol. ¹H-NMR δ (ppm, DMSO-*d*₆): 1.23 (s, 1H, COOH), 3.33–3.39 (m, 2H, CH₂ β), 5.04–5.07 (m, 1H, CH α), 6.81 (d, 1H, *J* = 8 Hz, CH Phenyl), 6.89 (d, 1H, *J* = 4 Hz, CH Phenyl), 6.91 (d, 1H, *J* = 8 Hz, CH Phenyl), 7.05–7.08 (m, 1H, CH 7), 7.17 (t, 1H, *J* = 8 Hz, CH Phenyl), 7.26 (t, 2H, *J* = 8 Hz, CH Phenyl), 7.31–7.333 (m, 1H, CH 8), 7.34 (dd, 1H, *J* = 4 Hz, *J* = 8 Hz, CH 6), 7.36–7.37 (m, 2H, CH Phenyl), 7.48 (s, 1H, CH 2), 7.61 (dd, 1H, *J* = 4 Hz, *J* = 8 Hz, CH 9), 7.76–7.77 (m, 1H, NH), 9.39 (s, 2H, C-OH Phenyl). ¹³C-NMR δ (ppm, DMSO-*d*₆): 35.61 (CH₂ β), 5.31 (CH α), 114.91 (CH 6), 115.40 (CH Phenyl), 116.75 (CH Phenyl), 119.75 (Cq 1), 120.96 (CH Phenyl), 122.23 (CH 7), 124.71 (Cq 5a), 125.64 (CH 9), 125.88 (CH 8), 127.67 (CH Phenyl), 128.58 (CH Phenyl), 130.78 (Cq Phenyl), 131.35 (CH 2), 137.26 (Cq 3a), 138.42 (Cq 9a), 144.98 (Cq Phenyl), 146.14 (Cq 4), 157.48 (Cq Phenyl), 157.77 (Cq Phenyl), 172.35 (C=O). MS (ESI +, QTof, *m/z*): 441.2 [M + H]⁺. HRMS calculated for C₂₅H₂₁N₄O₄ 441.1563, found 441.1569.

2-((1-(3,4-Dihydroxyphenyl)imidazo[1,2-a]quinoxalin-4-yl)amino)-3-(4-hydroxyphenyl)-propanoic acid (11h): Following the same procedure for the synthesis of **11a**, to a cooled (0 °C) solution of **9h** (0.030, 0.06 mmol) in anhydrous CH₂Cl₂ (10 mL) was added TFA (5 mL). The product was purified by flash chromatography eluted with cyclohexane/ethyl acetate 90/20 to 40/50. The compound is obtained as

a white solid (89% yield). $C_{25}H_{20}N_4O_5$. MW: 456.45 g/mol. 1H -NMR δ (ppm, DMSO- d_6): 1.29 (s, 1H, COOH), 3.21–3.23 (m, 2H, CH₂ β), 4.94–4.98 (m, 1H, CH α), 6.71 (d, 2H, J = 8 Hz, CH Phenyl), 6.86 (dd, 1H, J = 4 Hz, J = 8 Hz, CH Phenyl), 6.94 (d, 1H, CH Phenyl), 6.98 (d, 1H, J = 8 Hz, CH Phenyl), 7.04–7.08 (m, 1H, CH 7), 7.12 (d, 2H, J = 8 Hz, CH Phenyl), 7.31–7.32 (m, 1H, CH 8), 7.35 (dd, 1H, J = 4 Hz, J = 8 Hz, CH 6), 7.47 (s, 1H, CH 2), 7.59–7.60 (m, 1H, NH), 7.64 (dd, 1H, J = 4 Hz, J = 8 Hz, CH 9), 9.32–9.35 (m, 2H, C-OH Phenyl). ^{13}C -NMR δ (ppm, DMSO- d_6): 36.01 (CH₂ β), 55.24 (CH α), 115.56 (2 \times CH Phenyl), 115.96 (CH 6), 116.47 (CH Phenyl), 117.82 (CH Phenyl), 120.86 (Cq 1), 122.05 (CH Phenyl), 123.19 (CH 7), 125.81 (Cq 5a), 126.68 (CH 9), 126.70 (CH 8), 130.59 (2 \times CH Phenyl), 132.35 (Cq 3a), 132.48 (CH 2), 137.32 (Cq 9a), 146.03 (Cq 4), 147.05 (Cq Phenyl), 147.19 (Cq Phenyl), 156.44 (Cq Phenyl), 173.55 (C=O). MS (ESI +, QTof, m/z): 457.1 [M + H]⁺. HRMS calculated for $C_{25}H_{21}N_4O_5$ 457.1512, found 457.1514.

2-Amino-5-((1-(3,4-dihydroxyphenyl)imidazo[1,2-a]quinoxalin-4-yl)amino)pentanoic acid (11i): Following the same procedure for the synthesis of **11a**, to a cooled (0 °C) solution of **9i** in anhydrous CH₂Cl₂ (10 mL) was added TFA (5 mL). The product was purified by flash chromatography eluted with cyclohexane/ethyl acetate 90/20 to 40/50. The compound is obtained as a white solid (79% yield). $C_{21}H_{21}N_5O_4$. MW: 407.42 g/mol. 1H -NMR δ (ppm, DMSO- d_6): 1.23 (s, 1H, COOH), 1.85–1.89 (m, 4H, CH₂ γ , CH₂ β), 3.64–3.66 (m, 2H, CH₂ δ), 3.99–4.01 (m, 1H, CH α), 6.80 (dd, 1H, J = 4 Hz, J = 8 Hz, CH Phenyl), 6.89 (d, 1H, J = 4 Hz, CH Phenyl), 6.92 (d, 1H, J = 8 Hz, CH Phenyl), 7.07–7.11 (m, 1H, CH 7), 7.35 (dd, 1H, J = 4 Hz, J = 8 Hz, CH 6), 7.37–7.39 (m, 1H, CH 8), 7.51 (s, 1H, CH 2), 7.55 (dd, 1H, J = 4 Hz, J = 8 Hz, CH 9), 7.66 (t, 1H, J = 4 Hz, NH-CH₂ δ), 8.24 (s, 2H, NH₂), 9.40 (s, 2H, C-OH Phenyl). ^{13}C -NMR δ (ppm, DMSO- d_6): 24.80 (CH₂ γ), 28.04 (CH₂ β), 39.99 (CH₂ δ), 52.30 (CH α), 116.12 (CH 6), 116.51 (CH Phenyl), 117.77 (CH Phenyl), 120.74 (Cq 1), 121.96 (CH Phenyl), 123.27 (CH 7), 125.76 (Cq 5a), 126.83 (CH 8), 129.28 (CH 9), 132.68 (CH 2), 138.42 (Cq 3a), 146.12 (Cq 4), 147.29 (Cq Phenyl), 158.41 (Cq Phenyl), 158.75 (Cq 9a), 171.54 (C=O). MS (ESI +, QTof, m/z): 408.2 [M + H]⁺. HRMS calculated for $C_{21}H_{22}N_5O_4$ 408.1672, found 408.1668.

3.1.6. 3,4-Dihydroxyphenylboronic Acid (12)

To a cooled (0 °C) solution of 3,4-dimethoxyphenylboronic acid (0.800 g, 4.39 mmol) in anhydrous CH₂Cl₂ (50 mL) was added boron tribromide (10 mL, 10 mmol). The resulting solution was allowed to warm to room temperature and stirred until complete consumption of the starting material (1–2h, monitored by TLC). The solution was neutralized by addition of methanol (50 mL). The crude mixture was concentrated under reduced pressure. The compound was obtained as a white solid (84% yield) and used without purification. $C_6H_7BO_4$. MW: 153.93 g/mol. 1H -NMR δ (ppm, DMSO- d_6): 2.08 (s, 2H, B-OH), 6.47 (d, 1H, CH Phenyl), 6.60 (d, 1H, CH Phenyl), 6.71 (d, 1H, CH Phenyl), 8.00 (s, 2H, C-OH Phenyl). ^{13}C -NMR δ (ppm, DMSO- d_6): 108.10 (CH Phenyl), 116.14 (CH Phenyl), 119.73 (CH Phenyl), 145.73 (C-OH). MS (ESI +, QTof, m/z): 153.2 [M – H][–]. HRMS calculated for $C_6H_6O_4B$ 153.0359, found 153.0358.

3.2. Cell Line and Culture Techniques

The melanoma (A375) human cancer cell line is obtained from American Type Culture Collection (Rockville, MD, USA). Cells were cultured in RPMI Gibco medium containing RPMI-1640 (Waltham, MA, USA), 10% heat-inactivated (56 °C) foetal bovine serum (FBS) (Polylabo, Paris, France), 2 mM L-glutamine, 100 IU/mL penicillin G sodium, 100 mg/mL streptomycin sulfate, and 0.25 mg/mL amphotericin B. Cells were maintained in a humidified atmosphere of 5% CO₂ in air at 37 °C.

3.3. In Vitro Cytotoxicity Assay

Previously to the experiments, the number of cells by well, the doubling time and the MTT concentration have been optimized. In all the experiments, A375 cells were seeded at a final concentration of 5000 cells/well in 96-well microtiter plates and allowed to attach overnight. After

24 h incubation, the medium (phosphate-buffer saline pH 7.3) was aspirated carefully from the plates using a sterile Pasteur pipette, and cells were exposed (i) to vehicle controls (0.15% DMSO/culture medium (*v/v*) and culture medium alone), (ii) to EAPB02303, EAPB02302 and the synthesized compounds at concentrations of 10^{-5} – 3.2×10^{-9} M dissolved in a mixture 0.15% DMSO/culture medium (*v/v*). After 96 h of incubation, cell supernatant was removed and 100 μ L of a MTT (3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyltetrazolium bromide) solution in fresh medium was added per well (MTT final concentration of 0.5 mg/mL) and incubated for 4 h at 37 °C. This colorimetric assay is based on the ability of live and metabolically unimpaired tumor-cell targets to reduce MTT to a blue formazan product. At the end of the incubation period, the supernatant was carefully aspirated, then, 100 μ L of a mixture of isopropyl alcohol and 1 M hydrochloric acid (96/4, *v/v*) was added to each well. After 10 min of incubation and vigorous shaking to solubilize formazan crystals, the optical density was measured at 570 nm in a microculture plate reader (Zaragoza, Spain). For each assay, at least three experiments were performed in triplicate. The individual cell line growth curves confirmed that all A375 line in control medium remained in the log phase of cell growth 96 h after plating. Cell survival was expressed as percent of vehicle control. The IC₅₀ values defined as the concentrations of drugs which produced 50% cell growth inhibition; 50% reduction of absorbance, were estimated from the sigmoidal dose–response curves.

4. Conclusions

The synthesis and study of the amino acid groups grafted on position 4 within the imiquiline series highlight the fact that the nature of the substituent on position 4 is not essential for the biological activity. Indeed, large modifications between EAPB02302, which only has a primary amine, and the new compounds with a complete amino acid residue do not significantly modify the activity, which remains similar to that of our first imiquiline generation. However, these modulations allow one to significantly increase the theoretical water solubility. The presence of dihydroxy groups on the phenyl appears to be necessary for the conservation of the cytotoxic activity on the melanoma cell line tested. These encouraging results obtained on the representative A375 melanoma cell line will prompt us to study further in vivo evaluation on xenografted mice.

Supplementary Materials: The following are available online. NMR ¹H and ¹³C spectra of all compounds evaluated on A375 melanoma cells.

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Sample Availability: Samples of the compounds are not available from the authors.



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