RSC Advances

PAPER

View Article Online
View Journal | View Issue

Cite this: *RSC Adv.*, 2015, **5**, 107400

Synthesis of optically pure (*S*)-2-amino-5-arylpent-4-ynoic acids by Sonogashira reactions and their potential use as highly selective potent inhibitors of aldose reductase†

Silvio Parpart,[a] Andranik Petrosyan,[abc] Syed Jawad Ali Shah,[e] Raji Akeem Adewale,[e] Peter Ehlers,[a] Tatevik Grigoryan,[ad] Anna F. Mkrtchyan,[cd] Zorayr Z. Mardiyan,[c] Ani J. Karapetyan,[c] Avetis H. Tsaturyan,[c] Ashot S. Saghyan,[cd] Jamshed Iqbal[e] and Peter Langer*[ab]

Received 26th October 2015
Accepted 10th December 2015

DOI: 10.1039/c5ra22407a

www.rsc.org/advances

A new and convenient synthesis of optically pure (*S*)-2-amino-5-[aryl]pent-4-ynoic acids (alkynylated amino acids) is reported. (*S*)-2-Aminopent-4-ynoic acid-Ni-(*S*)-BPB was prepared and then functionalized *via* Sonogashira cross-coupling reactions to give (*S*)-2-amino-5-[aryl]pent-4-ynoic acid-Ni-(*S*)-BPB. The reaction conditions for the cross-coupling reaction were optimized and twelve derivatives were synthesized. Afterwards the Ni-complexes were cleaved to obtain the free (*S*)-2-amino-5-[aryl]pent-4-ynoic acids with excellent optical purity. The prepared (*S*)-2-amino-5-[aryl]pent-4-ynoic acids were tested for biological activity and selectively showed high inhibitory activity against aldose reductase (ALR2) over ALR1. Molecular docking studies have also been carried out to identify the putative binding mode of the compounds in these enzymes.

Introduction

Amino acids and peptides are of great significance in life sciences and can be found in many areas of everyday life. Thus, the application of amino acids and their oligomers or polymers range from biotechnology, medicine, microbiology to the food industry. Some examples are given in Fig. 1. L-Thyroxine is the treatment of choice for patients with hypothyroidism. L-Glutamic acid is used as a flavor-enhancing compound which provides an umami (savory) taste to food. While its activity is similar to normal L-DOPA, the 6-fluorinated L-DOPA can be used as a radiolabeled molecular imaging probe useful for *in vivo* imaging for biological research and drug discovery. Consequently, many strategies for the synthesis of amino acids and their derivatives have been developed since the first synthesis of alanine by Strecker in 1850.[1] In contrast to the classical synthetic routes, modern chemistry focuses on the synthesis of optically pure amino acids. Therefore, a chiral substrate, reagent, catalyst or environment is required to perform the asymmetric induction.[2]

In line with this background, amino acid–Ni–BPB complexes (BPB = *N*-(benzylprolyl)aminobenzophenone) were developed in the last decades as a chiral starting material.[3] The chiral auxiliary BPB performs the asymmetric induction, while Ni increases the stability and reactivity of the amino acid–BPB adduct. The amino acid–Ni–BPB complex is stable to air and moisture and it is synthesized starting from easily available building blocks (benzylchloride, proline, 2-aminobenzophenone). The use of this chemical strategy has some advantages over microbiological and enzymatic asymmetric synthesis protocols. In particular, the reactions can be carried out in concentrated solutions using commercially available organic solvents. The amino acids are easy to separate from the reaction mixture and the reactions are highly reproducible. Over all, it is often difficult to find enzymatic protocols for the preparation of new non-protein amino acids, because of their unusual structure.

Previously, such amino acid–nickel complexes were incorporated in enantioselective Michael additions,[4] Mannich reactions,[5] aldol reactions[6] and S_N2 reactions.[7,8] After functionalization, the free amino acid can be obtained by refluxing the Ni-complex in acidic methanol. Recently, (*S*)-2-aminopent-4-ynoic acid-Ni-(*S*)-BPB **1** was obtained in good yield

[a]*Universität Rostock, Institut für Chemie, A.-Einstein-Str. 3a, 18059 Rostock, Germany. E-mail: peter.langer@uni-rostock.de*

[b]*Leibniz-Institut für Katalyse e.V. an der Universität Rostock, A.-Einstein-Str. 29a, 18059 Rostock, Germany*

[c]*SPC "Armbiotechnology" SNPO NAS RA, Gyurjyan Str. 14, 0056 Yerevan, Armenia*

[d]*Yerevan State University, Faculty of Pharmacology and Chemistry, Alex Manoogian Str. 1, 0025 Yerevan, Armenia*

[e]*Centre for Advanced Drug Research, COMSATS Institute of Information Technology, 22060 Abbottabad, Pakistan. E-mail: drjamshed@ciit.net.pk*

† Electronic supplementary information (ESI) available. See DOI: 10.1039/c5ra22407a

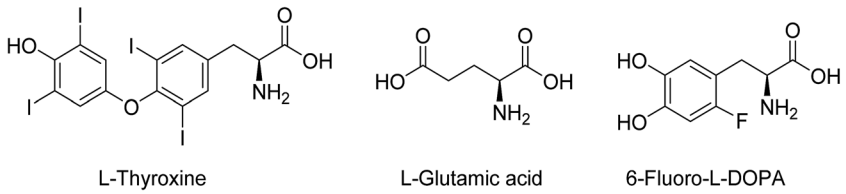
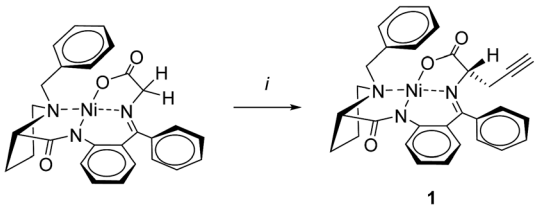


Fig. 1 Examples for amino acids and their applications.



Scheme 1 Synthesis of **1**: i (1) glycine-Ni-(*S*)-BPB, Bu_4NI, NaOH (30%), 3-bromopropyne, DCE, 20 °C (2) MeONa, MeOH, 20 °C.[8]

and with >95% diastereomeric excess using the procedure described in Scheme 1.[8] The cleavage of complex **1** in MeOH/HCl leads to (*S*)-2-aminopent-4-ynoic acid.

Terminal alkynes, like (*S*)-2-aminopent-4-ynoic acid, can be functionalized *via* the Sonogashira cross-coupling reaction.[9] Halogenated sp^2-hybridized compounds, like alkenes or aryls, are the coupling partner, while palladium and a copper salt are used as catalysts. However, the palladium catalyzed cross-coupling of amino acids is difficult to be carried out successfully, due to interactions between palladium and the free carboxyl and amino groups. For free (*S*)-2-aminopent-4-ynoic acid, the Sonogashira reaction has been reported to be successfully only when highly reactive iodobenzenes were employed.[10] Bromobenzenes can be used after protecting the carboxyl and amino groups.[11]

In (*S*)-2-aminopent-4-ynoic acid-Ni-(*S*)-BPB **1** both the amino and carboxyl group are ligated to nickel. Therefore, we reasoned that the Sonogashira reaction with bromobenzenes should be possible. Herein, we report Sonogashira cross-coupling reactions of Ni complex **1**. The subsequent cleavage of the complex afforded a variety of free alkynylated amino acids in good yields with high enantiomeric excess. This strategy provides a convenient approach to optically pure alkynylated amino acids.

Furthermore the obtained (*S*)-2-amino-(5)-[aryl]pent-4-ynoic acids were tested for their biological activities and were found to be highly selective inhibitors of ALR2 over ALR1.

This enzyme plays an important role in the polyol pathway of glucose metabolism. The polyol pathway of glucose metabolism is associated to the development of various diabetes complications, a global and continually growing epidemic.[12] Hyperglycemia in diabetes is believed to be the primary cause of the long term diabetics complications such as nephropathy, cataractogenesis, retinopathy, and neuropathy and many other mechanisms which include increased aldose reductase (AR)-related polyol pathway, excessive oxidative stress and increased advanced glycation end product (AGE) formation.[13] The increase in polyol pathway flux always result to accumulation of sorbitol in the fibre of the lens, leading to an influx of water, generation of osmotic stress, and cataract formation in which cataractogenesis leads to blindness the world over in diabetic patients.[14,15] Also, the accumulation of sorbitol and its metabolites in the nerves, retina, and kidneys which are connected to the onset and progression of long-term diabetic complications (*i.e.*, retinopathy, neuropathy, nephropathy and vascular complications) that are caused due to poor glycemic control.[16]

Aldehyde reductase (ALR1; EC 1.1.1.2) and aldose reductase (ALR2; EC 1.1.1.21) belong to the class of aldo-keto reductase (AKR) superfamily of enzymes whose members are believed to play critical roles in various biological functions which are associated to long-term diabetic complications.[17] The two enzymes have been isolated and purified from a number of tissues including the brain, kidney, liver, lens and skeletal muscle.[18,19] Both ALR1 and ALR2 catalyse the NADPH dependent reduction of aldehyde, xenobiotic aldehyde, ketones, trioses and triose phosphates.[20,21] ALR1 reduces aromatic aldehyde[22] while ALR2 is the first enzyme in the polyol pathway that converts glucose to sorbitol, which is subsequently transformed to fructose by sorbitol dehydrogenase. During a hyperglycaemic event, the increased in glucose level enhances ALR2 activity, increasing the glucose flux through the polyol pathway which impacts other NADPH-dependent enzymes shown to play a key role in long-term diabetic onset complications such as neuropathy and nephropathy.[22] Inhibition of ALR2, thus offers patients suffering from diabetes mellitus a viable therapeutic measure against this debilitating pathologies associated with chronic hyperglycaemia.[23,24]

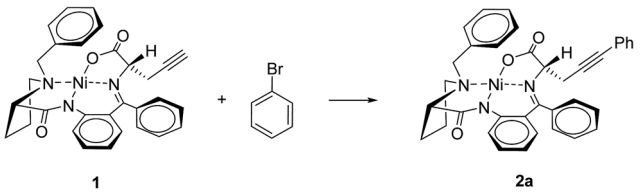
Many ARIS have been reported in the literature but adverse side effects and lack of efficacy have curtailed the prospect of many drug candidates for clinical use. As a result of this, the development of potent (ALR2) inhibitors is an obvious and attractive strategy to prevent or delay the onset and progression of these complications. In this present study, different derivatives of amino acids were synthesized as selective potent inhibitors of ALR2 over ALR1.

Results and discussion

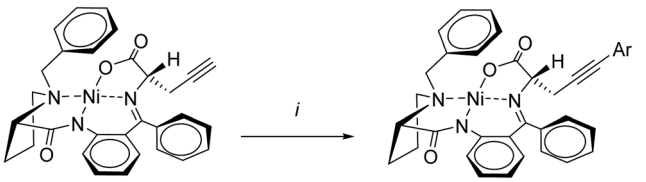
Chemical synthesis

Starting with the complex **1** a number of reaction conditions for the Sonogashira cross-coupling reaction were tested using bromobenzene as aryl halide (Scheme 2, Table 1).

Yields up to 83% of (*S*)-2-amino-5-phenylpent-4-ynoic acid-Ni-(*S*)-BPB **2a** were obtained using 5 mol% of the inexpensive



Scheme 2 Optimization for the synthesis of **2a**.



Scheme 3 Synthesis of **2a–k**: i, **1** (1.0 eq.), ArBr (1.2 eq.), $Pd(PPh_3)_4$ (5 mol%), CuI (10 mol%), $HNiPr_2$ (1 ml/0.25 mmol **1**), 1,4-dioxane (1 ml/0.25 mmol **1**), 90 °C, 3–4.5 h.

and commercially available catalyst $Pd(PPh_3)_4$. Attempts to reduce the amount of catalyst decreased the yield. The solvent of choice was 1,4-dioxane, while DMF, THF and acetonitrile gave slightly lower yields of **2a**. The base $HNiPr_2$ gave good yields, while Et_3N drastically decreased the yield. The best ratio between base and solvent proved to be 1 : 1. A reaction time of 3 hours was sufficient for the complete conversion of the starting material. To obtain good yields, either **1** or the bromobenzene has to be used in excess. For these reactions we decided to use commercially available bromobenzenes in excess, even if the isolated yields are slightly lower.

With the optimized reaction conditions in hand, derivatives **2a–k** were prepared (Scheme 3, Table 2).

Most of the derivatives **2a–k** were obtained in good yields. The established conditions were applied for electron rich as well as electron poor bromobenzenes and gave good yields, ranging from 67–78%. In case of compound **2d** only a moderate yield (46%) was achieved, which is probably due to steric effects of the methyl-group in *ortho*-position. For **2k** only 7% yield was obtained which might be explained by interactions of the nitro-group with palladium.

In addition, the twofold Sonogashira cross-coupling reaction was successfully carried out using 1,4-dibromobenzene (Scheme 4). Compound **2l** was obtained in 46% yield, which amounts to 68% for each coupling-step.

Subsequently, we studied the cleavage of complexes **2a–j** and **2l** to obtain the corresponding free amino acids. Compounds **2a–j** and **2l** were refluxed in a $MeOH/H_2O/HCl$ solvent mixture for 20 minutes to give the desired free amino acids **3a–j** and **3l** in a fast and simple manner (Schemes 5 and 6, Table 3).

The free amino acids **3a–j** and **3l** were obtained in very good to excellent yields. Electron donating and electron withdrawing groups on the benzene ring were not affecting the yield. Compound **3e** resulted in lower yield caused by difficulties during the work up process *via* cation-exchange column due to its low water solubility. Finally the enantiomeric excess of **3g**

Table 2 Derivatives **2a–k**

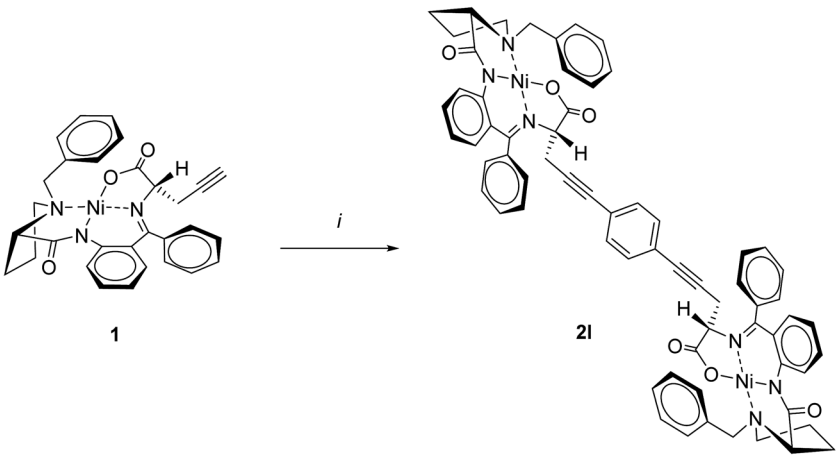
	Ar	Time [h]	Yield[a] [%]
2a	Phenyl	3.0	79
2b	4-Tolyl	3.0	67
2c	3-Tolyl	3.0	71
2d	2-Tolyl	3.0	46
2e	Naphth-1-yl	4.5	68
2f	Thiophen-2-yl	3.5	78
2g	4-Fluorobenzene	3.0	71
2h	4-Chlorobenzene	3.0	72
2i	4-(Trifluoromethyl)benzene	3.0	76
2j	3-Methoxybenzene	3.5	67
2k	4-Nitrobenzene	3.0	7

[a] Isolated yield.

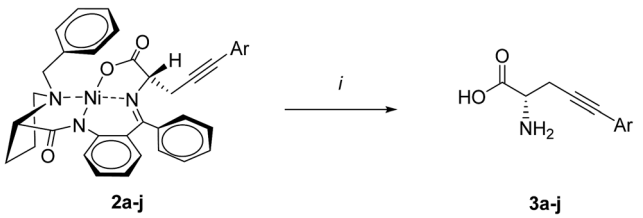
Table 1 Optimization for the synthesis of **2a** (all experiments were carried out with 0.25 mmol of **1** in 1 ml solvent)

Pd source [mol%]	CuI [mol%]	Solvent	PhBr [eq.]	Base [ml]	Temp. [°C]	Time [h]	Yield[a] [%]
$PdCl_2(PPh_3)_2$ (5)	10	1,4-Dioxane	0.84	$HNiPr_2$ (0.5)	90	6	46
$Pd(PPh_3)_4$ (5)	10	1,4-Dioxane	0.84	$HNiPr_2$ (0.5)	90	6	70
$Pd(PPh_3)_4$ (5)	10	THF	0.84	$HNiPr_2$ (0.5)	90	6	58
$Pd(PPh_3)_4$ (5)	10	DMF	0.84	$HNiPr_2$ (0.5)	90	6	64
$Pd(PPh_3)_4$ (5)	10	MeCN	0.84	$HNiPr_2$ (0.5)	90	6	59
$Pd(PPh_3)_4$ (5)	10	1,4-Dioxane	0.84	Et_3N (0.5)	90	6	45
$Pd(PPh_3)_4$ (5)	5	1,4-Dioxane	0.84	$HNiPr_2$ (0.5)	90	6	57
$Pd(PPh_3)_4$ (2.5)	5	1,4-Dioxane	0.84	$HNiPr_2$ (0.5)	90	6	40
$Pd(PPh_3)_4$ (5)	10	DMF	0.84	$HNiPr_2$ (0.5)	140	6	69
$Pd(PPh_3)_4$ (5)	10	1,4-Dioxane	0.84	$HNiPr_2$ (0.25)	90	6	33
$Pd(PPh_3)_4$ (5)	10	1,4-Dioxane	0.84	$HNiPr_2$ (1.0)	90	6	83
$Pd(PPh_3)_4$ (5)	10	1,4-Dioxane	0.84	$HNiPr_2$ (1.5)	90	6	71
$Pd(PPh_3)_4$ (5)	10	1,4-Dioxane	1	$HNiPr_2$ (1.0)	90	6	70
$Pd(PPh_3)_4$ (5)	10	1,4-Dioxane	1.2	$HNiPr_2$ (1.0)	90	6	79
$Pd(PPh_3)_4$ (5)	10	1,4-Dioxane	1.2	$HNiPr_2$ (1.0)	90	3	76

[a] Isolated yield.



Scheme 4 Synthesis of **2l**: i, **1** (1.0 eq.), 1,4-$Br_2C_6H_4$ (0.5 eq.), $Pd(PPh_3)_4$ (5 mol%), CuI (10 mol%), $HNiPr_2$ (1 ml/0.25 mmol **1**), 1,4-dioxane (1 ml/0.25 mmol **1**), 90 °C, 4.5 h.



Scheme 5 Synthesis of **3a–j**: i, **2a–j** (0.4–1.1 mmol), MeOH (10 ml), HCl (12 M, 1.5 ml), H_2O (5 ml), 60 °C, 20 min.

Table 3 Derivatives **3a–j** and **3l**

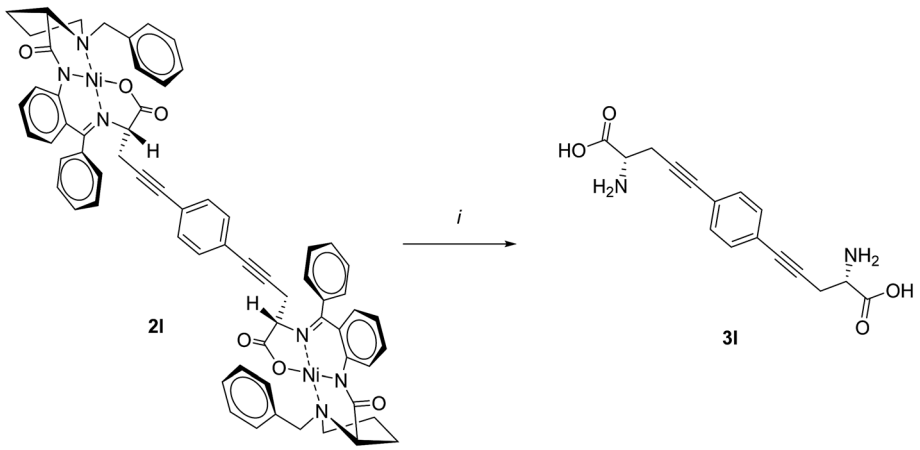
	Ar	Yield[a] [%]
3a	Phenyl	87
3b	4-Tolyl	89
3c	3-Tolyl	86
3d	2-Tolyl	72
3e	Naphth-1-yl	52
3f	Thiophen-2-yl	88
3g	4-Fluorobenzene	90
3h	4-Chlorobenzene	84
3i	4-(Trifluoromethyl)benzene	92
3j	3-Methoxybenzene	99
3l	1,4-Benzene	85

[a] Isolated yield.

and **3j** was checked by chiral HPLC (CrownpakCR(−) column). The enantiomeric excess of the amino acids **3g** and **3j** were estimated as >99%. This proves that the optically purity is not effected by the Sonogashira cross-coupling reaction or the cleavage step.

OSIRIS drug properties and toxicity profile

All of the newly synthesized compounds were found in good agreement with Lipinski's rule of five[25] as calculated by OSIRIS property explorer.[26] The overall OSIRIS drug score of compounds was in the range of 4.5–4.7, which showed that they were very good drug candidates. However, there is an exemption of compound **3e**, which exhibited 2.5 OSIRIS drug score. When



Scheme 6 Synthesis of **3l**: i, **2l** (0.5 mmol), MeOH (10 ml), HCl (12 M, 1.5 ml), H_2O (5 ml), 60 °C, 20 min.

the compounds were screened for drug toxicity on tumorigenic, mutagenic, irritability and reproductive toxicity they were found non-toxic. However, compound **3e** showed a mild tumorigenic toxicity due to the presence of napth-1-yl substitution.

Biological tests

ALR1 inhibitory activity. Aldehyde reductase is a cytosolic enzyme of an aldo-keto reductase superfamily member like aldose reductase (ALR2). It also catalyzes different physiological functions, among them, is detoxification of toxic aldehydes.[27–29] More so, these enzymes share a high level of sequence of about 65% and structural homology[30] as well as chemical and physical characteristics.[27] This increased tendency of a lot of substrates or ligands to bind to them.[29] In this study, two different derivatives of amino acids (phenyl and aliphatic) series were examined on purified ALR1 from bovine kidney to determine the one that would be a selective inhibitor of ALR2 over ALR1 as a potent inhibitor for future treatment of diabetic complications, expressed as IC_{50} values followed by their pIC_{50} ($-\log IC_{50}$) presented in Table 4. The results obtained from this study were presented on Table 4 and it was observed that among all the tested compounds, compounds **3h**, **3i**, and **3d** found to be strongly inhibited by ALR1 as compared to the other compounds which are potent inhibitors of ALR2 with the IC_{50} values of 0.041 ± 0.08, 0.065 ± 0.07 and 0.09 ± 0.01 respectively. The chlorine substituted derivative compound 3 h (IC_{50} 0.041 ± 0.08) was found to be inhibiting ALR1 with high IC_{50} value.

Finally, it was observed that increase in the electro negativity groups on different derivatives further decrease the inhibitory activity of these tested compounds against ALR1, therefore this could be a hint and re-examined critically in future as it could be a search light for the synthesis of high selective inhibitor of aldose reductase (ARIS).

ALR2 inhibitory activity. ALR2 inhibitors, many of which were potent both *in vitro* and *in vivo* experimental evaluations using animals, but on clinical trials they were failed which could be as a result of their side effects or poor efficacy. These side effects may be due to their failures to selective inhibit the ALR2 with respect to ALR1 (aldehyde reductase).[31] One of the most important attributes of pharmacological relevance of ARIs is their high selectivity over other members of the aldo-keto reductase family while the simultaneous inhibition of other structural related physiological important oxido-reductases may create undesirable effects but to ascertain the selectivity of the aldose reductase (ALR2), the closely related aldehyde reductase (ALR1) is always studied along.[32] In sequence, ALR1 and ALR2 similarity is close to about 65%.[33] In this present study, ALR 2 was selective studied over ALR1 using a purified calf lenses.

The inhibitory activity of aldose reductase was conducted on different derivatives of phenyl and aliphatic amino acids series at 1 mM concentration and compound having percentage inhibition greater than 50% was further diluted to the concentrations of eight to produce dose–response curve for determination of IC_{50} value which was basically the monitoring of NADPH oxidation by spectrophotometric method which is known to be a reliable standard method[30] and quercetin was used as the standard control. All the compounds tested on this enzyme shown to be highly selective potent inhibitors and their inhibitory activities were at the micro molar level as to the value obtained for standard inhibitor.

As shown in Table 4, the most active/potent compounds among the tested compounds against ALR2 with the high inhibitory activities were compounds, **3e**, **3i** and **3l** with the IC_{50} values of 0.012 ± 0.09, 0.068 ± 0.01, 0.078 ± 0.001 and 0.10 ± 0.03 with the pIC_{50} values of 7.9, 7.2, 7.1 and 7.0 respectively. The value of pIC_{50} is a good indicator to determine the potent inhibitor, because the higher its value the more potent the inhibitor. The least potent compounds as compared to the other compounds which show least inhibitory activity was compound **3c** with the IC_{50} value of 4.32 ± 0.04 by compounds **3h** with the IC_{50} values of 3.29 ± 0.20. The other tested amino acids were also promising inhibitors of the enzyme ALR2 and their pIC_{50} values are in the range of 5.9–6.9 as presented in Table 4.

Generally, in this series of compounds, the unsubstituted phenyl (compound **3a**) was the most potent inhibitor of ALR2. Finally, the strong inhibitory potency of this compound

Table 4 The IC_{50} and pIC_{50} values for ALR1 and ALR2 activities against amino acids 3a–j and 3l

	Aryl-rest	$IC_{50}^{ALR1} \pm SEM^a$ [μM]	pIC_{50}	$IC_{50}^{ALR2} \pm SEM^a$ [μM]	pIC_{50}
3a	Phenyl	1.05 ± 0.03	6.0	0.012 ± 0.09	7.9
3b	4-Tolyl	0.13 ± 0.05	6.8	1.10 ± 0.28	5.9
3c	3-Tolyl	5.20 ± 0.17	5.3	4.32 ± 0.04	5.3
3d	2-Tolyl	0.09 ± 0.01	7.0	0.45 ± 0.18	6.3
3e	Naphth-1-yl	0.40 ± 0.02	6.4	0.068 ± 0.001	7.2
3f	Thiophen-2-yl	0.60 ± 0.10	6.22	0.37 ± 0.08	6.4
3g	4-Fluorobenzene	1.53 ± 0.02	5.8	0.13 ± 0.02	6.9
3h	4-Chlorobenzene	0.041 ± 0.08	7.4	3.29 ± 0.20	5.5
3i	4-(Trifluoromethyl)benzene	0.065 ± 0.07	7.2	0.078 ± 0.001	7.1
3j	3-Methoxybenzene	0.14 ± 0.05	6.9	0.17 ± 0.02	6.8
3l	1,4-Benzene	1.05 ± 0.03	6.0	0.10 ± 0.03	7
	Valproic acid	56.01 ± 0.59	4.3	—	—
	Quercetin	—	—	3.04 ± 0.50	5.51

[a] $n = 3$; – not determined.

indicates that the presence of an additional groups on it may not be a prerequisite feature for ARIs activity, the potency and selectivity of this compounds as compared to the standard control and ALR1 are worthy of further development.

Molecular docking

As evident from the *in vitro* results compound **3a** was the most suitable compound for docking studies because of its potent and selective nature toward the ALR-2 enzyme. Molecular docking of compound **3a** was carried out after successfully reproducing poses similar to the reference ligand pose. The deviation (RMSD value) from the co-crystallized reference ligand poses were around 1.89 Å and 0.69 Å in case of ALR-1 and ALR-2, respectively. After reproducing the reference ligand poses, the compound **3a** was docked inside the active site.

The molecular docking of compound **3a** revealed perfect orientation of the test compound inside the ALR-2 as compared to ALR-1. The compound forms perfect orientation inside the ALR-2 active site by forming hydrogen bonding interactions with catalytic amino acid residues of Tyr48, His110 and Trp111. The benzene ring of the compound **3a** is perfectly oriented inside the specificity determining pocket of ALR-2 formed by amino acids Typ111, Thr113, Phe122, Ala299 and Leu300 as described previously.[34] Furthermore, the compound forms Pi–Pi stacking interaction with amino acid Trp111. Amino acid Trp20 was also found to form Pi–charge interactions with compound, which further stabilizes the pose. The HYDE assessment of the compound inside the ALR-2 shows that the compounds binds to the receptor with a very high binding affinity (*i.e.* -32 kJ mol^{-1}) as compared to its binding affinity inside the active pocket of ALR-1 (*i.e.* -17 kJ mol^{-1}).

Inside ALR-1 the compound **3a** forms hydrogen bonding interactions with amino acid Trp114 and Arg312. Such hydrogen bonding interactions are similar to the previously reported interactions formed by 3,5-dichlorosalicylic acid.[35] However, hydrogen bonding interactions previously reported[35] with amino acid Trp22, Tyr50 and His113 have not been observed. Furthermore, inside ALR-1 the compound was also found to have weak hydrophobic interaction with amino acid Trp22 and amino acid His113 was found to form Pi–charge interaction with our compound. The difference in binding affinity of our compound **3a** against ALR-1 and ALR-2 enzymes calculated by HYDE assessment may be attributed to differences in IC_{50} value against such enzymes. The putative binding mode of compound **3a** can be seen in Fig. 2.

Conclusion

We have described a straight forward strategy to prepare a variety of optically pure (*S*)-2-amino-5-arylpent-4-ynoic acids (alkynylated amino acids) with a broad preparative scope. Substrates and catalysts are readily available. The synthesized amino acids were tested for biological activity and were found to be highly selective inhibitors of ALR2 over ALR1 and were confirmed by molecular docking study. This enzyme plays an important role in the polyol pathway of glucose metabolism and is associated to the development of various diabetes complications.

Experimental section

Chemical synthesis

The Sonogashira reaction was performed in anhydrous solvents (DMF, THF, dioxane, MeCN) under argon using a vacuum-line and standard Schlenk techniques. Ethyl acetate, heptane and dichloromethane were distilled before usage. All other solvents and reagents were of reagent grade and used as received. For column chromatography Fluka silica gel 60 (0.063–0.200 mm, 70–320 mesh) was used. For the cation exchange column Dowex 50WX8 H^+ was used. NMR spectra were recorded with Bruker AV 500 (75 MHz), Bruker AV 300 III (62.9 MHz) and Bruker AV 250 II

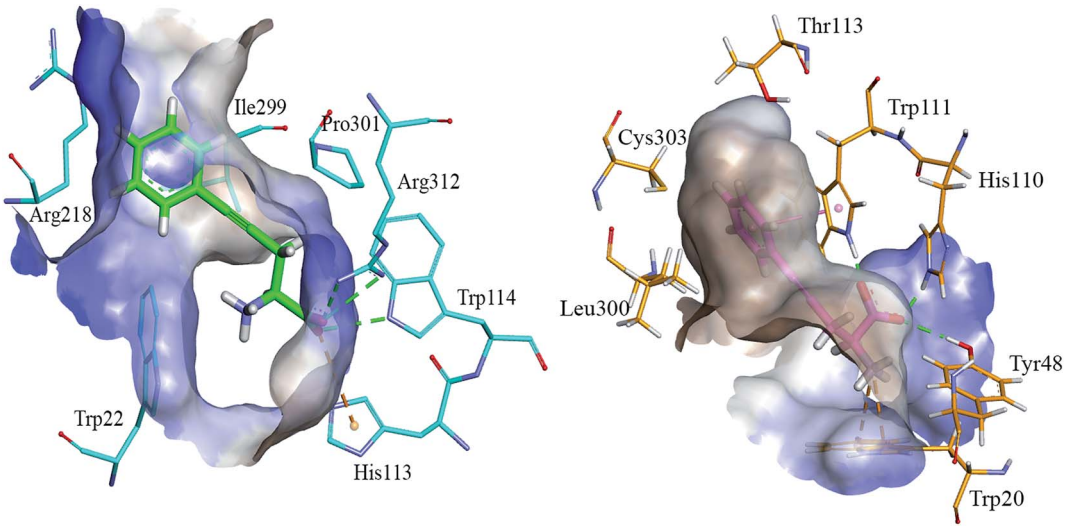


Fig. 2 Putative binding mode of compound **3a** inside active site of porcine ALR-1 (coloured cyan) and inside active site of human ALR-2 (coloured brown).

(62.9 MHz) spectrometers and are reported in ppm. The NMR spectra are calibrated by solvent at 7.26 ($CDCl_3$), 3.31 (D_3COD) 4.79 (D_2O) for ^1H and 77.23 ($CDCl_3$), 49.15 (D_3COD) for ^{13}C. MS and HRMS spectra were recorded with a Finnigan MAT 95 XP spectrometer. IR spectra were recorded with a Nicolet 6700 FT-IR spectrometer. EA spectra were recorded with a Flash EA 112 Series. Specific rotations were measured with a Gyromat-HP, 20 mm cell. Melting points were measured with a Micro-Hot-Stage GalenTM III Cambridge Instruments.

General procedure for 2a–l

(*S*)-2-Aminopent-4-ynoic acid-Ni-(*S*)-BPB **1** (1.0 eq.) was added to a stirred solution of $Pd(PPh_3)_4$ (5 mol%), CuI (10 mol%), bromobenzene (1.2 eq. (0.5 eq. for **2l**)), $HNiPr_2$ (4 ml $mmol^{-1}$ **1**) and 1,4-dioxane (4 ml $mmol^{-1}$ **1**). The mixture was stirred for 3–4.5 h at 90 °C. After cooling to room temperature the mixture was diluted with ethyl acetate and washed two times with water. The organic layer was dried with Na_2SO_4 and filtered. Afterwards the solvent was removed under reduced pressure and the residue was purified by column chromatography (EE/Hep, 5 : 1) to obtain **2a–l** as a red solid.

(*S*)-2-Amino-5-[phenyl]pent-4-ynoic acid-Ni-(*S*)-BPB (2a). Reaction of **1** (134 mg, 0.250 mmol), $Pd(PPh_3)_4$ (14.4 mg, 0.013 mmol), CuI (4.8 mg, 0.025 mmol) and bromobenzene (31.6 μl, 0.300 mmol) in $HNiPr_2$ (1 ml) and 1,4-dioxane (1 ml) for 3 h gave **2a** as a red solid (116 mg, 76%); mp 126–128 °C. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.53–1.67 (m, 1H, $CH_{2,Pro}$), 1.98–2.14 (m, 3H, $CH_{2,Pro}$), 2.52 (dd, ^3J = 6.4 Hz, ^2J = 17.0 Hz, 1H, $CH_{2,Gly}$), 2.93 (d, ^2J = 17.0 Hz, 1H, $CH_{2,Gly}$), 3.04–3.20 (m, 1H, $CH_{2,Pro}$), 3.36 (pt, ^3J = 8.3 Hz, 1H, CH_{Pro}), 3.56 (d, ^2J = 12.6 Hz, 1H, CH_2Ph), 3.59–3.71 (m, 1H, $CH_{2,Pro}$), 4.12 (d, ^3J = 6.4 Hz, 1H, CH_{Gly}), 4.42 (d, ^2J = 12.6 Hz, 1H, CH_2Ph), 6.70 (d, J = 3.9 Hz, 2H, C_6H_4), 7.11 (d, J = 7.3 Hz, 1H, Ar), 7.16–7.25 (m, 2H, Ar), 7.27–7.40 (m, 6H, Ar), 7.46–7.60 (m, 5H, Ar), 8.09 (d, J = 7.3 Hz, 2H, C_6H_5), 8.26 (d, J = 8.6 Hz, 1H, C_6H_4). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 23.3, 24.5, 30.3, 57.5, 63.3 (CH_2), 70.1 (CH), 84.4, 85.7 (C≡C), 120.5, 123.7, 126.7, 127.6, 128.3, 128.4, 128.7, 128.8, 129.0, 129.8, 131.5, 132.1, 132.4, 133.3 (CH), 123.2, 126.1, 133.4, 134.1, 142.9 (C_{Ar}), 171.8, 180.5 (C). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3436 (br, w), 2954 (w), 1671 (s), 1636 (s), 1585 (m), 1541 (m), 1438 (m), 1337 (s), 1254 (s), 1164 (m), 1064 (w), 922 (w), 752 (s), 701 (s), 540 (m). MS (EI, 70 eV): m/z (%) = 611 (M^+, 34), 567 (25), 476 (8), 380 (8), 164 (6), 217 (56), 160 (100), 91 (98). HRMS (ESI): calcd for $C_{36}H_{32}N_3NiO_3$ ($[M + H]^+$) 612.17917, found 612.17906, calcd for $C_{36}H_{31}N_3NaNiO_3$ ($[M + Na]^+$) 634.16111, found 634.16131.

(*S*)-2-Amino-5-[4-tolyl]pent-4-ynoic acid-Ni-(*S*)-BPB (2b). Reaction of **1** (804 mg, 1.5 mmol), $Pd(PPh_3)_4$ (86.0 mg, 0.075 mmol), CuI (28.6 mg, 0.150 mmol) and 4-bromotoluene (307.9 mg, 1.8 mmol) in $HNiPr_2$ (6 ml) and 1,4-dioxane (6 ml) for 3 h gave **2b** as a red solid (614 mg, 66%); mp 218–219 °C. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.51–1.66 (m, 1H, $CH_{2,Pro}$), 1.94–2.12 (m, 3H, $CH_{2,Pro}$), 2.33 (s, 3H, CH_3), 2.48 (dd, ^3J = 6.7 Hz, ^2J = 17.2 Hz, 1H, $CH_{2,Gly}$), 2.90 (dd, ^3J = 2.7 Hz, ^2J = 17.2 Hz, 1H, $CH_{2,Gly}$), 3.04–3.19 (m, 1H, $CH_{2,Pro}$), 3.33 (pt, ^3J = 8.6 Hz, 1H, CH_{Pro}), 3.54 (d, ^2J = 12.6 Hz, 1H, CH_2Ph), 3.55–3.65 (m, 1H, $CH_{2,Pro}$), 4.09 (dd, ^3J = 2.7 Hz, ^3J = 6.7 Hz, 1H, CH_{Gly}), 4.42 (d, ^2J = 12.6 Hz, 1H, CH_2Ph), 6.68 (d, J = 4.0 Hz, 2H, C_6H_4), 7.05–7.56 (m, 13H, Ar), 8.06 (d, J = 7.2 Hz, 2H, C_6H_5), 8.24 (d, J = 8.7 Hz, 1H, C_6H_4). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.7 (CH_3), 23.6, 24.8, 30.6, 57.7, 63.5 (CH_2), 68.3, 70.4 (CH), 83.8, 86.1 (C≡C), 120.7, 123.9, 127.0, 128.0, 129.0, 129.0, 129.3, 129.3, 129.4, 130.1, 131.8, 132.2, 132.6, 133.6, (CH_{Ar}), 120.4, 126.4, 133.6, 134.4, 138.6, 143.2 (C_{Ar}), 172.0, 179.2, 180.8 (C). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3054 (br, w), 3007 (br, w), 2871 (br, w), 1675 (s), 1620 (s), 1585 (m), 1543 (w), 1435 (w), 1337 (s), 1258 (s), 1162 (m), 1085 (w), 1029 (w), 860 (w), 828 (m), 774 (m), 756 (s), 747 (s), 699 (s), 629 (w), 567 (w). MS (EI, 70 eV): m/z (%) = 625 (M^+, 34), 581 (25), 490 (7), 394 (10), 251 (9), 217 (46), 205 (9), 160 (86), 91 (100). HRMS (ESI): calcd for $C_{37}H_{34}N_3NiO_3$ ($[M + H]^+$) 626.19482, found 626.19498, calcd for $C_{37}H_{33}N_3NaNiO_3$ ($[M + Na]^+$) 648.17676, found 648.17663.

(*S*)-2-Amino-5-[3-tolyl]pent-4-ynoic acid-Ni-(*S*)-BPB (2c). Reaction of **1** (804 mg, 1.5 mmol), $Pd(PPh_3)_4$ (86.0 mg, 0.075 mmol), CuI (28.6 mg, 0.150 mmol) and 3-bromotoluene (219.0 μl, 1.8 mmol) in $HNiPr_2$ (6 ml) and 1,4-dioxane (6 ml) for 3 h gave **2c** as a red solid (653 mg, 71%); mp 115–116 °C. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.51–1.62 (m, 1H, $CH_{2,Pro}$), 1.95–2.09 (m, 3H, $CH_{2,Pro}$), 2.27 (s, 3H, CH_3), 2.48 (dd, ^3J = 6.8 Hz, ^2J = 17.2 Hz, 1H, $CH_{2,Gly}$), 2.89 (dd, ^3J = 2.7 Hz, ^2J = 17.2 Hz, 1H, $CH_{2,Gly}$), 3.01–3.15 (m, 1H, $CH_{2,Pro}$), 3.33 (pt, ^3J = 8.4 Hz, 1H, CH_{Pro}), 3.51 (d, ^2J = 12.6 Hz, 1H, CH_2Ph), 3.55–3.64 (m, 1H, $CH_{2,Pro}$), 4.09 (dd, ^3J = 6.8 Hz, ^3J = 2.7 Hz, 1H, CH_{Gly}), 4.38 (d, ^2J = 12.6 Hz, 1H, CH_2Ph), 6.63–6.68 (m, 2H, C_6H_4), 7.06–7.54 (m, 13H, Ar), 8.06 (d, J = 7.1 Hz, 2H, C_6H_5), 8.25 (d, J = 8.6 Hz, 1H, C_6H_4). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.3 (CH_3), 23.5, 24.7, 30.4, 57.7, 63.5 (CH_2), 70.3 (CH), 84.1, 86.1 (C≡C), 120.6, 123.9, 126.9, 127.9, 128.4, 128.9, 129.0, 129.2, 129.4, 130.0, 131.7, 132.5, 132.9, 133.5 (CH_{Ar}), 123.1, 126.3, 134.4, 138.3, 143.1 (C_{Ar}), 171.9, 179.1, 180.7 (C). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3057 (br, w), 3027 (br, w), 2952 (br, w), 2869 (br, w), 1732 (w), 1671 (s), 1634 (s), 1585 (m), 1541 (m), 1438 (m), 1363 (m), 1336 (s), 1310 (m), 1253 (s), 1164 (s), 1063 (w), 882 (w), 750 (s), 701 (s), 625 (m), 567 (m), 540 (m). MS (EI, 70 eV): m/z (%) = 625 (M^+, 78), 581 (39), 490 (12), 424 (7), 394 (14), 264 (10), 219 (32), 217 (85) 205 (10), 160 (100), 129 (8), 91 (93), 44 (9). HRMS (EI): calcd for $C_{37}H_{33}N_3NiO_3$ ($[M]^-$) 625.18699, found 625.18724.

(*S*)-2-Amino-5-[2-tolyl]pent-4-ynoic acid-Ni-(*S*)-BPB (2d). Reaction of **1** (804 mg, 1.5 mmol), $Pd(PPh_3)_4$ (86.0 mg, 0.075 mmol), CuI (28.6 mg, 0.150 mmol) and 2-bromotoluene (219.0 μl, 1.8 mmol) in $HNiPr_2$ (6 ml) and 1,4-dioxane (6 ml) for 3 h gave **2d** as a red solid (427 mg, 46%); mp 107–108 °C. ^1H NMR (250 MHz, $CDCl_3$): δ = 1.52–1.63 (m, 1H, $CH_{2,Pro}$), 1.73–1.86 (m, 1H, $CH_{2,Pro}$), 1.92–2.05 (m, 2H, $CH_{2,Pro}$), 2.32 (s, 3H, CH_3), 2.52 (dd, ^3J = 7.0 Hz, ^2J = 17.1 Hz, 1H, $CH_{2,Gly}$), 2.92 (dd, ^3J = 2.2 Hz, ^2J = 17.1 Hz, 1H, $CH_{2,Gly}$), 2.98–3.10 (m, 1H, $CH_{2,Pro}$), 3.30 (dd, ^3J = 6.4 Hz, ^3J = 10.5 Hz, 1H, CH_{Pro}), 3.50 (d, ^2J = 12.6 Hz, 1H, CH_2Ph), 3.53–3.63 (m, 1H, $CH_{2,Pro}$), 4.11 (d, ^3J = 7.0 Hz, 1H, CH_{Gly}), 4.38 (d, ^2J = 12.6 Hz, 1H, CH_2Ph), 6.67 (d, J = 3.4 Hz, 2H, C_6H_4), 7.03–7.57 (m, 13H, Ar), 8.06 (d, J = 7.3 Hz, 2H, C_6H_5), 8.22 (d, J = 8.6 Hz, 1H, C_6H_4). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 20.7 (CH_3), 23.5, 24.7, 30.4, 57.8, 63.5 (CH_2), 70.2 (CH), 84.8, 88.4 (C≡C), 120.6, 123.9, 125.8, 126.9, 127.8, 128.6, 128.9, 129.0, 129.2, 129.7, 130.1, 131.8, 132.5, 133.5, 133.6 (CH_{Ar}), 123.1, 126.2, 134.4, 140.9, 143.2 (C_{Ar}), 171.9, 179.2, 180.8 (C). IR (ATR,

cm^{-1}): $\tilde{\nu}$ = 3059 (br, w), 2952 (br, w), 2870 (br, w), 1672 (s), 1635 (s), 1585 (m), 1438 (m), 1363 (m), 1337 (s), 1254 (s), 1164 (m), 1074 (br, w), 752 (s), 701 (s), 540 (m). MS (EI, 70 eV): *m*/*z* (%) = 625 (M^+, 20), 583 (14), 581 (13), 490 (5), 394 (5), 219 (14), 217 (37), 165 (8), 160 (86), 128 (7), 91 (100), 44 (19). HRMS (EI): calcd for $C_{37}H_{33}N_3NiO_3$ ([M]$^-$) 625.18699, found 625.18781.

(*S*)-2-Amino-5-[naphth-1-yl]pent-4-ynoic acid-Ni-(*S*)-BPB (2e). Reaction of **1** (804 mg, 1.5 mmol), $Pd(PPh_3)_4$ (86.0 mg, 0.075 mmol), CuI (28.6 mg, 0.150 mmol) and 1-bromonaphthalene (259.0 μl, 1.8 mmol) in $HNiPr_2$ (6 ml) and 1,4-dioxane (6 ml) for 4.5 h gave **2e** as a red solid (676 mg, 68%); mp 185–186 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.36–1.52 (m, 1H, $CH_{2,Pro}$), 1.62–1.87 (m, 2H, $CH_{2,Pro}$), 1.93–2.03 (m, 1H, $CH_{2,Pro}$), 2.52–2.72 (m, 2H, $CH_{2,Gly}$), 2.98–3.04 (m, 1H, $CH_{2,Pro}$), 3.08–3.21 (m, 1H, CH_{Pro}), 3.36 (d, ^2J = 12.5 Hz, 1H, CH_2Ph), 3.39–3.54 (m, 1H, $CH_{2,Pro}$), 3.99–4.20 (m, 1H, CH_{Gly}), 4.29 (d, ^2J = 12.5 Hz, 1H, CH_2Ph), 6.54–6.77 (m, 2H, C_6H_4), 7.01–7.77 (m, 15H, Ar), 7.98 (d, J = 7.5 Hz, 2H, C_6H_5), 8.22–8.29 (m, 2H, C_6H_4). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 23.3, 25.1, 30.2, 57.9, 63.5 (CH_2), 70.2 (CH), 84.0, 89.5 (C≡C), 120.7, 121.0, 124.1, 125.4, 126.2, 126.3, 126.7, 126.9, 127.3, 127.9, 128.3, 128.9, 129.0, 129.3, 130.1, 131.1, 131.8, 132.7, 133.3, 133.6, 133.7, 133.7, 134.5, 143.4 (C_{Ar}/CH_{Ar}), 172.2, 179.3, 180.8 (C). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3057 (br, w), 2953 (br, w), 2869 (br, w), 1732 (w), 1672 (m), 1634 (s), 1584 (m), 1438 (m), 1336 (s), 1253 (s), 1164 (m), 1063 (br, w), 802 (m), 774 (m), 750 (s), 700 (s), 567 (m), 539 (m). MS (EI, 70 eV): *m*/*z* (%) = 661 (M^+, 70), 617 (31), 526 (7), 264 (9), 217 (48), 165 (25) 160 (100), 91 (85). HRMS (EI): calcd for $C_{40}H_{33}N_3NiO_3$ ([M]$^-$) 661.18699, found 661.18873.

(*S*)-2-Amino-5-[thiophen-2-yl]pent-4-ynoic acid-Ni-(*S*)-BPB (2f). Reaction of **1** (804 mg, 1.5 mmol), $Pd(PPh_3)_4$ (86.0 mg, 0.075 mmol), CuI (28.6 mg, 0.150 mmol) and 2-bromothiophene (174.3 μl, 1.8 mmol) in $HNiPr_2$ (6 ml) and 1,4-dioxane (6 ml) for 3.5 h gave **2f** as a red solid (716 mg, 78%); mp 123–124 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.61–1.76 (m, 1H, $CH_{2,Pro}$), 2.02–2.25 (m, 3H, $CH_{2,Pro}$), 2.52 (dd, ^3J = 6.6 Hz, ^2J = 17.3 Hz, 1H, $CH_{2,Gly}$), 2.94 (dd, ^3J = 2.3 Hz, ^2J = 17.3 Hz, 1H, $CH_{2,Gly}$), 3.11–3.25 (m, 1H, $CH_{2,Pro}$), 3.37 (pt, ^3J = 8.0 Hz, 1H, CH_{Pro}), 3.56 (d, ^2J = 12.6 Hz, 1H, CH_2Ph), 3.59–3.66 (m, 1H, $CH_{2,Pro}$), 4.05–4.12 (m, 1H, CH_{Gly}), 4.40 (d, ^2J = 12.6 Hz, 1H, CH_2Ph), 6.67 (d, J = 4.0 Hz, 2H, C_6H_4), 6.97 (pt, J = 4.5 Hz, 1H, Ar), 7.09 (d, J = 6.7 Hz, 1H, Ar), 7.15–7.58 (m, 10H, Ar), 8.06 (d, J = 7.3 Hz, 2H, C_6H_5), 8.24 (d, J = 8.5 Hz, 1H, C_6H_4). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 23.5, 24.8, 30.5, 57.5, 63.3 (CH_2), 67.8, 70.2 (CH), 88.5 (C≡C), 120.6, 123.7, 126.7, 127.0, 127.2, 127.7, 128.8, 129.1, 129.9, 131.6, 132.5, 132.6, 133.4 (CH_{Ar}), 123.2, 126.2, 133.3, 134.1, 143.0 (C_{Ar}), 171.9, 178.8, 180.5 (C). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3061 (br, w), 2954 (br, w), 2858 (br, w), 1731 (w), 1672 (s), 1633 (s), 1585 (m), 1438 (m), 1364 (m), 1336 (s), 1253 (s), 1164 (s), 750 (s), 700 (s), 625 (m), 568 (m), 538 (m). MS (EI, 70 eV): *m*/*z* (%) = 617 (M^+, 37), 573 (18), 217 (34), 160 (100), 91 (85). HRMS (EI): calcd for $C_{34}H_{30}N_3NiO_3S$ ([M + H]$^+$) 618.13559, found 618.13638, calcd for $C_{34}H_{29}N_3NaNiO_3S$ ([M + Na]$^+$) 640.11753, found 640.11793.

(*S*)-2-Amino-5-[4-fluorobenzene]pent-4-ynoic acid-Ni-(*S*)-BPB (2g). Reaction of **1** (804 mg, 1.5 mmol), $Pd(PPh_3)_4$ (86.0 mg, 0.075 mmol), CuI (28.6 mg, 0.150 mmol) and 1-bromo-4-fluorobenzene (196.4 μl, 1.8 mmol) in $HNiPr_2$ (6 ml) and 1,4-dioxane (6 ml) for 3 h gave **2g** as a red solid (665 mg, 71%); mp 118 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.53–1.69 (m, 1H, $CH_{2,Pro}$), 1.95–2.16 (m, 3H, $CH_{2,Pro}$), 2.49 (dd, ^3J = 6.8 Hz, ^2J = 17.2 Hz, 1H, $CH_{2,Gly}$), 2.88 (dd, ^3J = 2.4 Hz, ^2J = 17.2 Hz, 1H, $CH_{2,Gly}$), 3.07–3.22 (m, 1H, $CH_{2,Pro}$), 3.36 (pt, ^3J = 8.3 Hz, 1H, CH_{Pro}), 3.48–3.63 (m, 2H, CH_2Ph/$CH_{2,Pro}$), 4.03–4.16 (m, 2H, $CH_{2,Pro}$/CH_{Gly}), 4.39 (d, ^2J = 12.6 Hz, 1H, CH_2Ph), 6.67 (d, J = 4.1 Hz, 2H, C_6H_4), 6.95–7.08 (m, 3H, Ar), 7.13–7.22 (m, 2H, Ar), 7.25–7.38 (m, 3H, Ar), 7.42–7.56 (m, 5H, Ar), 8.05 (d, J = 7.4 Hz, 2H, C_6H_5), 8.22 (d, J = 8.7 Hz, 1H, C_6H_4). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 23.5, 24.7, 30.5, 57.6, 60.5 (CH_2), 63.6, 70.3 (CH), 84.4, 84.8 (C≡C), 115.9 (d, ^2J = 22.2 Hz, CH_{FPh}), 119.5 (d, ^4J = 3.3 Hz, C_{FPh}), 120.8, 123.9 (CH_{Ar}), 126.3 (C_{Ar}), 126.9, 127.9, 129.0, 129.3, 130.1, 131.7, 132.7, 133.6 (CH_{Ar}), 133.5 (C_{Ar}), 134.2 (d, ^3J = 8.2 Hz, CH_{FPh}), 134.3, 143.1 (C_{Ar}), 162.7 (d, ^1J = 249 Hz, C_{FPh}), 172.0, 179.1, 180.8 (C). ^{19}F NMR (282.4 MHz, $CDCl_3$): δ = −110.6. IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3058 (br, w), 2692 (br, w), 2868 (br, w), 1732 (w), 1670 (s), 1632 (s), 1585 (m), 1505 (s), 1438 (m), 1364 (m), 1335 (s), 1254 (s), 1219 (m), 1164 (m), 1063 (m), 836 (m), 750 (s), 700 (s), 625 (m), 537 (m). MS (EI, 70 eV): *m*/*z* (%) = 629 (M^+, 43), 585 (39), 494 (10), 398 (9), 217 (77), 160 (100), 91 (100), 44 (22). HRMS (ESI): calcd for $C_{36}H_{31}FN_3NiO_3$ ([M + H]$^+$) 630.16974, found 630.17039, calcd for $C_{36}H_{30}N_3NaNiO_3$ ([M + Na]$^+$) 652.15169, found 652.15267.

(*S*)-2-Amino-5-[4-chlorobenzene]pent-4-ynoic acid-Ni-(*S*)-BPB (2h). Reaction of **1** (804 mg, 1.5 mmol), $Pd(PPh_3)_4$ (86.0 mg, 0.075 mmol), CuI (28.6 mg, 0.150 mmol) and 1-bromo-4-chlorobenzene (344.7 mg, 1.8 mmol) in $HNiPr_2$ (6 ml) and 1,4-dioxane (6 ml) for 3 h gave **2h** as a red solid (693 mg, 72%); mp 133–134 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.50–1.65 (m, 1H, $CH_{2,Pro}$), 1.88–2.13 (m, 3H, $CH_{2,Pro}$), 2.37–2.51 (m, 1H, $CH_{2,Gly}$), 2.83 (dd, ^3J = 3.7 Hz, ^2J = 17.0 Hz, 1H, $CH_{2,Gly}$), 3.02–3.18 (m, 1H, $CH_{2,Pro}$), 3.30 (d, ^3J = 8.1 Hz, 1H, CH_{Pro}), 3.42–3.55 (m, 2H, CH_2Ph/$CH_{2,Pro}$), 3.97–4.10 (m, 1H, CH_{Gly}), 4.26–4.38 (m, 1H, CH_2Ph), 6.54–6.66 (m, 2H, C_6H_4), 6.96–7.58 (m, 13H, Ar), 7.93–8.05 (m, 2H, C_6H_5), 8.11–8.21 (m, 1H, C_6H_4). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 23.6, 24.7, 30.5, 57.5, 63.5 (CH_2), 70.3 (CH), 84.7, 85.8 (C≡C), 120.8, 123.9, 126.9, 127.8, 128.9, 129.0, 129.2, 129.3, 130.1, 131.7, 132.6, 133.5, 133.5 (CH_{Ar}), 121.9, 126.3, 133.6, 134.2, 134.6, 143.0 (C_{Ar}), 172.0, 178.9, 180.7 (C). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3059 (br, w), 2953 (br, w), 2870 (br, w), 1732 (w), 1672 (s), 1634 (S), 1439 (m), 1364 (m), 1336 (s), 1254 (s), 1164 (m), 1088 (m), 750 (s), 701 (s), 687 (m), 570 (w). MS (EI, 70 eV): *m*/*z* (%) = 645 (M^+, 52), 601 (31), 510 (11), 453 (12), 414 (8), 264 (16), 217 (98), 160 (100), 91 (89), 65 (13), 44 (16). HRMS (ESI): calcd for $C_{36}H_{30}{}^{35}Cl_1N_3NiO_3$ ([M]$^-$) 645.13237, found 645.13405, calcd for $C_{36}H_{30}{}^{37}Cl_1N_3NiO_3$ ([M]$^-$) 647.12942, found 647.13164.

(*S*)-2-Amino-5-[4-(trifluoromethyl)benzene]pent-4-ynoic acid-Ni-(*S*)-BPB (2i). Reaction of **1** (134 mg, 0.25 mmol), $Pd(PPh_3)_4$ (14.4 mg, 0.013 mmol), CuI (4.8 mg, 0.025 mmol) and 1-bromo-4-(trifluoromethyl)benzene (41.4 μl, 0.3 mmol) in $HNiPr_2$ (1 ml) and 1,4-dioxane (1 ml) for 3 h gave **2i** as a red solid (125 mg, 74%); mp 142–143 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.56–1.71 (m, 1H, $CH_{2,Pro}$), 1.94–2.15 (m, 3H, $CH_{2,Pro}$), 2.54 (dd, ^3J = 6.8 Hz, ^2J = 17.2 Hz, 1H, $CH_{2,Gly}$), 2.92 (dd, ^3J = 2.9 Hz, ^2J = 17.2 Hz, 1H, $CH_{2,Gly}$), 3.05–3.24 (m, 1H, $CH_{2,Pro}$), 3.36 (dd, ^3J = 7.5 Hz, ^3J = 9.3 Hz, 1H, CH_{Pro}), 3.54 (d, ^2J = 12.6 Hz, 1H, CH_2Ph), 3.50–

3.60 (m, 1H, $CH_{2,Pro}$), 4.07–4.14 (m, 1H, CH_{Gly}), 4.40 (d, ^2J = 12.6 Hz, 1H, CH_2Ph), 6.68 (d, J = 4.2 Hz, 2H, C_6H_4), 7.06 (d, J = 6.7 Hz, 1H, Ar), 7.13–7.39 (m, 5H, Ar), 7.44–7.61 (m, 7H, Ar), 8.05 (d, J = 7.2 Hz, 2H, C_6H_5), 8.22 (d, J = 8.7 Hz, 1H, C_6H_4). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 23.6, 24.8, 30.5, 57.5, 63.6 (CH_2), 68.0, 70.3 (CH), 84.5, 87.5 (C≡C), 120.9, 124.0 (CH_{Ar}), 125.6 (q, ^3J = 3.8 Hz, CH_{CF_3Ph}), 126.3 (C_{Ar}), 127.0 (CH_{Ar}), 127.2 (bs, C_{CF_3Ph}), 127.9, 129.1, 129.2, 129.3, 129.4, 130.2 (CH_{Ar}), 130.4 (q, ^2J = 32.0 Hz, CH_{CF_3Ph}), 131.8, 132.6, 132.8, 133.7 (CH_{Ar}), 133.5, 134.3, 143.1 (C_{Ar}), 172.2, 178.9, 180.7 (C). ^{19}F NMR (282.4 MHz, $CDCl_3$): δ = −62.8. IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3059 (br, w), 2964 (br, w), 2870 (br, w), 1733 (w), 1673 (m), 1635 (s), 1321 (s), 1255 (s), 1163 (s), 1121 (s), 1104 (s), 1065 (s), 1015 (m), 843 (m), 750 (s), 701 (s), 686 (m), 599 (m), 569 (m). MS (EI, 70 eV): m/z (%) = 679 (M^+, 58), 635 (33), 544 (9), 264 (7), 217 (56), 160 (100), 91 (95). HRMS (EI): calcd for $C_{37}H_{30}F_3N_3NiO_3$ ($[M]^-$) 679.15873, found 679.16111. Anal. calcd for $C_{37}H_{30}F_3N_3NiO_3$ (680.4): C, 65.32; H, 4.44; N, 6.18. Found: C, 65.12; H, 4.33; N, 5.84.

(*S*)-2-Amino-5-[3-methoxybenzene]pent-4-ynoic acid-Ni-(*S*)-BPB (2j). Reaction of **1** (134 mg, 0.25 mmol), $Pd(PPh_3)_4$ (14.4 mg, 0.013 mmol), CuI (4.8 mg, 0.025 mmol) and 1-bromo-4-methoxybenzene (37.7 μl, 0.3 mmol) in $HNiPr_2$ (1 ml) and 1,4-dioxane (1 ml) for 3 h gave **2j** as a red solid (96 mg, 60%); mp 200–201 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.53–1.69 (m, 1H, $CH_{2,Pro}$), 1.97–2.17 (m, 3H, $CH_{2,Pro}$), 2.50 (dd, ^3J = 6.7 Hz, ^2J = 17.2 Hz, 1H, $CH_{2,Gly}$), 2.91 (dd, ^3J = 2.9 Hz, ^2J = 17.2 Hz, 1H, $CH_{2,Gly}$), 3.04–3.22 (m, 1H, $CH_{2,Pro}$), 3.32 (dd, ^3J = 7.5 Hz, ^3J = 9.4 Hz, 1H, CH_{Pro}), 3.54 (d, ^2J = 12.6 Hz, 1H, CH_2Ph), 3.58–3.69 (m, 1H, $CH_{2,Pro}$), 3.74 (s, 3H, CH_3), 4.05–4.15 (m, 1H, CH_{Gly}), 4.40 (d, ^2J = 12.6 Hz, 1H, CH_2Ph), 6.67 (d, J = 3.7 Hz, 2H, C_6H_4), 6.83–6.90 (m, 1H, Ar), 6.97–7.01 (m, 1H, Ar), 7.06–7.56 (m, 11H, Ar), 8.06 (d, J = 7.1 Hz, 2H, C_6H_5), 8.24 (d, J = 8.7 Hz, 1H, C_6H_4). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 23.7, 24.8, 30.6, 57.8, 63.6 (CH_2), 55.5 (CH_3), 70.4 (CH), 84.5, 85.9 (C≡C), 115.7, 116.5, 120.8, 124.0, 124.9, 126.3, 127.9, 129.0, 129.3, 129.7, 130.1, 131.8, 132.6, 133.6 (CH_{Ar}), 124.4, 127.0, 133.6, 134.4, 143.2, 159.6 (C_{Ar}), 172.0, 179.0, 180.8 (C). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3058 (br, w), 2955 (br, w), 2869 (br, w), 1732 (w), 1672 (s), 1634 (s), 1583 (m), 1438 (m), 1364 (m), 1335 (s), 1314 (m), 1286 (m), 1254 (s), 1163 (s), 750 (s), 701 (s), 687 (s), 540 (m). MS (EI, 70 eV): m/z (%) = 641 (M^+, 62), 597 (21), 506 (8), 410 (9), 264 (8), 217 (54), 160 (100), 91 (85), 44 (6). HRMS (EI): calcd for $C_{37}H_{33}N_3NiO_4$ ($[M]^-$) 641.18191, found 641.18378.

(*S*)-2-Amino-5-[4-nitrobenzene]pent-4-ynoic acid-Ni-(*S*)-BPB (2k). Reaction of **1** (804 mg, 1.5 mmol), $Pd(PPh_3)_4$ (86.0 mg, 0.075 mmol), CuI (28.6 mg, 0.150 mmol) and 1-bromo-4-nitrobenzene (363.6 mg, 1.8 mmol) in $HNiPr_2$ (6 ml) and 1,4-dioxane (6 ml) for 3 h gave **2k** as a red solid (66 mg, 7%); mp 145–146 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.58–1.73 (m, 1H, $CH_{2,Pro}$), 1.94–2.19 (m, 3H, $CH_{2,Pro}$), 2.60 (dd, ^3J = 7.0 Hz, ^2J = 17.3 Hz, 1H, $CH_{2,Gly}$), 2.95 (dd, ^3J = 3.0 Hz, ^2J = 17.3 Hz, 1H, $CH_{2,Gly}$), 3.14–3.28 (m, 1H, $CH_{2,Pro}$), 3.34–3.43 (m, 1H, CH_{Pro}), 3.50–3.60 (m, 2H, $CH_2Ph/CH_{2,Pro}$), 4.05–4.16 (m, 1H, CH_{Gly}), 4.39 (d, J = 12.6 Hz, 1H, CH_2Ph), 6.68 (d, J = 3.2 Hz, 2H, C_6H_4), 7.05 (d, J = 7.2 Hz, 1H, Ar), 7.15–7.63 (m, 11H, Ar), 8.05 (d, J = 7.0 Hz, 2H, C_6H_5), 8.17–8.20 (m, 2H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 23.7, 25.0, 30.6, 57.4, 63.6 (CH_2), 70.3 (CH), 84.0, 90.6 (C≡C), 121.0, 123.9, 124.0, 127.0, 127.8, 129.1, 129.2, 129.4, 129.5, 130.3, 131.8, 132.9, 133.0, 133.5 (CH_{Ar}), 126.2, 130.2, 133.7, 134.2, 143.0, 147.4 (C_{Ar}), 172.4, 178.7, 180.8 (C). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3060 (br, w), 2963 (br, w), 2868 (br, w), 1673 (m), 1635 (s), 1590 (m), 1515 (m), 1438 (m), 1338 (s), 1309 (m), 1164 (m), 852 (m), 749 (s), 700 (s), 689 (m), 541 (m). MS (EI, 70 eV): m/z (%) = 656 (M^+, 20), 626 (11), 612 (18), 439 (9), 342 (17), 217 (40), 180 (7), 160 (100), 91 (98), 44 (18). HRMS (EI): calcd for $C_{36}H_{30}N_4NiO_5$ ($[M]^-$) 656.15642, found 656.15590.

5,5′-[1,4-Benzene]bis((*S*)-2-aminopent-4-ynoic acid-Ni-(*S*)-BPB) (2l). Reaction of **1** (1600 mg, 3.00 mmol), $Pd(PPh_3)_4$ (173.3 mg, 0.15 mmol), CuI (57.2 mg, 0.30 mmol) and 1,4-dibromobenzene (353.9 mg, 1.50 mmol) in $HNiPr_2$ (12 ml) and 1,4-dioxane (12 ml) for 4.5 h gave **2l** as a red solid (785 mg, 46%); mp 205–206 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.56–1.75 (m, 2H, $CH_{2,Pro}$), 1.92–2.18 (m, 6H, $CH_{2,Pro}$), 2.45–2.64 (m, 2H, $CH_{2,Gly}$), 2.90 (d, ^2J = 16.9 Hz, 2H, $CH_{2,Gly}$), 3.18–3.38 (m, 4H, $CH_{2,Pro}/CH_{Pro}$), 3.57 (d, ^2J = 12.7 Hz, 2H, CH_2Ph), 3.47–3.62 (m, 2H, $CH_{2,Pro}$), 4.02–4.14 (m, 2H, CH_{Gly}), 4.40 (d, J = 12.7 Hz, 2H, CH_2Ph), 6.67 (d, J = 3.2 Hz, 4H, C_6H_4), 7.04–7.60 (m, 22H, Ar), 8.04 (d, J = 7.1 Hz, 4H, C_6H_5), 8.21 (d, J = 8.1 Hz, 2H, C_6H_4). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 23.7, 24.9, 30.7, 57.5, 63.5 (CH_2), 68.5, 70.3 (CH), 85.3, 86.7 (C≡C), 120.8, 123.9, 126.9, 127.9, 129.0, 129.0, 129.3, 130.2, 131.8, 132.3, 132.7, 133.7, (CH_{Ar}), 123.4, 126.4, 133.5, 134.3, 143.1 (C_{Ar}), 172.0, 179.0, 180.7 (C). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3057 (br, w), 2960 (br, w), 2867 (br, w), 1673 (m), 1634 (s), 1585 (m), 1438 (m), 1362 (m), 1334 (s), 1312 (m), 1252 (s), 1163 (m), 749 (s), 701 (s), 687 (m), 547 (m). HRMS (ESI): calcd for $C_{66}H_{56}N_6Ni_2O_6$ ($[M + H]^+$) 1145.30411, found 1145.30343, calcd for $^{13}C_1{}^{12}C_{65}H_{56}N_6Ni_2O_6$ ($[M + H]^+$) 1146.30730, found 1146.30674, calcd for $^{13}C_2{}^{12}C_{64}H_{56}N_6Ni_2O_6$ ($[M + H]^+$) 1147.30248, found 1147.30206, calcd for $C_{66}H_{56}N_6NaNi_2O_6$ ($[M + Na]^+$) 1167.28605, found 1167.28519, calcd for $^{13}C_1{}^{12}C_{65}H_{56}N_6NaNi_2O_6$ ($[M + Na]^+$) 1168.28925, found 1168.28788, calcd for $^{13}C_2{}^{12}C_{64}H_{56}N_6NaNi_2O_6$ ($[M + Na]^+$) 1169.28443, found 1169.28372.

General procedure for 3a–j and 3l

Starting with **2a–j** and **2l** (0.4–1.1 mmol) respectively: the Ni-complex was dissolved in 10 ml MeOH and afterwards 5 ml H_2O as well as 1.5 ml HCl (12 M) were added. The stirred mixture was heated to 60 °C for 20 min (the color chanced from red to green). After cooling to room temperature the mixture was diluted with water and extracted with DCM four times to remove (*S*)-BPB. The H_2O layer was treated with 5% NH_4OH until pH 1. Afterwards the amino acid was separated from the mixture by cation exchange column (Dowex 50WX8 H^+) to obtain **3a–j** and **3l** as a white solid.

(*S*)-2-Amino-5-[phenyl]pent-4-ynoic acid (3a). Reaction of **2a** (580 mg, 0.949 mmol) gave **3a** as a white solid (156 mg, 87%). Mp 238–239 °C; $[\alpha]_D^{27}$ −10.4 (*c* 0.20, 1 M HCl). ^{1}H NMR (300 MHz, CD_3OD, pH = 1): δ = 3.12 (dd, ^2J = 17.9 Hz, ^3J = 5.0 Hz, 1H, CH_2), 3.22 (d, ^2J = 17.9 Hz, ^3J = 5.4 Hz, 1H, CH_2), 4.26 (dd, ^3J = 5.0 Hz, ^3J = 5.4 Hz, 1H, CH), 7.31–7.37 (m, 3H, Ph), 7.43–7.48 (m, 2H, Ph). ^{13}C NMR (75 MHz, CD_3OD, pH = 1): δ = 22.4 (CH_2), 52.9 (CH), 82.4, 85.8 (C≡C), 124.0 (C_{Ph}), 129.5, 129.8, 133.0

(CH_{Ph}), 170.5 (COOH). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2914 (br, w), 2079 (br, w), 1577 (s), 1504 (s), 1489 (s), 1424 (s), 1403 (s), 1318 (s), 1136 (m), 1112 (m), 1069 (m), 844 (m), 752 (s), 691 (s), 527 (m), 500 (m). MS (EI, 70 eV): *m*/*z* (%) = 190 (M^+, 10), 162 (40), 133 (58), 109 (9), 47 (100), 44 (8). HRMS (ESI): calcd for $C_{11}H_{12}NO_2$ ($[M + H]^+$) 190.08626, found 190.08617.

(*S*)-2-Amino-5-[4-tolyl]pent-4-ynoic acid (3b). Reaction of **2b** (510 mg, 0.816 mmol) gave **3b** as a white solid (147 mg, 89%). Mp 239–240 °C; $[\alpha]_D^{27}$ −16.2 (*c* 0.20, 1 M HCl). ^{1}H NMR (300 MHz, CD_3OD, pH = 1): δ = 2.33 (s, 3H, CH_3), 3.15 (dd, ^2J = 17.8 Hz, ^3J = 5.0 Hz, 1H, CH_2), 3.16 (dd, ^2J = 17.8 Hz, ^3J = 5.5 Hz, 1H, CH_2), 4.26 (dd, ^3J = 5.0 Hz, ^3J = 5.5 Hz, CH), 7.14 (d, ^3J = 7.9 Hz, 2H, Ar), 7.33 (d, ^3J = 7.9 Hz, 2H, Ar). ^{13}C NMR (75 MHz, CD_3OD, pH = 1): δ = 21.6 (CH_3), 22.4 (CH_2), 52.9 (CH), 81.7, 86.1 (C≡C), 121.0, 140.1 (C_{Ar}), 130.2, 132.9 (CH_{Ar}), 170.5 (COOH). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3128 (br, m), 3026 (br, m), 2865 (br, m), 2081 (br, w), 1759 (br, w), 1605 (m), 1576 (m), 1508 (s), 1489 (m), 1423 (s), 1401 (s), 1367 (m), 1321 (s), 1134 (m), 1107 (m), 816 (s), 528 (s). MS (EI, 70 eV): *m*/*z* (%) = 203 (M^+, 7), 186 (5), 171 (3), 159 (100), 143 (11), 129 (41), 115 (16), 105 (48), 91 (11), 74 (11), 44 (29). HRMS (ESI): calcd for $C_{12}H_{12}NO_2$ ($[M - H]^-$) 202.08735, found 202.0696.

(*S*)-2-Amino-5-[3-tolyl]pent-4-ynoic acid (3c). Reaction of **2c** (521 mg, 0.833 mmol) gave **3c** as a white solid (144 mg, 87%). Mp 228–229 °C; $[\alpha]_D^{24}$ −11.3 (*c* 0.20, 1 M HCl). ^{1}H NMR (300 MHz, D_2O, pH = 1): δ = 2.09 (s, 3H, CH_3), 2.93 (dd, ^2J = 18.0 Hz, ^3J = 4.9 Hz, 1H, CH_2), 3.04 (dd, ^2J = 18.0 Hz, ^3J = 5.8 Hz, 1H, CH_2), 4.19 (dd, ^3J = 4.9 Hz, ^3J = 5.8 Hz, 1H, CH), 7.05–7.10 (m, 3H, Ar), 7.13 (bs, 1H, Ar). ^{13}C NMR (62.9 MHz, D_2O, pH = 1): δ = 20.1 (CH_3), 20.7 (CH_2), 51.4 (CH), 81.2, 84.8 (C≡C), 121.5, 138.7 (C_{Ar}), 128.4, 128.6, 129.7, 134.0 (CH_{Ar}), 170.2 (COOH). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3174 (br, w), 2962 (br, m), 1599 (s), 1581 (s), 1505 (s), 1486 (m), 1425 (s), 1402 (s), 1351 (m), 1319 (s), 1113 (m), 798 (m), 784 (s), 693 (s), 530 (m). MS (EI, 70 eV): *m*/*z* (%) = 204 (M^+, 2), 186 (76), 158 (28), 144 (10), 129 (100), 115 (22), 91 (7), 75 (41), 36 (26). HRMS (ESI): calcd for $C_{12}H_{14}NO_2$ ($[M + H]^+$) 204.10191, found 204.10209, calcd for $C_{12}H_{13}NaNO_2$ ($[M + Na]^+$) 226.08385, found 226.0839.

(*S*)-2-Amino-5-[2-tolyl]pent-4-ynoic acid (3d). Reaction of **2d** (379 mg, 0.606 mmol) gave **3d** as a white solid (88 mg, 72%). Mp 197–198 °C; $[\alpha]_D^{25}$ −10.4 (*c* 0.23, 1 M HCl). ^{1}H NMR (250 MHz, D_2O, pH = 1): δ = 2.37 (s, 3H, CH_3), 3.16 (dd, ^2J = 17.9 Hz, ^3J = 4.8 Hz, 1H, CH_2), 3.31 (dd, ^2J = 17.9 Hz, ^3J = 5.5 Hz, 1H, CH_2), 4.40 (dd, ^3J = 4.8 Hz, ^3J = 5.5 Hz, 1H, CH), 7.12–7.47 (m, 4H, Ar). ^{13}C NMR (62.9 MHz, D_2O, pH = 1): δ = 19.7 (CH_3), 21.1 (CH_2), 51.7 (CH), 83.6, 85.5 (C≡C), 121.4, 140.8 (C_{Ar}), 125.7, 129.1, 129.5, 132.1 (CH_{Ar}), 170.4 (COOH). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3117 (br, w), 3043 (br, m), 2956 (br, m), 1606 (s), 1419 (m), 1403 (s), 1331 (m), 752 (s), 549 (m), 531 (s). MS (EI, 70 eV): *m*/*z* (%) = 203 (M^+, 3), 186 (3), 171 (3), 158 (27), 143 (8), 128 (44), 115 (20), 91 (6), 74 (100), 44 (8). HRMS (ESI): calcd for $C_{12}H_{12}NO_2$ ($[M - H]^-$) 202.08735, found 202.08696.

(*S*)-2-Amino-5-[naphth-1-yl]pent-4-ynoic acid (3e). Reaction of **2e** (604 mg, 0.914 mmol) gave **3e** as a white solid (129 mg, 54%). Mp 223–224 °C; $[\alpha]_D^{26}$ −11.4 (*c* 0.19, 1 M HCl). ^{1}H NMR (300 MHz, CD_3OD, pH = 1): δ = 3.30 (dd, ^2J = 17.8 Hz, ^3J = 5.0 Hz, 1H, CH_2), 3.40 (d, ^2J = 17.8 Hz, ^3J = 5.4 Hz, 1H, CH_2), 4.37 (dd, ^3J = 5.0 Hz, ^3J = 5.4 Hz, 1H, CH), 7.44 (dd, ^3J = 7.1 Hz, ^3J = 8.0 Hz, 1H, Ar), 7.51–7.63 (m, 2H, Ar), 7.70 (dd, ^4J = 0.8 Hz, ^3J = 7.1 Hz, 1H, Ar), 7.88 (d, ^3J = 8.4 Hz, 2H, Ar), 8.30 (d, ^3J = 8.0 Hz, 1H, Ar). ^{13}C NMR (75 MHz, CD_3OD, pH = 1): δ = 22.7 (CH_2), 53.0 (CH), 84.0, 87.5 (C≡C), 121.5 (C_{Ar}), 126.4, 127.2, 127.7, 128.1, 129.5, 130.2, 132.1 (CH_{Ar}), 134.7, 134.8 (C_{Ar}), 170.6 (COOH). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3120 (br, m), 3041 (br, m), 2832 (br, m), 1756 (br, w), 1587 (m), 1504 (m), 1396 (s), 1322 (m), 1097 (br, m), 1063 (br, m), 1016 (m), 799 (s), 770 (s), 615 (m), 564 (m). MS (EI, 70 eV): *m*/*z* (%) = 239 (M^+, 54), 222 (13), 167 (82), 165 (100), 152 (10), 139 (8), 128 (9), 74 (26). HRMS (ESI): calcd for $C_{15}H_{12}NO_2$ ($[M - H]^-$) 238.08735, found 238.0869.

(*S*)-2-Amino-5-[thiophen-2-yl]pent-4-ynoic acid (3f). Reaction of **2f** (649 mg, 1.050 mmol) gave **3f** as a white solid (180 mg, 88%). Mp 230–231 °C; $[\alpha]_D^{28}$ −9.3 (*c* 0.20, 1 M HCl). ^{1}H NMR (300 MHz, CD_3OD, pH = 1): δ = 3.15 (d, ^2J = 17.8 Hz, ^3J = 5.0 Hz, 1H, CH_2), 3.32 (d, ^2J = 17.8 Hz, ^3J = 5.6 Hz, 1H, CH_2), 4.26 (dd, ^3J = 5.0 Hz, ^3J = 5.6 Hz, 1H, CH), 7.00 (dd, ^3J = 3.6 Hz, ^3J = 5.1 Hz, 1H, Ar), 7.25 (dd, ^4J = 1.1 Hz, ^3J = 3.6 Hz, 1H, Ar), 7.25 (dd, ^4J = 1.1 Hz, ^3J = 5.1 Hz, 1H, Ar). ^{13}C NMR (62.9 MHz, CD_3OD, pH = 1): δ = 22.6 (CH_2), 52.7 (CH), 79.2, 86.5 (C≡C), 133.0 (C_{Ar}), 128.2, 128.8, 133.8 (CH_{Ar}), 170.3 (COOH). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3012 (br, m), 2600 (br, w), 2084 (br, w), 1576 (m), 1504 (s), 1420 (s), 1405 (s), 1316 (m), 828 (m), 695 (s). MS (EI, 70 eV): *m*/*z* (%) = 195 (M^+, 0), 152 (84), 123 (100), 109 (21), 96 (18), 45 (9). HRMS (ESI): calcd for $C_9H_8NO_2S$ ($[M - H]^-$) 194.02812, found 194.02767.

(*S*)-2-Amino-5-[4-fluorobenzene]pent-4-ynoic acid (3g). Reaction of **2g** (529 mg, 0.841 mmol) gave **3g** as a white solid (156 mg, 90%). Mp 228–229 °C; $[\alpha]_D^{25}$ −9.8 (*c* 0.20, 1 M HCl); ee > 99% (HPLC). ^{1}H NMR (250 MHz, D_2O, pH = 1): δ = 3.08 (dd, ^2J = 18.0 Hz, ^3J = 5.4 Hz, 1H, CH_2), 3.17 (dd, ^2J = 18.0 Hz, ^3J = 5.8 Hz, 1H, CH_2), 4.33 (dd, ^3J = 5.4 Hz, ^3J = 5.8 Hz, 1H, CH), 7.01–7.13 (m, 2H, Ar), 7.41–7.60 (m, 2H, Ar). ^{13}C NMR (62.9 MHz, D_2O, pH = 1): δ = 22.4 (CH_2), 53.1 (CH), 82.7, 85.5 (C≡C), 117.2 (d, ^2J = 22.3 Hz, CH_{Ar}), 119.4 (d, ^4J = 3.4 Hz, C_{Ar}), 135.4 (d, ^3J = 8.7 Hz, CH_{Ar}), 164.1 (d, ^1J = 247.3 Hz, CF), 171.9 (COOH). ^{19}F NMR (282.4 MHz, CD_3OD, pH = 1): δ = −111.0. IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3161 (br, m), 2991 (br, m), 2914 (br, m), 1601 (s), 1505 (s), 1479 (s), 1426 (s), 1405 (s), 1356 (m), 1323 (m), 1219 (s), 1148 (m), 1110 (m), 1094 (m), 833 (s), 811 (m), 628 (m), 526 (s). MS (EI, 70 eV): *m*/*z* (%) = 207 (M^+, 2), 190 (11), 162 (49), 133 (61), 115 (18), 91 (7), 74 (100), 44 (37). HRMS (ESI): calcd for $C_{11}H_{19}FNO_2$ ($[M - H]^-$) 206.06228, found 206.06284.

(*S*)-2-Amino-5-[4-chlorobenzene]pent-4-ynoic acid (3h). Reaction of **2h** (612 mg, 0.949 mmol) gave **3h** as a white solid (179 mg, 84%). Mp 225–226 °C; $[\alpha]_D^{27}$ −21.0 (*c* 0.20, 1 M HCl). ^{1}H NMR (300 MHz, CD_3OD, pH = 1): δ = 3.13 (dd, ^2J = 18.0 Hz, ^3J = 4.9 Hz, 1H, CH_2), 3.19 (dd, ^2J = 18.0 Hz, ^3J = 5.3 Hz, 1H, CH_2), 4.27 (dd, ^3J = 4.9 Hz, ^3J = 5.3 Hz, 1H, CH), 7.34 (d, ^3J = 8.6 Hz, 2H, Ar), 7.44 (d, ^3J = 8.6 Hz, 2H, Ar). ^{13}C NMR (75 MHz, CD_3OD, pH = 1): δ = 22.4 (CH_2), 52.9 (CH), 83.9, 84.8 (C≡C), 122.8, 135.7 (C_{Ar}), 129.8, 134.5 (CH_{Ar}), 170.4 (COOH). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3130 (br, m), 3039 (br, m), 1771 (br, w), 1604 (m), 1591 (m), 1508 (m), 1488 (s), 1425 (m), 1401 (s), 1367 (m), 1356 (m), 1323 (s), 1149 (m), 1110 (m), 1089 (s), 1069 (m), 1016 (m), 823 (s), 637 (m). MS (EI, 70 eV): *m*/*z* (%) = 223 (M^+, 2), 206 (5), 178 (47), 149 (19), 125 (11), 115 (35), 59 (7), 74 (100), 63 (6), 44 (19). HRMS

(ESI): calcd for $C_{11}H_9{}^{35}ClNO_2$ ([M − H]$^-$) 222.03273, found 222.03226, calcd for $C_{11}H_9{}^{37}ClNO_2$ ([M − H]$^-$) 224.03007, found 224.02953.

(*S*)-2-Amino-5-[4-(trifluoromethyl)benzene]pent-4-ynoic acid (3i). Reaction of **2i** (748 mg, 1.100 mmol) gave **3i** as a white solid (261 mg, 92%). Mp 220–221 °C; $[\alpha]_D^{27}$ −10.7 (*c* 0.25, 1 M HCl). ^{1}H NMR (300 MHz, CD_3OD, pH = 1): δ = 3.22 (d, ^3J = 5.0 Hz, 1H, CH_2), 3.22 (d, ^3J = 5.4 Hz, 1H, CH_2), 4.32 (dd, ^3J = 5.0 Hz, ^3J = 5.4 Hz, 1H, CH), 7.63–7.67 (m, 4H, Ar). ^{13}C NMR (75 MHz, CD_3OD, pH = 1): δ = 22.4 (CH_2), 52.7 (CH), 84.5, 85.7 (C≡C), 125.5 (q, ^1J = 271 Hz, CF_3), 126.5 (q, ^3J = 3.8 Hz, CH_{Ar}), 128.2 (C_{Ar}), 131.3 (q, ^2J = 32.2 Hz, C_{Ar}), 133.6 (CH_{Ar}), 170.3 (COOH). ^{19}F NMR (282.4 MHz, CD_3OD, pH = 1): δ = −64.3. IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3132 (br, m), 3040 (br, m), 2619 (br, w), 2088 (br, w), 1767 (br, w), 1607 (m), 1575 (m), 1507 (m), 1480 (m), 1425 (m), 1404 (s), 1321 (s), 1291 (m), 1168 (s), 1126 (s), 1104 (s), 1068 (s), 1019 (m), 842 (s), 596 (m). MS (EI, 70 eV): *m*/*z* (%) = 257 (M$^+$, 1), 240 (12), 212 (47), 183 (31), 164 (16), 143 (21), 115 (24), 74 (100). HRMS (ESI): calcd for $C_{12}H_9F_3NO_2$ ([M − H]$^-$) 256.05909, found 256.05876.

(*S*)-2-Amino-5-[3-methoxybenzene]pent-4-ynoic acid (3j). Reaction of **2j** (280 mg, 0.436 mmol) gave **3j** as a white solid (94 mg, 99%). Mp 209–210 °C; $[\alpha]_D^{26}$ −10.2 (*c* 0.20, 1 M HCl); ee > 99% (HPLC). ^{1}H NMR (250 MHz, D_2O, pH = 1): δ = 3.15 (dd, ^2J = 18.0 Hz, ^3J = 5.2 Hz, 1H, CH_2), 3.22 (dd, ^2J = 18.0 Hz, ^3J = 6.0 Hz, 1H, CH_2), 3.79 (s, 3H, CH_3) 4.25 (dd, ^3J = 5.2 Hz, ^3J = 6.0 Hz, 1H, CH), 6.98–7.17 (m, 3H, Ar), 7.28–7.45 (m, 1H, Ar). ^{13}C NMR (62.9 MHz, D_2O, pH = 1): δ = 22.4 (CH_2), 53.1 (CH), 57.0 (CH_3), 82.3, 86.0 (C≡C), 116.7, 118.5, 126.2, 131.5 (CH_{Ar}), 124.5, 160.2 (C_{Ar}), 172.0 (COOH). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3126 (br, m), 3009 (br, m), 2835 (br, m), 2087 (br, w), 1766 (br, w), 1583 (s), 1507 (s), 1489 (s), 1469 (m), 1404 (s), 1351 (m), 1317 (s), 1288 (s), 1267 (m), 1208 (s), 1179 (m), 1108 (br, m), 1037 (s), 860 (s), 785 (s), 689 (m), 615 (m), 534 (s). MS (EI, 70 eV): *m*/*z* (%) = 219 (M$^+$, 26), 202 (27), 174 (100), 159 (11), 145 (36), 115 (21), 91 (9), 74 (76), 44 (20). HRMS (ESI): calcd for $C_{12}H_{12}NO_3$ ([M − H]$^-$) 218.08227, found 218.08186.

5,5′-[1,4-Benzene]bis((*S*)-2-aminopent-4-ynoic acid) (3l). Reaction of **2l** (602 mg, 0.525 mmol) gave **3l** as a white solid (133 mg, 85%). Mp 260 °C (decomposition); $[\alpha]_D^{27}$ −31.1 (*c* 0.18, 1 M HCl). ^{1}H NMR (300 MHz, CD_3OD, pH = 1): δ = 3.14 (dd, ^2J = 17.9 Hz, ^3J = 5.0 Hz, 2H, CH_2), 3.21 (dd, ^2J = 17.9 Hz, ^3J = 5.4 Hz, 2H, CH_2), 4.28 (dd, ^3J = 5.0 Hz, ^3J = 5.4 Hz, 2H, CH), 7.43 (s, 4H, Ar). ^{13}C NMR (62.9 MHz, CD_3OD, pH = 1): δ = 22.4 (CH_2), 52.8 (CH), 84.7, 85.4 (C≡C), 124.3 (C_{Ar}), 133.0 (CH_{Ar}), 170.4 (COOH). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3120 (br, w), 2993 (br, m), 2660 (br, w), 1607 (br, s), 1541 (s), 1502 (m), 1424 (m), 1403 (s), 1370 (s), 1332 (s), 1070 (m), 842 (s), 610 (m), 560 (m), 531 (s). HRMS (ESI): calcd for $C_{16}H_{15}N_2O_4$ ([M − H]$^-$) 299.10373, found 299.10457.

OSIRIS drug properties and toxicity profile

The novel synthesized series of compounds were evaluated for their potential to qualify as drug candidate by using OSIRIS property explorer[26] based on Lipinski's rule of five.[25] Additionally, the OSIRIS property explorer was also used to determine the toxicity of the synthesized series. Toxicity profiles such as tumorigenic, mutagenic, irritability and reproductive toxicity were calculated using the same software.

Enzyme part

Materials. Coenzyme nicotinamide adenine dinucleotide phosphate (NADPH), (D, L-glyceraldehyde), quercetin were purchased from Sigma-Aldrich Chemical Co. (St. Louis, MO, USA). All the solvents of highest purity used were bought from Merck, Fluka while valproate acid was purchased from local pharmaceutical store.

Extraction and activity of ALR1 and ALR2

Isolation and purification of aldehyde reductase enzyme (ALR1). ALR1 was purified from bovine kidney using extraction method previously described.[31] Briefly, bovine kidneys were collected from a local abattoir were diced and homogenised in three volumes of 10 mM sodium phosphate buffer (pH 7.2) containing 0.25 M sucrose, 2.0 mM EDTA and 2.5 mM b-mercaptoethanol. The homogenate was centrifuged at 10 000 g and −4 °C for 30 min, obtained supernatant was fractionated by the addition of 40–60% ammonium sulphate. The ammonium sulphate concentration was further increased to 75% to have ALR1 been precipitated. And this was performed at the operation condition of −4 °C. The purified enzyme in pellet form was suspended in 10 mM sodium phosphate buffer (pH 7.2) with 2.0 mM of EDTA and 2.5 mM b-mercaptoethanol in it and dialyzed over the night with the same buffer. The volume dialyzed enzyme was noted and stored at −80 °C and was subsequently used for enzymatic assays.[36]

Isolation and purification of aldose reductase enzyme (ALR2). Isolation and purification of ALR2 enzyme was carried out using calf lenses according to the modified method previously described.[37] The lenses were quickly removed from the calf eyes into a glass homogenizer surrounded with ice and homogenized with 10 ml of 10 mM phosphate buffer of pH 7.0 that contains the mixture of 1 mM b-mercaptoethanol and 1 mM EDTA, centrifuged at 18 000 g at −4 °C for 20 min. Ammonium sulphate was slowly added to the stirred supernatant fraction that yielded a 35% saturated solution. After the completion of the stirring for 3 h, the solution was further centrifuged at 18 000*g* for the period of 20 min and precipitated. The precipitates were dissolved in buffer of phosphate (pH 7.0) and dialysed for two days using the same buffer. The purified ALR2 was store at −80 °C until was used in the enzyme assays.

ALR1 and ALR2 enzyme assays

ALR1 enzyme assay. The enzymatic activities of ALR1 and ALR2 were determined by assayed spectrophotometrically using a microplate reader (Bio-Tek ELx 800™, Instruments Inc., Winooski, VT, USA) which measures the decrease in the absorption of NADPH that follows by the oxidation of NADPH catalyzed by both enzymes. The activity of ALR1 was measured according to the reported procedure,[38] assayed spectrophotometrically by determining NADPH consumption at 340 nm. The reaction mixture consists of 20 μl of the inhibitor, 0.1 mM NADPH, 0.1 M sodium phosphate buffer (pH 6.2), 10 mM of sodium D-glucuronate and enzyme to make a total volume of 200 μl. The reaction was initiated by the addition of substrate after the incubation for 10 min at 37 °C. The change in absorbance was measured on a microplate at a wavelength of 340 nm after 5 min of incubation at 37 °C. Correction of oxidation

associated with NADPH was employed by appropriate blank while 20 μl of valproic acid (10 mM) was used as the positive control. A unit of the enzyme is defined as an amount of it required in catalyzing the oxidation of 1 mM of NADPH per minute in the assay condition.

ALR2 enzyme assay. ALR2 activity was assayed according to the prescribed method,[39] the reaction mixture contained 40 μl of 10 mM DL-glyceraldehyde (substrate) and all other reagents were added in the way according to the ALR1 assay procedure. More so, 20 μl of quercetin (1 mM) was used as the positive control. All the reactions were performed in triplicate. The absorbance was recorded and the data was analyzed using PRISM 5.0 (GraphPad, San Diego, California, USA) to calculate the IC50 value of the test sample which percentage inhibition is above 50%. The percentage inhibition was calculated using the equation below, $100 - (OD_{testwell}/OD_{control}) \times 100$.[40]

Molecular docking

Molecular docking study of compound **3a** was performed using LeadIT from BioSolveIT, GmbH Germany.[41] The compound structure was drawn using ACD/ChemSketch[42] and was 3D optimized. Crystal structure of human aldose reductase PDB ID 1US0 was downloaded from RCSB protein data bank,[43] while crystal structure of porcine aldehyde reductase PDB ID 3FX4 was downloaded to carry out docking studies.

Using 'Load or Prepare' utility of LeadIT software, the receptor structures were prepared. In case of ALR-1, nicotinamide adenine dinucleotide phosphate (NADP) was selected as a co-factor, while in case of ALR-2, dihydro nicotinamide adenine dinucleotide phosphate (NADPH) was selected. Active site of the receptor was defined as the amino acid residues in 7.5 Å radii of the co-crystallized reference ligand. The co-crystallized reference ligand in case of ALR-1 was FX4 ([(5*Z*)-5-{[3-(carboxymethoxy)-4-methoxyphenyl]methylidene}-2,4-dioxo-1,3-thiazolidin-3-yl]acetic acid) while in case of ALR-2, the reference ligand was IDD594 (2-(2-{[(4-bromo-2-fluorophenyl) methyl]carbamothioyl}-5-fluorophenoxy)acetic acid).

Using default docking parameters of the software, molecular docking studies were carried out. The docking parameters were first optimized by re-docking of the reference ligands and determining their RMSD values with the co-crystallized structures. After successful re-docking of the reference ligand, molecular docking of compound **3a** was carried out. Top ranking 30 poses of the compound **3a** was generated. The putative binding mode of the compound was then carefully selected after visual as well as HYDE assessment[44] and 3D docking figure of the compound was then prepared using Discovery Studio Visualizer v4.0.[45]

Acknowledgements

Financial support by the Volkswagenstiftung (Az86223) and by the State of Mecklenburg-Vorpommern is gratefully acknowledged.

References

1 A. Strecker, *Justus Liebigs Ann. Chem.*, 1850, 27–45.

2 (*a*) *Asymmetric Catalysis on Industrial Scale*, ed. H.-U. Blaser and H.-J. Federsel, Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim, Germany, 2010; (*b*) R. O. Duthaler, *Tetrahedron*, 1994, **50**, 1539–1650; (*c*) D. E. Patterson, S. Xie, L. A. Jones, M. H. Osterhout, C. G. Henry and T. D. Roper, Large-Scale Application of Asymmetric Phase-Transfer Catalysis for Amino Acid Synthesis, in *Asymmetric Catalysis on Industrial Scale*, ed. H.-U. Blaser and H.-J. Federsel, Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim, Germany, 2010, pp. 473–484; (*d*) B. Weiner, W. Szymański, D. B. Janssen, A. J. Minnaard and B. L. Feringa, *Chem. Soc. Rev.*, 2010, **39**, 1656.

3 (*a*) J. L. Aceña, A. E. Sorochinsky, H. Moriwaki, T. Sato and V. A. Soloshonok, *J. Fluorine Chem.*, 2013, **155**, 21–38; (*b*) M. Nádvorník, V. Langer, R. Jirásko, M. Holčapek, T. Weidlich, A. Lyčka and A. Popkov, *Polyhedron*, 2008, **27**, 3477–3483; (*c*) A. Popkov and B. de Spiegeleer, *Dalton Trans.*, 2012, **41**, 1430–1440; (*d*) V. Soloshonok, H. Ueki and T. Ellis, *Synlett*, 2009, **2009**, 704–715; (*e*) A. E. Sorochinsky, J. L. Aceña, H. Moriwaki, T. Sato and V. Soloshonok, *Amino Acids*, 2013, **45**, 1017–1033; (*f*) J. Wang, L. Zhang, H. Jiang, K. Chen and H. Liu, *Chimia*, 2011, **65**, 919–924.

4 (*a*) V. A. Soloshonok, C. Cai and V. J. Hruby, *Tetrahedron: Asymmetry*, 1999, **10**, 4265–4269; (*b*) V. A. Soloshonok, C. Cai, V. J. Hruby, L. van Meervelt and T. Yamazaki, *J. Org. Chem.*, 2000, **65**, 6688–6696.

5 V. A. Soloshonok, D. V. Avilov, V. P. Kukhar, L. van Meervelt and N. Mischenko, *Tetrahedron Lett.*, 1997, **38**, 4671–4674.

6 (*a*) V. A. Soloshonok, V. P. Kukhar, S. V. Galushko, N. Y. Svistunova, D. V. Avilov, N. A. Kuz'mina, N. I. Raevski, Y. T. Struchkov, A. P. Pysarevsky and Y. N. Belokon, *J. Chem. Soc., Perkin Trans. 1*, 1993, 3143; (*b*) V. A. Soloshonok, D. V. Avilov, V. P. Kukhar', V. I. Tararov, T. F. Savel'eva, T. D. Churkina, N. S. Ikonnikov, K. A. Kochetkov, S. A. Orlova, A. P. Pysarevsky, Y. T. Struchkov, N. I. Raevsky and Y. N. Belokon', *Tetrahedron: Asymmetry*, 1995, **6**, 1741–1756.

7 A. E. Sorochinsky, J. L. Aceña, H. Moriwaki, T. Sato and V. A. Soloshonok, *Amino Acids*, 2013, **45**, 691–718.

8 D. Houck, J. Luis Aceña and V. A. Soloshonok, *Helv. Chim. Acta*, 2012, **95**, 2672–2679.

9 (*a*) R. Chinchilla and C. Nájera, *Chem. Rev.*, 2007, **107**, 874–922; (*b*) R. Chinchilla and C. Nájera, *Chem. Soc. Rev.*, 2011, **40**, 5084–5121; (*c*) A. M. Thomas, A. Sujatha and G. Anilkumar, *RSC Adv.*, 2014, **4**, 21688.

10 H. Dibowski and F. P. Schmidtchen, *Angew. Chem., Int. Ed.*, 1998, **37**, 476–478.

11 (*a*) R. J. Brea, M. P. López-Deber, L. Castedo and J. R. Granja, *J. Org. Chem.*, 2006, **71**, 7870–7873; (*b*) G. T. Crisp and J. Gore, *Tetrahedron*, 1997, **53**, 1523–1544; (*c*) G. T. Crisp and T. A. Robertson, *Tetrahedron*, 1992, **48**, 3239–3250; (*d*) P. D. Greenspan, K. L. Clark, R. A. Tommasi, S. D. Cowen, L. W. McQuire, D. L. Farley, J. H. van Duzer, R. L. Goldberg, H. Zhou, Z. Du, J. J. Fitt, D. E. Coppa, Z. Fang, W. Macchia, L. Zhu, M. P. Capparelli, R. Goldstein, A. M. Wigg, J. R. Doughty, R. S. Bohacek and A. K. Knap, *J. Med. Chem.*, 2001, **44**, 4524–4534; (*e*)

M. J. Pérez-Alvite, M. Mosquera, L. Castedo and J. R. Granja, *Amino Acids*, 2011, **41**, 621–628; (*f*) G. T. Shchetnikov, M. A. Zotova, C. Bruneau, P. H. Dixneuf and S. N. Osipov, *Eur. J. Org. Chem.*, 2010, **2010**, 1587–1592.

12 P. Zimmet, K. G. Alberti and J. Shaw, *Nature*, 2001, **414**, 782–787.

13 O. El-Kabbani, F. Ruiz, C. Darmanin and R. P.-T. Chung, *Cell. Mol. Life Sci.*, 2004, **61**, 750–762.

14 E. Kubo, N. Miyoshi, M. Fukuda and Y. Akagi, *Exp. Eye Res.*, 1999, **68**, 457–464.

15 A. Y. Lee and S. S. Chung, *FASEB J.*, 1999, **13**, 23–30.

16 P. F. Kador, J. H. Kinoshita, W. H. Tung and L. T. Chylack Jr, *Invest. Ophthalmol. Visual Sci.*, 1980, **19**, 980–982.

17 S. Srivastava, M. Spite, J. O. Trent, M. B. West, Y. Ahmed and A. Bhatnagar, *J. Biol. Chem.*, 2004, **279**, 53395–53406.

18 B. Tabakoff and V. G. Erwin, *J. Biol. Chem.*, 1970, **245**, 3263–3268.

19 D. R. Tulsiani and O. Touster, *J. Biol. Chem.*, 1977, **252**, 2545–2550.

20 A. Hara, Y. Deyashiki, T. Nakayama and H. Sawada, *Eur. J. Biochem.*, 1983, **133**, 207–214.

21 H. Sawada, A. Hara, T. Nakayama and F. Kato, *J. Biochem.*, 1980, **87**, 1153–1165.

22 B. Wermuth, J. D. Münch and J. P. von Wartburg, *J. Biol. Chem.*, 1977, **252**, 3821–3828.

23 M. Dunlop, *Kidney Int.*, 2000, **58**, 3–12.

24 C. Yabe-Nishimura, *Pharmacol. Rev.*, 1998, **50**, 21–33.

25 C. A. Lipinski, F. Lombardo, B. W. Dominy and P. J. Feeney, *Adv. Drug Delivery Rev.*, 2012, **64**, 4–17.

26 T. Sander, *OSIRIS property explorer. Allschwil*, Actelion Pharmaceuticals Ltd, 2001, http://www.organic-chemistry.org/prog/peo/index.html.

27 V. Carbone, M. Giglio, R. Chung, T. Huyton, J. Adams, R. Maccari, R. Ottana, A. Hara and O. El-Kabbani, *Eur. J. Med. Chem.*, 2010, **45**, 1140–1145.

28 O. A. Barski, K. H. Gabbay and K. M. Bohren, *Genomics*, 1999, **60**, 188–198.

29 O. El-Kabbani, V. Carbone, C. Darmanin, M. Oka, A. Mitschler, A. Podjarny, C. Schulze-Briese and R. P.-T. Chung, *J. Med. Chem.*, 2005, **48**, 5536–5542.

30 O. El-Kabbani, L. Sthanam, V. L. Narayana, K. M. Moore, N. C. Green, T. G. Flynn and L. J. Delucas, *Acta Crystallogr., Sect. D: Biol. Crystallogr.*, 1993, **49**, 490–496.

31 A. Del Corso, L. Costantino, G. Rastelli, F. Buono and U. Mura, *Exp. Eye Res.*, 2000, **71**, 515–521.

32 O. El-Kabbani, D. K. Wilson, J. M. Petrash and F. A. Quiocho, *Mol. Vision*, 1998, **4**, 19–25.

33 S. Hayman and J. H. Kinoshita, *J. Biol. Chem.*, 1965, **240**, 877.

34 O. El-Kabbani, C. Darmanin, T. R. Schneider, I. Hazemann, F. Ruiz and M. Oka, *Proteins: Struct., Funct., Bioinf.*, 2004, **55**(4), 805–813.

35 V. Carbone, R. Chung, S. Endo, A. Hara and O. El-Kabbani, *Arch. Biochem. Biophys.*, 2008, **479**(1), 82–87.

36 A. K. Daly and T. J. Mantle, *J. Biochem.*, 1982, **205**, 373–380.

37 P. F. Kador, J. H. Kinoshita, D. R. Brittain, D. J. Mirrlees, C. M. Sennitt and D. Stribling, *J. Biochem.*, 1986, **240**, 233–237.

38 L. Costantino, G. Rastelli, M. C. Gamberini, J. A. Vinson, P. Bose, A. Iannone, M. Staffieri, L. Antolini, A. Del Corso, U. Mura and A. Albasini, *J. Med. Chem.*, 1999, **42**, 1881–1893.

39 F. Da Settimo, G. Primofiore, C. La Motta, S. Salerno, E. Novellino, G. Greco, A. Lavecchia, S. Laneri and E. Boldrini, *Bioorg. Med. Chem.*, 2005, **13**, 491–499.

40 M. Saraswat, P. Muthenna, P. Suryanarayana, J. M. Petrash and G. B. Reddy, *Asia Pac. J. Clin. Nutr.*, 2008, **17**, 558–565.

41 *LeadIT: BioSolveIT GmbH*, Germany, 2014.

42 *ACD/ChemSketch. 14.00 ed*, Advanced Chemistry Development, Inc., Toronto, On, Canada, 2015.

43 H. M. Berman, J. Westbrook, Z. Feng, G. Gilliland, T. Bhat and H. Weissig, *Nucleic Acids Res.*, 2000, **28**(1), 235–242.

44 N. Schneider, G. Lange, S. Hindle, R. Klein and M. J. Rarey, *J. Comput.-Aided Mol. Des.*, 2013, **27**(1), 15–29.

45 *Discovery StudioVisualizer. 4.0 ed*, Accelrys Software Inc, 2005.

