Bioorganic & Medicinal Chemistry 20 (2012) 6687–6708

Contents lists available at SciVerse ScienceDirect

Bioorganic & Medicinal Chemistry

journal homepage: www.elsevier.com/locate/bmc

Homo- and heterodimeric Smac mimetics/IAP inhibitors as in vivo-active pro-apoptotic agents. Part I: Synthesis

Leonardo Manzoni [a], Laura Belvisi [b], Aldo Bianchi [c], Annalisa Conti [d], Carmelo Drago [c], Marilenia de Matteo [c], Luca Ferrante [c], Eloise Mastrangelo [e], Paola Perego [d], Donatella Potenza [b], Carlo Scolastico [c], Federica Servida [f], Gabriele Timpano [c], Francesca Vasile [b], Vincenzo Rizzo [c], Pierfausto Seneci [b,c,*]

[a] Istituto di Scienze e Tecnologie Molecolari (ISTM), Consiglio Nazionale delle Ricerche (CNR), Via Golgi 19, Milan I-20133, Italy
[b] Dipartimento di Chimica, Università degli Studi di Milano, Via Golgi 19, Milan I-20133, Italy
[c] CISI scrl, Via Fantoli 16/15, Milan I-20138, Italy
[d] Dipartimento di Oncologia Sperimentale e Medicina Molecolare, Fondazione IRCCS Istituto Nazionale dei Tumori, Via Amadeo 42, Milan I-20133, Italy
[e] Dipartimento di Bioscienze e CNR-IBF, Università degli Studi di Milano, Via Celoria 26, Milan I-20133, Italy
[f] Fondazione Matarelli, Dipartimento di Farmacologia, Chemioterapia e Tossicologia Medica, Università degli Studi di Milano, Via Vanvitelli 32, Milan I-20129, Italy

ARTICLE INFO

Article history:
Available online 21 September 2012

Keywords:
IAP inhibitors
Smac mimetics
Apoptosis
Oncology
Peptidomimetics

ABSTRACT

Novel pro-apoptotic, homo- and heterodimeric Smac mimetics/IAPs inhibitors based on the N-AVPI-like 4-substituted 1-aza-2-oxobicyclo[5.3.0]decane scaffold were prepared from monomeric structures connected through a head–head (**8**), tail–tail (**9**) or head–tail (**10**) linker. The selection of appropriate decorating functions for the scaffolds, and of rigid and flexible linkers connecting them, is described. The synthesis, purification and analytical characterization of each prepared dimer **8–10** is thoroughly described.

1. Introduction

The apoptotic process of programmed cell death is dysfunctional in its regulation in a variety of human pathologies, among which cancer,[1–3] inflammation[4,5] and neurodegeneration,[6,7] where it has become the focus of extensive pharmaceutical research. Pathways leading to apoptosis include the extrinsic or death receptor-dependent path[8,9] and the intrinsic or mitochondrial path,[8,10] both caspase-dependent; and some caspase-independent mechanisms, involving other proteases as apoptosis executioners.[11]

In a complex scenario, hitting more than one putative significant target with a lead should maximize the chances of therapeutic success. Thus, we focused on targeting molecular entities involved in several apoptotic pathways, rather than extremely targeted agents. Such polypharmacology[12] approach is precedented in target classes such as kinases[13] and GPCRs.[14]

The family of Inhibitor of Apoptosis Proteins (IAPs)[15,16] is characterized by the presence of one or more Baculovirus IAP Repeat (BIR) domains. Since the discovery of the first viral *iap* gene and its linkage with apoptosis,[17] IAPs were considered putative targets for pro-apoptotic drugs in oncology.[18] The initial assumption of a common anti-apoptotic mechanism for the whole IAP target family through interference with caspase-dependent pathways[19,20] has been proven wrong, or at least only partially correct for other IAP proteins,[21,22] but their interest as oncology targets related to apoptosis has not been seriously challenged.[23]

The most caspase-connected IAP is the X-Inhibitor of Apoptosis Protein[24,25] (XIAP). XIAP is capable of binding caspase 9 (the initiator caspase) and both caspases 3 and 7 (the executioner caspases).[26] XIAP binding prevents activation of caspases and, consequently, prevents cells from entering apoptosis.

A protein released from mitochondria, the Second Mitochondria-derived Activator of Caspases (Smac)[27]/Direct IAP Binding protein with LOw pI (DIABLO)[28] binds XIAP as a dimer[29] on the same binding sites of caspase 9 (BIR3 domain).[30–32] Smac interferes also with the XIAP binding site of caspases 3 and 7 (linker-BIR2 domain),[33] promoting both the extrinsic and intrinsic apoptosis paths. The delicate balance of this binding equilibrium is altered in various diseases; for example, several tumor cell lines show overexpression of XIAP and, consequently, a caspase-dependent resistance to enter apoptosis.[34,35] Thus, XIAP inhibition via Smac mimetics' binding is considered a validated mechanism for intervention in cancer therapy.[36–38]

* Corresponding author. Tel.: +39 0250314060; fax: +39 0250314075.
E-mail address: pierfausto.seneci@unimi.it (P. Seneci).

0968-0896/$ - see front matter © 2012 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.bmc.2012.09.020

Smac binding to other human IAP family members such as cIAP1[39] and cIAP2[40] through their BIR domains is also proven, although not related to their NF-κB activation-related anti-apoptotic properties.[41–43] Thus, Smac mimetics may modulate the pathological action of any IAP oncology target,[44–46] although the complex network of IAP-dependent interactions still needs to be fully elucidated to understand any drawback for the use of Smac mimetics in therapy.[47]

Several authors have shown how monomeric Smac mimetics/IAP inhibitors such as **1a** (Fig. 1, top left), inspired by the Smac N-terminal AVPI sequence and built on aza-containing bicycloalkane carboxylate scaffolds, bind XIAP, cIAP1 and cIAP2 on their BIR domains with sub-micromolar potency, induce rapid cIAP1 degradation, and affect apoptosis in tumor cells when given in combination with cytotoxic agents.[48] The same authors reported diazabicyclic scaffolds as potent, orally active pan-IAP antagonists.[49] Among them, **2a** (AT406, Fig. 1, bottom left) is in clinical development for the treatment of solid and hematological tumors.[50] Recently, another orally active clinical candidate **3a** (GDC-0152, Fig. 1, top right) was fully described.[51]

We have reported a structure-driven approach to potent, monomeric Smac mimetics/IAP inhibitors of general formula **4** (Fig. 1, middle), where introduction of a 4-substitution on the 1-aza-2-oxobicyclo[5.3.0]decane scaffold established novel molecular interactions with the binding linker-BIR2 and/or BIR3 sites.[52,53] Our early lead **4a**[52] (Fig. 1, bottom right) showed good in vitro—cell-free and cellular—potency. The optimized lead **4b**[54] (Fig. 1, bottom right) showed a significant improvement in solubility and penetration through biological membranes.

Dimeric Smac mimetics/IAP inhibitors such as **5–7** (Fig. 2) were also presented as bifunctional ligands able to simultaneously bind to BIR2 and BIR3 domains of XIAP, and to induce rapid cIAP1 and cIAP2 degradation.[55–57] Their structure includes two AVPI-related peptidomimetics connected through one (**5**, **7**) or two (**6**) linkers of varying length, rigidity and lipophilicity. The observed cytotoxic effects on selected cell lines[55] and significant activity in animal models[57] suggested a downstream developability for such 'non drug-like' dimers.

Here we report novel, dimeric Smac mimetics/IAP inhibitors **8**–**10** (Fig. 3) which take advantage of their characteristic 4-substitution to exploit three connection strategies. Labeling as 'head' the 4-substituent and 'tail' the C-terminus amide of the 1-aza-2-oxobicyclo[5.3.0]decane scaffold (Fig. 3), we have designed, synthesized and biologically characterized several head–head (**8**) and tail–tail homodimers (**9**), together with unprecedented heterodimeric head–tail compounds (**10**, Fig. 3). We aimed to introduce symmetrical and unsymmetrical substitution patterns on the two linker-connected monomer units, and to assess a few synthetic strategies fully compatible with a wide variety of functional groups. We reasoned that, if fully achieved, such goals should have allowed to understand the influence of structural modifications on in vitro and in vivo efficacy of dimeric Smac mimetics/IAP inhibitors **8**–**10**, and to select at least one suitable candidate for preclinical evaluation.

The rational design and the chemical synthesis of dimeric Smac mimetics/IAP inhibitors **8**–**10** is presented and discussed in this paper. Their structural and biological characterization, including NMR and X-ray studies, cell-free, cellular and in vivo efficacy testing on selected compounds, are reported in the following paper.[58]

2. Synthesis

2.1. Rationale

Some of us recently reported[52,59] an innovative synthesis strategy to access monomeric compounds of general formula **4**, which differ from known structures **1** for the additional 4-substitution on the 1-aza-2-oxobicyclo[5.3.0]decane scaffold (Fig. 1). Having secured synthetic access to such structures, and having established a preliminary SAR on the 4-position, we decided to study how two such structures could be connected, through a suitable linker attached onto a chemically modifiable functional group, to take advantage of a simultaneous interaction with two BIR domains, as previously reported by others.[55,57]

As to the connecting chemical function between the monomer unit and the linker, it has to be both chemically replaceable-modifiable, and compatible with preserving BIR-binding properties even after substantial structural modifications. Two such groups were known at the time when we designed our dimer assembly strategy: the C-terminus amide portion, used in several papers as an anchor point for dimer synthesis,[55,57] and the 4-substitution, which was proven by us to tolerate the introduction of various functional groups, including bulky substituents.[52] We named the latter compounds as head–head dimers **8**, while the former were labelled as tail–tail compounds **9**.

We reasoned that, in order to reach both binding sites in two BIR domains of a given IAP protein, the two monomeric AVPI mimetics would need to adopt specific—and possibly rather

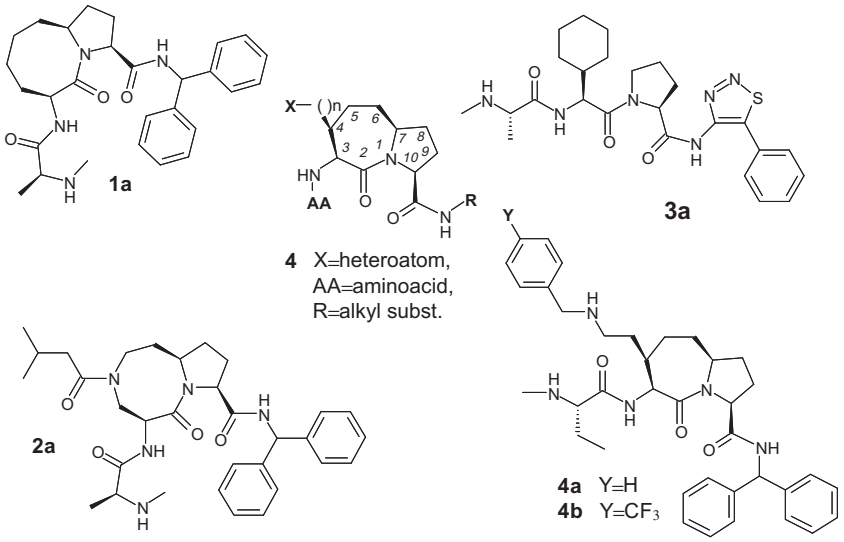


Figure 1. Monomeric Smac mimetics/IAP inhibitors.

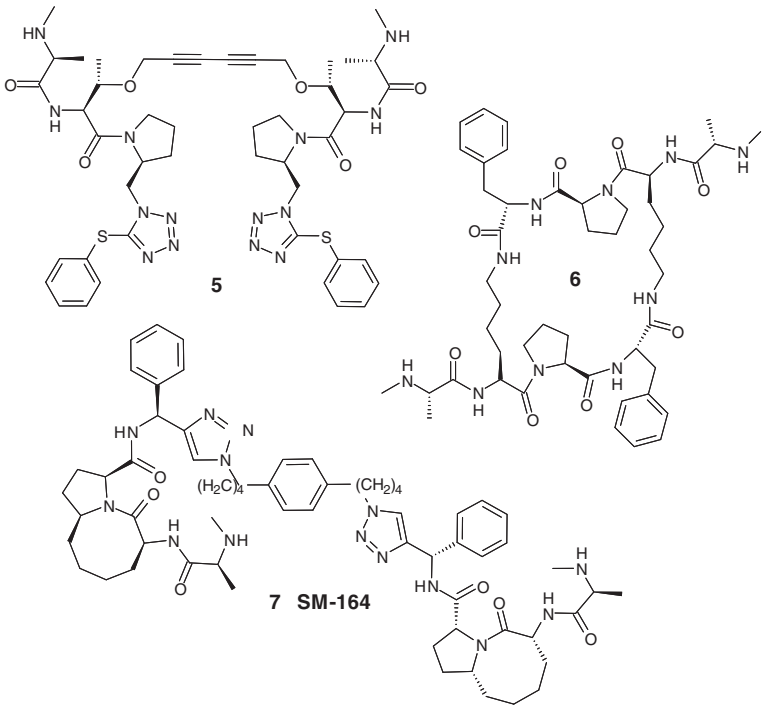


Figure 2. Previously reported dimeric Smac mimetics/IAP inhibitors.

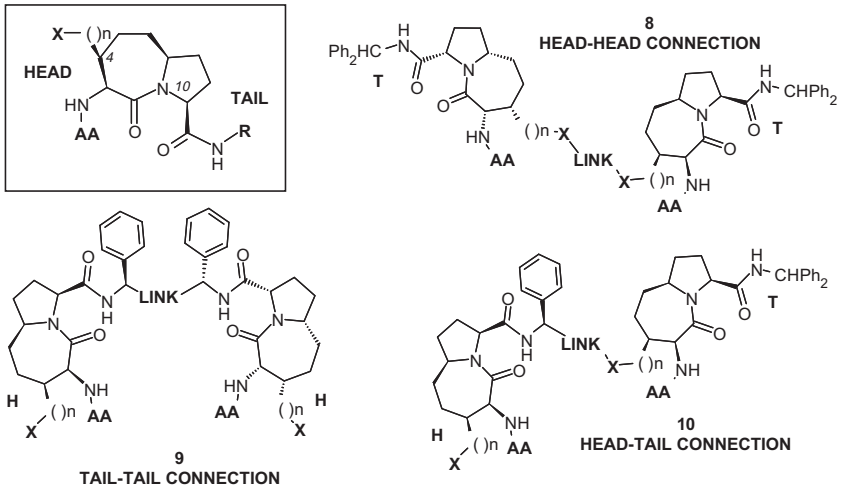


Figure 3. Head–head (**8**), tail–tail (**9**) and head–tail (**10**) dimeric Smac mimetics/IAP inhibitors based on the 1-aza-2-oxobicyclo[5.3.0]decane scaffold.

constrained—conformations. A graphically effective pictorial analogy of head–head, head–tail and tail–tail dimers is reported in Figure 4. It is likely that, to assume a relative orientation of both monomers in a given dimer **8** or **9** which would allow to bind simultaneously to two BIR targets, either one or both of the linked monomers should move away from their minimum energy state. It's also reasonable that their capability to reach such dimer binding conformation would be different, due to the constraints induced in dimer regions by a tail-tail or a head-head connection. We then reasoned that, if synthetically feasible, head-tail heterodimers **10** would also provide useful information in terms of binding modes, and obviously of dimers' structural requirements to maximize their pro-apoptotic effects (Fig. 4).

The linker unit, connecting two AVPI mimetics, is also going to influence the bi-functional binding potential of dimeric Smac mimetics. We selected several linking backbones, taking also advantage of reported efforts by other groups,[60] with the aim to explore how, *inter alia*, their length, flexibility and lipophilicity would influence the dimer activity. Some preferred linker structures are depicted in Figure 5.

2.2. Key monomers

Six monomeric intermediates were selected as synthetic gateways to our dimers. Their structure is shown in Figure 6, while their synthesis was previously reported.[52]

Namely, compound **4c** corresponds to the product of step ii, Scheme 1, Ref. 52; compound **4d** corresponds to the product of step iv, Scheme 1, Ref. 52; compounds **4e,f** and **4g,h** correspond, respectively, to compounds **8a,b** and **9a,b**, Scheme 1 in Ref. 52.

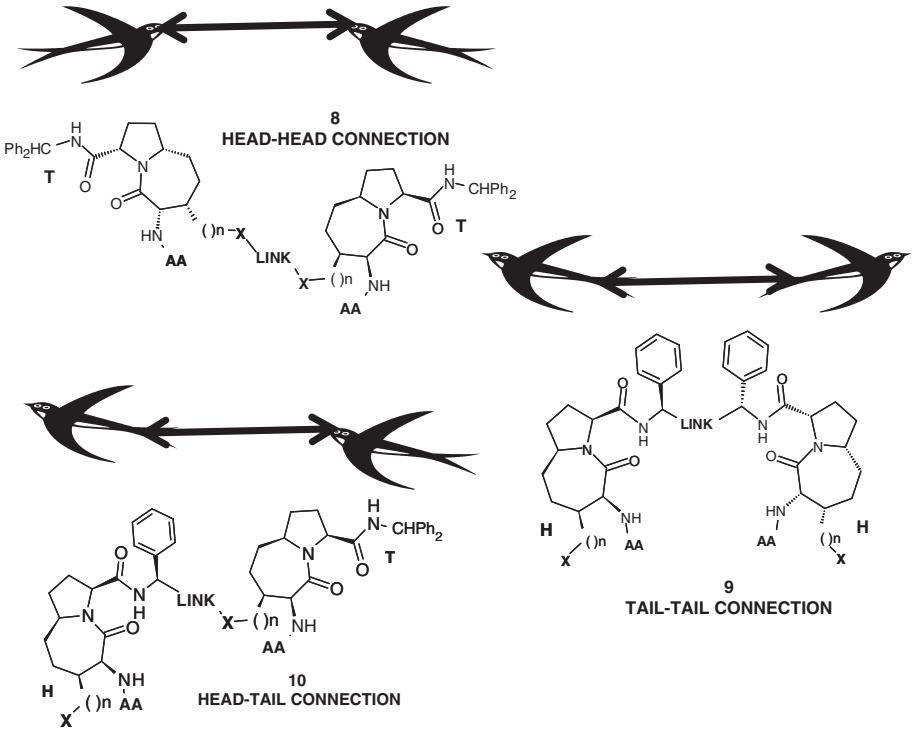


Figure 4. Heads, tails and swallows.

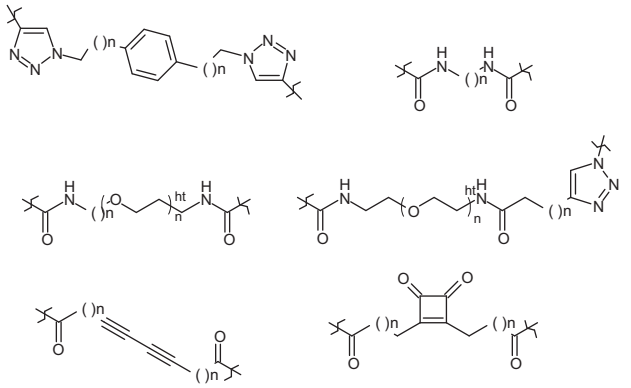


Figure 5. Preferred linker structures.

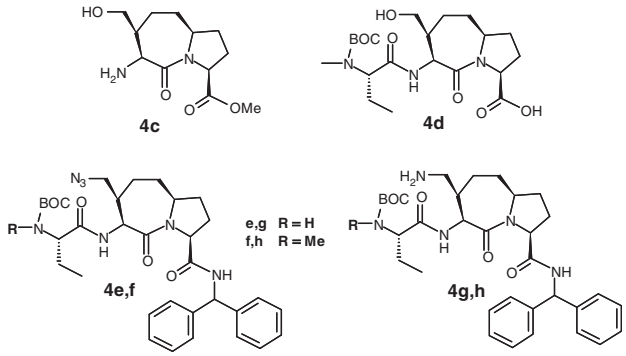


Figure 6. Key monomeric synthons for the synthesis of dimers **8**–**10**.

2.3. Head–head homodimers 8

Nine head–head homodimers **8** were synthesized. A diphenylmethylamide was the tail for all compounds **8**, while three of them contained (*S*)-ethylglycine and six contained *N*-methyl(*S*)-ethylglycine (AA, Fig. 3).

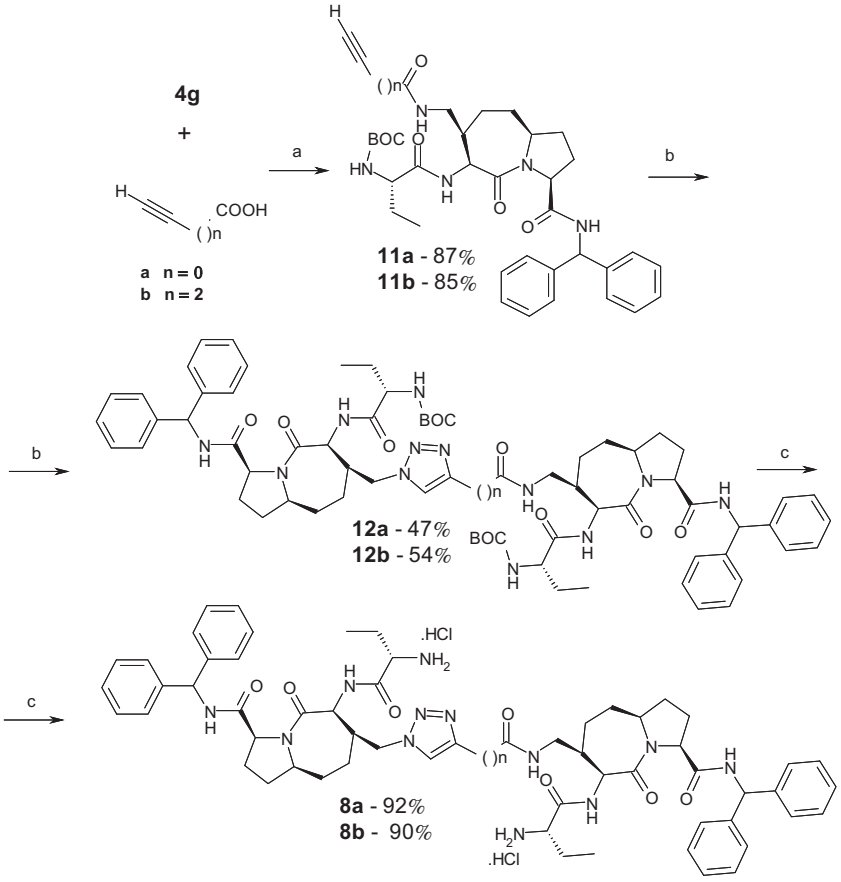
Amine **4g** was reacted with two alkynyl carboxylic acids (step a, Scheme 1) to provide high yields of 4-alkynyl amides **11a,b**. The amides were reacted with azide **4e** in a Cu-catalyzed click chemistry reaction (step b, Scheme 1) to provide good yields of *N*-Boc-protected dimers **12a**,**b**. Acidic deprotection with methanolic HCl (step c) provided high yields of head–head dimers **8a,b** as bishydrochlorides (Scheme 1). The unoptimized overall yields for **8a** and **8b** were, respectively, 38% and 42%.

Alkynylamide **11b** was oxidatively dimerized[55] in moderate yields (step a, Scheme 2) using copper (II) acetate, and the resulting symmetrical *N*-Boc-protected dimer **12c** was deprotected (step b) to provide quantitative yields of head–head dimer **8c** as a dihydrochloride (Scheme 2). The unoptimized overall yield for **8c** was 36%.

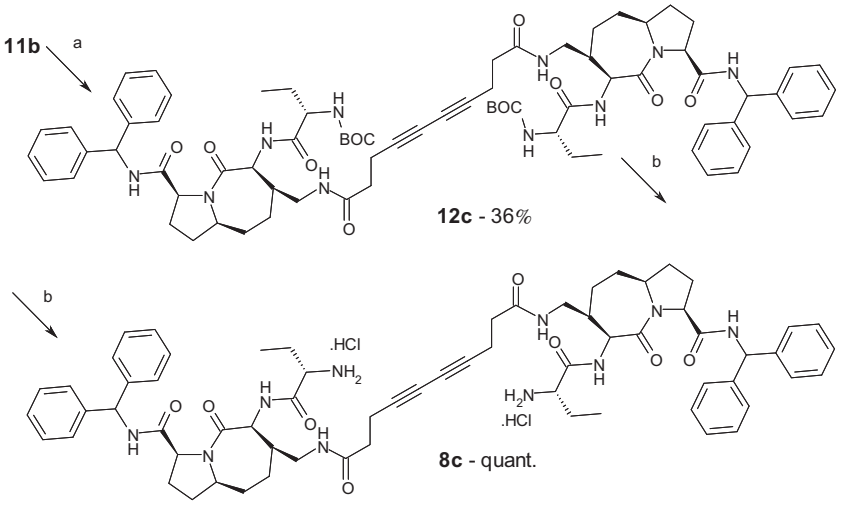
N-Methylamine **4h** was reacted with three biscarboxylates (step a, Scheme 3) to provide good yields of *N*-Boc-protected dimers **12d–f**. Acidic deprotection with TFA (step b) provided good to excellent yields of head–head dimers **8d–f** as bistrifluoroacetates (Scheme 3). The unoptimized overall yields for **8d**, **8e** and **8f** were, respectively, 44%, 53% and 39%.

N-Methylamine **4h** was also reacted with an alkynyl heptanoate (step a, Scheme 4) to provide *N*-methyl, 4-alkynyl amide **11c** in excellent yield. This was oxidatively dimerized[55] in excellent yields (step b) using copper (II) acetate, and the resulting symmetrical *N*-Boc-protected dimer **12g** was deprotected (step c) to provide moderate yields of head–head dimer **8g** as a dihydrochloride (Scheme 4). The unoptimized overall yield for **8g** was 30%.

The amide **11c** was also reacted with a known bis-azide[61] in a Cu-catalyzed click chemistry reaction (step a, Scheme 5) to provide moderate yields of the *N*-Boc-protected dimer **12h**. Acidic deprotection with TFA (step b) provided quantitative yields of the head–head dimer **8h** as a bistrifluoroacetate (Scheme 5). The unoptimized overall yield for **8h** was 29%.

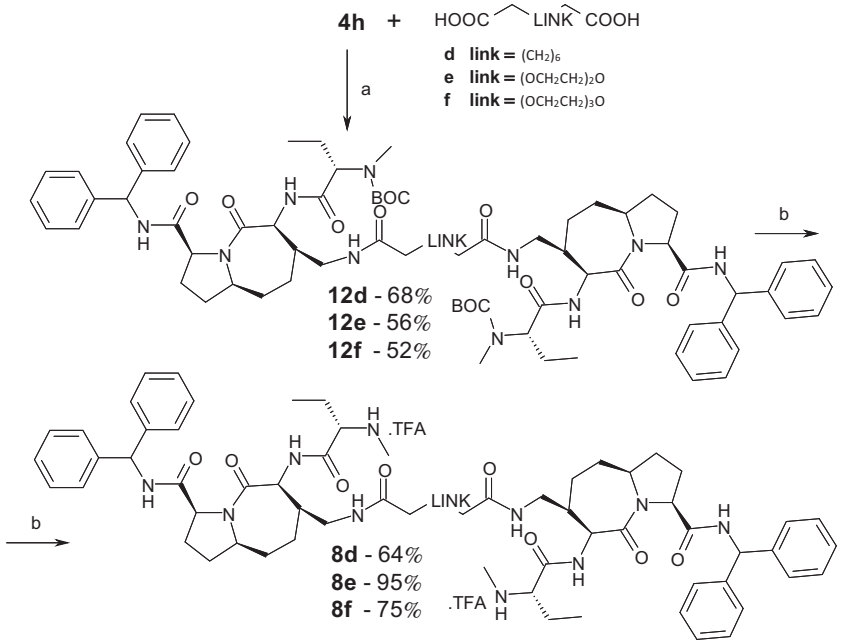


Scheme 1. Synthesis of head–head dimers **8a**,**b**.



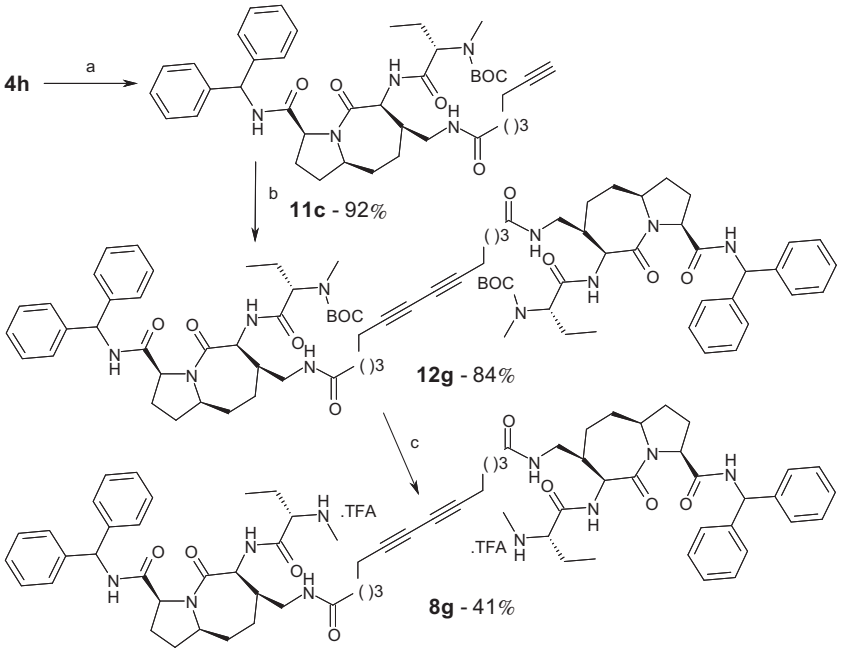
Scheme 2. Synthesis of head–head dimer **8c**.

Finally, *N*-methylamine **4h** was reacted with *N*-Cbz beta alanine (step a, Scheme 6) to provide *N*-methyl amide **11d** in quantitative yield. The amide was hydrogenolytically deprotected (step b) and reacted with diethyl squarate (step c) to give the symmetrical, *N*-Boc-protected dimer **12i** in excellent yield. Acidic deprotection with TFA (step d) provided excellent yields of the head–head dimer **8i** as a bistrifluoroacetate (Scheme 6). The unoptimized overall yield for **8i** was 75%.



a, EDC, HOBt, DIPEA, CH_2Cl_2, rt, 2 hrs; b, TFA, CH_2Cl_2, rt, 4 hrs.

Scheme 3. Synthesis of head–head dimers **8d–f**.



a, 6-heptynoic acid, EDC, HOBt, DIPEA, CH_2Cl_2, rt, 4 hrs; b, $Cu(OAc)_2$, CH_3CN, reflux, 0.5 hrs; c, TFA, CH_2Cl_2, rt, 4 hrs.

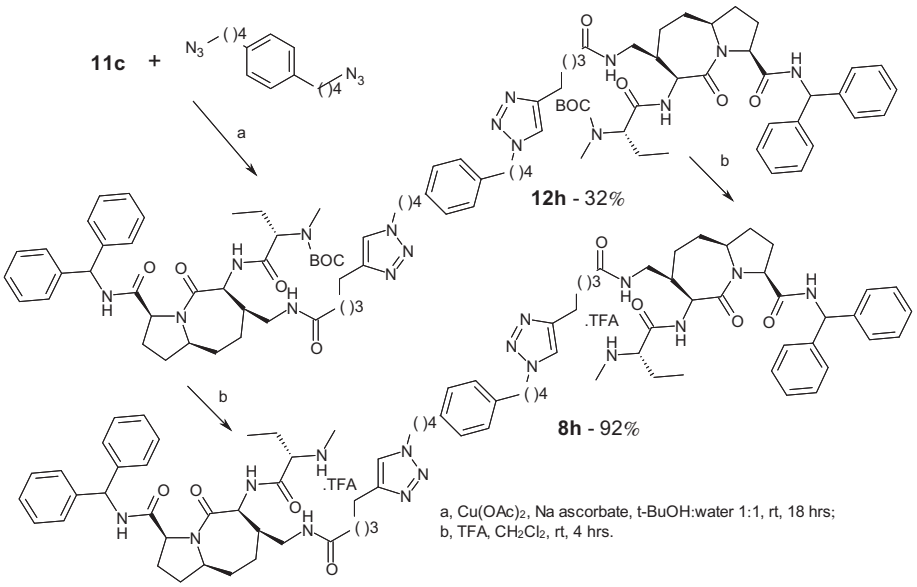
Scheme 4. Synthesis of head–head dimer **8g**.

2.4. Tail–tail homodimers 9

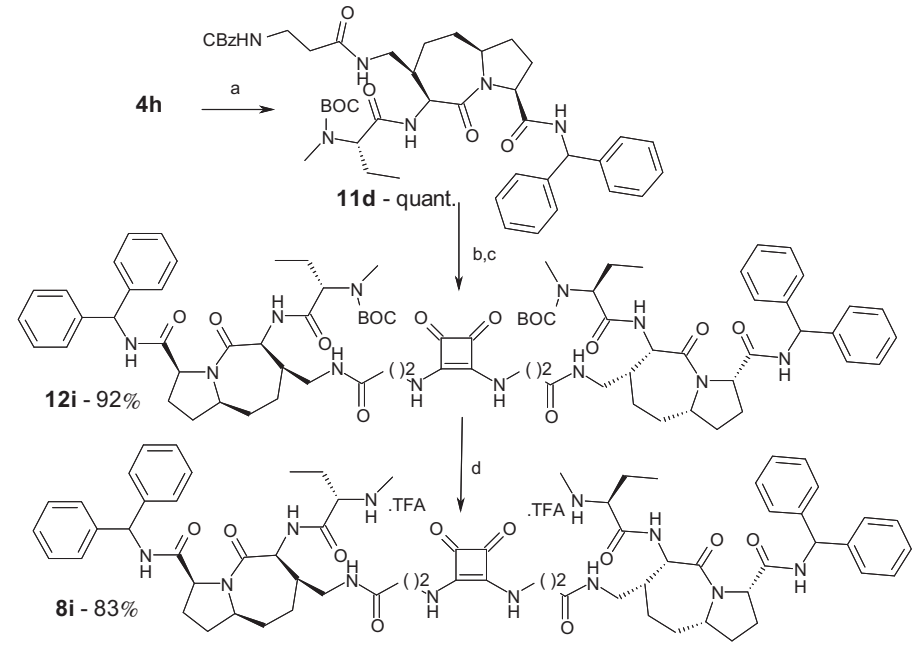
Seven tail–tail homodimers **9** were synthesized. *N*-methyl(*S*)-ethylglycine was present in all compounds **9** (AA, Fig. 3), while three different 4-substitutions (–CH_2OH in five compounds, -CH_2NHCH_2Ph and elongated –$CH_2CH_2NH_2$ in one compound) were introduced.

Carboxylic acid **4d** was reacted with an optically active alkynyl amine (step a, Scheme 7) to provide C-terminus-alkynyl amide **13a** in good yield. The amide was reacted with a known bis-azide[58] in a Cu-catalyzed click chemistry reaction (step b) to provide the *N*-Boc-protected dimer **14a** in good yield. Acidic deprotection with TFA (step c) provided tail–tail dimer **9a** as bistrifluoroacetate in good yield (Scheme 7). The unoptimized overall yield for **9a** was 29%.

A set of four tail–tail dimers **9b–e** was prepared by reaction of the same carboxylic acid **4d** with four bis-amine linkers **17a–d**. Such bis-amines were prepared from bis-amines **15a–d**[62] by



Scheme 5. Synthesis of head–head dimer **8h**.

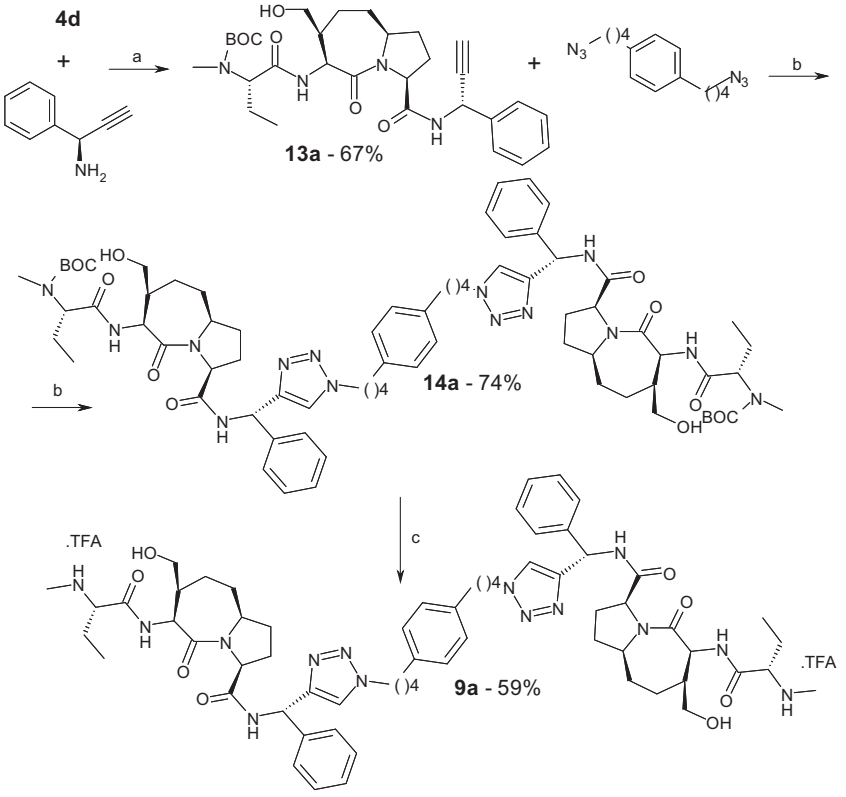


Scheme 6. Synthesis of head–head dimer **8i**.

condensation with (*S*)-phenylglycine (step a, Scheme 8) to give *N*-Boc protected compounds **16a–d** in excellent yields. Desired bis-amine linkers **17a–d** were obtained by TFA deprotection (step b) in quantitative yields (Scheme 8).

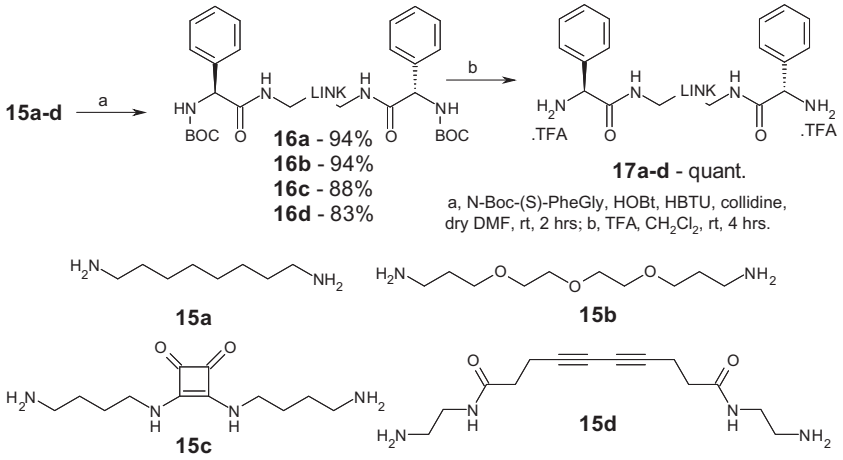
Carboxylic acid **4d** was reacted with four bis-amine linkers **17a–d** (step a, Scheme 9) to give, with good to excellent yields, *N*-Boc protected dimers **14b–e**. Acidic deprotection with TFA (step b) provided tail–tail dimers **9b–e** as bistrifluoroacetates in good to excellent yields (Scheme 9). The unoptimized overall yields for **9b–e**, starting from **4d** and **17a–d**, were, respectively, 53%, 73%, 31% and 56%.

N-Boc protected dimer **14a** was decorated on its 4-substitution to provide tail–tail dimer **9f** (Scheme 10). Namely, **14a** was mesylated and reacted with sodium azide (steps a, b) to give azide **14f** in good yield. The azide was reduced in a Staudinger reaction (step c) to give the amine **14g** in quantitative yield, and the amine was N-alkylated in a reductive amination protocol (step d) to provide the N-protected, benzylated dimer **14h** in moderate yields. Acidic



a, EDC, HOBt, DIPEA, dry CH_2Cl_2, rt, 2 hrs; b, $Cu(OAc)_2$, Na ascorbate, tBuOH:water 1:1, rt, 18 hrs; c,TFA, CH_2Cl_2, rt, 4 hrs.

Scheme 7. Synthesis of tail–tail dimer **9a**.



a, N-Boc-(S)-PheGly, HOBt, HBTU, collidine, dry DMF, rt, 2 hrs; b, TFA, CH_2Cl_2, rt, 4 hrs.

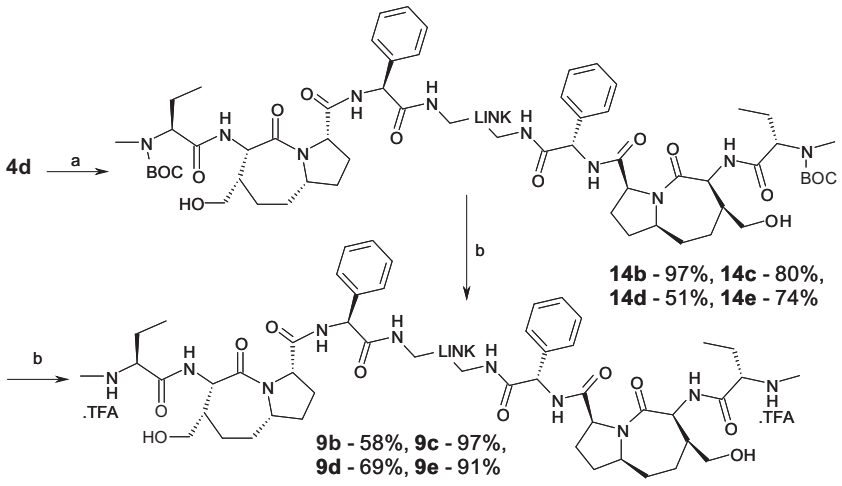
Scheme 8. Synthesis of bis-amine linkers **17a–d**.

deprotection with TFA (step e) provided tail–tail dimer **9f** as a tetratrifluoroacetate in good yield (Scheme 10). The unoptimized overall yield for **9f** from **14a** was 24%.

Finally, 4-hydroxymethyl methyl ester **4c** was *N*-Boc protected, mesylated and reacted with a tetraalkyl ammonium cyanide (steps a–c, Scheme 11) to provide the cyano compound **13b** in good yield. After N-deprotection and condensation with N-protected and methylated (*S*)-ethylglycine (steps d,e) to yield **13c**, the cyano group was reduced, and the resulting amine was protected with Boc in a one-pot reaction protocol (steps f,a) to give the *N*-Boc protected, elongated amine **13d** in moderate yield. After quantitative basic hydrolysis of the methyl ester (step g), the acid **13e** was reacted with previously described bis-amine **17b** (step h) to give tetra *N*-Boc protected dimer **14i** in good yields. Acidic deprotection with TFA (step i) provided elongated tail–tail dimer **9g** as a tetratrifluoroacetate in good yield (Scheme 11). The unoptimized overall yield for **9g** was 12%.

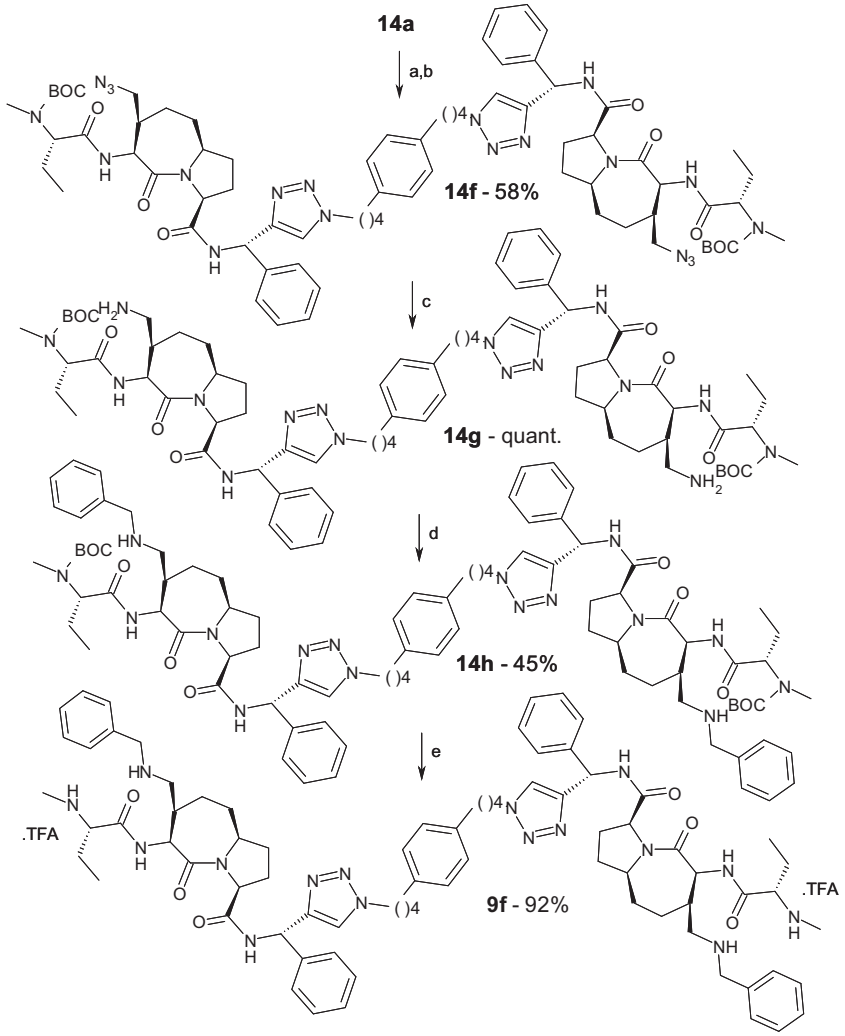
2.5. Head–tail heterodimers 10

Three head–tail heterodimers **10** were synthesized together with a hybrid heterodimeric structure. *N*-Methyl(*S*)-ethylglycine



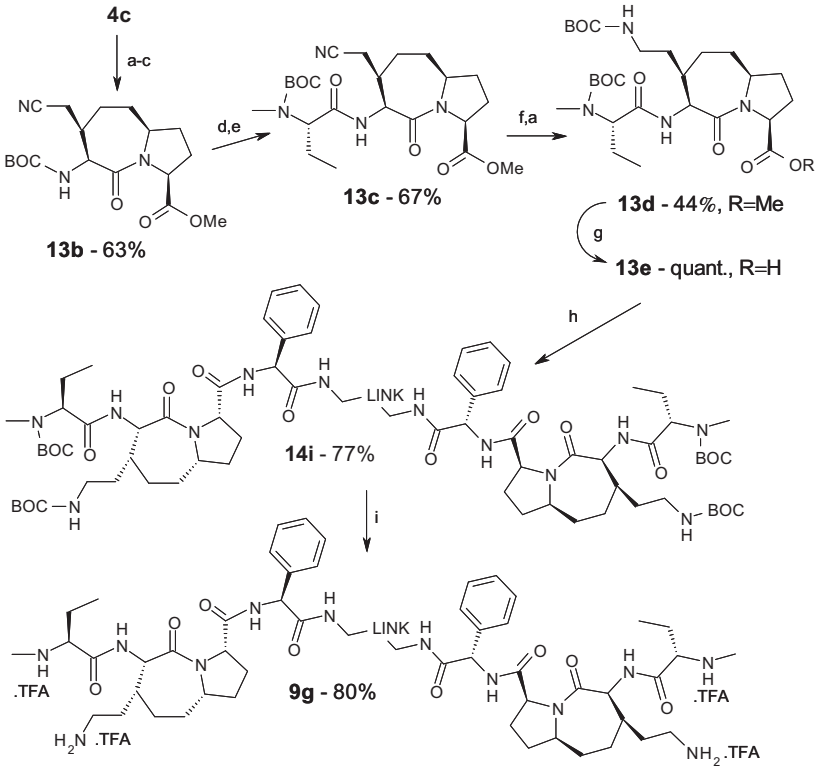
a, **17a-d**, HOBt, HBTU, collidine, dry DMF, 0° to rt, 2 hrs; b, TFA, CH_2Cl_2, rt, 4 hrs.

Scheme 9. Synthesis of tail–tail dimers **9b**–**e**.



a, MsCl, TEA, dry CH_2Cl_2, 0° to rt, 2 hrs; b, NaN_3, dry DMF, 100° C, 0.5hrs; c, Me_3P, dry CH_2Cl_2, rt, 2 hrs; d, PhCHO, $NaBH(OAc)_3$, dry CH_2Cl_2, rt, 18 hrs; e, TFA, CH_2Cl_2, rt, 4 hrs.

Scheme 10. Synthesis of tail–tail dimer **9f**.



a, Boc_2O, TEA, CH_2Cl_2, rt, 2 hrs; b, MsCl, TEA, CH_2Cl_2, rt, 2 hrs; c, $nBu_4N^+CN^-$, DMF, microwave, 80°C, 1.5 hrs; d, 3N HCl in MeOH, rt, 18 hrs; e, N-Boc,N-Me-(S)-2aminobutanoic acid, EDC, HOBt, DIPEA, dry CH_2Cl_2, rt, 2 hrs; f, Ni Raney, EtOH, continuous flow, 60 bar, 60°C, 6 hrs; g, 2N LiOH, 1,4-dioxane:water, 0°C to rt, 1 hr; h, **17b**, HOBt, HBTU, collidine, dry DMF, rt, 18 hrs; i, TFA, CH_2Cl_2, rt, 4 hrs.

Scheme 11. Synthesis of tail–tail dimer **9g**.

(AA, Fig. 3), 4-CH_2OH substitution, and a diphenylmethyl amide tail were conserved in the three heterodimers, while the hybrid structure connected the head of a 1-aza-2-oxobicyclo[5.3.0]decane scaffold-based AVPI mimetic with a structurally different, known[55] monomeric unit.

Four key tail-linker monomeric intermediates **18a–d** were prepared as shown in Scheme 12. Commercially available azidoamine **15e** was first reacted with (*S*)-phenylglycine (step a) to give intermediate **16e** in good yield, then N-deprotected (step b). Coupling with **4d** (step c) provided the linker-bearing monomeric azide **18a** in excellent yield. After catalytic hydrogenation (step d) of the same azide to provide quantitatively the linker-bearing monomeric amine **18b**, the same amine was either coupled with 4-pentynyl-butanoic acid (step e) to give the linker-bearing monomeric alkyne **18c** with excellent yield, or with diglycolic anhydride (step f) to give the linker-bearing monomeric carboxylate **18d** (Scheme 12).

Linker-bearing monomeric azide **18a** was coupled in a click chemistry reaction with 4-alkynyl amide **11e** (step b, Scheme 13), this last prepared from **4h** (step a), to provide in good yield the N-protected head–tail heterodimer **19a**. Acidic deprotection with TFA (step c) provided head–tail heterodimer **10a** as a bistrifluoroacetate in excellent yield (Scheme 13). The unoptimized overall yield for **10a** was 55% from **18a**.

Linker-bearing alkyne **18c** was coupled in a click chemistry reaction with azide **4f** (step a, Scheme 14) to provide in very good yield the N-protected head–tail heterodimer **19b**. Acidic deprotection with TFA (step b) provided head–tail heterodimer **10b** as a bistrifluoroacetate in excellent yield (Scheme 14). The unoptimized overall yield for **10b** was 69% from **18c**.

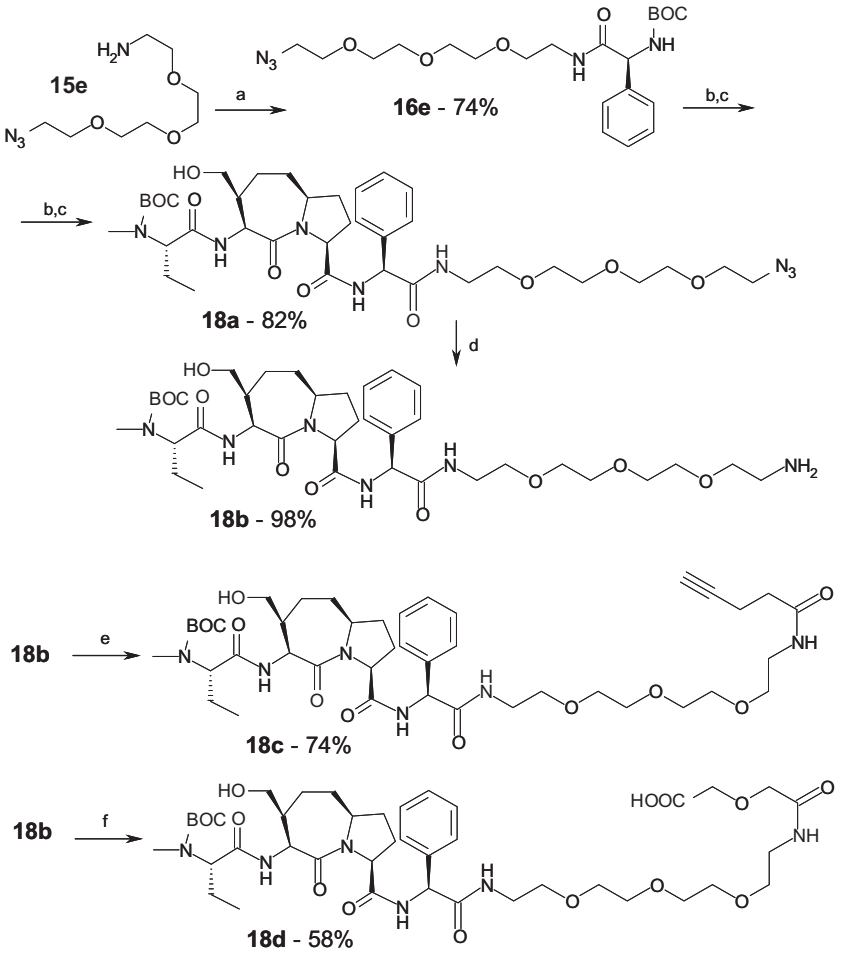
Linker-bearing carboxylate **18d** was coupled with amine **4h** (step a, Scheme 15) to provide in very good yield the N-protected head–tail heterodimer **19c**. Acidic deprotection with TFA (step b) provided head–tail heterodimer **10c** as a bistrifluoroacetate in excellent yield (Scheme 15). The unoptimized overall yield for **10c** was 59% from **18d**.

Finally, a heterodimer containing two linker-connected AVPI mimetics based on different scaffolds was prepared as in Scheme 16. Namely, azide **4e** was coupled in a click chemistry reaction with N-protected alkyne-containing Smac mimetic **20a**[55] (step a) to give *N*-Boc, *N*-Fmoc protected heterodimer **19d** in good yield. Sequential deprotection in basic (step b) and acidic (step c) conditions produced the hybrid heterodimer **10d** in excellent yield. The unoptimized overall yield for **10d** was 51%.

3. Conclusions

The chemical feasibility of head head-**8**, tail tail-**9** and head tail-**10** dimers based on 4-substituted 1-aza-2-oxobicyclo[5.3.0]decane scaffolds was successfully proven through the synthesis of 20 compounds, bearing various 4-substitutions. The monomer units in each dimer were connected through linkers with varying length, lipophilicity and flexibility.

Extensive details regarding the biological activity of each prepared dimer, and the structural characterization of selected homodimers using NMR, X-ray crystallography and gel filtration are provided in the following paper.[58] Their activity profiling will drive our future synthetic efforts towards the more prospective homo- and heterodimers. Such efforts will be reported in due time.



a, N-Boc-(S)-phenylglycine, HOBt, HBTU, collidine, dry DMF, 0° to rt, 2 hrs; b, TFA, CH_2Cl_2, rt, 4 hrs; c, **4d**, HOBt, HBTU, collidine, dry DMF, 0° to rt, 2 hrs; d, H_2, Pd/C, continuous flow, 10 bar, 35°C; e, 4-pentynoic acid, DCC, DMAP, dry CH_2Cl_2, 0° to rt, 4 hrs; f, diglycolic anhydride, pyridine, dry DMF, rt, 4 hrs.

Scheme 12. Synthesis of tail-linker monomeric intermediates **18a–d**.

4. Experimental part

4.1. General methods

^{1}H NMR spectra were recorded on a Bruker Avance instrument in $CDCl_3$, CD_3OD or D_2O as solvent at 400 or 600 MHz. ^{13}C NMR spectra were recorded in $CDCl_3$, CD_3OD or D_2O as solvent at 100 or 125 MHz. Coupling constants are given in Hertz, Hz, and are rounded to the nearest 0.1 Hz.

Purifications were carried out either by flash chromatography on silica gel (particle size 60 μm, 230–400 mesh), Kieselgel, or by Biotage™ flash chromatography [Biotage columns Si-12-M (150 × 12 mm; silica gel (40–63 lm), flow rate 12 mL/min); Si-25-M (150 × 25 mm; silica gel (40–63 μm), flow rate 25 mL/min)], or by Biotage™ C_{18} reverse phase chromatography [Biotage column C_{18}HS (150 × 25 mm; KP-C_{18}-HS (35–70 μm), flow rate 25 mL/min)]. Final products were purified by C_{18} reverse phase semi-preparative HPLC using either a Waters X-Terra RP_{18} OBD column (19 mm × 10.0 cm, 5 μm) or a Supelco Ascentis C_{18} column (21.2 mm × 15.0 cm, 5 μm).

LC–MS data were collected with an Agilent 1100 HPLC connected to a Bruker Esquire 3000$^+$ ion trap mass spectrometer through an ES interface.

Optical rotations $[\alpha]_{20}^{D}$ were measured in cells of 1 dm pathlength and 1 mL capacity with a Perkin Elmer 241 polarimeter.

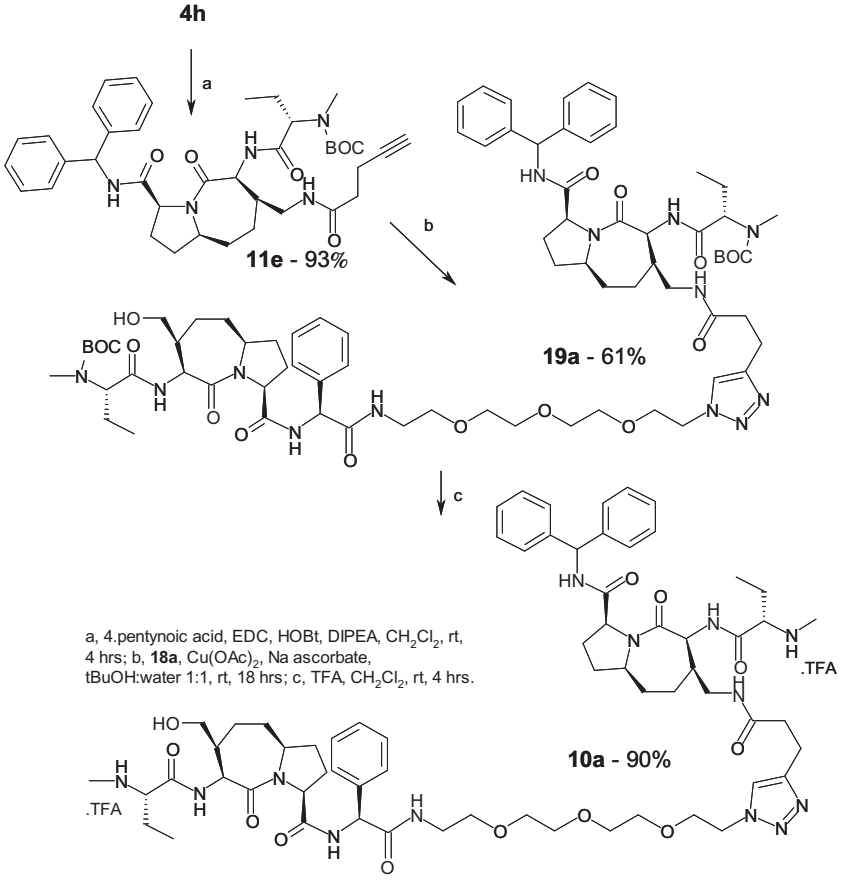
Solvents were distilled and dried according to standard procedures, and reactions requiring anhydrous conditions were performed under nitrogen or argon. Solvents for the reactions were used directly from the bottle if not differently specified.

Standard dimers **3**[55] and **5**[57] were prepared according to the published procedure.

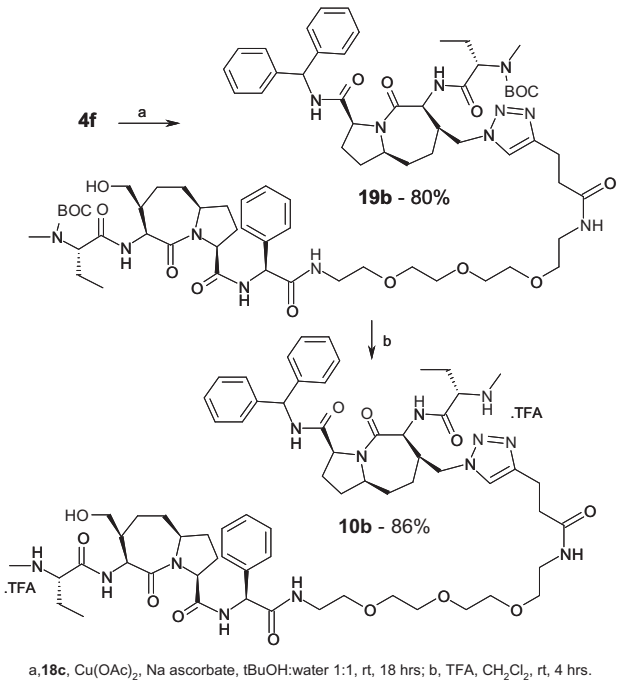
4.2. Head–head dimer 8a—Scheme 1

4.2.1. Compound 11a

A solution of DCC (20.6 mg, 0.10 mmol) and DMAP (2.4 mg, 0.02 mmol) in dry CH_2Cl_2 (10 mL) was added dropwise to a stirred solution of compound **4g (**59.2 mg, 0.10 mmol) and propiolic acid (6.2 μL, 0.10 mmol) in dry CH_2Cl_2 (10 mL) at 0 °C. After the addition, the reaction mixture was warmed to room temperature over a period of 1 h. After reaction completion, the reaction mixture was filtered, and the filtrate was washed with diethyl ether (2 × 10 mL). The combined organic phase was concentrated under reduced pressure, and the crude product was purified by Biotage™ flash chromatography, eluant conditions: 1% of MeOH and 99% of CH_2Cl_2 to 10% of MeOH and 90% of CH_2Cl_2. Yield 85% (55 mg, MW 644.32, 0.085 mmol) of pure **11a**. Analytical characterization: $[\alpha]_{20}^{D}$ −81.4 (c 0.75, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$): δ: 7.91 (d, J = 8.8 Hz, 1H), 7.50–7.10 (m, 11H), 6.24 (d, J = 8.4 Hz, 1H), 5.00 (d, J = 6.4 Hz, 1H), 4.75 (d, J = 7.2 Hz, 1H), 4.64 (t, J = 9.2 Hz, 1H), 4.20 (dd,



Scheme 13. Synthesis of head–tail dimer **10a**.



Scheme 14. Synthesis of head–tail dimer **10b**.

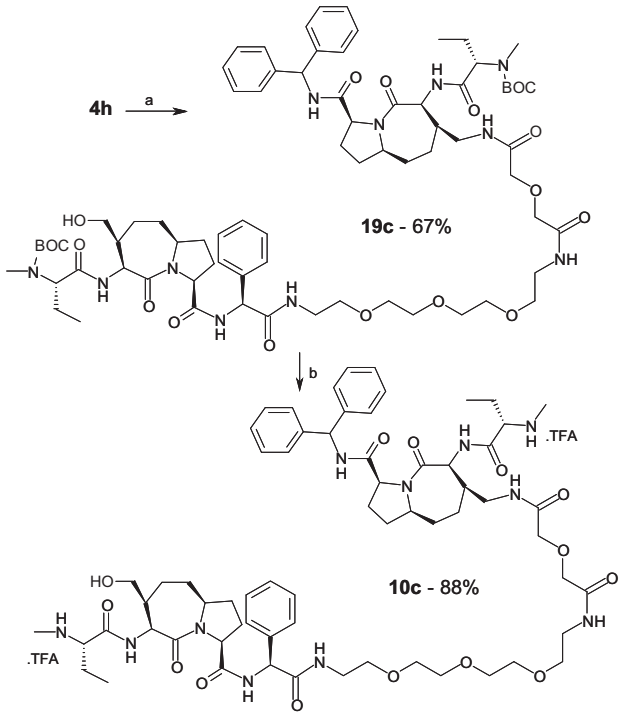
J = 10.8, 7.2 Hz, 1H), 4.06 (m, 2H), 3.85 (q, J = 8.4 Hz, 1H), 2.95 (s, 1H), 2.45 (m, 1H), 2.28 (m, 1H), 2.0–1.55 (m, 7H), 1.47 (s, 9H), 1.35–1.10 (m, 2H), 0.97 (t, J = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ: 172.4, 171.3, 169.5, 155.5, 152.2, 142.1, 141.1, 128.7, 127.3, 80.2, 74.6, 68.0, 61.0, 58.7, 56.8, 53.0, 39.1, 34.2, 33.3, 31.3, 28.3, 25.6, 10.4.

4.2.2. Compound 12a

A 0.9 M water solution of sodium ascorbate (45 μL, 0.4 mmol) and a 0.3 M water solution of $Cu(OAc)_2$ (65 μL, 0.02 mmol) were sequentially added to a stirred solution of compounds **4e** (61.8 mg, 0.10 mmol) and **11a** (64.4 mg, 0.10 mmol) in a 1:1 mixture of H_2O/^{t}BuOH (300 μL). The reaction mixture was stirred overnight at room temperature, and then the solvent was removed under reduced pressure. Finally, the residue was purified by Biotage™ flash chromatography, eluant conditions: 1% of MeOH and 99% of CH_2Cl_2 to 10% of MeOH and 90% of CH_2Cl_2. Yield 47% (59 mg, MW 1261.54, 0.047 mmol) of pure **11a**. Analytical characterization: $[\alpha]^D_{20}$ −64.3 (c 0.51, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ: 7.82 (d, J = 14.0, 1H), 7.73 (d, J = 8.4 Hz, 1H), 7.32–7.00 (m, 24H), 6.12 (t, J = 8 Hz, 2H), 5.07 (d, J = 5.6 Hz, 1H), 4.91 (d, J = 11.2 Hz, 1H), 4.64 (t, J = 6.4 Hz, 2H), 4.55 (m, 3H), 4.14 (t, J = 11.6 Hz, 1H), 3.98 (m, 2H), 3.73 (m, 3H), 3.14 (d, J = 12.0 Hz, 1H), 2.34 (m, 2H), 2.16 (m, 2H), 2.0–1.40 (m, 16H), 1.31 (s, 18H), 1.19 (s, 2H), 0.90 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ: 173.1, 171.7, 170.6, 169.4, 169.2, 160.4, 142.1, 141.8, 141.0, 128.8, 128.7, 127.7, 127.5, 127.4, 127.2, 127.1, 61.3, 61.1, 58.8, 56.8, 56.7, 54.0, 53.7, 40.7, 40.6, 40.2, 34.4, 33.8, 33.3, 33.2, 31.4, 25.7, 25.5, 25.4, 10.3.

4.2.3. Compound 8a

A 3 N solution of HCl in MeOH (0.5 mL) was added to a stirred solution of compound **12a** (7.6 mg, 0.006 mmol) in MeOH (2 mL). The reaction mixture was left stirring at room temperature overnight and then concentrated under reduced pressure. The



Scheme 15. Synthesis of head–tail dimer **10c**.

residue did not require any further purification, and was lyophilized. Yield 92% (6 mg, MW 1134.22, 0.0055 mmol) of pure **8a**. Analytical characterization: $[\alpha]_{20}^{D}$ −39.1 (*c* 0.23, H_2O); ^{1}H NMR (400 MHz, D_2O): δ: 8.35 (s, 1H), 7.32–7.18 (m, 20H), 5.97 (m, 2H), 4.61 (m, 3H), 4.48 (m, 2H), 4.35 (m, 1H), 3.9 (m, 4H), 3.50 (dd, *J* = 13.6, 8.4 Hz, 1H), 3.28 (dd, *J* = 12.8, 8.4 Hz,1H), 2.25–1.35 (m, 22H), 0.95 (m, 6H); ^{13}C NMR (100 MHz, D_2O): δ: 172.7, 170.5, 169.8, 169.7, 161.9, 142.2, 141.0, 140.9, 129.0, 128.9, 127.8, 127.4, 127.1, 61.9, 58.6, 58.4, 57.6, 54.5, 54.4, 54.3, 41.0, 38.6, 38.1, 32.4, 32.3, 27.8, 24.4, 8.5, 8.4. ESI-MS: m/z 1061.5 $[M+H]^+$1083.6 $[M+Na]^+$, 531.3 $[M+2H]^{2+}$.

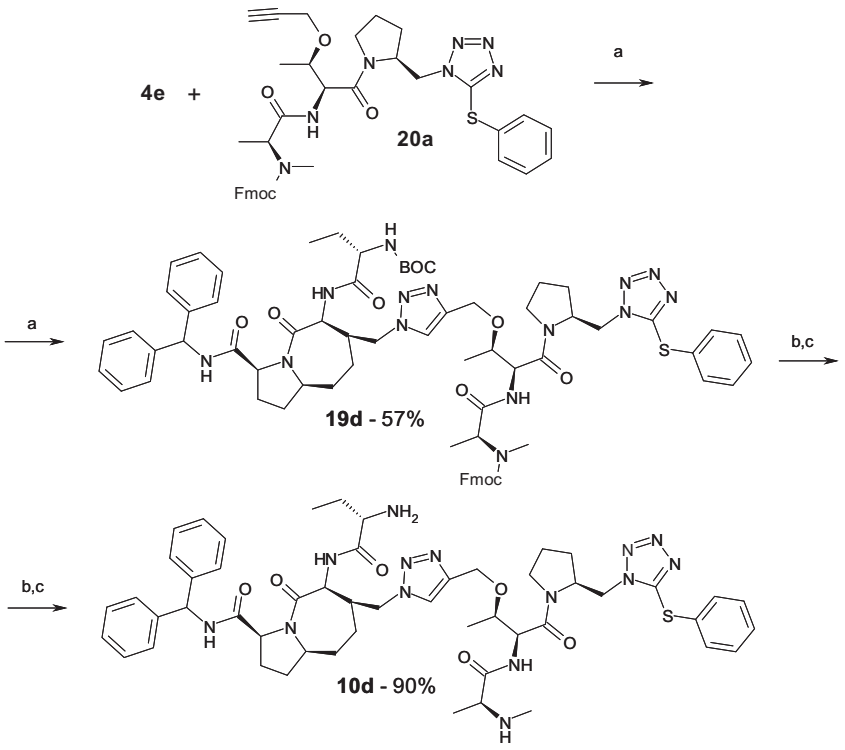
4.3. Head–head dimer 8b—Scheme 1

The head–head dimer **8b** was prepared similarly to **8a**. The detailed synthetic protocol leading to its synthesis, and its full synthetic characterization are reported in the Supplementary data.

4.4. Head–head dimer 8c—Scheme 2

4.4.1. Compound 12c

A stirred suspension of compound **11b** (67.2 mg, 0.10 mmol) and $Cu(OAc)_2$ (127.1 mg, 0.70 mmol) in acetonitrile (20 mL) was refluxed for 30 min After reaction completion, the solvent was removed under reduced pressure, the residue was dissolved in CH_2Cl_2 and Cu(II) salts were removed by filtering over a short pad of silica gel eluting with 9/1 CH_2Cl_2/MeOH. Finally, the crude products was purified by Biotage™ flash chromatography, eluant conditions: 1% of MeOH and 99% of CH_2Cl_2 to 10% of MeOH and 90% of CH_2Cl_2. Yield 36% (48 mg, MW 1341.67, 0.036 mmol) of pure **12c**. Analytical characterization: $[\alpha]_{20}^{D}$ −69.3 (*c* 0.96, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ: 7.90 (d, J = 6.8 Hz, 2H), 7.36–7.16 (m, 25H), 6.22 (d, J = 8.0 Hz, 1H), 5.05 (bd, *J* = 6.4 Hz, 2H), 4.72 (d, *J* = 8.0 Hz, 2H), 4.49 (t, *J* = 9.6 Hz, 2H), 3.98 (dd, *J* = 13.6, 7.6 Hz, 2H), 3.81 (dd, *J* = 17.6, 8.8, 2H), 3.58 (m, 2H), 3.01 (m, 1H), 2.58 (m, 4H), 2.40 (m, 6H), 2.25 (m, 2H), 1.95–1.55 (m, 16H), 1.45 (s, 18H), 1.30–1.10 (m, 2H), 1.00 (t, *J* = 7.6 Hz, 6H); ^{13}C NMR13C NMR (100 MHz, $CDCl_3$): δ: 173.6, 171.7, 170.8, 169.4, 141.2, 140.8, 128.6, 127.5, 127.4, 127.2, 80.5, 66.0, 61.2, 58.9, 57.0, 56.8,



Scheme 16. Synthesis of head–tail dimer **10d**.

54.0, 41.3, 40.0, 35.3, 34.5, 33.2, 28.3, 25.7, 25.2, 15.9, 10.3. ESI-MS: m/z 1342.9 $[M+H]^+$, 1363.9 $[M+Na]^+$.

4.4.2. Compound 8c

A 3 N solution of HCl in MeOH (0.5 mL) was added to a stirred solution of compound **12c** (18.5 mg, 0.014 mmol) in MeOH (2 mL). The reaction mixture was left stirring at room temperature overnight and then concentrated under reduced pressure. The residue did not require any further purification, and was lyophilized. Quantitative yield (17 mg, MW 1214.35, 0.014 mmol) of pure **8c**. Analytical characterization: $[\alpha]_{20}^{D}$ −43.1 (*c* 0.90, H_2O); ^1H NMR (400 MHz, D_2O): δ: 7.35–7.20 (m, 20H), 5.95 (s, 2H), 4.56 (d, *J* = 10.4 Hz, 2H), 4.50 (dd, *J* = 7.6, 4.8 Hz, 2H), 3.98 (m, 4H), 3.23 (dd, *J* = 13.6, 3.2 Hz, 2H), 3.06 (m, 2H), 2.45–2.30 (m, 4H), 2.25–1.40 (m, 26H), 0.97 (t, *J* = 7.2 Hz, 6H); ^{13}C NMR (100 MHz, D_2O): δ: 174.3, 172.4, 170.4, 169.6, 141.1, 140.9, 129.0, 128.9, 127.9, 127.8, 127.4, 127.0, 65.8, 61.7, 58.4, 57.7, 54.5, 54.4, 40.7, 37.6, 34.3, 32.6, 30.7, 27.8, 24.4, 15.5, 8.5. ESI-MS: m/z 1163.3 $[M+Na]^+$, 571.1 $[M+2H]^{2+}$.

4.5. Head–head dimer 8d—Scheme 3

4.5.1. Compound 12d

EDC·HCl (23 mg, 0.12 mmol), HOBt (16.2 mg, 0.12 mmol) and DIPEA (69.7 μL, 0.40 mmol) were sequentially added to a stirred solution of 1,10-decanedioic acid (9.7 mg, 0.048 mmol) in dry CH_2Cl_2 (2 mL) at room temperature. The reaction mixture was left stirring for 15 min and then added to a stirred solution of **4h** (60.6 mg, 0.10 mmol) in dry CH_2Cl_2 (2 mL). The reaction mixture was stirred at room temperature overnight and then, after reaction completion, the solvent was removed under reduced pressure. The crude product was diluted with EtOAc (20 mL) and washed with a saturated solution of ammonium chloride (3 × 20 mL), saturated solution of sodium bicarbonate (3 × 20 mL) and brine (1 × 20 mL). The organic layer was dried over Na_2SO_4, and then the solvent removed under reduced pressure. The residue was purified by Biotage™ flash chromatography, eluant conditions: 1% of MeOH and 99% of CH_2Cl_2 to 10% of MeOH and 90% of CH_2Cl_2. Yield 68% (48 mg, MW 1376.71, 0.034 mmol) of pure **12d**. Analytical characterization: $[\alpha]_{20}^{D}$ −96 (*c* 1.34, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ: 7.82 (bs, 2H), 7.30–7.05 (m, 22H), 6.07 (m, 2H), 6.14 (d, *J* = 8.0 Hz, 2H), 4.66 (d, *J* = 7.2 Hz, 2H), 4,38 (m, 4H), 3.68 (m, 2H), 3.54 (m, 2H), 2.77 (m, 8H), 2.35 (m, 2H), 2.15 (m, 2H), 2.10 (m, 4H), 1.95–1.45 (m, 22H), 1.40 (s, 18H), 1.30–1.15 (m, 10H), 1.05 (m, 2H), 0.85 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ: 173.6, 172.8, 171.8, 169.3, 142.2, 128.6, 127.4, 127.3, 127.2, 61.1, 60.5, 58.9, 56.8, 53.7, 40.0, 37.0, 34.5, 33.2, 29.4, 28.3, 25.8, 25.5, 21.5, 10.7. ESI-MS: m/z 1377.4 $[M+H]^+$, 589.2 $[M+2H]^{2+}$.

4.5.2. Compound 8d

TFA (450 μL, 5.0 mmol) was added to a stirred solution of compound **12d** (37.8 mg, 0.028 mmol) in CH_2Cl_2 (2 mL). The reaction mixture was left stirring at room temperature overnight and then concentrated under reduced pressure. The residue was purified by chromatography on a C_{18} reverse phase semi-preparative hplc column, eluant conditions: from 70% of H_2O (0.2% TFA) and 30% of CH_3CN (0.2% TFA) to 30% of H_2O (0.2% TFA) and 70% of CH_3CN (0.2% TFA), flow rate 12 mL/min, 20 min runs. Yield 64% (25.3 mg, MW 1405.59, 0.018 mmol) of pure **8d**. Analytical characterization: $[\alpha]_{20}^{D}$ −61 (*c* 1.06, CH_3OH); ^1H NMR (400 MHz, D_2O): δ: 8.80 (m, 2H), 7.40–7.20 (m, 20H), 6.14 (s, 2H), 4.67 (m, 4H), 4.00 (m, 2H), 3.87 (bs, 2H), 3.44 (d, *J* = 13.6 Hz, 2H), 3.01 (t, *J* = 10 Hz, 2H), 2.70 (s, 6H), 2.85–2.70 (m, 6H), 2.70–1.75 (m, 16H), 1.70–1.55 (m, 8H), 1.32 (s, 8H), 1.05 (d, *J* = 7.0 Hz, 6H); ^{13}C NMR (100 MHz, D_2O): δ: 175.1, 171.6, 169.6, 167.5, 141.7, 141.5, 128.3, 128.1, 127.2, 127.1, 126.9, 62.6, 61.5, 58.2, 57.0, 54.3, 40.9, 38.2, 35.7, 32.7, 31.7, 31.0, 30.0, 28.9, 27.5, 25.6, 23.3, 8.0. ESI-MS: m/z 1177.6 $[M+H]^+$, 589.2 $[M+2H]^{2+}$.

4.6. Head–head dimers 8e,f—Scheme 3

The head–head dimers **8e** and **8f** were prepared similarly to **8d**. The detailed synthetic protocols leading to their synthesis, and their full synthetic characterization are reported in the Supplementary data.

4.7. Head–head dimer 8g—Scheme 4

4.7.1. Compound 11c

EDC·HCl (23 mg, 0.12 mmol), HOBt (16.2 mg, 0.12 mmol) and DIPEA (69.7 μL, 0.40 mmol) were sequentially added to a stirred solution of 6-heptynoic acid (15.2 μL, 0.12 mmol) in CH_2Cl_2 (2 mL) at room temperature. The reaction mixture was left stirring for 15 min and then added to a stirred solution of **4h** (60.6 mg, 0.10 mmol) in dry CH_2Cl_2 (2 mL). The reaction mixture was stirred at room temperature overnight and then, after reaction completion, the solvent was removed under reduced pressure. The crude product was diluted with EtOAc (20 mL) and washed with a saturated solution of ammonium chloride (3 × 20 mL), saturated solution of sodium bicarbonate (3 × 20 mL) and brine (1 × 20 mL). The organic layer was dried over Na_2SO_4, and then the solvent removed under reduced pressure. The residue was purified by Biotage™ flash chromatography, eluant conditions: from 50% of EtOAc and 50% of Petroleum ether to 100% of EtOAc. Yield 92% (65 mg, MW 713.42, 0.092 mmol) of pure **11c**. Analytical characterization: $[\alpha]_{20}^{D}$ −75 (*c* 0.90, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ: 7.92 (bs, 1H), 7.40–7.15 (m, 11H), 6.23 (d, *J* = 8.4 Hz, 1H), 4.75 (d, *J* = 7.6 Hz, 1H), 4.46 (m, 2H), 3.77 (m, 1H), 3.60 (m, 1H), 2.88 (s, 6H), 2.85 (m, 1H), 2.47 (m, 1H), 2.23 (m, 4H), 2.00–1.55 (m, 14H), 1.50 (s, 9H), 1.45–1.05 (m, 2H), 0.94 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ: 173.1, 172.9, 171.7, 169.3, 142.1, 128.5, 127.5, 127.4, 127.3, 127.2, 68.4, 61.1, 58.9, 56.8, 53.8, 40.0, 36.2, 34.5, 33.2, 28.4, 28.1, 25.5, 24.8, 21.6, 18.2, 10.8. ESI-MS: m/z 714.2 $[M+H]^+$.

4.7.2. Compound 12g

A stirred suspension of compound **11c** (71.4 mg, 0.10 mmol) and $Cu(OAc)_2$ (127.1 mg, 0.70 mmol) in acetonitrile (20 mL) was refluxed for 30 min. After reaction completion, the solvent was removed under reduced pressure. The crude product was diluted with EtOAc (20 mL) and washed with a saturated solution of amonium chloride (3 × 10 mL) and brine (1 × 10 mL). Finally, the crude product was purified by Biotage™ flash chromatography, eluant conditions: 1% of MeOH and 99% of CH_2Cl_2 to 10% of MeOH and 90% of CH_2Cl_2. Yield 84% (60 mg, MW 1425.83, 0.042 mmol) of pure **12g**. Analytical characterization: $[\alpha]_{20}^{D}$ −85 (*c* 1.1, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ: 7.83 (bs, 2H), 7.35–7.05 (m, 22H), 6.80 (m, 2H), 6.14 (m, 2H), 4.65 (bs, 2H), 4.37 (m, 4H), 3.68 (m, 2H), 3.52 (m, 2H), 2.78 (s, 6H), 2.66 (m, 2H), 2.36 (m, 2H), 2.25–2.10 (m, 10H), 1.95–1.45 (m, 22H), 1.40 (s, 18H), 1.35–1.00 (m, 4H), 0.87 (bs, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ: 172.9, 171.7, 169.3, 142.1, 128.6, 127.5, 127.4, 127.3, 65.6, 61.1, 60.6, 58.9, 56.8, 53.7, 41.1, 40.0, 36.2, 34.5, 33.2, 31.8, 28.3, 28.0, 25.5, 24.9, 21.6, 19.0, 10.8. ESI-MS: m/z 1426.6 $[M+H]^+$, 613.2 $[M+2H]^{2+}$.

4.7.3. Compound 8g

TFA (450 μL, 5.0 mmol) was added to a stirred solution of compound **12g** (94.1 mg, 0.066 mmol) in CH_2Cl_2 (2 mL). The reaction mixture was left stirring at room temperature overnight and then concentrated under reduced pressure. The residue was purified by chromatography on a C_{18} reverse phase semi-preparative hplc column, eluant conditions: from 70% of H_2O (0.2% TFA) and 30% of CH_3CN (0.2% TFA) to 30% of H_2O (0.2% TFA) and 70% of CH_3CN (0.2% TFA), flow rate 12 mL/min, 20 min runs. Yield 41% (39 mg,

MW 1453.64, 0.027 mmol) of pure **8g**. Analytical characterization: $[\alpha]_{20}^{D}$ −84 (*c* 1.16, CH_3OH); ^1H NMR (400 MHz, D_2O): *δ*: 8.80 (m, 2H), 7.40–7.20 (m, 20H), 6.14 (s, 2H), 4.67 (m, 4H), 4.02 (bs, 2H), 3.87 (bs, 2H), 3.44 (d, *J* = 13.2 Hz, 2H), 3.07 (t, *J* = 11.2 Hz, 2H), 2.72 (s, 6H), 2.40–2.20 (m, 10H), 2.20–180 (m, 16H), 1.75–1.60 (m, 8H), 1.60–1.45 (m, 4H), 1.05 (d, *J* = 7.1 Hz, 6H); ^{13}C NMR (100 MHz, D_2O): *δ*: 174.6, 171.6, 169.6, 167.5, 141.7, 141.5, 128.3, 128.1, 127.3, 127.2, 127.0, 126.9, 76.3, 65.4, 62.6, 61.6, 58.3, 57.0, 54.3, 40.9, 38.3, 35.1, 32.7, 31.7, 31.0, 30.2, 27.7, 27.5, 24.8, 23.2, 18.1, 7.8. ESI-MS: m/z 1226.0 $[M+H]^+$, 613.7 $[M+2H]^{2+}$.

4.8. Head–head dimer 8h—Scheme 5

4.8.1. Compound 12h

A 0.9 M aqueous solution of sodium ascorbate (61 μL, 0.055 mmol) and a 0.3 M aqueous solution of $Cu(OAc)_2$ (83 μL, 0.025 mmol) were sequentially added to a stirred solution of compound **11c** (0.10 mmol) and 1,4-(4′-azidobutyl)benzene[61] (13.6 mg, 0.05 mmol) in a 1:1 mixture of H_2O/^{t}BuOH (300 μL). The reaction mixture was stirred overnight at room temperature and then the solvent was removed under reduced pressure. The crude product was diluted with EtOAc (20 mL) and washed with a saturated solution of amonium chloride (3 × 20 mL) and brine (1 × 20 mL). The residue was purified by Biotage™ flash chromatography, eluant conditions: 1% of MeOH and 99% of CH_2Cl_2 to 10% of MeOH and 90% of CH_2Cl_2. Yield 32% (27 mg, MW 1700.21, 0.016 mmol) of pure **12h**. Analytical characterization: $[\alpha]_{20}^{D}$ −84 (*c* 1.16, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): *δ*: 7.84 (bs, 2H), 7.37 (bs, 2H), 7.35–7.15 (m, 22H), 7.09 (d, *J* = 6.8 Hz, 2H), 6.98 (s, 4H), 6.13 (d, *J* = 7.6 Hz, 2H), 4.65 (d, *J* = 6.8 Hz, 2H), 4.48 (m, 4H), 4.20 (m, 4H), 3.70 (m, 2H), 3.46 (m, 2H), 2.78 (s, 6H), 2.75 (m, 2H), 2.65 (s, 4H), 2.53 (t, *J* = 6.4 Hz, 4H), 2.34 (m, 2H), 2.17 (m, 6H), 1.95–1.50 (m, 28H), 1.40 (s, 18H), 1.39 (m, 2H), 1.05 (m, 2H), 0.85 (bs, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): *δ*: 174.9, 173.0, 171.8, 169.4, 150.0, 140.5, 139.0, 1.38.0, 138.6, 128.4, 127.5, 127.3, 120.6, 80.5, 61.2, 60.6, 59.0, 56.9, 53.8, 50.0, 41.3, 40.1, 36.3, 34.8, 34.4, 33.2, 31.8, 30.5, 29.8, 28.9, 28.3, 25.6, 25.3, 21.7, 20.7, 10.8. ESI-MS: m/z 1699.6 $[M+H]^+$, 850.8 $[M+2H]^{2+}$.

4.8.2. Compound 8h

TFA (450 μL, 5.0 mmol) was added to a stirred solution of compound **12h** (21.2 mg, 0.013 mmol) in CH_2Cl_2 (2 mL). The reaction mixture was left stirring at room temperature overnight and then concentrated under reduced pressure. The residue was purified by chromatography on a C_{18} reverse phase semi-preparative hplc column, eluant conditions: from 70% of H_2O (0.2% TFA) and 30% of CH_3CN (0.2% TFA) to 30% of H_2O (0.2% TFA) and 70% of CH_3CN (0.2% TFA), flow rate 12 mL/min, 20 min runs. Yield 92% (24 mg, MW 1728.01, 0.011 mmol) of pure **8h**. Analytical characterization: $[\alpha]_{D}^{20}$ −99 (*c* 1.16, CH_3OH); ^1H NMR (400 MHz, D_2O): *δ*: 8.80 (m, 2H), 7.76 (s, 2H), 7.40–7.15 (m, 20H), 7.06 (s, 4H), 6.14 (s, 2H), 4.66 (m, 4H), 4.37 (t, *J* = 6.4 Hz, 4H), 4.00 (m, 2H), 3.87 (m, 2H), 3.44 (d, *J* = 13.2 Hz, 2H), 3.05 (t, *J* = 11.6 Hz, 2H), 2–74–2.68 (m, 10H), 2.59 (t, *J* = 6.8 Hz, 4H), 2.26 (m, 6H), 2.15–1.75 (m, 21H), 1.70–1.50 (m, 17H), 1.06 (t, *J* = 7.2 Hz, 6H); ^{13}C NMR (100 MHz, D_2O): *δ*: 174.7, 171.6, 169.6, 167.5, 147.1, 141.7, 141.6, 139.2, 128.3, 128.1, 127.3, 127.1, 126.9, 122.2, 62.6, 61.6, 58.3, 57.1, 54.3, 50.0, 41.0, 38.3, 35.3, 34.2, 32.7, 31.7, 31.0, 30.2, 29.3, 28.5, 28.0, 27.6, 25.0, 24.3, 23.2, 7.8. ESI-MS: m/z 1500.2 $[M+H]^+$, 751.2 $[M+2H]^{2+}$.

4.9. Head–head dimer 8i—Scheme 6

4.9.1. Compound 11d

EDC·HCl (23 mg, 0.12 mmol), HOBt (16.2 mg, 0.12 mmol) and DIPEA (69.7 μL, 0.40 mmol) were sequentially added to a stirred solution of Cbz-β-Ala-OH (26.8 mg, 0.12 mmol) in CH_2Cl_2 (2 mL) at room temperature. The reaction mixture was left stirring for 15 min and then added to a stirred solution of **4h** (60.6 mg, 0.10 mmol) in dry CH_2Cl_2 (2 mL). The reaction mixture was stirred at room temperature overnight and then, after reaction completion, the solvent was removed under reduced pressure. The crude product was diluted with EtOAc (20 mL) and washed with a saturated solution of ammonium chloride (3 × 20 mL), saturated solution of sodium bicarbonate (3 × 20 mL) and brine (1 × 20 mL). The organic layer was dried over Na_2SO_4, and then the solvent removed under reduced pressure. The residue was purified by Biotage™ flash chromatography, eluant conditions: from 50% of EtOAc and 50% of Petroleum ether to 100% of EtOAc. Yield 99% (80 mg, MW 811.00, 0.099 mmol) of pure **11d**. Analytical characterization: $[\alpha]_{20}^{D}$ −118 (*c* 1.14, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): *δ*: 7.80 (d, *J* = 8.0 Hz, 2H), 7.30–7.15 (m, 14H), 7.10 (d, *J* = 7.6 Hz, 2H), 6.13 (d, *J* = 8.8 Hz, 2H), 5.02 (t, *J* = 12.0 Hz, 2H), 4.63 (d, *J* = 7.6 Hz, 1H), 4.31 (m, 2H), 3.62 (m, 1H), 3.40 (m, 3H), 2.75 (m, 3H), 2.35 (m, 3H), 2.12 (m, 1H), 1.90–1.50 (m, 8H), 1.39 (s, 9H), 1.35 (m, 1H), 1.05 (m, 1H), 0.85 (t , *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): *δ*:.173.0, 171.6, 169.3, 156.4, 136.7, 128.7, 128.6, 128.4, 128.0, 127.4, 127.3, 127.2, 80.4, 66.5, 61.1, 60.8, 58.8, 56.8, 53.8, 41.3, 40.1, 37.3, 35.9, 34.5, 33.1, 32.0, 30.1, 28.4, 25.5, 21.8, 10.8. ESI-MS: m/z 811.6 $[M+H]^+$.

4.9.2. Compound 12i

A solution of compound **11d** (67.6 mg, 0.1 mmol) in EtOH/H_2O 9:1 (10 mL) was Cbz-deprotected by continuous flow hydrogenation using the H-Cube™ system. The hydrogenation was performed using a Pd/C catalyst cartridge column (CatCart™). The reactor pressure and temperature were fixed at 10 bar and 40 °C, and a flow rate of 0.8 ml/min was set. After reaction completion, the solvent was removed under reduced pressure.

The crude hydrogenation product was dissolved in EtOH (1 mL), and then diethyl squarate (7.1 μL, 0.048 mmol), Et_3N (55.8 μL, 0.4 mmol) and a catalytic amount of DMAP (1.2 mg, 0.01 mmol) were sequentially added at room temperature. The reaction mixture was left stirring overnight at room temperature. After reaction completion, the solvent was removed under reduced pressure, the crude product was diluted with EtOAc (20 mL) and washed with water (3 × 20 mL). The organic layer was dried over Na_2SO_4, and then the solvent was removed under reduced pressure. Finally, the crude product was purified by Biotage™ flash chromatography, eluant conditions: 1% of MeOH and 99% of CH_2Cl_2 to 10% of MeOH and 90% of CH_2Cl_2. Yield 92% (63 mg, MW 1431.75, 0.044 mmol) of pure **12i**. Analytical characterization: $[\alpha]_{20}^{D}$ −88 (*c* 1.60, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): *δ*: 7.76 (d, *J* = 8.4 Hz, 2H), 7.30–7.10 (m, 22H), 6.13 (d, *J* = 8.8 Hz, 2H), 4.63 (d, *J* = 7.2 Hz, 2H), 4.35 (m, 4H), 3.75 (m, 5H), 3.25 (bs, 2H), 2.95 (bs, 2H), 2.73 (s, 6H), 2.42 (bs, 4H), 2.30 (m, 2H), 2.18 (m, 2H), 1.95–1.60 (m, 14H), 1.50 (m, 2H), 1.40 (s, 18H), 1.20 (m, 2H), 0.84 (t, *J* = 6.8 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): *δ*: 171.4, 169.6, 142.1, 141.2, 128.7, 127.4, 127.2, 61.2, 58.8, 56.8, 53.8, 41.5, 40.8, 39.9, 36.9, 34.0, 33.1, 31.8, 30.7, 25.8, 21.6, 10.5. ESI-MS: m/z 1432.0 $[M+H]^+$.

4.9.3. Compound 8i

TFA (450 μL, 5.0 mmol) was added to a stirred solution of compound **12i** (41.5 mg, 0.029 mmol) in CH_2Cl_2 (2 mL). The reaction mixture was left stirring at room temperature overnight and then concentrated under reduced pressure. The residue was purified by chromatography on a C_{18} reverse phase semi-preparative hplc column, eluant conditions: from 70% of H_2O (0.2% TFA) and 30% of CH_3CN (0.2% TFA) to 30% of H_2O (0.2% TFA) and 70% of CH_3CN (0.2% TFA), flow rate 12 mL/min, 20 min runs. Yield 83% (35 mg, MW 1459.56, 0.024 mmol) of pure **8i**. Analytical characterization: $[\alpha]_{20}^{D}$ −113 (*c* 1.20, CH_3OH); ^1H NMR (400 MHz, D_2O): *δ*:

7.35–7.25 (m, 20H), 6.00 (s, 2H), 4.57 (d, J = 10.0 Hz, 2H), 4.48 (dd, J = 7.6, 5.2 Hz, 2H), 3.95 (m, 2H), 3.88 (dd, J = 7.2, 5.2 Hz, 2H), 3.71 (m, 4H), 3.30 (dd, J = 13.6, 3.6 Hz, 2H), 2.99 (dd, J = 13.6, 9.6 Hz, 2H), 2.64 (s, 6H), 2.44 (m, 4H), 2.20–2.05 (m, 4H), 1.95–1.85 (m, 8H), 1.80–1.60 (m, 6H), 1.50–1.35 (m, 4H), 0.94 (t, J = 7.2 Hz, 6H); ^{13}C NMR (100 MHz, D_2O): δ: 181.7, 172.9, 172.0, 169.9, 168.4, 167.9, 141.3, 141.0, 128.8, 127.6, 127.5, 127.3, 127.0, 62.7, 61.6, 58.2, 57.4, 54.5, 40.7, 37.5, 37.0, 32.4, 31.6, 30.7, 27.7, 23.4, 8.3. ESI-MS: m/z 1231.9 $[M+H]^+$, 616.5 $[M+2H]^{2+}$.

4.10. Tail–tail dimer 9a—Scheme 7

4.10.1. Compound 13a

EDC·HCl (69 mg, 0.36 mmol), HOBt (48.6 mg, 0.36 mmol) and DIPEA (209 μL, 1.20 mmol) were sequentially added to a stirred solution of **4d** (132.5 mg, 0.3 mmol) in CH_2Cl_2 (10 mL) at room temperature. The reaction mixture was left stirring for 15 min and then added to a stirred solution of (*S*)-3-amino-3-phenylprop-1-yne (13.1 mg, 0.10 mmol) in dry CH_2Cl_2 (10 mL). The reaction mixture was stirred at room temperature overnight and then, after reaction completion, the solvent was removed under reduced pressure. The crude product was diluted with EtOAc (20 mL) and washed with a saturated solution of ammonium chloride (3 × 20 mL), saturated solution of sodium bicarbonate (3 × 20 mL) and brine (1 × 20 mL). The organic layer was dried over Na_2SO_4, and then the solvent was removed under reduced pressure. The residue was purified by Biotage™ flash chromatography, eluant conditions: 50% of EtOAc and 50% of Petroleum ether to 100% of EtOAc. Yield 67% (112 mg, MW 554.69, 0.201 mmol) of pure **13a**. Analytical characterization: $[\alpha]_{20}^{D}$ −116 (*c* 1.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ: 7.65 (d, J = 7.6 Hz, 1H), 7.36 (m, 3H), 7.20 (m, 3H), 5.87 (d, J = 6.8 Hz, 1H), 4.61 (d, J = 6.0 Hz, 1H), 4.42–4.30 (m, 2H), 3.67 (m, 1H), 3.47 (d, J = 11.6 Hz, 1H), 3.14 (d, J = 12.0, 1H), 2.78 (s, 3H), 2.42 (s, 1H), 2.36 (m, 1H), 2.18 (m, 1H), 2.00–1.70 (m, 4H), 1.70–1.55 (m, 3H), 1.44 (s, 9H), 0.97 (m, 1H), 0.84 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ: 171.7, 138.9, 128.9, 126.8, 73.0, 64.1, 60.8, 60.2, 58.7, 53.6, 44.4, 41.5, 34.6, 33.2, 31.0, 30.0, 28.4, 25.4, 21.4, 10.6. ESI-MS: m/z 555.4 $[M+H]^+$, 577.3 $[M+Na]^+$.

4.10.2. Compound 14a

A 0.9 M water solution of sodium ascorbate (61 μL, 0.055 mmol) and a 0.3 M water solution of $Cu(OAc)_2$ (83 μL, 0.025 mmol) were sequentially added to a stirred solution of compound **13a** (61 mg, 0.11 mmol) and 1,4-(4′-azidobutyl)benzene[61] (13.6 mg, 0.05 mmol) in a 1:1 mixture of H_2O/^{t}BuOH (300 μL). The reaction mixture was stirred overnight at room temperature and then the solvent was removed under reduced pressure. The crude product was diluted with EtOAc (20 mL) and washed with a saturated solution of ammonium chloride (3 × 20 mL) and brine (1 × 20 mL). The organic layer was dried over Na_2SO_4, and then the solvent was removed under reduced pressure. Finally, the residue was purified by Biotage™ flash chromatography, eluant conditions: 1% of MeOH and 99% of CH_2Cl_2 to 10% of MeOH and 90% of CH_2Cl_2. Yield 74% (51 mg, MW 1381.74, 0.037 mmol) of pure **14a**. Analytical characterization: $[\alpha]_{20}^{D}$ −83 (*c* 1.15, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ: 7.94 (m, 2H), 7.42 (m, 2H), 7.30–7.10 (m, 12H), 6.96 (s, 4H), 6.20 (d, J = 6.4 Hz, 2H), 4.64 (bs, 2H), 4.38 (m, 4H), 4.23 (bs, 4H), 3.70 (m, 2H), 3.53 (d, J = 12.0 Hz, 2H), 3.21 (d, J = 12.0 Hz, 2H), 2.79 (s, 6H), 2.53 (bs, 4H), 2.27 (m, 2H), 2.16 (m, 2H), 2.05–1.60 (m, 18H), 1.56 (m, 4H), 1.42 (s, 18H), 1.14 (m, 4H), 0.84 (bs, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ: 173.0, 171.5, 169.6, 140.9, 139.0, 128.6, 128.4, 127.7, 127.1, 121.4, 80.0, 64.3, 61.2, 60.2, 58.8, 53.8, 50.2, 50.0, 41.6, 34.7, 34.5, 33.1, 31.1, 29.7, 28.4, 28.2, 26.0, 21.5, 10.7. ESI-MS: m/z 1382.1 $[M+H]^+$, 691.7 $[M+2H]^{2+}$.

4.10.3. Compound 9a

TFA (450 μL, 5.0 mmol) was added to a stirred solution of compound **14a** (30.4 mg, 0.022 mmol) in CH_2Cl_2 (2 mL). The reaction mixture was left stirring at room temperature overnight and then concentrated under reduced pressure. The residue was purified by chromatography on a C_{18} reverse phase semi-preparative hplc column, eluant conditions: from 90% of H_2O (0.2% TFA) and 10% of MeOH/^{i}PrOH 6:4 (0.2% TFA) to 100% of MeOH/^{i}PrOH 6:4 (0.2% TFA), flow rate 12 ml/min, 20 min runs. Yield 59% (18 mg, MW 1409.54, 0.013 mmol) of pure **9a**. Analytical characterization: $[\alpha]_{20}^{D}$ −110 (*c* 0.41, CH_3OH); ^{1}H NMR (400 MHz, D_2O): δ: 7.53 (s, 2H), 7.20–7.05 (m, 10H), 6.59 (s, 4H), 6.10 (s, 2H), 4.57 (d, J = 9.2 Hz, 2H), 4.38 (bs, 2H), 3.96 (bs, 4H), 3.81 (m, 4H), 3–49 (bs, 4H), 2.62 (s, 6H), 2.08 (bs, 4H), 2.00–1.80 (m, 10H), 1.75–1.55 (m, 8H), 1.50–1.35 (m, 8H), 1.08 (bs, 4H), 0.88 (d, J = 7.2 Hz, 6H); ^{13}C NMR (100 MHz, D_2O): δ: 172.3, 170.7, 168.0, 147.9, 139.4, 139.1, 128.8, 128.2, 128.0, 127.0, 123.0, 63.1, 62.7, 61.6, 58.5, 54.3, 50.0, 49.9, 39.0, 32.3, 31.5, 29.4, 28.9, 27.7, 27.5, 23.4, 8.3. ESI-MS: m/z 1181.9 $[M+H]^+$, 1204.2 $[M+Na]^+$, 591.8 $[M+2H]^{2+}$.

4.11. Tail–tail dimer 9b—Schemes 8 and 9

4.11.1. Compound 16a

HOBt (104 mg, 0.77 mmol), HBTU (292 mg, 0.77 mmol) and Sym-collidine (169.1 μL, 1.28 mmol) were sequentially added to a stirred solution of commercially available 15a (46.2 mg, 0.32 mmol) and *N*-Boc-(*S*)-2-Phenylglycine (200.9 mg, 0.80 mmol) in dry DMF (2 mL) at 0 °C. The reaction mixture was left stirring for 2 h and then, after reaction completion, the mixture was diluted with EtOAc (20 mL) and washed with a saturated solution of ammonium chloride (3 × 20 mL), saturated solution of sodium bicarbonate (3 × 20 mL) and brine (1 × 20 mL. The organic layers were dried over Na_2SO_4, and then the solvent was removed under reduced pressure. The residue was purified by Biotage™ flash chromatography, eluant conditions: from 1% of MeOH and 99% of CH_2Cl_2 to 10% of MeOH and 90% of CH_2Cl_2. Yield 94% (183 mg, MW 610.80, 0.30 mmol) of pure 16a. Analytical characterization: ^{1}H NMR (400 MHz, $CDCl_3$):δ: 7.38–7.25 (m, 10H), 5.76 (m, 2H), 5.25 (m, 2H), 3.32 (bs, 1H), 3.23 (m, 2H), 3.13 (bs, 1H), 1.57 (s, 4H), 1.42 (m, 18H), 1.21 (d, J = 11.2 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ: 129.0, 128.9, 128.3, 127.2, 39.7, 39.7, 29.2, 28.8, 28.3, 26.4. ESI-MS: m/z 611.4 $[M+H]^+$.

4.11.2. Compound 17a

TFA (450 μL, 5.0 mmol) was added to a stirred solution of compound 16a (165 mg, 0.27 mmol) in CH_2Cl_2 (3 mL). The reaction mixture was left stirring at room temperature and then concentrated under reduced pressure to give a crude residue which was used without purification. Quantitative yield (172.4 mg, MW 638.56, 0.27 mmol) of 17a.

4.11.3. Compound 14b

HOBt (32.4 mg, 0.24 mmol), HBTU (91 mg, 0.24 mmol) and Sym-collidine (52.9 μL, 0.4 mmol) were sequentially added to a stirred solution of **4d** (110.4 mg, 0.25 mmol) and **17a** (63.9 mg, 0.10 mmol) in dry DMF (2 mL) at 0 °C. The reaction mixture was left stirring for 2 h and then, after reaction completion, the mixture was diluted with EtOAc (20 mL) and washed with a saturated solution of ammonium chloride (3 × 20 mL), saturated solution of sodium bicarbonate (3 × 20 mL) and brine (1 × 20 mL). The organic layers were dried over Na_2SO_4, and then the solvent was removed under reduced pressure. The residue was purified by Biotage™ flash chromatography, eluant conditions: 1% of MeOH and 99% of CH_2Cl_2 to 10% of MeOH and 90% of CH_2Cl_2. Yield 97% (122 mg, MW 1257.59, 0.094 mmol) of pure **14b**. Analytical characteriza-

tion: $[\alpha]_{20}^{D}$ −118 (*c* 1.23, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ: 8.43 (d, *J* = 8 Hz, 2H), 8.17 (t, *J* = 5.6 Hz, 2H), 7.86 (bs, 2H), 7.40–7.25 (m, 10H), 5.36 (d, *J* = 8 Hz, 2H), 4.61 (dd, *J* = 7.2, 4 Hz, 2H), 4.48–4.36 (m, 4H), 3.89 (m, 2H), 3.45 (bs, 2H), 3.25 (m, 2H), 3.00 (m, 4H), 2.70 (s, 6H), 2.16 (m, 2H), 2.14 (m, 2H), 2.00–1.75 (m, 8H), 1.70–1.45 (m, 10H), 1.40 (s, 18H), 1.35 (m, 4H), 1.15 (s, 8H), 0.80 (bs, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ: 171.2, 170.3, 169.9, 139.4, 128.6, 127.8, 127.5, 79.5, 63.1, 61.1, 58.0, 56.8, 53.9, 41.0, 39.0, 33.2, 32.8, 30.2, 29.3, 29.0, 28.5, 28.1, 26.6, 11.2 . ESI-MS: m/z 1257.9 $[M+H]^+$.

4.11.4. Compound 9b

TFA (450 μL, 5.0 mmol) was added to a stirred solution of compound **14b** (93.1 mg, 0.074 mmol) in CH_2Cl_2 (2 mL). The reaction mixture was left stirring at room temperature overnight and then concentrated under reduced pressure. The residue was purified by chromatography on a C_{18} reverse phase semi-preparative hplc column, eluant conditions: from 70% of H_2O (0.2% TFA) and 30% of CH_3CN (0.2% TFA) to 30% of H_2O (0.2% TFA) and 70% of CH_3CN (0.2% TFA), flow rate 12 ml/min, 20 min runs. Yield 58% (55 mg, MW 1285.35, 0.043 mmol) of pure **9b**. Analytical characterization: $[\alpha]_{20}^{D}$ −94 (*c* 1.44, CH_3OH); ^{1}H NMR (400 MHz, D_2O): δ: 7.41 (m, 10H), 5.29 (s, 2H), 4.70 (m, 2H), 4.53 (dd, *J* = 8.0, 4.4 Hz, 2H), 4.05 (m, 2H), 3.88 (dd, *J* = 7.2, 5.2 Hz, 2H), 3.61 (m, 2H), 3.25 (m, 2H), 3.05 (m, 2H), 2.68 (s, 6H), 2.25 (m, 2H), 2.15 (m, 2H), 2.05 (m, 4H), 1.95 (m, 6H), 1.85 (m, 3H), 1.75 (m, 4H), 1.60 (m, 2H), 1.35 (m, 4H), 1.012(bs, 8H), 0.96 (t, *J* = 8.0 Hz, 6H); ^{13}C NMR (100 MHz, D_2O): δ: 173.2, 171.6, 171.2, 168.3, 136.1, 129.2, 129.0, 127.3, 63.2, 62.8, 61.8, 58.8, 58.2, 54.5, 39.3, 39.0, 32.4, 31.5, 31.4, 29.5, 28.1, 27.8, 25.6, 23.4, 8.2. ESI-MS: m/z 1057.9 $[M+H]^+$.

4.12. Tail–tail dimers 9c–e—Schemes 8 and 9

The tail–tail dimers **9c**, **9d** and **9e** were prepared similarly to **9b**. The detailed synthetic protocols leading to their synthesis, and their full synthetic characterization are reported in the Supplementary data.

4.13. Tail–tail dimer 9f—Scheme 10

4.13.1. Compound 14f

Dry TEA (83.6 μL, 0.6 mmol) and MsCl (46.4 μL, 0.6 mmol) were sequentially added to a stirred solution of compound **14a** (0.1 mmol) in dry CH_2Cl_2 (4 mL) under argon at 0 °C. The reaction mixture was stirred at room temperature for 2 h. After reaction completion, the resulting mixture was diluted with CH_2Cl_2 (20 mL) and washed with a saturated solution of ammonium chloride (3 × 20 mL). The combined organic layers were dried over Na_2SO_4, and then the solvent was removed under reduced pressure.

The crude mesylate was dissolved in dry DMF (10 mL) under argon at room temperature, and then NaN_3 (130 mg, 2 mmol) was added. The reaction mixture was heated at 100 °C for 30 min, while being irradiated in a microwave reactor. After reaction completion most of the DMF was removed under reduced pressure, the crude was diluted with EtOAc (20 mL) and washed with water (3 × 20 mL). The organic layer was dried over Na_2SO_4, and then the solvent was removed under reduced pressure. Finally, the crude product was purified by Biotage™ flash chromatography. eluant conditions: 1% of MeOH and 99% of CH_2Cl_2 to 10% of MeOH and 90% of CH_2Cl_2. Yield 58% (83 mg, MW 1431.77, 0.058 mmol) of pure **14f**. Analytical characterization: $[\alpha]_{20}^{D}$ −105 (*c* 1.31, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ: 8.03 (m, 2H), 7.40–7.20 (m, 12H), 7.05 (m, 6H), 6.29 (d, *J* = 7.6 Hz, 2H), 4.71 (d, *J* = 6.4 Hz, 2H), 4.58 (m, 2H), 4.49 (m, 2H), 4.33 (bs, 4H), 3.83 (m, 2H), 3.42 (bd, *J* = 11.6 Hz, 2H), 3.16 (t, *J* = 12.8 Hz, 2H), 2.86 (s, 6H), 2.62 (m, 4H), 2.36 (m, 2H), 2.23 (m, 2H), 2.05–2.60 (m, 22H), 1.55 (bs, 20H), 1.22 (m, 2H), 0.85 (bs, 6H) ; ^{13}C NMR (100 MHz, $CDCl_3$): δ: 171.5, 171.0, 169.6, 140.7, 139.0, 128.7, 128.4, 127.9, 127.1, 121.6, 61.0, 59.0, 58.7, 53.6, 53.2, 50.3, 50.0, 34.7, 34.1, 33.3, 32.1, 29.7, 28.4, 28.2, 26.0, 21.4, 10.6. ESI-MS: m/z 1433.1 $[M+H]^+$, 666.7 $[M+2H]^{2+}$.

4.13.2. Compound 14g

A 1 N solution of $(CH_3)_3P$ in toluene (105 μL, 0.105 mmol) was added dropwise to a stirred solution of compound **14f** (50.1 mg, 0.035 mmol) in dry CH_2Cl_2 (10 mL) under argon at room temperature. After 2 h, a 1 N HCl aqueous solution (10 mL) was added to the reaction mixture, and stirring at room temperature was continued for further 20 min. After reaction completion, the reaction mixture was neutralized with sodium bicarbonate and extracted with CH_2Cl_2 (3 × 20 mL). The organic layers were combined and dried over Na_2SO_4, and the solvent was removed under reduced pressure. The crude product did not require any further purification, and was characterized as such. Yield 99% (48 mg, MW 1379.77, 0.035 mmol) of pure **14g**. Analytical characterization: $[\alpha]_{20}^{D}$ −120 (*c* 0.48, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ: 8.35 (m, 4H), 7.88 (m, 2H), 7.35–7.15 (m, 12H), 6.93 (m, 4H), 6.14 (d, *J* = 6.4 Hz, 2H), 4.62 (bs, 2H), 4.40 (m, 4H), 4.24 (bs, 4H), 3.70 (m, 2H), 3.00–2.65 (m, 10H), 2.52 (bs, 4H), 2.30–2.05 (m, 4H), 2.00–1.55 (m, 20H), 1.54 (m, 4H), 1.39 (s, 18H), 1.19 (m, 4H), 0.84 (bs, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ: 173.2, 171.7, 169.2, 141.9, 139.3, 129.6, 128.2, 127.5, 127.4, 122.4, 81.0, 64.5, 61.4, 60.1, 58.8, 53.8, 50.2, 50.0, 41.6, 35.7, 33.5, 33.1, 31.5, 29.7, 28.4, 28.2, 26.0, 21.5, 10.4. ESI-MS: m/z 1380.1 $[M+H]^+$, 691.2 $[M+2H]^{2+}$.

4.13.3. Compound 14h

$NaBH(OAc)_3$ (16.5 mg, 0.078 mmol) was added to a stirred solution of compound **14g** (41.4 mg, 0.03 mmol) and benzaldehyde (5.5 μL, 0.054 mmol) in dry CH_2Cl_2 (5 mL). The reaction mixture was stirred overnight at room temperature, and then the solvent was removed under reduced pressure. Finally, the crude product was purified by Biotage™ flash chromatography, eluant conditions: 1% of MeOH and 99% of CH_2Cl_2 to 10% of MeOH and 90% of CH_2Cl_2. Yield 45% (21 mg, MW 1560.32, 0.0135 mmol) of pure **14h**. Analytical characterization: $[\alpha]_{20}^{D}$ −150 (*c* 0.70, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ: 8.25 (bs, 2H), 8.03 (m, 2H), 7.40–7.24 (m, 20H), 7.18 (m, 2H), 7.05 (s, 4H), 6.28 (d, *J* = 7.6 Hz, 2H), 4,73 (bs, 2H), 4.49 (m, 4H), 4.30 (s, 4H), 3.95–3.75 (m, 6H), 2.95–2.75 (m, 6H), 2.70–2.50 (m, 8H), 2.35 (m, 2H), 2.23 (m, 2H), 2.25–1.55 (m, 22H), 1.49 (m, 20H), 1.24 (m, 2H), 0.93 (bs, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ: 169.9, 147.8, 141.0, 139.1, 128.8, 128.6, 127.6, 127.2, 127.0, 121.5, 61.0, 58.4, 50.2, 50.0, 38.1, 34.7, 33.3, 33.2, 29.7, 28.5, 28.2, 26.0, 22.1, 10.6. ESI-MS: m/z 1561.4 $[M+H]^+$, 781.0 $[M+2H]^{2+}$.

4.13.4. Compound 9f

TFA (90 μL, 1.0 mmol) was added to a stirred solution of compound **14h** (20.3 mg, 0.013 mmol) in CH_2Cl_2 (2 mL). The reaction mixture was left stirring at room temperature overnight and then concentrated under reduced pressure. The residue was purified by chromatography on a C_{18} reverse phase semi-preparative hplc column, eluant conditions: from 90% of H_2O (0.2% TFA) and 10% of MeOH/^{i}PrOH 6:4 (0.2% TFA) to 100% of MeOH/^{i}PrOH 6:4 (0.2% TFA), flow rate 12 ml/min, 20 min runs. Yield 92% (19 mg, MW 1587.83, 0.012 mmol) of pure **9f**. Analytical characterization: $[\alpha]_{20}^{D}$ −121 (*c* 0.95, CH_3OH); ^{1}H NMR (400 MHz, D_2O): δ: 7.52 (s, 2H), 7.35 (s, 10H), 7.25–7.05 (m, 10H), 6.64 (s, 4H), 6.06 (s, 2H), 4.56 (d, *J* = 9.2 Hz, 2H), 4.37 (bs, 2H), 4.14 (s, 4H), 4.045 (bs, 4H), 3.89 (bs, 2H), 3.76 (bs, 2H), 3.03 (d, *J* = 12.0 Hz, 2H), 2.95 (t, *J* = 11.2 Hz, 2H), 2.49 (s, 6H), 2.15 (bs, 4H), 2.12–1.90 (m, 8H), 1.90–1.70 (m, 8H), 1.70–1.65 (m, 2H), 1.50 (bs, 8H), 1.13 (bs, 4H), 0.84 (t, *J* = 7.2 Hz, 6H); ^{13}C NMR (100 MHz, D_2O): δ: 172.5, 168.9,

168.7, 147.5, 139.3, 139.1, 130.1, 129.9, 129.8, 129.3, 128.9, 128.2, 128.1, 127.0, 132.2, 62.5, 61.7, 58.0, 54.1, 51.4, 50.2, 50.1, 47.8, 35.2, 33.7, 32.2, 31.5, 29.7, 28.7, 28.4, 27.9, 27.4, 23.4, 8.1. ESI-MS: m/z 1360.0 $[M+H]^+$, 680.6 $[M+2H]^{2+}$.

4.14. Tail–tail dimer 9g—Scheme 11

4.14.1. Compound 13b

Dry TEA (223 μL, 1.6 mmol) and Boc_2O (349.2 mg, 1.6 mmol) were sequentially added to a stirred solution of compound **4c** (205 mg, 0.8 mmol) in dry CH_2Cl_2 (4 mL). The reaction mixture was stirred at room temperature and monitored by LC–MS. After reaction completion, the solution was diluted with CH_2Cl_2 (5 mL) and washed once with 5% citric acid and saturated $NaHCO_3$. The organic layer was dried over Na_2SO_4 and evaporated under reduced pressure. The crude product was used as such in the next reaction step.

Dry TEA (335 μL, 2.4 mmol) and MsCl (92.9 μL, 1.2 mmol) were sequentially added to a stirred solution of crude alcohol (270 mg, 0.78 mmol) in dry CH_2Cl_2 (4 mL) under argon at 0 °C. The reaction mixture was stirred at room temperature overnight. After reaction completion, the resulting mixture was diluted with CH_2Cl_2 (20 mL) and washed with a saturated ammonium chloride solution (2 × 20 mL). The organic layer was dried over Na_2SO_4, and then the solvent was removed under reduced pressure.

The crude product was dissolved in dry DMF (10 mL) and treated with $Bu_4N^+CN^-$ (322.2 mg, 1.2 mmol). The reaction mixture was heated at 80 °C for 90 min in a microwave reactor. After reaction completion most of the DMF was removed under reduced pressure, the crude was diluted with EtOAc (20 mL) and washed with water (3 × 20 mL). The organic layer was dried over Na_2SO_4, and then the solvent was removed under reduced pressure. The crude product was purified by Biotage™ flash chromatography, eluant conditions: from 1% of MeOH and 99% of CH_2Cl_2 to 10% of MeOH and 90% of CH_2Cl_2. Yield 63% (245 mg, MW 365.0, 0.493 mmol) of pure **13b**. Analytical characterization: ^{1}H NMR (400 MHz, $CDCl_3$): δ: 5.83 (d, J = 6.8 Hz, 1H), 4.61 (dd, J = 8.0, 4.4 Hz, 1H), 4.25 (t, J = 9.6 Hz, 1H); 3.92 (dd, J = 14.8, 7.6 Hz, 1H), 3.77 (s, 3H), 2.76 (dd, J = 15.2, 4.4 Hz, 1H), 2.42–2.25 (m, 3H), 2.15–1.65 (m, 7H), 1.45 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ: 172.2, 169.5, 118.9, 80.2, 60.4, 58.7, 56.2, 52.4, 37.7, 34.0, 33.3, 32.8, 28.3, 27.7,20.9. ESI-MS: m/z 753.4 [2 M+Na]$^+$.

4.14.2. Compound 13c

Compound **13b** (0.49 mmol) was dissolved in 3 N methanolic HCl solution (3 mL). The resulting mixture was stirred at room temperature overnight, and then evaporated under reduced pressure. The crude product was re-dissolved in CH_2Cl_2 (20 mL) and washed once with a saturated solution of $NaHCO_3$. The organic layer was dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure. The crude product was used as such in the next reaction step.

Dry DIPEA (341.4 μL, 1.96 mmol) was added to a solution of *N*-Boc, *N*-Me-(*S*)-ethylglycine (134.7 mg, 0.62 mmol), EDC·HCl (115 mg, 0.6 mmol) and HOBt (73.3 mg, 0.6 mmol) in dry CH_2Cl_2 (3 mL) at room temperature under a nitrogen atmosphere. The solution was stirred for 10 min before adding a solution of the crude amine (180 mg, 0.49 mmol) in CH_2Cl_2 (2 mL). The reaction mixture was stirred at room temperature and monitored by LC–MS. After reaction completion, the solution was diluted with CH_2Cl_2 (20 mL) and washed once with 5% citric acid and saturated $NaHCO_3$. The organic layer was dried over Na_2SO_4 and evaporated under reduced pressure. The crude product was purified by flash chromatography, eluant conditions: from 1% of MeOH and 99% of CH_2Cl_2 to 10% of MeOH and 90% of CH_2Cl_2. Yield 67% (152 mg, MW 464.57, 0.327 mmol) of pure **13c**. Analytical characterization: ^{1}H NMR (400 MHz, $CDCl_3$): δ: 7.14 (d, J = 7.2 Hz, 1H); 4.62 (dd, J = 7.6, 4.0, 1H), 4.56 (t, J = 9.6 Hz, 1H), 4.38 (bs, 1H), 3.97 (dd, J = 14.8, 7.2 Hz, 1H), 3.78 (s, 3H), 2.87 (s, 3H), 2.65 (bd, 1H), 2.45–2.28 (m, 3H), 2.20–1.70 (m, 9H), 1.50 (s, 9H), 0.92 (t, J = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ: 172.3, 169.0, 60.4, 58.6, 54.4, 52.5, 37.5, 33.9, 33.4, 32.7, 28.4, 27.7, 21.6, 20.8, 10.7. ESI-MS: m/z 465.5 $[M+H]^{+\cdot}$.

4.14.3. Compound 13d

A solution of nitrile **13c** (0.31 mmol) in EtOH (4 mL), and the was flowed through a Raney Nickel catalyst cartridge (hydrogen pressure 60 bar, temperature 60 °C, flow rate 0.5 mL/min) in a continuous flow hydrogenation H-Cube™ system. After reaction completion, the solvent was removed under reduced pressure and the crude was used as such in the next reaction step.

Dry TEA (86.4 μL, 0.62 mmol) and Boc_2O (135.3 mg, 0.62 mmol) were sequentially added to a stirred solution of the crude amine in dry CH_2Cl_2 (3 mL). The reaction mixture was stirred at room temperature and monitored by LC–MS. After reaction completion, the solution was diluted with CH_2Cl_2 (5 mL) and washed once with 5% citric acid and saturated $NaHCO_3$. The organic layer was dried over Na_2SO_4 and evaporated under reduced pressure. The crude product was purified by flash chromatography, eluant conditions: from 10% of EtOAc and 90% of petroleum ether to 100% of EtOAc. Yield 44% (78 mg, MW 568.60, 0.137 mmol) of pure **13d**. Analytical characterization: ^{1}H NMR (400 MHz, $CDCl_3$): δ: 6.88 (d, J = 4.8 Hz, 1H), 4.57 (m, 2H), 4.41 (dd, J = 9.2, 6.0 Hz, 1H), 4.94 (bd, J = 8.4 Hz, 1H), 3.75 (s, 3H), 3.06 (bs, 2H), 2.84 (s, 3H), 2.25 (m, 1H), 2.20–2.03 (m, 3H), 2.0–1.85 (m, 2H), 1.80–1.55 (m, 6H), 1.49 (s, 9H), 1.43 (s, 9H), 1.28 (t, J = 7.2 Hz, 1H), 0.91 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ: 172.5, 170.7, 155.9, 79.0, 60.2, 58.5, 55.0, 52.3, 38.4, 37.2, 33.5, 32.8, 32.3, 28.4, 27.8, 21.7, 21.0, 14.2, 10.7. ESI-MS: m/z 569.5 $[M+H]^+$.

4.14.4. Compound 13e

A 2 N aqueous LiOH solution (0.5 mL) was slowly added to an iced cooled, stirred solution of **13d** (74 mg, 0.13 mmol) in 1,4-dioxane (1 mL). The reaction mixture was then stirred at room temperature until complete hydrolysis of the starting material. After reaction completion, the cloudy solution was concentrated, the residue was taken up in CH_2Cl_2 (10 mL) and water (10 mL), and acidified to pH ≈3 with 2 N aqueous HCl. The mixture was extracted with CH_2Cl_2 (2 × 10 mL), the combined organic layers were dried over Na_2SO_4, and then the solvent was removed under reduced pressure. Crude **13e** was used without purification in the next reaction step.

4.14.5. Compound 14i

HOBt (16.2 mg, 0.12 mmol), HBTU (45.5 mg, 0.12 mmol) and Sym-collidine (26.4 μL, 0.2 mmol) were sequentially added to a stirred solution of **17b** (39.3 mg, 0.055 mmol) and crude **13e** (72.1 mg, 0.13 mmol) in dry DMF (2 mL) at 0 °C. The reaction mixture was left stirring and monitored by LC–MS. After reaction completion, the mixture was diluted with EtOAc (20 mL) and sequentially washed with 5% aqueous citric (20 mL) acid, saturated aqueous sodium bicarbonate (20 mL) and brine (2 × 20 mL). The organic layer was dried over Na_2SO_4, and then the solvent removed under reduced pressure. The residue was purified by Biotage™ flash chromatography, eluant conditions: from 10% of EtOAc and 90% of petroleum ether to 100% of EtOAc. Yield 77% (66 mg, MW 1559.97, 0.042 mmol) of pure **7**. Analytical characterization: ^{1}H NMR (400 MHz, $CDCl_3$): δ: 8.03 (d, J = 4.5 Hz, 2H), 7.32–7.02 (m, 10H), 7.01 (d, J = 8.4 Hz, 2H), 6.85 (bs, 2H), 5.32 (d, J = 4.5 Hz, 2H), 4.68 (d, J = 7.2 Hz, 2H), 4.48 (bs, 2H), 4.45 (dd, J = 9.6, 4.0 Hz, 2H), 3.86 (m, 2H), 3.62–3.25 (m, 16H), 3.10 (m, 4H), 2.86 (s, 6H), 2.32–2.15 (M, 4H), 2.05–1.60 (m, 24H), 1.52 (s, 18H), 1.43 (s, 18H), 1.28 (m, 2H), 0.93 (t, J = 7.2 Hz, 6H); ^{13}C NMR (100 MHz,

$CDCl_3$): δ: 171.9, 169.4, 156.0, 138.4, 128.9, 128.8, 128.2, 128.1, 127.2, 70.5, 70.0, 69.6, 61.2, 58.7, 57.3, 54.8, 38.1, 37.3, 34.5, 33.2, 28.5, 26.6, 10.8. ESI-MS: m/z 1559.9 $[M+H]^+$.

4.14.6. Compound 9g

TFA (270 μL, 3.0 mmol) was added to a stirred solution of compound **14i** (61 mg, 0.04 mmol) in CH_2Cl_2 (5 mL). The reaction mixture was left stirring at room temperature overnight and then concentrated under reduced pressure. The residue was purified by chromatography on a C_{18} reverse phase semi-preparative hplc column, eluant conditions: from 70% of H_2O (0.2% TFA) and 30% of CH_3CN (0.2% TFA) to 30% of H_2O (0.2% TFA) and 70% of CH_3CN (0.2% TFA), flow rate 12 ml/min, 20 min runs. Yield 80% (52 mg, MW 1615.57, 0.032 mmol) of pure **9g**. Analytical characterization: ^{1}H NMR (400 MHz, D_2O): δ: 7.47 (m, 10H), 5.28 (s, 2H), 4.60 (d, J = 9.6 Hz, 2H), 4.49 (dd, J = 8.0, 5.2 hz, 2H), 4.05 (m, 2H), 3.50 (dd, J = 6.4, 3.2 Hz, 4H), 3.43 (dd, J = 5.2, 3.2 Hz, 4H), 3.32 (t, J = 6.4 Hz, 4H), 3.29 (t, J = 6.8 Hz, 2H), 3.20–3.00 (m, 4H), 2.95 (m, 2H), 2,67 (s, 6H), 2.25 (m, 2H), 2.15 (m, 2H), 2.03 (m, 4H), 1.90 (m, 6H), 1.85–1.55 (m, 16H), 0.92 (t, J = 7.6, Hz, 6H); (100 MHz, D_2O): δ: 173.3, 171.8, 170.4, 168.6, 135.9, 129.3, 127.3, 69.4, 69.3, 68.0, 62.6, 61.6, 58.4, 58.3, 56.1, 37.3, 36.4, 35.1, 32.4, 31.6, 30.5, 29.8, 29.1, 28.1, 27.9, 23.5, 8.1. ESI-MS: m/z 580.6 $[M+H]^{2+}$, 1159.7 $[M+H]^+$.

4.15. Head–tail dimer 10a—Schemes 12 and 13

4.15.1. Compound 16e

HOBt (81 mg, 0.6 mmol), HBTU (227.5 mg, 0.6 mmol) and Sym-collidine (132.1 μL, 1 mmol) were sequentially added to a stirred solution of commercially available **15e** (110 mg, 0.503 mmol) and *N*-Boc-(*S*)-2-Phenylglycine (158 mg, 0.63 mmol) in dry DMF (3 mL) at 0 °C . The reaction mixture was left stirring and monitored by LC–MS. After reaction completion, the mixture was diluted with EtOAc (20 mL) and sequentially washed with 5% aqueous citric acid (20 mL), saturated aqueous sodium bicarbonate (20 mL) and brine (2 × 20 mL). The organic layer was dried over Na_2SO_4, and then the solvent was removed under reduced pressure. The residue was purified by Biotage™ flash chromatography, eluant conditions: from 1% of MeOH and 99% of CH_2Cl_2 to 10% of MeOH and 90% of CH_2Cl_2. Yield 74% (167 mg, MW 451.53, 0.37 mmol) of pure **16e**. Analytical characterization: ^{1}H NMR (400 MHz, $CDCl_3$): δ: 7.32.7.20 (m, 5H), 6.28 (bs, 1H), 5.77 (bs, 1H), 5.07 (bs, 1H), 3.6–3.28 (m, 16H), 1.35 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ: 129.0, 128.3, 127.2, 70.7, 70.6, 70.5, 70.3, 70.0, 69.6, 68.8, 58.5, 50.7, 39.6, 28.3. ESI-MS: m/z 452.5 $[M+H]^+$, 474.5 $[M+Na]^+$.

4.15.2. Compound 18a

TFA (900 μL, 10 mmol) was added to a stirred solution of compounds **16e** (95 mg, 0.27 mmol) in CH_2Cl_2 (3 mL). The reaction mixture was left stirring at room temperature and then concentrated under reduced pressure. The crude product was used in the next reaction step without further purification.

HOBt (74.6 mg, 0.55 mmol), HBTU (208.6 mg, 0.55 mmol) and sym-collidine (132.1 μL, 1 mmol) were sequentially added to a stirred solution of the crude residue (theoretically 0.27 mmol) and compound **4d** (150 mg, 0.034 mmol) in dry DMF (3 mL) at 0 °C. The reaction mixture was left stirring and monitored by LC–MS. After reaction completion, the mixture was diluted with EtOAc (20 mL) and washed with 5% aqueous citric acid (20 mL), saturated aqueous sodium bicarbonate (20 mL) and brine (2 × 20 mL). The organic layer was dried over Na_2SO_4, and then the solvent was removed under reduced pressure. The residue was purified by Biotage™ flash chromatography, eluant conditions: from 1% of MeOH and 99% of CH_2Cl_2 to 10% of MeOH and 90% of CH_2Cl_2. Yield 82% (170 mg, MW 774.92, 0.220 mmol) of pure **18a**. Analytical characterization: ^{1}H NMR (400 MHz, $CDCl_3$): δ: 7.93 (d, J = 6.8 Hz, 1H), 7.51 (d, J = 8.0 Hz, 1H), 7.36–7.27 (m, 5H), 6.37 (bs, 1H), 5.38 (d, J = 7 Hz, 1H), 4.71 (d, J = 6.8 Hz, 1H), 4.48 (m, 2H), 3.68 (m, 1H), 3.65 (m, 8H), 3.55 (m, 4H), 3.45 (m, 4H), 3.38 (m, 2H), 3.32 (m, 1H), 2.87 (s, 3H), 2.32 (m 1H), 2.22 (m, 1H), 2.10–1.40 (m, 3H), 1.35–1.70 (m, 5H), 1.52 (s, 9H), 1.30 (m, 2H), 0.93 (t, J = 7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ: 173.2, 172.4, 171.4, 170.0, 169.5, 138.2, 128.9, 128.2, 127.2, 70.7, 70.6, 70.5, 70.3, 70.0, 69.5, 64.3, 61.4, 61.0, 59.1, 58.8, 57.4, 53.9, 50.6, 41.6, 39.7, 34.4, 33.0, 32.8, 30.4, 28.4, 26.4, 21.6, 10.7 . ESI-MS: m/z 775.5 $[M+H]^+$, 797.5 $[M+Na]^+$.

4.15.3. Compound 11e

DCC (22.7 mg, 0.11 mmol) and DMAP (2.4 mg, 0.02 mmol) were sequentially added to a stirred solution of compound **4h** (60 mg, 0.1 mmol) and 4-pentynoic acid (9.8 mg, 0.1 mmol) in dry CH_2Cl_2 (4 mL) at 0 °C. The reaction mixture was warmed to room temperature over a period of 1 h. After reaction completion, the reaction mixture was filtered, and the filtrate was washed with diethyl ether. The organic phase was removed under reduced pressure, and the crude product was purified by Biotage™ flash chromatography, eluant conditions: from 1% of MeOH and 99% of CH_2Cl_2 to 10% of MeOH and 90% of CH_2Cl_2. Yield 93% (64 mg, MW 685.87, 0.093 mmol) of pure **11e**. Analytical characterization: $[\alpha]_{20}^{D}$ −116.0 (c 0.90, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ: 7.90 (d, J = 6.8 Hz, 1H), 7.28–7.09 (m, 11H), 6.13 (d, J = 8.0 Hz, 1H), 4.64 (d, J = 7.0 Hz, 1H), 4.45 (bs, 1H), 4.34 (m, 1H), 3.67 (m, 1H), 3.35 (m, 1H), 3.00–2.60 (m, 4H), 2.50–2.30 (m, 5H), 2.15 (m, 1H), 2.00–1.50 (m, 9H), 1.45 (m, 1H), 1.40 (s, 9H), 1.35–1.05 (m, 1H), 0.91 (t, J = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ: 172.8, 171.7, 171.3, 169.3, 142.0, 141.2, 128.7, 128.6, 127.5, 127.4, 127.3, 127.2, 80.7, 69.0, 62.0, 58.9, 56.8, 54.0, 41.8, 39.9, 35.4, 34.5, 33.3, 33.0, 32.0, 28.3, 27.5, 25.5, 21.9, 15.1, 10.8. ESI-MS: m/z 686.5 $[M+H]^+$, 703.5 $[M+Na]^+$.

4.15.4. Compound 19a

A 0.9 M aqueous solution of sodium ascorbate (70 μL) and a 0.3 M aqueous solution of $Cu(OAc)_2$ (50 μL) were sequentially added to a stirred solution of compound **18a** (44 mg, 0.057 mmol) and compound **11e** (38 mg, 0.057 mmol) in a 1:1 mixture of H_2O/^{t}BuOH (1 mL). The reaction mixture was stirred overnight at room temperature and then the solvent was removed under reduced pressure. The residues were purified by Biotage™ flash chromatography, eluant conditions: from 1% of MeOH and 99% of CH_2Cl_2 to 10% of MeOH and 90% of CH_2Cl_2. Yield 61% (51 mg, MW 1460.79, 0.035 mmol) of pure **19a**. Analytical characterization: ^{1}H NMR (400 MHz, $CDCl_3$): δ: 7.95 (d, J = 6.8 Hz, 2H), 7.51 (m, 2H), 7.35–7.20 (m, 15H), 7.16 (d, J = 9.2 Hz, 2H), 6.75 (bs, 1H), 6.22 (d, J = 6.8 Hz, 1H), 5.43 (d, J = 7.2 Hz, 1H), 4.72 (dd, J = 16, 7.6 Hz, 2H), 4.48 (m, 6H), 3.82 (m, 4H), 3.70–3.30 (m, 15H), 3.07 (t, J = 7.6 Hz, 2H), 2.85 (m, 6H), 2,.67 (m, 3H), 2.48 (m, 1H), 2.25 (m, 3H), 2.05 (m, 1H), 2.00–1.80 (m, 5H), 1.80–1.65 (m, 7H), 1.52 (s, 9H), 1.48 (s, 9H), 1.35 (m, 1H), 1.25 (m, 2H), 1.10 (m, 1H), 0.94 (t, J = 7.2 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ: 173.1, 171.4, 169.6, 169.4, 146.1, 142.1, 138.4, 128.8, 128.7, 128.6, 127.3, 127.2, 127.1, 123.0, 70.5, 70.4, 70.2, 69.5, 69.3, 64.3, 61.4, 61.1, 58.8, 57.2, 56.8, 53.9, 53.7, 50.4, 41.7, 39.6, 35.5, 34.5, 33.2, 33.0, 31.2, 28.4, 28.3, 26.4, 25.6, 21.6, 21.3, 10.7. ESI-MS: m/z 1461.7 $[M+H]^+$, 1482.7 $[M+Na]^+$.

4.15.5. Compound 10a

TFA (270 μL, 3.0 mmol) was added to a stirred solution of compound **19a** (54 mg, 0.030 mmol) in CH_2Cl_2 (5 mL). The reaction mixture was left stirring at room temperature overnight and then concentrated under reduced pressure. The residue was purified by chromatography on a C_{18} reverse phase semi-preparative hplc

column, eluant conditions: from 40% of H_2O (0.1% TFA) and 60% of CH_3CN (0.1% TFA) to 25% of H_2O (0.1% TFA) and 75% of CH_3CN (0.1% TFA), flow rate 15 ml/min, 22 min runs. Yield 90% (41 mg, MW 1488.60, 0.027 mmol) of pure **10a**. Analytical characterization: ^{1}H NMR (400 MHz, D_2O): δ: 8.77 (s, 1H), 7.39–7.29 (m, 15H), 6.04 (s, 1H), 5.33 (s, 1H), 4.67 (d, J = 10.0 Hz, 2H), 4.60–4.40 (m, 5H), 4.00 (m, 2H), 3.90 (m, 2H), 3.79 (m, 2H), 3.58 (d, J = 3.6 Hz, 2H), 3.55–38 (m, 11H), 3.35–3.20 (m, 2H), 2.96 (m, 3H), 2.67 (s, 6H), 2.57 (t, J = 7.2 Hz, 2H), 2.23 (m, 2H), 2.12 (m, 2H), 2.07–1.85 (m, 8H), 1.85–1.62 (m, 7H), 1.55 (m, 1H), 1.50–1.30 (m, 2H), 0.95 (m, 6H); ^{13}C NMR (100 MHz, D_2O): δ:174.8, 173.2, 172.7, 171.8, 171.1, 169.9, 168.4, 168.2, 146.0, 141.0, 140.8, 135.9, 129.2, 129.0, 128.8, 127.8, 127.3, 127.1, 123.9, 69.5, 69.4, 68.7, 68.6, 63.2, 62.7, 62.6, 61.7, 58.7, 58.3, 58.0, 57.6, 54.5, 54.4, 50.0, 40.7, 39.2, 38.9, 37.2, 35.1, 32.4, 31.5, 31.4, 30.1, 29.4, 27.9, 27.7, 23.4, 21.0, 8.2. ESI-MS: m/z 631.3 $[M+H]^{2+}$, 1260.8 $[M+H]^+$, 1282.7 $[M+Na]^+$.

4.16. Head–tail dimer 10b—Schemes 12 and 14

4.16.1. Compound 18b

A 1.0 M aqueous citric acid solution (250 μL) was added to a solution of **18a** (170 mg, 0.220 mmol) in H_2O/EtOH 1:9 (3 mL**).** The solution was hydrogenated by flowing through a 10% Pd/C catalyst cartridge (hydrogen pressure 10 bar, temperature 35 °C, flow rate 0.5 mL/min) using the H-Cube™ system. After reaction completion, the solvent was removed under reduced pressure. The crude product was used without any further purification, and only an analytical sample was purified by semi-preparative HPLC reverse phase chromatography, eluant conditions: from 90% H_2O (1% CH_3COOH) and 10% CH_3CN (1% CH_3COOH) to 100% CH_3CN (1% CH_3COOH). Yield 98% (162 mg, MW 748.95, 0.219 mmol) of pure **18b**. Analytical characterization: ^{1}H NMR (400 MHz, CD_{3OD}): $_\delta$: 8.6 (bs, 1H), 7.44–7.33 (m, 5H), 5.40 (s, 1H), 4.67 (dd, J = 5.2, 2.8 Hz, 1H), 4.53 (m, 2H), 4.01 (m, 1H), 3.67 (m, 5H), 3.65–3.47 (m, 8H), 3.39 (m, 2H), 3.09 (bs, 2H), 2.85 (s, 3H), 2.27 (m, 1H), 2.16 (m, 1H), 2.10- 1.88 (m, 4H), 1.82–1.65 (m, 4H), 1.55 (m, 1H), 1.50 (s, 9H), 1.42 (bs, 2H), 0.94 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, CD_3OD): δ: 172.3, 171.8, 171.0, 137.6, 128.4, 127.9, 127.2, 70.1, 69.8, 69.0, 67.4, 63.9, 61.4, 58.5, 57.3, 40.3, 39.6, 39.2, 33.2, 32.8, 30.7, 29.5, 27.3, 27.2, 26.9, 9.6. ESI-MS: m/z 749.6 $[M+H]^+$, 771.7 $[M+Na]^+$.

4.16.2. Compound 18c

DCC (24.8 mg, 0.12 mmol) and DMAP (3 mg, 0.025 mmol) were sequentially added to a stirred solution of compound **18b (**83 mg, 0.11 mmol) and 4-pentynoic acid (0.11 mmol) in dry CH_2Cl_2 (4 mL) at 0 °C. The reaction mixture was warmed to room temperature over a period of 1 h. After reaction completion, the reaction mixture was filtered, and washed with diethyl ether. The combined solvents were removed under reduced pressure, and the crude product was purified by Biotage™ flash chromatography, eluant conditions: : from 1% of MeOH and 99% of CH_2Cl_2 to 10% of MeOH and 90% of CH_2Cl_2. Yield 74% (67 mg, MW 829.01, 0.081 mmol) of pure **18c**. Analytical characterization: ^{1}H NMR (400 MHz, $CDCl_3$): δ: 7.98 (d, J = 7.0 Hz, 1H), 7.51 (d, J = 6.8 Hz, 1H), 7.45–7.25 (m, 5H), 6.68 (bs, 1H), 5.43 (d, J = 7.2 Hz, 1H), 4.71 (d, J = 6.8 Hz, 1H); 4.48 (bs, 2H), 3.8 (m, 1H), 3.70- 3.30 (m, 18H), 2.87 (s. 3H), 2.48 (m, 2H), 2.40–2.15 (m, 4H), 2.15–1.65 (m, 9H), 1.52 (s, 9H), 1.40–1.25 (m, 2H), 0.93 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ: 173.4, 173.2, 171.4, 171.3, 170.1, 169.5, 138.2, 128.8, 128.2, 127.2, 83.2, 70.6, 70.5, 70.4, 70.3, 70.1, 69.8, 69.5, 69.2, 64.3, 61.4, 58.8, 57.2, 53.9, 41.6, 39.7, 39.6, 39.1, 35.1, 34.5, 33.0, 31.2, 28.4, 26.6, 21.6, 20.6, 14.8, 10.6. ESI-MS: m/z 829.6 $[M+H]^+$, 851.5 $[M+Na]^+$.

4.16.3. Compound 19b

A 0.9 M aqueous solution of sodium ascorbate (60 μL) and a 0.3 M aqueous solution of $Cu(OAc)_2$ (40 μL) were sequentially added to a stirred solution of compound **19c** (37 mg, 0.045 mmol) and compound **4f** (29 mg, 0.045 mmol) in a 1:1 mixture of H_2O/^{t}BuOH (750 μL). The reaction mixture was stirred overnight at room temperature and then the solvent was removed under reduced pressure. The residues were purified by Biotage™ flash chromatography, eluant conditions: from 1% of MeOH and 99% of CH_2Cl_2 to 10% of MeOH and 90% of CH_2Cl_2. Yield 80% (52 mg, MW 1460.79, 0.036 mmol) of pure **19b**. Analytical characterization: ^{1}H NMR (400 MHz, $CDCl_3$): δ: 7.89 (d, J = 6.8 Hz, 1H), 7.71 (d, J = 7.0 Hz, 1H), 7.47 (m, 1H), 7.35–7.12 (m, 15H), 7.08 (d, J = 7.2 Hz, 1H), 6.85 (bs, 1H), 6.55 (bs, 1H), 6.10 (d, J = 8.8 Hz, 1H), 5.36 (d, J = 7.2 Hz, 1H), 4.56 (m, 3H), 4.38 (m, 4H), 4.10 (bs, 1H), 3.75 (m, 2H), 3.60–3.20 (m, 18H), , 2.97 (bs, 2H), 2.75 (s, 6H), 2.55 (m, 3H), 2.32 (m, 1H), 2.15 (m, 3H), 1.95–1.60 (m, 13H), 1.43 (s, 9H), 1.38 (s, 9H); 1.35–1.15 (m, 3H), 1.02 (m, 1H), 0.85 (t, J = 7.2 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ: 171.9, 171.4, 170.7, 169.6, 141.8, 141.2, 138.4, 128.8, 128.7, 128.1, 127.6, 127.5, 127.3, 127.2, 127.1, 70.4, 70.1, 69.9, 69.8, 69.5, 64.3, 61.4, 61.3, 58.8, 57.2, 56.9, 53.9, 53.6, 41.6, 40.4, 39.6, 39.2, 34.4, 33.6, 33.3, 33.0, 31.1, 28.4, 28.3, 26.5, 25.9, 21.7, 21.2, 10.7. ESI-MS: m/z 681.2 $[M+H]^{2+}$,1461.0 $[M+H]^+$, 1483.0 $[M+Na]^+$.

4.16.4. Compound 10b

TFA (180 μL, 2.0 mmol) was added to a stirred solution of compound **19b** (30 mg, 0.022 mmol) in CH_2Cl_2 (4 mL). The reaction mixture was left stirring at room temperature overnight and then concentrated under reduced pressure. The residue was purified by chromatography on a C_{18} reverse phase semi-preparative hplc column, eluant conditions: from 40% of H_2O (0.1% TFA) and 60% of CH_3CN (0.1% TFA) to 25% of H_2O (0.1% TFA) and 75% of CH_3CN (0.1% TFA), flow rate 15 ml/min, 22 min runs. Yield 86% (28 mg, MW 1488.60, 0.019 mmol) of pure **10b**. Analytical characterization: ^{1}H NMR (400 MHz, D_2O): δ: 7.78 (s, 1H), 7.37–7.28 (m, 15H), 6.04 (s, 1H), 5.34 (s, 1H), 4.78 (d, J = 10.4 Hz, 1H), 4.66 (m, 1H), 4.53 (m, 3H), 4.36 (m, 1H), 4.03 (m, 2H), 3.88 (t, J = 6.0 Hz, 2H), 3.60–3.25 (m, 16H), 3.28 (m, 3H), 2.94 (t, J = 14.4 Hz, 2H), 2.70 (s, 3H), 2.58 (s, 3H), 2.56 (t, J = 7.2 Hz, 2H), 2.35–2.05 (m, 5H), 2.05–1.88 (m, 9H), 1.85–1.65 (m, 6H), 1.62–1.46 (m, 3H), 0.95 (m, 6H); ^{13}C NMR (100 MHz, D_2O): δ: 174.9, 173.2, 172.7, 171.1, 169.5, 168.7, 146.5, 141.0, 140.9, 136.0, 129.2, 129.0, 128.9, 127.8, 127.4, 127.3, 127.1, 69.6, 69.4, 68.8, 68.7, 63.2, 62.8, 62.6, 61.9, 61.8, 58.7, 58.2, 58.0, 57.6, 54.5, 54.4, 52.0, 39.3, 39.0, 38.1, 35.0, 32.4, 32.3, 31.8, 31.5, 27.9, 27.7, 23.5, 23.4, 20.9, 8.2, 8.1. ESI-MS: m/z 631.1 $[M+H]^{2+}$, 1260.8 $[M+H]^+$, 1282.7 $[M+Na]^+$.

4.17. Head–tail dimer 10c—Schemes 12 and 15

4.17.1. Compound 18d

Diglycolic anhydride (25.5 mg, 0.22 mmol) and pyridine (36.4 μL, 0.45 mmol) were sequentially added to a stirred solution of compound **18b (**83 mg, 0.11 mmol) in DMF (3 mL). The reaction mixture was stirred at room temperature for 4 h. After reaction completion, water (20 mL) was added to the reaction mixture. The mixture was diluted with EtOAc (20 mL) and washed with 5% aqueous citric acid (20 mL), saturated aqueous sodium bicarbonate (20 mL) and brine (2 × 20 mL). The combined organic layer was dried over Na_2SO_4, and then the solvent was removed under reduced pressure. Finally, the crude product was purified by flash chromatography on a Biotage™ C_{18} reverse phase column, eluant conditions: from 90% H_2O (1% CH_3COOH) and 10% CH_3CN (1% CH_3COOH) to 100% CH_3CN (1% CH_3COOH). Yield 58% (55 mg, MW 865.00, 0.064 mmol) of pure **18d**. Analytical characterization: ^{1}H

NMR (400 MHz, $CDCl_3$): δ: 8.01 (d, J = 7.0 Hz, 1H), 7.61 (bs, 1H), 7.53 (d, J = 6.8 Hz, 1H), 7.40–7.28 (m, 5H), 6.98 (bs, 1H), 4.52 (d, J = 7.2 Hz, 1H), 4.71 (d, J = 6.8 Hz, 1H), 4.5 (m, 2H), 4.10 (m, 3H), 3.82 (m, 1H); 3.70–3.30 (m, 18H), 2.88 (s, 3H), 2.25 (m, 2H), 2.08 (s, 2H), 2.05–1.70 (m, 8H), 1.51 (s, 9H), 1.39 (m, 2H), 0.93 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ: 175.2, 173.0, 171.9, 171.4, 169.8, 169.8, 137.9, 128.8, 128.3, 127.2, 77.3, 77.0, 76.8, 71.4, 70.4, 70.0, 69.7, 69.5, 69.2, 64.3, 61.6, 58.9, 57.2, 54.0, 41.5, 39.7, 38.8, 34.3, 33.0, 31.2, 28.4, 26.7, 21.6, 20.6, 10.6. ESI-MS: m/z 865.4 $[M+H]^+$, 887.4 $[M+Na]^+$.

4.17.2. Compound 19c

HOBt (9.5 mg, 0.078 mmol), HBTU (29.6 mg, 0.078 mmol) and sym-collidine (33 μL, 0.25 mmol) were sequentially added to a stirred solution of compound **18d** (54 mg, 0.063 mmol) and compound **4h** (52 mg, 0.08 mmol) in dry DMF (1 mL) at 0 °C. The reaction mixture was left stirring and monitored by LC–MS. After reaction completion, the mixture was diluted with EtOAc (20 mL) and washed with 5% aqueous citric acid (20 mL), saturated aqueous sodium bicarbonate (20 mL) and brine (2 × 20 mL). The organic layer was dried over Na_2SO_4, and then the solvent was removed under reduced pressure. The residue was purified by Biotage™ flash chromatography, eluant conditions: from 1% of MeOH and 99% of CH_2Cl_2 to 10% of MeOH and 90% of CH_2Cl_2. Yield 67% (61 mg, MW 1457.77, 0.042 mmol) of pure **19c**. Analytical characterization: ^{1}H NMR (400 MHz, $CDCl_3$): δ: 7.87 (d, J = 7.2 Hz, 1H), 7.76 (d, J = 6.8 Hz, 1H), 7.63 (d, J = 6.0 Hz, 1H), 7.46 (m, 2H), 7.35–7.10 (m, 15H), 6.72 (bs, 1H), 6.15 (d, J = 8.4 Hz, 1H), 5.35 (d, J = 7.2 Hz, 1H), 4.64 (dd, J = 19.2, 7.2 Hz, 2H), 4.40 (m, 4H), 3.95 (m, 4H), 3.72 (m, 3H), 3.6–3.20 (m, 18H), 2.79 (s, 3H), 2.75 (s, 3H), 2.52 (m, 2H), 2.35 (m, 1H), 2.18 (m, 2H), 1.90–1.55 (m, 14H), 1.43 (s, 9H), 1.41 (s, 9H), 1.30–1.10 (m, 4H), 0.85 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ: 172.7, 171.3, 169.6, 168.9, 168.9, 142.2, 138.4, 128.8, 128.6, 128.5, 128.1, 127.4, 127.3, 127.2, 70.7, 70.5, 70.4, 70.3, 70.1, 69.6, 69.5, 64.3, 61.7, 61.4, 61.3, 60.5, 58.9, 58.8, 57.2, 56.8, 53.9, 53.5, 41.6, 40.0, 39.7, 39.6, 38.7, 34.4, 34.3, 33.1, 33.0, 31.1, 28.4, 28.3, 26.4, 25.7, 21.7, 21.3, 10.7, 10.6. ESI-MS: m/z 1452.9 $[M+H]^+$, 1475.0 $[M+Na]^+$.

4.17.3. Compound 10c

TFA (360 μL, 4.0 mmol) was added to a stirred solution of compound **19c** (58 mg, 0.040 mmol) in CH_2Cl_2 (5 mL). The reaction mixture was left stirring at room temperature overnight and then concentrated under reduced pressure. The residue was purified by chromatography on a C_{18} reverse phase semi-preparative hplc column, eluant conditions: from 40% of H_2O (0.1% TFA) and 60% of CH_3CN (0.1% TFA) to 25% of H_2O (0.1% TFA) and 75% of CH_3CN (0.1% TFA), flow rate 15 ml/min, 22 min runs. Yield 88% (55 mg, MW 1480.57, 0.037 mmol) of pure **10c**. Analytical characterization: ^{1}H NMR (400 MHz, D_2O): δ: 7.41–7.30 (m, 15H), 6.06 (s, 1H), 5.36 (s, 1H), 4.67 (d, J = 8.4 Hz, 2H), 4.55 (m, 2H), 4.10 (d, J = 5.2 hz, 4H), 4.05 (m, 2H), 3.93 (t, J = 6.4 Hz, 1H), 3.89 (t, J = 5.6 Hz, 1H), 2.70 (s, 3H), 2.69 (s, 3H), 2.25 (m, 2H), 2.15 (m, 2H), 2.08–1-68 (m, 17H), 1.65–1.50 (m, 3H), 0.97 (m, 6H) ; ^{13}C NMR (100 MHz, D_2O): δ: 172.8, 171.8, 171.7, 171.1, 170.1, 168.5, 168.3, 141.0, 140.9, 129.2, 129.0, 128.9, 127.8, 127.4, 127.3, 127.2, 70.0, 69.9, 69.6, 69.4, 68.8, 68.7, 63.2, 62.8, 62.7, 61.9, 61.8, 58.8, 58.5, 58.0, 57.7, 54.6, 54.5, 40.7, 39.3, 39.0, 38.6, 37.4, 32.4, 31.6, 31.5, 30.5, 29.5, 29.0, 27.9, 27.7, 23.4, 8.2, 8.1. ESI-MS: m/z 627.1 $[M+H]^{2+}$, 1252.8 $[M+H]^+$, 1274.8 $[M+Na]^+$.

4.18. Head–tail dimer 10d—Schemes 12 and 16

4.18.1. Compound 19d

A 0.9 M aqueous solution of sodium ascorbate (45 μL, 0.4 mmol) and a 0.3 M aqueous solution of $Cu(OAc)_2$ (65 μL, 0.02 mmol) were added to A stirred solution of compound **4e** (61.8 mg, 0.10 mmol) and of the alkyne **20a**[55] (70.8 mg, 0.10 mmol) in a 1:1 mixture of H_2O/^{t}BuOH (300 μL). The reaction mixture was stirred overnight at room temperature, and then the solvent was removed under reduced pressure. Finally, the residue was purified by flash chromatography, eluant conditions: isocratic, CH_2Cl_2/MeOH 95/5. Yield 57% (76 mg, MW 1324.62, 0.057 mmol) of pure **19d**. Analytical characterization: $[\alpha]_{20}^{D}$ −55.6 (c 0.54, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$): δ: 7.83 (d, J = 7.2 Hz, 1H), 7.76 (d, J = 7.2 Hz, 2H), 7.57 (m, 5H), 7.49 (bd, 1H), 7.45–7.13 (m, 18H), 6.17 (d, J = 8.2 Hz, 1H), 5.23 (bd, J = 7.2 Hz, 1H), 4.80–4.30 (m, 9H), 4.30–3.90 (m, 6H), 3.90–3.50 (m, 4H), 2.87 (s, 3H), 2.38 (m, 1H), 2.21 (m, 1H), 2.02 (m, 1H), 1.94–1.45 (m, 10H), 1.43–1.32 (m, 11H), 1.30–1.05 (m, 6H), 0.93 (t, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ: 173.0, 171.2, 170.7, 169.4, 169.3, 155.7, 153.3, 143.9, 141.8, 141.3, 133.0, 129.8, 128.8, 127.7, 127.4, 127.3, 127.2, 127.1, 125.0, 120.0, 80.1, 74.6, 68.0, 62.6, 61.2, 58.7, 56.8, 56.3, 54.9, 54.6, 53.7, 51.8, 48.4, 47.7, 47.2, 40.4, 33.5, 33.2, 31.1, 28.5, 27.2, 26.0, 25.6, 24.0, 16.3, 10.2. ESI-MS: m/z 1325.4 $[M+H]^+$, 1347.4 $[M+Na]^+$.

4.18.2. Compound 10d

Compound **19d** (59.7 mg, 0.045 mmol) was dissolved into a 20% solution of piperidine in CH_2Cl_2 (2 mL). The reaction mixture was stirred for 30 min at room temperature. and then concentrated in vacuo. The residue was used as such in the next reaction step.

A 3 N solution of HCl in MeOH (0.5 mL) was added to a stirred solution of crude (theoretically 0.045 mmol) in MeOH (2 mL). The reaction mixture was left stirring at room temperature overnight and then concentrated under reduced pressure. The residue was purified by chromatography on a C_{18} reverse phase semi-preparative hplc column, eluant conditions: from 80% of H_2O (0.1% TFA) and 20% of CH_3CN (0.1% TFA) to 50% of H_2O (0.1% TFA) and 50% of CH_3CN, flow rate 20 ml/min, 10 min runs. Yield 90% (45 mg, MW 1231.29, 0.040 mmol) of pure **10d**. Analytical characterization: $[\alpha]_{20}^{D}$ −29.0 (c 0.88, H_2O); ^{1}H NMR (400 MHz, D_2O): δ: 7.86 (s, 1H); 7.43–7.05 (m, 15H), 5.91 (s, 1H), 4.63–4.10 (m, 10H), 3.95–3.80 (m, 4H), 3.48 (m, 2H), 2.59 (s, 3H), 2.25–1.38 (m, 16H), 1.23 (m, 2H), 1.14 (m, 3H), 0.96 (m, 3H); ^{13}C NMR (100 MHz, D_2O): δ: 172.0, 169.7, 169.5, 154.7, 144.5, 141.2, 141.0, 134.0, 133.3, 130.2, 130.0, 128.7, 127.6, 127.3, 127.0, 126.6, 125.2, 74.0, 61.5, 58.1, 57.4, 57.0, 56.5, 56.0, 54.3, 54.1, 51.8, 48.9, 47.6, 38.6, 32.3, 31.0, 29.6, 28.6, 27.7, 26.9, 24.4, 23.5, 16.0, 15.3, 8.4. ESI-MS: m/z 1025.7 $[M+Na]^+$, 502.4 $[M+2H]^{2+}$.

Acknowledgment

The authors are thankful to 'FONDAZIONE CARIPLO' for financing through Project 2009-2534, titled 'Inhibitors of Apoptosis Proteins (IAPs) as anticancer therapeutics'.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bmc.2012.09.020.

References and notes

1. Fulda, S.; Debatin, K. M. *Curr. Cancer Drug Targets* **2004**, *4*, 569.
2. Kim, R. *Nat. Rev. Cancer* **2005**, *103*, 1551.
3. Cotter, T. G. *Nat. Rev. Cancer* **2009**, *9*, 501.
4. Damgaard, R. B.; Gyrd-Hansen, M. *Discov. Med.* **2011**, *11*, 221.
5. Nagata, S. *Ann. N. Y. Acad. Sci.* **2010**, *1209*, 10.
6. Okouchi, M.; Ekshyyan, O.; Maracine, M.; Aw, T. Y. *Antioxid. Redox Signal.* **2007**, *9*, 1059.
7. Baratchi, S.; Kanwar, R. K.; Kanwar, J. R. *Crit. Rev. Biochem. Mol. Biol.* **2010**, *45*, 535.
8. Fulda, S.; Debatin, K. M. *Oncogene* **2006**, *25*, 4798.
9. Wiezorek, J.; Holland, P.; Graves, J. *Clin. Cancer Res.* **2010**, *16*, 1701.

10. Brenner, D.; Mak, T. W. *Curr. Opin. Cell Biol.* **2009**, *21*, 871.
11. Constantinou, C.; Papas, K. A.; Constantinou, A. I. *Curr. Cancer Drug Targets* **2009**, *9*, 717.
12. Metz, J. T.; Hajduk, P. J. *Curr. Opin. Chem. Biol.* **2010**, *14*, 498.
13. Knight, Z. A.; Lin, H.; Shokat, K. M. *Nat. Rev. Cancer* **2010**, *10*, 130.
14. Allen, J. A.; Roth, B. A. *Annu. Rev. Pharmacol. Toxicol.* **2011**, *51*, 117.
15. Danson, S.; Dean, E.; Dive, C.; Ranson, M. *Curr. Cancer Drug Targets* **2007**, *7*, 785.
16. Altieri, D. C. J. *Biochem.* **2010**, *430*, 199.
17. Crook, N. E.; Clem, R. J.; Miller, L. K. *J. Virol.* **1993**, *67*, 2168.
18. Hunter, M.; LaCasse, E. C.; Korneluk, R. G. *Apoptosis* **2007**, *12*, 1543.
19. Shi, Y. *Protein Sci.* **2004**, *13*, 1979.
20. Eckelman, P.; Salvesen, G. S.; Scott, F. L. *EMBO Rep.* **2006**, *7*, 988.
21. Srinivasula, S. M.; Ashwell, J. D. *Mol. Cell* **2008**, *30*, 123.
22. Dubrez-Daloz, L.; Dupoux, A.; Cartier, J. *Cell Cycle* **2008**, *7*, 1036.
23. Gyrd-Hansen, M.; Meier, P. *Nat. Rev. Cancer* **2010**, *10*, 561.
24. Mufti, R.; Burstein, E.; Duckett, C. S. *Arch. Biochem. Biophys.* **2007**, *463*, 168.
25. Kashar, H. *Clin. Cancer Res.* **2010**, *16*, 4496.
26. Deveraux, Q. L.; Leo, E.; Stennicke, H. R.; Welsh, K.; Salvesen, G. S.; Reed, J. C. *EMBO J.* **1999**, *18*, 5242.
27. Du, M.; Fang, Y.; Li, L.; Wang, X. *Cell* **2000**, *102*, 33.
28. Verhagen, M.; Ekert, P. G.; Pakusch, M.; Silke, J.; Connolly, L. M.; Reid, G. E.; Moritz, R. L.; Simpson, R. J.; Vaux, D. L. *Cell* **2000**, *102*, 43.
29. Chai, J.; Du, C.; Wu, J.-W.; Kyin, S.; Wang, X.; Shi, Y. *Nature* **2000**, *406*, 855.
30. Liu, Z.; Sun, C.; Olejniczak, E. T.; Meadows, R. P.; Betz, S. F.; Oost, T.; Herrmann, J.; Wu, J. C.; Fesik, S. W. *Nature* **2000**, *408*, 1004.
31. Wu, G.; Chai, J.; Suber, T. L.; Wu, J. W.; Du, C.; Wang, X.; Shi, Y. *Nature* **2000**, *408*, 1008.
32. Shiozaki, N.; Chai, J.; Rigotti, D. J.; Riedl, S. J.; Li, P.; Srinivasula, S. M.; Alnemri, E. S.; Fairman, R.; Shi, Y. *Mol. Cell* **2003**, *11*, 519.
33. Riedl, S. J.; Renatus, M.; Schwarzenbacher, R.; Zhou, Q.; Sun, C.; Fesik, S. W.; Liddington, R. C.; Salvesen, G. S. *Cell* **2001**, *104*, 791.
34. Shi, Z.; Liang, Y. J.; Chen, Z. S.; Wang, X. H.; Ding, Y.; Chen, L. M. L.; Fu, W. *Oncol. Rep.* **2007**, *17*, 969.
35. Mizutani, Y.; Nakanishi, H.; Li, Y. N.; Matsubara, H.; Yamamoto, K.; Sato, N.; Shiraishi, T.; Nakamura, T.; Mikami, K.; Okihara, K.; Takaha, N.; Ukimura, O.; Kawauchi, A.; Nonomura, N.; Bonavida, B.; Miki, T. *Int. J. Oncol.* **2007**, *30*, 919.
36. Holcik, M.; Gibson, H.; Korneluk, R. G. *Apoptosis* **2001**, *6*, 253.
37. Dean, J.; Ranson, M.; Blackhall, F.; Dive, C. *Expert Opin. Ther. Targets* **2007**, *11*, 1459.
38. Rajapakse, H. A. *Curr. Top. Med. Chem.* **2007**, *7*, 966.
39. Rothe, M.; Pan, M. G.; Henzel, W. J.; Ayres, T. M.; Goeddel, D. V. *Cell* **1995**, *83*, 1243.
40. Baud, V.; Karin, M. *Nat. Rev. Drug Disc.* **2009**, *8*, 33.
41. Eckelman, B. P.; Salvesen, G. S. *J. Biol. Chem.* **2006**, *281*, 3254.
42. Bertrand, M. J. M.; Milutinovic, S.; Dickson, K. M.; Ho, W. C.; Boudreault, A.; Durkin, J.; Gillard, J. W.; Jaquith, J. B.; Morris, S. J.; Barker, A. P. *Mol. Cell* **2008**, *30*, 689.
43. Bertrand, M. J. M.; Doiron, K.; Labbè, K.; Korneluk, R. G.; Barker, A. P.; Saleh, M. *Immunity* **2009**, *30*, 789.
44. Chen, D. J.; Huerta, S. *Anticancer Drugs* **2009**, *20*, 646.
45. Mannhold, R.; Fulda, S.; Carosati, E. *Drug Discovery Today* **2010**, *15*, 210.
46. Flygare, J. A.; Fairbrother, W. J. *Expert Opin. Ther. Pat.* **2010**, *20*, 251.
47. Krieg, A.; Reed, C. J. *Cell Cycle* **2010**, *9*, 426.
48. Sun, H.; Nikolovska-Coleska, Z.; Lu, J.; Qiu, S.; Yang, C.-Y.; Gao, W.; Meagher, J.; Stuckey, J.; Wang, S. *J. Med. Chem.* **2006**, *49*, 7916.
49. Peng, Y.; Sun, H.; Nikolovska-Coleska, Z.; Qiu, S.; Yang, C.-Y.; Lu, J.; Cai, Q.; Yi, H.; Kang, S.; Yang, D.; Wang, S. *J. Med. Chem.* **2008**, *51*, 8158.
50. Cai, Q.; Sun, H.; Peng, Y.; Lu, J.; Nikolovska-Coleska, Z.; McEachern, D.; Liu, L.; Qiu, S.; Yang, C.-Y.; Miller, R.; Yi, H.; Zhang, T.; Sun, D.; Kang, S.; Guo, M.; Leopold, L.; Yang, D.; Wang, S. *J. Med. Chem.* **2011**, *54*, 2714.
51. Flygare, J. A.; Beresini, M.; Budha, N.; Chan, H.; Chan, I. T.; Cheeti, S.; Cohen, F.; Deshayes, K.; Doerner, K.; Eckhardt, S. G.; Elliott, L. O.; Feng, B.; Franklin, M. C.; FrankovitzReisner, S.; Gazzard, L.; Halladay, J.; Hymowitz, S. G.; La, H.; LoRusso, P.; Maurer, B.; Murray, L.; Plise, E.; Quan, C.; Stephan, J.-P.; Young, S. G.; Tom, J.; Tsui, V.; Um, J.; Varfolomeev, E.; Vucic, D.; Wagner, A. J.; Wallweber, H. J. A.; Wang, L.; Ware, J.; Wen, Z.; Wong, H.; Wong, J. M.; Wong, M.; Wong, S.; Yu, R.; Zobel, K.; Fairbrother, W. J. *J. Med. Chem.* **2012**, *55*, 4101.
52. Seneci, P.; Bianchi, A.; Battaglia, C.; Belvisi, L.; Bolognesi, M.; Caprini, A.; Cossu, F.; De Franco, E.; De Matteo, M.; Delia, D.; Drago, C.; Khaled, A.; Lecis, D.; Manzoni, L.; Marizzoni, M.; Mastrangelo, E.; Milani, M.; Motto, I.; Potenza, D.; Rizzo, V.; Servida, F.; Turlizzi, E.; Varrone, M.; Vasile, F.; Scolastico, C. *Bioorg. Med. Chem.* **2009**, *17*, 5834.
53. Cossu, F.; Malvezzi, F.; Canevari, G.; Mastrangelo, E.; Lecis, D.; Delia, D.; Seneci, P.; Scolastico, C.; Bolognesi, M.; Milani, M. *Protein Sci.* **2010**, *17*, 2418.
54. Bianchi, A.; Ugazzi, M.; Ferrante, L.; Lecis, D.; Scavullo, C.; Mastrangelo, E.; Seneci, P. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 2204.
55. Li, L.; Thomas, R. M.; Suzuki, H.; De Brabander, J. K.; Wang, X.; Harran, P. G. *Science* **2004**, *305*, 1471.
56. Nikolovska-Coleska, Z.; Meagher, J. L.; Jiang, S.; Yang, C.-Y.; Qiu, S.; Roller, P. P.; Stuckey, J. A.; Wang, S. *Biochemistry* **2008**, *47*, 9811.
57. Lu, J.; Bai, L.; Sun, H.; Nikolovska-Coleska, Z.; McEachern, D.; Qiu, S.; Miller, R. S.; Yi, H.; Shangary, S.; Sun, Y.; Meagher, J. L.; Stuckey, J. A.; Wang, S. *Cancer Res.* **2008**, *68*, 9384.
58. Lecis, D.; Mastrangelo, E.; Belvisi, L.; Bolognesi, M.; Civera, M.; Cossu, F.; De Cesare, M.; Delia, D.; Manenti, G.; Manzoni, L.; Milani, M.; Moroni, E.; Perego, P.; Potenza, D.; Rizzo, V.; Scavullo, C.; Scolastico, C.; Servida, F.; Vasile, F.; Seneci, P. *Bioorg. Med. Chem.* **2012**.
59. Manzoni, L.; Arosio, D.; Belvisi, L.; Bracci, A.; Colombo, M.; Invernizzi, D.; Scolastico, C. *J. Org. Chem.* **2005**, *70*, 4124.
60. Sun, H.; Liu, L.; Lu, J.; Bai, L.; Li, X.; Nikolovska-Coleska, Z.; McEachern, D.; Yang, C.-Y.; Qiu, S.; Yi, H.; Sun, D.; Wang, S. *J. Med. Chem.* **2011**, *54*, 3306.
61. Sun, H.; Nikolovska-Coleska, Z.; Lu, J.; Meagher, J. L.; Yang, C.-Y.; Qiu, S.; Tomita, Y.; Ueda, Y.; Yiang, S.; Krajewski, K.; Roller, P. P.; Stuckey, J. A.; Wang, S. *J. Am. Chem. Soc.* **2007**, *129*, 15279.
62. Bis-amino linkers **15a** and **15b** are commercially available. The synthesis of compounds **15c** and **15d** is described in the Section 4.