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A plug and play approach to structural variations of bio-inspired anticancer lipidic phenyl dialkynylcarbinols

Margaux Bossuat,[a] Nadège Preuilh,[b] Patrick Seigneur,[a] Isabelle Fabing,[a] Christian Pradel,[c] Antonio Peixoto,[b] Valérie Maraval,[d] Vania Bernardes-Génisson,[d] Stéphanie Ballereau,[a] Sébastien Britton *[b] and Yves Génisson *[a]

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Phenyl dialkynylcarbinols (PACs) are analogues of natural acetylenic lipids acting on human cells as cytotoxic prodrugs enantiospecifically bioactivated by HSD17B11. Here, we report a highly convergent and modular synthetic strategy to accelerate the exploration of their anticancer structure–activity relationships. Late-stage PAC assembly was achieved by Pd/Cu-catalysed coupling of three chiral alkynylcarbinol warheads, racemic or enantioenriched, with various functionalised lipidic aryl iodides. The added value of this methodology to directly access enantioenriched PAC analogues from an enzymatically resolved alkynylcarbinol precursor was also demonstrated. A total of 22 new compounds were prepared, including two butadiynylcarbinol congeners, with IC_{50} values as low as 0.13 μM in HCT116 cancer cells. Enantiomeric comparisons confirmed strong eudismic ratios in this series. Genetic inactivation of HSD17B11 in U2OS cells demonstrated its key role in the cytotoxicity of most compounds, while 1,2,3-triazolyl allenyl alkynylcarbinols emerged as particularly promising, combining a novel chemotype, a potent activity, and an alternative mechanism of action.

Introduction

Acetylenic lipids represent a fascinating family of natural products[1] found both in marine[2,3] and terrestrial organisms.[4–6] Due to the combination of their unique structure and potent bioactivity, these so-called polyyne natural products have been the subject of numerous structural,[7–9] synthetic[10,11] and biological reports.[12–14] Extensive mechanism of action-driven and structure–activity relationship (SAR)-oriented chemical and biological studies remain however scarce in this series. We focused our attention on a sub-class of anticancer acetylenic lipids designated as lipidic alkynylcarbinols. Encompassing several emblematic representatives such as petrocortyne,[3,7] duryne,[3,7] lembehyne[2,3] and falcarindiol,[6,9,13] these natural compounds all share the presence of one or several chiral alkynylcarbinol pharmacophoric units along their lipidic backbone (Fig. 1).

An in-depth SAR exploration initiated by our groups,[15,16] originally inspired by the natural product (*S*,*E*)-eicos-4-en-3-ol (Fig. 2), was ultimately enlightened by the discovery of the cellular mechanism of action accounting for the cytotoxicity of representative synthetic analogues.[17] The pro-apoptotic behaviour of these prodrugs results from the enantiospecific oxidation of the pharmacophoric dialkynylcarbinol (DAC) unit into a highly protein-reactive dialkynylketone warhead. The lipidic

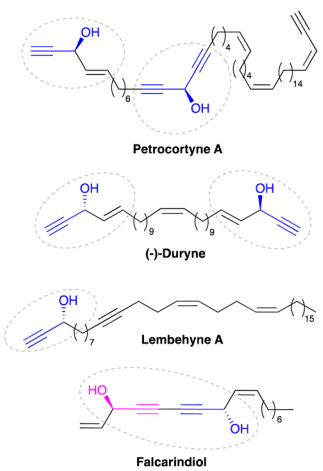


Fig. 1 Representative examples of natural lipids embedding alkynylcarbinol moieties.

[a]*Toulouse University, Laboratoire de Synthèse et de Physico-Chimie de Molécules d'Intérêt Biologie (SPCMIB), CNRS (UMR 5068), Toulouse, France. E-mail: yves.genisson@utoulouse.fr*

[b]*Institut de Pharmacologie et de Biologie Structurale (IPBS), Université de Toulouse, CNRS, Toulouse, France. E-mail: sebastien.britton@ipbs.fr*

[c]*Université de Toulouse, CNRS, LHFA – UMR 5069, 118 Route de Narbonne, 31062, France*

[d]*Toulouse University, Laboratoire de Chimie de Coordination du CNRS (UPR 8241), 205 Route de Narbonne, 31077, Toulouse, Cedex 4, France*

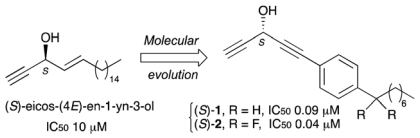


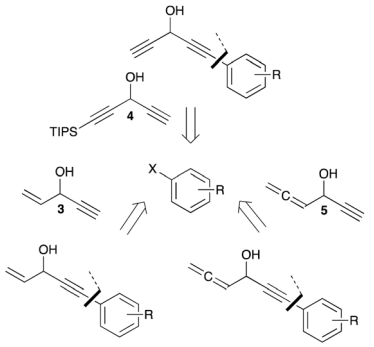
Fig. 2 Molecular evolution of an archetypical natural acetylenic lipid towards the last generation of synthetic phenyl dialkynylcarbinol (PAC) analogues.

portion of the molecule is considered to contribute both to the substrate recognition by Short-chain Dehydrogenase/Reductase (SDR) bioactivating enzymes and to the cellular toxicity of the resulting protein lipoxidation process. On these bases, we recently designed a new generation of lipidic phenyl dialkynylcarbinol (PAC) anticancer prodrugs (Fig. 2).[18] These compounds were conceived by conjugating the key DAC moiety to an (hetero)aromatic ring, such as a phenyl group, bearing the lipophilic appendage. Not only this modification led to a gain in stability and selectivity towards the main bioactivation enzyme, as compared to the earlier generation of synthetic DAC compounds, but it also afforded new opportunities for geometric and electronic structural optimization.[18]

A first set of 25 PAC derivatives was reported.[18] The SAR data allowed identification of the prototypical molecule (*S*)-**1** embedding a benzene ring *para*-substituted with an octyl chain. This compound exhibits a more than 100-fold increase in cytotoxicity against HCT116 colon cancer cells as compared to the natural product of reference (Fig. 2). A mechanistic study was carried out, using notably an enantioenriched ω-alkyne-tagged clickable probe. It confirmed the capacity of these new prodrugs, once bioactivated, to modify cellular proteins and to induce endoplasmic reticulum stress, ubiquitin-proteasome system inhibition and apoptosis, as previously reported for DACs.[17] Lipidic backbone functionalisation led to the *gem*-difluorinated analogue (*S*)-**2**, which displays an IC_{50} down to 0.042 μM. Additional structural diversification in racemic series showed that decoration of the benzene ring, or its replacement by a heteroaromatic nucleus, allowed increasing the levels of cytotoxicity and/or selectivity towards the main bioactivation enzyme HSD17B11 *vs.* its paralogue HSD17B13. Prompted by these promising results, we pursued the development of a versatile synthetic approach to further explore the molecular diversity in the PAC series. Our first results along this line are reported herein.

One of the assets of the PAC series lies in its synthetic accessibility, which arises from the smooth reactivity of terminal alkynes under transition metal-catalysis. Their retrosynthetic analysis thus privileged disconnection of the key Csp–Csp^2 bond between the alkyne moiety and the aromatic ring. Following this logic, our groups previously implemented two synthetic sequences relying on a late-stage formation of the dialkynylcarbinol unit.[18] The present work focuses on the retrosynthesis depicted in Scheme 1 as an alternative pathway offering increased convergence and modularity.

Thanks to the robust Sonogashira reaction, this so-called plug and play approach was expected to warrant direct access to a collection of analogues through the cross-coupling of a set



Scheme 1 The retrosynthetic analysis at the basis of the plug and play approach.

of halogenated (hetero)aromatic intermediates with different alkynylcarbinol precursors. Previous structural exploration indicated that replacing the typical dialkynylcarbinol pharmacophoric unit for an alkenyl-[19] or allenyl-alkynylcarbinol[20] moiety offers opportunities for the identification of new preferential bioactivation enzymes, while preserving significant levels of cytotoxicity.[17]

A similar trend was also observed in the PAC series, as shown by the relative activity of racemic **6**, **7** and **8** (Fig. 3) (see SI). We thus considered the three corresponding alkynylcarbinol precursors **3**, **4** and **5** as relevant building blocks for the PAC series diversification (Scheme 1). In addition, not only the early-stage assembly of the chiral alkynylcarbinol precursors **3–5** was planned to facilitate modulation of the lipophilic core, but their use in enantioenriched form could also afford direct access to the targeted PAC compounds in non-racemic series.

The alkenyl alkynylcarbinol precursor **3** has been used, under racemic or enantioenriched form, in several syntheses of falcarindiol,[21–23] panaxytriol[24,25] and other related polyacetylenic natural products.[26–28] The reactivity of the terminal alkyne moiety under smooth Cadiot–Chodkiewicz reaction conditions is indeed well-suited for the elaboration of the characteristic 1,3-diyne unit. In contrast, the *C*-silylated dialkynylcarbinol precursor **4** has only been scarcely used for the synthesis of acetylenic lipids. Elegant pioneering studies have taken advantage of the resolved enantiomers of the TBS-protected form of compound **4** for the concise preparation of the natural (*S*)-eicos-(4*E*)-en-1-yn-3-ol[29] and the synthetic (15*E*)-isomer of (3*R*,28*R*)-duryne.[30] Our groups applied the Crabbé-Ma asymmetric allenylation reaction to access stereoisomerically

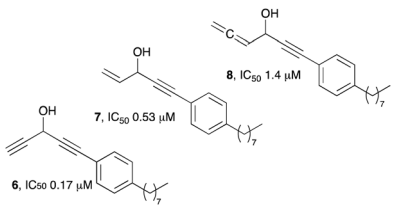


Fig. 3 Series of PAC analogues carrying three different alkynylcarbinol warheads.

enriched samples of lipidic allenyl alkynylcarbinols from both enantiomers of the TIPS-protected precursor **4**.[6] Finally, the preparation and lipase-mediated kinetic resolution of a TMS derivative of the allenyl alkynylcarbinol precursor **5** have been described, but no further use of this compound has been reported.[31]

Results and discussion

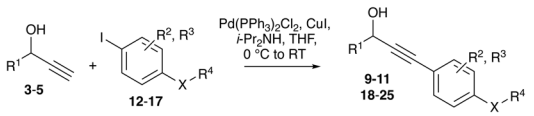
Preparation of the alkynylcarbinol precursors

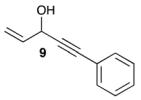
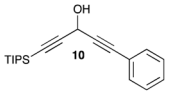
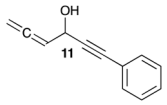
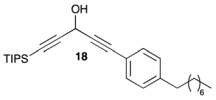
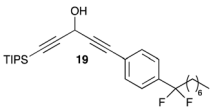
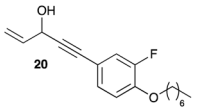
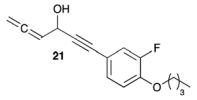
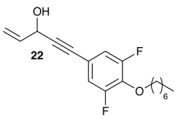
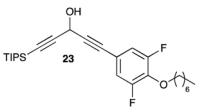
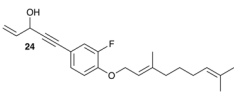
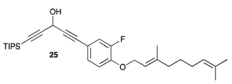
The alkenyl alkynylcarbinol precursor **3** was prepared from acrolein and ethynyl magnesium bromide as previously described (see SI).[32] The dialkynylcarbinol precursor **4** was obtained by addition of ethynyl magnesium bromide onto TIPS-protected propynal resulting from the formylation of TIPS-acetylene with DMF (see SI).[33] Finally, the allenyl alkynylcarbinol precursor **5** was synthesized from **4** thanks to the Crabbé-Ma procedure[34] with paraformaldehyde followed by desilylation with TBAF (see SI).

Preparation of racemic samples

Synthesis of benzene-containing PAC derivatives using Sonogashira coupling reactions. The study was initiated using phenyl iodide as a model reagent. Reaction of the alkynylcarbinol precursors **3**, **4**, or **5** with $Pd(PPh_3)_2Cl_2$, CuI and *i*-Pr_2NH in THF between 0 °C and RT[35] delivered the expected coupling products **9–11** with 39–52% yield after only 2 hours of reaction (Table 1).[36] In contrast, the use of phenyl bromide didn't give any transformation. This procedure was thus selected for the exploration of functionalised iodobenzene precursors. The methodology was first validated in targeting the direct precursors of the prototypical PACs **1** and **2** issued from our previous study.[18] Derivatives **18** and **19** were obtained in a single step with 36% yield by reacting the precursor **3** with iodoarenes **12** and **13**, respectively (Table 1). This highlighted the added value of this convergent route compared to the previous 3- to 4-step linear sequence.[18] Next, the preparation of new analogues by coupling precursors **3–5** with the fluorinated iodobenzene reagents **14–17** (Scheme 1 and Table 1) was investigated. Previous data indicated that alkyl aryl ether analogues possess significant levels of cytotoxic potency, possibly associated with the +M effect of oxygen, favouring the oxidative bioactivation. In particular, the analogue embedding a 3-fluoro-4-heptyloxy moiety displayed an IC_{50} of 0.36 μM towards HCT116 cells.[18] This *para*-alkoxy phenyl series, relying on readily accessible halobenzene reagents, was thus targeted. The latter, presenting different phenyl substitution patterns as well as varied lipophilic chain lengths and nature, were obtained in two steps from the corresponding commercially available fluorinated phenols (see SI). All compounds **20–25** were isolated with yields ranging from 40 to 73%. When compared to the results obtained with unsubstituted or *C*-substituted iodobenzene, the presence of substituents displaying −I/+M effects, and, notably, the oxygen atom in *para* position proved favourable to the Pd-catalysed coupling with alkynylcarbinol precursors **3–5**. This observation was consistent with previously reported substituent effects in Sonogashira cross-coupling.[37] Similarly, the presence of fluorine atoms on the benzene ring, chosen for the sake of pharmacomodulation, was also found to favour the reaction. The sensitivity of the *O*-

Table 1 Sonogashira coupling reactions to prepare benzene-containing PAC derivatives



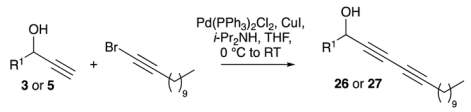
Alkyne	Iodide	Product	Yield
3	PhI	 **9**	52%
4	PhI	 **10**	45%
5	PhI	 **11**	39%
4	**12** $R^2 = R^3 = H$ $X = CH_2$ $R^4 = n$-heptyl	 **18**	36%
4	**13** $R^2 = R^3 = H$ $X = CF_2$ $R^4 = n$-heptyl	 **19**	36%
3	**14** $R^2 = 3$-F, $R^3 = H$ $X = O$ $R^4 = n$-heptyl	 **20**	50%
5	**15** $R^2 = 3$-F, $R^3 = H$ $X = O$ $R^4 = n$-butyl	 **21**	67%
3	**16** $R^2 = 3$-F, $R^3 = 5$-F $X = O$ $R^4 = n$-heptyl	 **22**	46%
3	**16** $R^2 = 3$-F, $R^3 = 5$-F $X = O$ $R^4 = n$-heptyl	 **23**	73%
3	**17** $R^2 = 3$-F, $R^3 = H$ $X = O$ R^4 = geranyl	 **24**	40%
3	**17** $R^2 = 3$-F, $R^3 = H$ $X = O$ R^4 = geranyl	 **25**	58%

geranyl chain required careful HPLC purification of **24** and **25** that lowered the isolated yields (see SI).

Synthesis of heterocyclic PAC derivatives using Cadiot–Chodkiewicz coupling reactions. Since the Cadiot–Chodkiewicz reaction has been widely applied to the alkenyl alkynylcarbinol precursor **3**, this benchmark transformation was included to our study (Table 2). Considering the particularly strong cytotoxicity of the butadiynyl alkynylcarbinol (BAC) derivative possessing a C17 skeleton,[38] the coupling with 1-bromododecyne was first attempted as a model transformation with precursor **3**. This reaction delivered the new butadiynyl alkenylcarbinol **26** in 58% yield (Table 2). The successful coupling of the dialkynylcarbinol precursor **4** with 1-bromotetradecyne was previously described by our groups.[39] The reaction between 1-bromododecyne and the allenyl alkynylcarbinol precursor **5** was also shown to proceed efficiently, affording **27** in 57% yield. Given the bioisosteric relationship between a phenyl and an alkynyl moiety,[40] the two butadiynylcarbinol analogues **26** and **27** represent additional elements of comparison with the extended PAC series exemplified with derivatives **7** and **8** (Fig. 3).

At this stage, the Cadiot–Chodkiewicz reaction with a trialkylsilyl-protected acetylene was considered (Table 3). The plan was to install an alkylated heterocyclic nucleus next to the alkynylcarbinol unit by means of a click-type 1,3-dipolar cycloaddition. Several examples of CuAAC reactions on the terminal position of the polyyne appendage of complex molecules being recently reported,[41–43] we investigated this versatile transformation. The three different alkynylcarbinol precursors **3–5** were alternatively tested. Due to the expected volatility and sensitivity of the intermediate diynes, the three consecutive steps, *i.e.*, the Cadiot–Chodkiewicz coupling, the *C*-desilylation and the CuAAC reaction, were carried out without isolation of the intermediates to ensure optimal global yields. Attempts to run the first two steps of this sequence using the dialkynylcarbinol precursor **4** invariably gave rise to decomposition of the starting material, potentially because of the instability of the butadiynyl alkynylcarbinol intermediate. In contrast, the approach proved viable with the precursors **3** and **5** (Table 3).

Table 2 Cadiot–Chodkiewicz reactions to prepare butadiynylcarbinol PAC surrogates



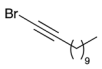
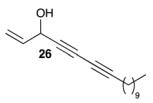
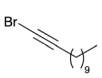
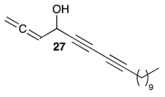
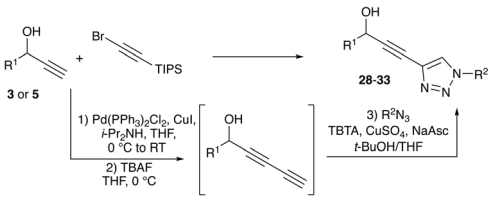
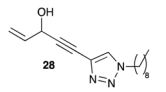
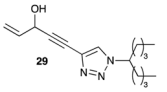
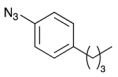
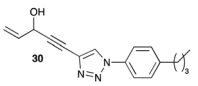
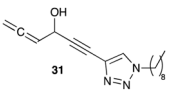
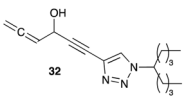
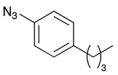
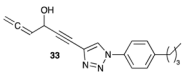
Alkyne	Bromide	Product	Yield
3			58%
5			57%

Table 3 Cadiot–Chodkiewicz coupling reaction-CuAAC sequence to prepare 1,2,3-triazole-containing PAC analogues

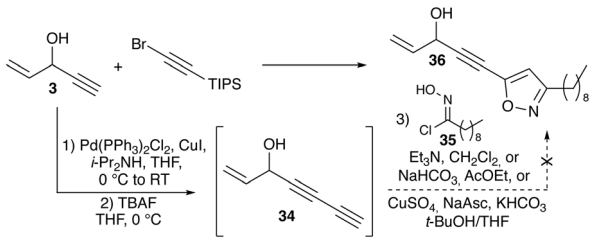


Alkyne	Azide	Product	Yield
3			34%
3			21%
3			2%
5			50%
5			34%
5			4%

A set of three representative aliphatic, either linear or branched, and aromatic azide reagents was selected. The transformation proved efficient with 1-azidononane, giving overall yields of 34–50% over 3 steps. The bulkier 5-azidononane led to a less productive transformation while the aromatic reagent 1-azido-4-butylbenzene gave only traces of expected cycloadduct, possibly due to its reduced stability associated to the longer needed reaction time. Overall, allenyl alkynylcarbinol precursor **5** gave better yields than its vinyl alkynylcarbinol counterpart **3**.

Encouraged by these first results, we envisioned to generalize this approach to isoxazole PAC analogues obtained by 1,3-dipolar cycloaddition with a nitrile oxide reagent. Base-promoted *in situ* generation of the latter from the chloro-oxime precursor **35** derived from decanal was selected as an appropriate option to explore the feasibility of this pathway (Scheme 2).

Several standard conditions were attempted with the more accessible alkynylcarbinol precursor **3**. Neither the use of Et_3N



Scheme 2 Attempted preparation of isoxazole-containing PAC analogues *via* Cadiot–Chodkiewicz coupling reaction-1,3-dipolar cycloaddition sequence.

in CH_2Cl_2,[44] nor $NaHCO_3$ in AcOEt,[45,46] nor $CuSO_4$ and NaAsc in the presence of $KHCO_3$ in *t*-BuOH/THF[47,48] gave the expected cycloadduct **36**, despite the complete consumption of the starting alkynylcarbinol **3**. Since model studies with the chlorooxime **35** and phenyl acetylene had shown that some of these procedures gave fair yields in the corresponding isoxazole (see SI), this failure may be explained by the sensitivity of the dipolarophile intermediate **34** combined to the reduced reactivity of the long chain nitrile oxide. The retrosynthetic approach presented in Scheme 1 was thus considered.

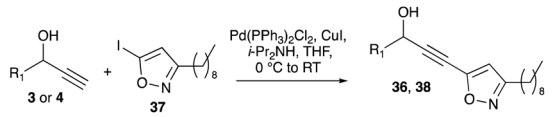
Synthesis of heterocyclic PAC analogues using Sonogashira coupling reactions. Implementation of this approach required access to the appropriate heteroaromatic iodide. In the case of the targeted isoxazole, the precursor **37** (Table 4) was obtained by means of the cycloaddition between the chlorooxime **35** and ethynyl tributylstannane followed by iododestanylation of the resulting isoxazole intermediate (see SI).[49,50] It was then engaged in the Sonogashira couplings with the alkynylcarbinol precursors **3** or **4** to deliver the expected PAC analogues **36** and **38** in 38% or 30% yield, respectively (Table 5).

In order to diversify the panel of analogues, the approach was challenged to generate new furan derivatives. The high level of cytotoxicity previously demonstrated for this heterocyclic series, potentially resulting from the favourable −I/+M effect of the conjugated oxygen atom, suggested an appropriate tuning of their reactivity towards the SDR-catalysed dehydrogenation.[4] The allenyl alkynylcarbinol derivative **40** was thus obtained in 18% yield through the coupling of precursor **5** with 2-hexyl-4-iodofuran (**39**), prepared following the methodology reported by Gevorgyan[51] (see SI) (Scheme 3).

With the aim of fully exploring the influence of nitrogenated heterocyclic nucleus, pyrazoles were selected as readily accessible analogues (Table 5). The intermediates **41** and **42** were prepared by simple *N*-alkylation of commercially available 4-iodo-1*H*-pyrazole (see SI).[52] Coupling reactions with alkynylcarbinol precursors **3–5** proceeded smoothly to deliver the targeted pyrazole-containing PAC analogues **43–45** in yields ranging from 20% to 52% (Table 5).

***C*-Desilylation step to access the targeted dialkynylcarbinol-type PAC derivatives.** Access to the dialkynylcarbinol PAC analogues required a final deprotection of the terminal alkyne unit of **23**, **25**, **38** and **44** (Table 6). *C*-Desilylation of TIPS-acetylene intermediates *en route* to the synthesis of elaborated lipidic alkynylcarbinol derivatives typically relies on the use of TBAF in THF.[19,20,23,53–55] However, treatment of the intermediate **23** with 1.3 equivalent of TBAF in anhydrous THF between 0 °C and RT allowed isolation of the expected product **46** in only 5% yield. Attempts to control the transformation by lowering the temperature proved unfeasible, either giving rise to a complete blockage of the reaction or a sudden decomposition upon warming up. Reasoning that participation of the free carbinol as

Table 4 Sonogashira coupling reactions to prepare isoxazole-containing PAC analogues



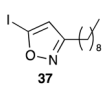
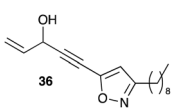
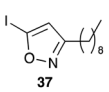
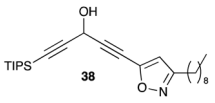
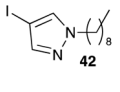
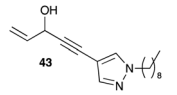
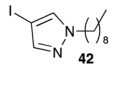
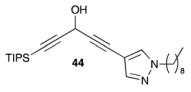
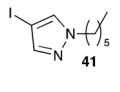
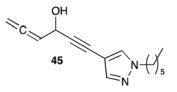
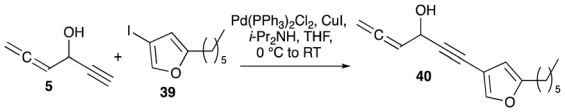
Alkyne	Iodide	Product	Yield
3	 **37**	 **36**	38%
4	 **37**	 **38**	30%

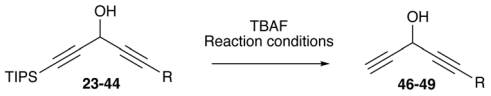
Table 5 Sonogashira coupling reactions to prepare pyrazole-containing PAC analogues

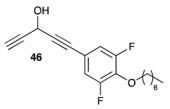
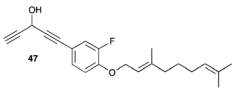
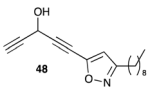
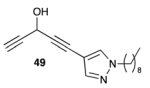
Alkyne	Iodide	Product	Yield
3	 **42**	 **43**	39%
4	 **42**	 **44**	52%
5	 **41**	 **45**	20%



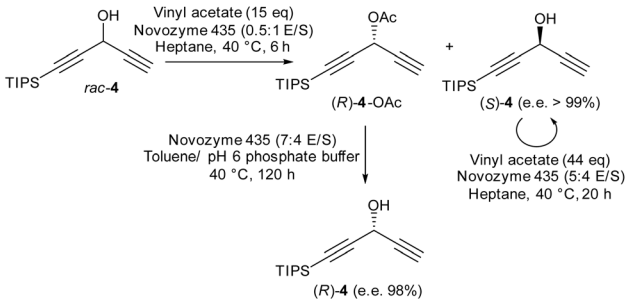
Scheme 3 Sonogashira coupling reaction to prepare a furan-containing PAC analogue.

Table 6 *C*-Desilylation of the dialkynylcarbinol-cored PAC analogues



Substrate	Conditions	Product	Yield
23	Dry THF + 3% H_2O, 1.5 eq. TBAF, 0 °C to RT, 3 h		60%
25	Dry THF, 1.3 eq. TBAF, 0 °C to RT, 0.5 h		40%
38	Dry THF + 2.5% H_2O, 4 eq. TBAF, 0 °C to RT, 24 h		54%
44	Dry THF, 1.5 eq. TBAF, −20 °C to 10 °C, 2.5 h		42%

a source of proton might contribute to this outcome, we looked at the use of wet THF to temper the reaction conditions.[56] Addition of water to THF, usually required for highly sensitive TIPS-acetylene substrates,[57–59] was thus considered. After extensive trials, it was found that the use of 3% of water in anhydrous THF, under otherwise standard conditions (1.5 eq. of TBAF, 0 °C to RT, 3 h), allowed obtaining **46** in 60% yield (Table 6). Similar conditions were employed to avoid decomposition during *C*-desilylation of the isoxazole-containing intermediate **38**. The vulnerability of dialkynylcarbinols **23** and **38** towards TBAF treatment may be correlated to the electron-withdrawing effect of their (hetero)aromatic moiety. Both **25** and **44** were, on the other hand, amenable to deprotection with TBAF under standard conditions with *ca.* 40% yield (Table 6).



Scheme 4 Lipase-catalysed enzymatic kinetic resolution of the precursor 4.

Preparation of enantioenriched samples

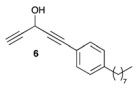
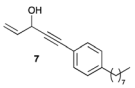
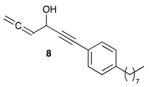
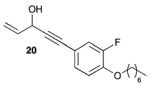
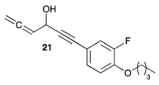
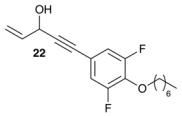
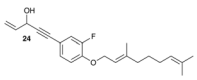
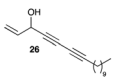
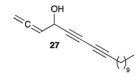
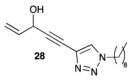
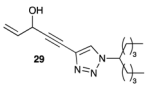
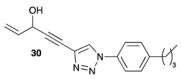
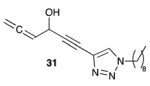
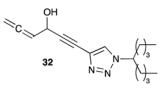
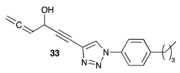
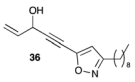
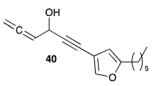
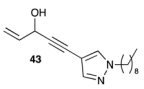
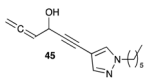
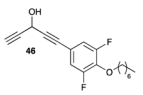
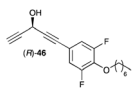
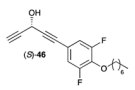
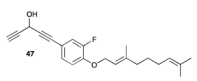
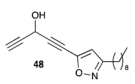
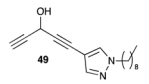
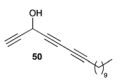
One of the potential advantages of the present strategy is to offer a direct access to enantioenriched PAC analogues starting from enantiomerically resolved alkynylcarbinol precursors. We previously separated and individually used both enantiomers of **4** to access original dialkynylcarbinol derivatives.[20] This precursor, otherwise scarcely exploited in the literature, was selected to implement the strategy. The racemic alkynylcarbinol **4** was thus subjected to enzymatic kinetic resolution by means of *Candida antartica* lipase B (Novozyme 435)-catalysed acetylation (Scheme 4). Treatment of *rac*-**4** with acrylic resin-immobilized enzyme and vinyl acetate in heptane at 40 °C for 6 h allowed isolation of the corresponding (*R*)-acetate in 41% yield. The latter was hydrolysed by use of the same enzyme in the presence of a pH 6 phosphate buffer solution for 120 h to give (*R*)-**4**. The unreacted alcohol (*S*)-**4** was subjected again to the enzymatic acetylation procedure for 20 h to upgrade its enantiomeric enrichment. (*R*)- and (*S*)-**4** were typically obtained with e.e. of 98 and >99%, respectively, according to chiral gas chromatography analysis of a re-acetylated sample (see SI).

The model coupling reaction with phenyl iodide was first explored with (*S*)-**4**. Chiral analytical supercritical fluid chromatography (SFC) analysis on Chiralpak IC column evidenced the formation of (*S*)-**10** with an e.e. >99%. Prompted by this result, assembly of the prototypical PAC framework was studied. Coupling of (*S*)- and (*R*)-**4** with iodide **12** delivered (*S*)- and (*R*)-**18**, respectively. Both compounds were isolated with e.e. >99% according to SFC analysis on Chiralpak IB column, confirming preservation of the enantiomeric enrichment of **4** during the Pd-catalysed Sonogashira coupling. Finally, the efficiency of this approach was illustrated with one of the most active PAC analogues. Enantioenriched (*R*)- and (*S*)-**46** were thus secured from coupling of the functionalised iodide **16** with (*S*)- or (*R*)-**4**, respectively, in a straightforward two-step sequence.

Biological evaluations

The cytotoxicity of all compounds was assessed in HCT116 colon cancer cells, a cell line of reference that was so far used to

Table 7 Cell viability data on HCT116 cells (IC_{50} values in μM)

Compound	IC_{50}	Compound	IC_{50}
	0.17		0.53
	1.47		0.48
	6.37		0.19
	0.35		0.09
	0.32		0.49
	6.50		2.51
	0.40		4.71
	1.49		0.76
	17.1		1.35
	21.1		0.26
	5.71		0.14
	0.13		2.21
	1.37		0.06

evaluate all analogues (Table 7). Comparing the relative potency of **50**, **26** and **27** allowed to directly assess the contribution of the pharmacophoric alkynylcarbinol moiety on cytotoxicity in the most active BAC series. The activity was gradually reduced when moving from the dialkynylcarbinol to the alkenyl alkynylcarbinol and the allenyl alkynylcarbinol warhead. The same trend was observed in the PAC series with IC_{50} increasing from 0.17 to 1.47 μM for **6**, **7** and **8**. Of note, the PAC derivatives revealed to be only 3 to 6 times less active than their BAC congeners. Since the unique potency of BAC **50** was previously shown to take place at the expense of both its stability and its selectivity towards the main bioactivation enzyme HSD17B11,[17] this observation confirmed the relevance of the PAC series.

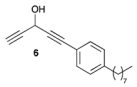
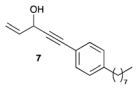
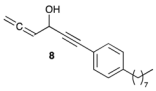
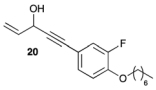
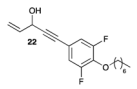
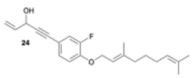
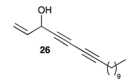
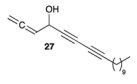
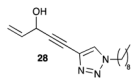
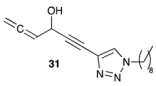
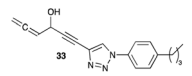
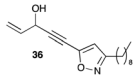
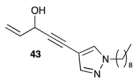
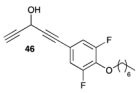
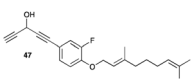
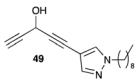
Five out of the six representatives of *para*-alkoxy phenyl series displayed a submicromolar level of IC_{50} with an average value of 0.26 μM. This result is in line with previously reported data for the PAC derivatives, indicating the combined favourable effect on cytotoxicity of the presence of fluorine and oxygen atoms at the positions 3 and 5 or 4 of the benzene ring, respectively.[17] Of note, comparison of compounds **46** and **22** evidenced that the alkenyl alkynylcarbinol pharmacophore can confer potent cytotoxicity with an IC_{50} 0.19 μM. This is also the case for **36**, which is three times more efficient than its dialkynylcarbinol analogue **48**. In agreement with our previous data, a significant eudismic ratio was found between (*S*)- and (*R*)-**46**, the dextrogyre (*S*)-eutomer being 40 times more potent than the levogyre (*R*)-distomer, with and IC_{50} of 0.14 μM. On the other hand, the dialkynylcarbinol derivative **47** was found to possess an IC_{50} of 0.13 μM, illustrating the favourable impact the bioinspired *O*-geranyl tail in comparison with its previously described *O*-heptyl congener displaying an IC_{50} of 0.36 μM.[18]

Regarding the 1,2,3-triazole-containing derivatives, cytotoxicity data were more contrasted. The influence of the lipophilic appendage was prominent, the branched non-5-yl chain in compounds **29** and **32** being unfavourable (IC_{50} of 6.5 and 4.7 μM, respectively), whereas the aromatic moiety in compounds **30** and **33** gave appreciable levels of cytotoxicity (IC_{50} of 2.5 and 1.5 μM, respectively). Interestingly, both linear *N*-nonyl compounds **28** and **31** showed equivalent potency, with the allenyl alkynylcarbinol **31** presenting an IC_{50} of 0.40 μM. This result illustrates the promise of this synthetic pharmacophore, which has been only scarcely exploited so far.

As far as the other five-membered ring heterocyclic derivatives were concerned, furan **40** and pyrazole **45** displayed only marginal cytotoxicity (IC_{50} of 17 and 21 μM, respectively), indicating the detrimental influence of the allenyl alkynylcarbinol combined with a shorter alkyl chain, whether with a pyrazole or a furan nucleus. On the other hand, isoxazole and pyrazole derivatives **43**, **48** and **49** displayed comparable IC_{50} values in the low μM, whereas isoxazole **36**, having an alkenyl alkynylcarbinol warhead, was the most potent compound of this group with an IC_{50} of 0.76 μM. When compared to that of the dialkynylcarbinol **48**, its three-time higher potency highlighted once again the favourable role of the alkenyl alkynylcarbinol pharmacophoric moiety on cytotoxicity.

Having previously identified several alkynylcarbinol-containing compounds as prodrugs enantiospecifically bioactivated by the human SDR HSD17B11 into reactive, cytotoxic alkynylketones,[17] we sought to determine whether our new series also depend on HSD17B11 for their cytotoxic activities. For this, racemic compounds with an IC_{50} below 2 μM on HCT116 cells were selected and their cytotoxic activity evaluated on the human osteosarcoma cell line U2OS, either wild-type (WT) or inactivated for HSD17B11 *via* CRISPR/Cas9 (KO HSD17B11).[17] The ratio between the IC_{50} on KO HSD17B11 *versus* WT U2OS was calculated as an indication of HSD17B11-dependent cytotoxicity (Table 8). The data showed that

Table 8 Cell viability data on U2OS WT or KO HSD17B11 (IC_{50} values in μM). IC_{50} values on U2OS for the reference compound **6** were reported previously[18]

Compound	WT	KO HSD17B11	Ratio IC_{50} KO/WT
	0.08	>5	>62.5
	0.33	12.0	36.3
	1.18	8.61	7.3
	0.48	11.1	23.2
	0.24	13.9	57.8
	1.74	7.38	4.2
	0.06	1.68	28.0
	0.15	1.34	8.9
	0.34	1.52	4.5
	0.14	0.21	1.5
	0.97	1.08	1.1
	0.22	0.49	2.2
	0.91	4.22	4.6
	0.21	>20	>95.2
	0.07	9.18	131.1
	0.58	4.20	7.2

compounds with a terminal dialkynylcarbinol motif are strongly dependent on HSD17B11 for their cytotoxicity (ratio greater than 62 for 3 out of 4 compounds), in agreement with our previous observations.[17] Compounds with a terminal alkenyl alkynylcarbinol motif had lower dependency on HSD17B11 for their activity (ratio between 2 and 57, eight compounds tested), which may result from their activation by RDH11, another human SDR for which we reported an ability to oxidize several alkenyl alkynylcarbinols.[17] Finally, allenyl alkynylcarbinols displayed the lowest dependency on HSD17B11 (ratio between 1 and 8.9, four compounds tested) and among those, two related 1,2,3-triazolyl allenyl alkynylcarbinol compounds, **31** and **33**, had a ratio close to 1, suggesting that their cytotoxicity is independent of HSD17B11 and mediated by another SDR or *via* an alternative mechanism.

Conclusions

Discovery of the latest generation analogues of natural acetylenic lipids, namely phenyl dialkynylcarbinol derivatives, has prompted the development of a highly convergent synthetic route to facilitate their structural exploration. Cadiot–Chodkiewicz or Sonogashira Pd/Cu-catalysed coupling of chiral alkynylcarbinol precursors with various functionalised acetylenic or aromatic halides was developed. Whereas the CuAAC click reaction of a 1,3-butadiyne intermediate led to a 1,2,3-triazole-containing series in a sequential process, phenyl, furyl, pyrazolyl and isoxazolyl congeners were produced in a single Sonogashira coupling step. The added-value of this modular approach for the direct access to enantioenriched compounds from a chemoenzymatically-resolved alkynylcarbinol precursor was demonstrated in the benzenic series. Cell viability data highlighted that the alkynylcarbinol warhead and the aromatic fragment display complementary contributions, giving rise to analogues with submicromolar IC_{50} of cytotoxicity against cancer cells when combined in an optimal fashion. Among these series, the 1,2,3-triazolyl allenyl alkynylcarbinols were identified as particularly interesting as their cytotoxic activity (IC_{50} of 0.14 μM for **31** on U2OS) is independent of HSD17B11, a finding that opens new prospects for further chemical and biological studies to decipher and exploit their mechanism of action.

Experimental section

General methods

All reagents were obtained from commercial suppliers and used without any further purification. If not specified, reactions were run under nitrogen atmosphere in oven-dried glassware. Standard inert atmosphere techniques were used in handling all air and moisture sensitive reagents. Toluene, dichloromethane (DCM), tetrahydrofuran (THF), dimethylformamide (DMF) and diethyl ether (Et_2O) were obtained by filtration through a drying column on a filtration system. Thin-layer chromatography (TLC) analyses were performed on precoated, aluminum-backed silica gel (Merck 60 F254). Visualization of the developed chromatogram was performed by UV light (254 nm) and using 10% phosphomolybdic acid in EtOH, or aqueous potassium permanganate ($KMnO_4$) stain. Flash chromatography columns were performed using flash silica gel (SDS 35–70 μm). Nuclear

magnetic resonance spectra were recorded on a Bruker Advance 300 or 400 or 600 MHz spectrometer. Chemical shifts for ^{1}H NMR spectra are given in parts per million (ppm) with the residual solvent resonance as the reference $CHCl_3$ (δ = 7.26 ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, m = multiplet and br = broad), coupling constant in Hz and integration. Chemical shifts for ^{13}C NMR spectra are given in ppm using the central peak of $CDCl_3$ (δ = 77.16 ppm) as the reference. All ^{13}C NMR spectra were obtained with complete proton decoupling. High-resolution mass spectrometry (HRMS) was performed on a Thermo-Finnigan MAT 95 XL instrument. Mass spectrometry *m*/*z* values are given in Dalton units.

General procedures

General procedure A (Sonogashira coupling). The carbinol precursor (1 eq.), the aryl iodide (1.4 eq.), $Pd(PPh_3)_2Cl_2$ (4 mol%) and CuI (4 mol%) were dissolved in dry THF under an atmosphere of N_2. At 0 °C, DIPA (1 eq.) was then added. After completion of the reaction, saturated aqueous solution of NH_4Cl was added to quench the reaction. The mixture was extracted with diethyl ether. The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel).

General procedure B (Cadiot–Chodkiewicz coupling). The carbinol precursor (1 eq.), CuCl (15 mol%), $NH_2OH{\cdot}HCl$ (30 mol%) and *n*-$BuNH_2$ (1.5 eq.) were dissolved in toluene at 0 °C. Then 1-bromododecyne (1.1 eq.) was added. The resulting solution was allowed to warm to RT and stirred overnight. After completion of the reaction, aqueous HCl (1 M) was added and the mixture turned from brown to green. The resulting mixture was extracted with diethyl ether. Combined organic layers were washed with saturated aqueous $NaHCO_3$ solution, brine and dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography.

General procedure C (synthesis of triazole derivatives). A reaction flask containing toluene was cooled to 0 °C. The carbinol precursor (1 eq.), CuCl (15 mol%), $NH_2OH{\cdot}HCl$ (30 mol%), *n*-$BuNH_2$ (1.5 eq.) and (bromoethynyl)triisopropylsilane (1.1 eq) were added. The mixture was stirred at RT overnight before being quenched by carefully adding aqueous HCl (1 M). The aqueous layer was extracted three times with diethyl ether. The combined organic layers were washed with a saturated aqueous solution of $NaHCO_3$, then with a saturated aqueous NaCl solution and dried over anhydrous $MgSO_4$. Solvents were removed by soft rotary evaporation and then the obtained protected diyne was used without further purification. At 0 °C under N_2 atmosphere, TBAF (1.3 eq., 1 M in THF) was added dropwise to a solution of the protected diyne (1 eq.) in dry THF. The mixture was stirred for 15 minutes. The reaction mixture was then quenched with aqueous NH_4Cl solution and extracted with Et_2O. The combined organic layers were washed with brine, dried over $MgSO_4$ and solvents were removed carefully by soft rotary evaporation. The resulting diyne was used without further purification. The diyne (1.3 eq.), the azide (1 eq.) and TBTA (0.2 eq.) were added to a degassed solution of *t*-BuOH and THF. Sodium ascorbate (0.4 eq.) and $CuSO_4$ (0.2 eq.) were mixed with degassed water until the mixture turned from brown to yellow. The mixture was then added to the previous solution. The reaction mixture was stirred at RT overnight. Aqueous layers were then extracted three times with Et_2O. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$ and solvents were removed under reduced pressure. The residue was purified by flash chromatography.

Experimental procedures for the tested compounds

5-(4-Octylphenyl)pent-1-en-4-yn-3-ol (7). To a solution of 3-(4-octylphenyl)propiolaldehyde[18] (38 mg, 0.157 mmol, 1.0 equiv.) in dry THF (2 mL) under N_2 at 0 °C was added vinyl magnesium bromide (190 μL, 0.19 mmol, 1.0 M solution in THF, 1.2 equiv.). The resulting solution was stirred at 0 °C for 1 h and allowed to warm to RT. After completion of the reaction, monitored by TLC, a saturated aqueous NH_4Cl solution was added to quench the reaction. The resulting mixture was extracted with diethyl ether. Combined organic layers were washed with brine and dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude mixture was purified by flash chromatography on silica gel using a gradient of up to 20% of diethyl ether in pentane. The alkenyl alkynylcarbinol **7** (11 mg, 26%) was isolated as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.41–7.31 (m, 2H), 7.17–7.07 (m, 2H), 6.06 (ddd, J = 17.0, 10.1, 5.3 Hz, 1H), 5.54 (dt, J = 17.0, 1.5, 1.2 Hz, 1H), 5.27 (dt, J = 10.1, 1.3 Hz, 1H), 5.10 (ddt, J = 6.7, 5.3, 1.3 Hz, 1H), 2.61 (t, J = 7.4 Hz 2H), 1.96 (s, J = 6.4 Hz, 1H), 1.65–1.57 (m, 2H), 1.33–1.16 (m, 10H), 0.94–0.82 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 143.8, 137.1, 131.7, 128.4, 119.5, 116.5, 87.0, 86.6, 63.8, 35.9, 31.9, 31.2, 29.5, 29.3 (*2), 22.7, 14.1. HRMS (DCI-CH_4): calcd for $C_{19}H_{27}O$ $[MH]^+$: 271.2062 *m*/*z*, found: 271.2055 *m*/*z*.

*1-(4-Octylphenyl)hexa-4,5-dien-1-yn-3-ol (**8**).* In a sealed tube, 1-(4-octylphenyl)penta-1,4-diyn-3-ol (**6**)[18] (50 mg, 0.186 mmol), CuI (2.6 mg, 7.5 mol%) and paraformaldehyde (8.9 mg, 0.014 mmol) were dissolved in dioxane. Then DIPA (37 μL, 0.261 mmol) was added. The reaction mixture was evacuated and backfilled with argon three times, then heated to 130 °C overnight. After completion of the reaction, the reaction mixture was cooled down to RT and directly concentrated under reduced pressure. The crude mixture was then purified by flash chromatography on silica gel using a gradient of up to 20% of diethyl ether in pentane. The allenyl alkynylcarbinol **8** (42 mg, 81%) was isolated as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.32 (d, J = 8.2 Hz, 2H), 7.12 (d, J = 8.0 Hz, 2H), 5.48 (q, J = 6.4 Hz, 1H), 5.14 (br s, 1H), 5.01 (dd, J = 6.4, 2.5 Hz, 2H), 2.59 (t, J = 7.8 Hz, 2H), 2.09 (br s, 1H), 1.68–1.52 (m, 2H), 1.34–1.25 (m, 10H), 0.94–0.84 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 207.8, 144.0, 131.8, 128.5, 119.5, 93.4, 87.5, 86.0, 79.1, 61.2, 36.0, 32.0, 31.4, 29.6, 29.4, 22.8, 14.2. HRMS (DCI-CH_4): calcd for $C_{20}H_{27}O$ $[MH]^+$: 283.2062 *m*/*z*, found: 283.2064 *m*/*z*.

*5-(3-Fluoro-4-(heptyloxy)phenyl)pent-1-en-4-yn-3-ol (**20**).* Following the general procedure A, the obtained crude mixture was purified by flash chromatography on silica gel using a gradient of up to 30% of diethyl ether in pentane. The alkenyl alkynylcarbinol **20** (35 mg, 50%) was isolated as a yellow oil. ^{1}H

NMR (300 MHz, $CDCl_3$) δ (ppm) 7.23–7.13 (m, 2H), 6.89 (t, J = 8.9 Hz, 1H), 6.07 (ddd, J = 17.0, 10.1, 5.4 Hz, 1H), 5.55 (dt, J = 17.0, 1.3 Hz, 1H), 5.30 (dt, J = 10.1, 1.3 Hz, 1H), 5.11 (ddt, J = 6.7, 5.4, 1.3 Hz, 1H), 4.05 (t, J = 6.5 Hz, 2H) 1.99 (d, J = 6.5 Hz, 1H), 1.92–1.76 (m, 2H), 1.54–1.25 (m, 8H), 0.96–0.87 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 151.9 (d, J = 246.8 Hz), 148.0 (d, J = 7.5 Hz), 136.9, 128.3 (d, J = 3.5 Hz), 119.4 (d, J = 19.8 Hz), 116.6, 114.6 (d, J = 8.5 Hz), 114.3 (d, J = 2.6 Hz), 86.9, 85.3 (d, J = 7.5 Hz), 69.4, 63.7, 31.7, 29.1, 29.0, 25.9, 22.6, 14.1. ^{19}F NMR (282 MHz, $CDCl_3$) δ (ppm) −134.2. HRMS (DCI-CH_4): calcd for $C_{18}H_{24}O_2F$ $[MH]^+$: 291.1760 m/z, found: 291.1750 m/z.

1-(4-Butoxy-3-fluorophenyl)hexa-4,5-dien-1-yn-3-ol ***(21).*** Following the general procedure A, the obtained crude mixture was purified by flash chromatography on silica gel using a gradient of up to 30% of diethyl ether in pentane. The allenyl alkynylcarbinol **21** (37 mg, 67%) was isolated as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.23–7.12 (m, 2H), 6.89 (t, J = 8.9 Hz, 1H), 5.49 (q, J = 6.4 Hz, 1H), 5.15 (s, 1H), 5.04 (dd, J = 6.4, 2.5 Hz, 2H), 4.06 (t, J = 6.5 Hz, 2H) 2.09 (d, J = 6.5 Hz, 1H), 1.90–1.75 (m, 2H), 1.55–1.46 (m, 2H), 0.94–0.84 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 207.9, 168.1, 151.8 (d, J = 246.7 Hz), 128.4 (d, J = 3.5 Hz), 119.4 (d, J = 19.8 Hz), 114.5 (d, J = 8.5 Hz), 114.2 (d, J = 2.6 Hz), 93.1, 87.3, 84.6 (d, J = 3.6 Hz), 79.0, 69.1, 61.0, 31.2, 19.1, 13.8. ^{19}F NMR (282 MHz, $CDCl_3$) δ (ppm) −134.2. HRMS (DCI-CH_4): calcd for $C_{16}H_{18}O_2F$ $[MH]^+$: 261.1291 m/z, found: 261.1285 m/z.

5-(3,5-Difluoro-4-(heptyloxy)phenyl)pent-1-en-4-yn-3-ol ***(22).*** Following the general procedure A, the obtained crude mixture was purified by flash chromatography on silica gel using a gradient of up to 30% of diethyl ether in pentane. The alkenyl alkynylcarbinol **22** (87 mg, 46%) was isolated as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.08–6.93 (m, 2H), 6.06 (ddd, J = 17.0, 10.1, 5.4 Hz, 1H), 5.54 (dt, J = 17.0, 1.2 Hz, 1H), 5.31 (dt, J = 10.1, 1.2 Hz, 1H), 5.10 (ddt, J = 6.7, 5.4, 1.2 Hz, 1H), 4.17 (tt, J = 6.7, 0.9 Hz, 2H) 2.00 (d, J = 6.7 Hz, 1H), 1.83–1.71 (m, 2H), 1.54–1.18 (m, 8H), 0.96–0.86 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 155.5 (dd, J = 248.6, 6.9 Hz), 136.8 (t, J = 14.1 Hz), 136.5, 116.9, 116.6 (t, J = 11.2 Hz), 116.1–115.3 (m), 88.5, 77.2, 74.9 (t, J = 3.2 Hz), 63.6, 29.9, 29.0, 25.6, 22.6, 14.1. ^{19}F NMR (282 MHz, $CDCl_3$) δ (ppm) −127.7. HRMS (DCI-CH_4): calcd for $C_{18}H_{23}O_2F_2$ $[MH]^+$: 309.1666 m/z, found: 309.1656 m/z.

(E)-5-(4-((3,6-Dimethylhepta-2,5-dien-1-yl)oxy)-3-fluorophenyl)-pent-1-en-4-yn-3-ol ***(24).*** Following the general procedure A, the obtained crude mixture was purified on preparative reversed phase HPLC Waters (XSelect C18, 5 μm (19 × 150 mm) column 80 : 20 to 70 : 30 then to 60 : 40H_2O/ACN, 20 mL min^{-1}). The geranyl alkenyl alkynylcarbinol **24** (10 mg, 40%) was isolated as a colorless oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) 7.19–7.13 (m, 2H), 6.91–6.85 (m, 1H), 6.05 (ddd, J = 17.0, 10.1, 5.4 Hz, 1H), 5.53 (dt, J = 17.0, 1.3 Hz, 1H), 5.47 (tq, J = 6.6, 1.3 Hz, 1H), 5.27 (dt, J = 10.1, 1.3 Hz, 1H), 5.12–5.07 (m, 2H), 4.64 (d, J = 6.6 Hz, 2H), 2.17–2.06 (m, 4H), 1.96 (d, J = 6.5 Hz, 1H), 1.73 (br s, 3H), 1.67 (d, J = 1.3 Hz, 3H), 1.60 (d, J = 1.4 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) 152.1 (d, J = 246.8 Hz), 147.6 (d, J = 10.6 Hz), 142.2, 136.9, 131.9, 128.2 (d, J = 3.4 Hz), 123.7, 119.4 (d, J = 20.1 Hz), 118.8, 116.6, 114.8 (d, J = 13.3 Hz), 109.9, 87.0, 85.2 (d, J = 2.8 Hz), 66.2, 63.7, 39.5, 26.2, 25.7, 17.7, 16.7. ^{19}F NMR (282 MHz, $CDCl_3$) δ (ppm) −133.7. HRMS (DCI-CH_4): calcd for $C_{21}H_{24}O_2F$ $[MH]^+$: 327.1760 m/z, found: 327.1758 m/z.

Heptadeca-1-en-4,6-diyn-3-ol ***(26).*** Following the general procedure B, the obtained crude mixture was purified by flash chromatography on silica gel using a gradient of up to 20% of diethyl ether in pentane. The butadiynyl alkenyl alkynylcarbinol **26** (87 mg, 58%) was isolated as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 5.95 (ddd, J = 17.0, 10.1, 5.3 Hz, 1H), 5.47 (ddd, J = 17.0, 1.4, 1.0 Hz, 1H), 5.24 (ddd, J = 10.1, 1.4, 1.0 Hz, 1H), 4.92 (ddt, J = 6.7, 5.3, 1.4 Hz, 1H), 2.28 (td, J = 7.0, 1.0 Hz, 2H), 1.91–1.82 (m, 1H), 1.61–1.45 (m, 2H), 1.43–1.23 (m, 14H), 0.93–0.83 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 136.4, 117.2, 82.7, 73.9, 71.6, 64.4, 63.7, 32.0, 29.7, 29.6, 29.4, 29.2, 29.0, 28.2, 22.8, 19.4, 14.3. HRMS (DCI-CH_4): calcd for $C_{17}H_{27}O$ $[MH]^+$: 247.2062 m/z, found: 247.2064 m/z.

Octadeca-1-en-4,6-diyn-3-ol ***(27).*** Following the general procedure B, the obtained crude mixture was purified by flash chromatography on silica gel using a gradient of up to 20% of diethyl ether in pentane. The butadiynyl allenyl alkynylcarbinol **27** (156 mg, 57%) was isolated as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 5.44–5.31 (m, 1H), 5.04–4.90 (m, 3H), 2.28 (td, J = 7.0, 0.9 Hz, 2H), 1.97 (dd, J = 6.2, 1.5 Hz, 1H), 1.63–1.42 (m, 2H), 1.44–1.20 (m, 14H), 0.94–0.81 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 207.8, 92.7, 82.8, 79.3, 74.2, 70.9, 64.4, 61.1, 32.0, 29.7, 29.6, 29.4, 29.2, 29.0, 28.2, 22.8, 19.4, 14.3. HRMS (DCI-CH_4): calcd for $C_{18}H_{27}O$ $[MH]^+$: 259.2062 m/z, found: 259.2068 m/z.

5-(1-Nonyl-1H-1,2,3-triazol-4-yl)pent-1-en-4-yn-3-ol ***(28).*** Following the general procedure C, the obtained crude mixture was purified by flash chromatography on silica gel using a gradient of up to 30% of a mixture of DCM/AcOEt (8/2) in pentane. The triazole **28** (41 mg, 34%) was isolated as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.66 (s, 1H), 6.08 (ddd, J = 17.1, 10.2, 5.4 Hz, 1H), 5.58 (dt, J = 17.1, 1.3 Hz, 1H), 5.32 (dt, J = 10.2, 1.3 Hz, 1H), 5.16 (dt, J = 5.4, 1.5 Hz, 1H), 4.38 (t, J = 7.2 Hz, 2H), 2.07–1.82 (m, 3H), 1.39–1.25 (m, 12H), 0.96–0.86 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 136.3, 130.6, 126.0, 117.0, 91.3, 75.7, 63.6, 50.6, 31.8, 30.2, 29.3, 29.2, 20.0, 26.4, 22.7, 14.1. HRMS (DCI-CH_4): calcd for $C_{16}H_{26}N_3O$ $[MH]^+$: 276.2076 m/z, found: 276.2089 m/z.

5-((1-Nonan-5-yl)-1H-1,2,3-triazol-4-yl)pent-1-en-4-yn-3-ol ***(29).*** Following the general procedure C, the obtained crude mixture was purified by flash chromatography on silica gel using a gradient of up to 30% of a mixture of DCM/AcOEt (8/2) in pentane. The triazole **29** (22 mg, 21%) was isolated as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.62 (s, 1H), 6.08 (ddd, J = 17.1, 10.2, 5.4 Hz, 1H), 5.57 (ddd, J = 17.1, 1.6, 1.0 Hz, 1H), 5.32 (dt, J = 10.2, 1.6 Hz, 1H), 5.16 (t, J = 5.4 Hz, 1H), 4.48 (quint, J = 7.2 Hz, 1H), 2.10 (d, J = 6.4 Hz, 1H), 1.97–1.78 (m, 4H), 1.43–0.97 (m, 8H), 0.87 (t, J = 7.2 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 136.4, 130.0, 124.6, 116.9, 91.5, 75.9, 63.5, 62.8, 35.4, 28.0, 22.2, 13.8. HRMS (DCI-CH_4): calcd for $C_{16}H_{26}N_3O$ $[MH]^+$: 276.2076 m/z, found: 276.2084 m/z.

5-(1-(4-Butylphenyl)-1H-1,2,3-triazol-4-yl)pent-1-en-4-yn-3-ol ***(30).*** Following the general procedure C, the obtained crude mixture was purified by flash chromatography on silica gel using a gradient of up to 30% of a mixture of DCM/AcOEt (8/2)

in pentane. The triazole **30** (3 mg, 2%) was isolated as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 8.03 (s, 1H), 7.50 (d, J = 8.33 Hz, 2H), 7.33 (d, J = 8.33 Hz, 2H), 6.07 (ddd, J = 17.1, 10.2, 5.4 Hz, 1H), 5.57 (ddd, J = 17.1, 1.6, 1.0 Hz, 1H), 5.31 (dt, J = 10.2, 1.6 Hz, 1H), 5.16 (dt, J = 5.4, 1.5 Hz, 1H), 2.68 (t, J = 7.6 Hz, 2H), 1.86 (br s, 1H), 1.71–1.55 (m, 2H), 1.46–1.28 (m, 2H), 0.94 (t, J = 7.6 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 144.5, 136.2, 134.3, 130.8, 129.8, 124.2, 120.6, 117.1, 92.0, 75.5, 63.6, 35.2, 33.5, 22.3, 13.9. HRMS (DCI-CH_4): calcd for $C_{17}H_{19}N_3O$ $[MH]^+$: 281.1506 *m*/*z*, found: 281.1509 *m*/*z*.

1-(1-Nonyl-1H-1,2,3-triazol-4-yl)hexa-4,5-dien-1-yn-3-ol ***(31)***. Following the general procedure C, the obtained crude mixture was purified by flash chromatography on silica gel using a gradient of up to 30% of a mixture of DCM/AcOEt (8/2) in pentane. The triazole **31** (58 mg, 51%) was isolated as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.63 (s, 1H), 5.49 (q, J = 6.4 Hz, 1H), 5.17 (dt, J = 6.4, 2.4 Hz, 1H), 5.03 (dd, J = 6.4, 2.4 Hz, 2H), 4.36 (t, J = 7.2 Hz, 2H), 2.06 (br s, 1H), 1.97–1.84 (m, 2H), 1.35–1.22 (m, 12H), 0.94–0.84 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 207.6, 126.0, 92.7, 91.6, 79.2, 75.2, 60.9, 50.6, 31.8, 30.2, 29.3,29.2, 28.9, 26.4, 22.7, 14.1. HRMS (DCI-CH_4): calcd for $C_{17}H_{26}N_3O$ $[MH]^+$: 288.2076 *m*/*z*, found: 288.2072 *m*/*z*.

1-(1-(Nonan-5-yl)-1H-1,2,3-triazol-4-yl)hexa-4,5-dien-1-yn-3-ol ***(32)***. Following the general procedure C, the obtained crude mixture was purified by flash chromatography on silica gel using a gradient of up to 30% of a mixture of DCM/AcOEt (8/2) in pentane. The triazole **32** (24 mg, 34%) was isolated as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.61 (s, 1H), 5.49 (q, J = 6.4 Hz, 1H), 5.17 (dt, J = 6.4, 2.4 Hz, 1H), 5.03 (dd, J = 6.4, 2.4 Hz, 2H), 4.54–4.39 (m, 1H), 1.95–1.76 (m, 4H), 1.41–0.94 (m, 8H), 0.85 (t, J = 7.5 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 207.7, 129.9, 124.7, 92.7, 91.8, 79.0, 75.2, 62.8, 60.9, 35.4, 28.0, 22.2, 13.8. HRMS (DCI-CH_4): calcd for $C_{17}H_{26}N_3O$ $[MH]^+$: 288.2076 *m*/*z*, found: 288.2072 *m*/*z*.

1-(1-(Nonan-5-yl)-1H-1,2,3-triazol-4-yl)hexa-4,5-dien-1-yn-3-ol ***(33)***. Following the general procedure C, the obtained crude mixture was purified by flash chromatography on silica gel using a gradient of up to 30% of a mixture of DCM/AcOEt (8/2) in pentane. The triazole **33** (4 mg, 4%) was isolated as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 8.03 (s, 1H), 7.63–7.57 (m, 2H), 7.36–7.28 (m, 2H), 5.50 (q, J = 6.3 Hz, 1H), 5.19 (dt, J = 6.3, 2.4 Hz, 1H), 5.02 (dd, J = 6.3, 2.4 Hz, 2H), 2.68 (t, J = 7.6 Hz, 2H), 1.68–1.58 (m, 2H), 1.41–1.33 (m, 2H), 0.94 (t, J = 7.4 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) 207.7, 144.4, 134.3, 130.8, 129.8, 124.2, 120.6, 92.6, 92.3, 79.2, 74.8, 61.0, 35.2, 33.3, 22.2, 13.8. HRMS (DCI-CH_4): calcd for $C_{18}H_{20}N_3O$ $[MH]^+$: 294.1606 *m*/*z*, found: 294.1609 *m*/*z*.

5-(3-Nonylisoxazol-5-yl)pent-1-en-4-yn-3-ol ***(36)***. Following the general procedure A, the obtained crude mixture was purified by flash chromatography on silica gel using a gradient of up to 30% of diethyl ether in pentane. The isoxazole **36** (26 mg, 38%) was isolated as a brown oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 6.31 (s, 1H), 6.04 (ddd, J = 17.0, 10.2, 5.4 Hz, 1H), 5.55 (dt, J = 17.0, 1.3 Hz, 1H), 5.33 (dt, J = 10.1, 1.3 Hz, 1H), 5.20–5.10 (m, 1H), 2.72 (d, J = 5.4 Hz, 1H), 2.67 (t, J = 7.6 Hz, 2H), 1.72–1.58 (m, 2H), 1.42–1.20 (m, 12H), 0.96–0.84 (m, 3H). ^{13}C NMR (75 MHz, CDCl3) δ (ppm) 164.2, 152.3, 135.5, 117.5, 108.0, 97.1, 72.9, 63.3, 31.9, 29.4, 29.3, 29.2, 29.1, 28.2, 25.9, 22.7, 14.1. HRMS (DCI-CH_4): calcd for $C_{17}H_{26}NO_2$ $[MH]^+$: 276.1964 *m*/*z*, found: 276.1968 *m*/*z*.

1-(6-Hexylfuran-2-yl) hexa-1,2-dien-5-yn-4-ol ***(40)***. Following the general procedure A, the obtained crude mixture was purified by flash chromatography on silica gel using a gradient of up to 20% diethyl ether in pentane. The allenyl alkynylcarbinol **40** (14 mg, 18%) was isolated as a brown oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.51 (d, J = 0.9 Hz, 1H), 6.04 (m, 1H), 5.48 (q, J = 6.4 Hz, 1H), 5.17–5.09 (m, 1H), 5.08–4.97 (m, 2H), 2.60 (td, J = 7.5, 0.9 Hz, 2H), 2.12 (br s, 1H), 1.71–1.55 (m, 2H), 1.50–1.21 (m, 6H), 0.99–0.84 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 207.6, 157.1, 144.4, 107.5, 106.9, 93.1, 89.4, 78.9, 77.7, 61.1, 31.5, 28.7, 27.8, 27.7, 22.6, 14.1. HRMS (DCI-CH_4): calcd for $C_{16}H_{21}O_2$ $[MH]^+$: 245.1542 *m*/*z*, found: 245.1547 *m*/*z*.

5-(1-Nonyl-1H-pyrazol-4-yl)pent-1-en-4-yn-3-ol ***(43)***. Following the general procedure A, the obtained crude mixture was purified by flash chromatography on silica gel using a gradient of up to 40% of diethyl ether in pentane. The alkenyl alkynylcarbinol **43** (91 mg, 39%) was isolated as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.60 (d, J = 0.7 Hz, 1H), 7.52 (d, J = 0.7 Hz, 1H), 6.06 (ddd, J = 17.0, 10.1, 5.5 Hz, 1H), 5.52 (dt, J = 17.0, 1.5 Hz, 1H), 5.27 (dt, J = 10.1, 1.5 Hz, 1H), 5.09 (ddt, J = 6.7, 5.5, 1.5 Hz, 1H), 4.09 (t, J = 7.1 Hz, 2H), 2.08 (d, J = 6.4 Hz, 1H), 1.85 (quint, J = 7.3 Hz, 2H), 1.37–1.22 (m, 12H), 0.93–0.83 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 141.9, 137.1, 131.9, 116.4, 101.9, 88.5, 78.0, 63.8, 52.5, 31.8, 30.2, 29.4, 29.2, 26.5, 22.6, 14.1. HRMS (DCI-CH_4): calcd for $C_{17}H_{27}N_2O$ $[MH]^+$: 275.2123 *m*/*z*, found: 275.2114 *m*/*z*.

1-(1-Hexyl-1H-pyrazol-4-yl)hexa-4,5-dien-1-yn-3-ol ***(45)***. Following the general procedure A, the obtained crude mixture was purified by flash chromatography on silica gel using a gradient of up to 30% of diethyl ether in pentane. The allenyl alkynylcarbinol **45** (26 mg, 20%) was isolated as a colourless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.60 (d, J = 0.6 Hz, 1H), 7.52 (d, J = 0.6 Hz, 1H), 5.48 (q, J = 6.4 Hz, 1H), 5.14, (br d, J = 6.5 Hz, 1H), 5.07–4.97 (m, 2H), 4.10 (t, J = 7.1 Hz, 2H), 2.22 (s, 1H), 1.85 (quint, J = 7.2 Hz, 2H), 1.38–1.22 (m, 6H), 0.97–0.84 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 207.6, 141.9, 132.0, 93.2, 88.8, 79.4, 78.9, 77.3, 61.1, 52.5, 31.2, 30.1, 26.1, 22.5, 14.0. HRMS (DCI-CH_4): calcd for $C_{15}H_{21}N_2O$ $[M]^+$: 245.1654 *m*/*z*, found: 245.1654 *m*/*z*.

1-(3,5-Difluoro-4-(heptyloxy)phenyl)penta-1,4-diyn-3-ol ***(46)***. Compound **23** (45.5 mg, 98.3 μmol) was dissolved in wet THF (1 mL, 3% v/v H_2O). At 0 °C under an atmosphere of N_2, TBAF (1 M in THF, 147 μL, 0.147 mmol, 1.5 equiv.) was added dropwise. After 3 h, a saturated aqueous solution of NH_4Cl was added to quench the reaction. The resulting mixture was extracted with diethyl ether. The combined organic layers were washed with brine and dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude mixture was purified by flash chromatography on silica gel using a gradient of up to 10% of diethyl ether in pentane. The dialkynylcarbinol **46** (21 mg, 60%) was isolated as an orange oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.08–6.93 (m, 2H), 5.31 (dd, J = 7.6, 2.3 Hz, 1H), 4.15 (tt, J = 6.6, 0.9 Hz, 2H), 2.63 (d, J = 2.3 Hz, 1H), 2.32 (d, J = 7.6 Hz, 1H), 1.88–1.64 (m, 2H), 1.50–1.24 (m, 8H), 0.94–0.84 (m, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 155.5 (dd, $J = 248.9$, 6.8 Hz), 137.2 (t, $J = 14.1$ Hz), 116.2–115.9 (m), 115.9–115.7 (m), 86.1, 82.5 (t, $J = 3.4$ Hz), 80.4, 74.9 (t, $J = 3.4$ Hz), 73.3, 52.5 (d, $J = 6.6$ Hz), 31.7, 29.9, 28.9, 25.6, 22.6, 14.1. ^{19}F NMR (282 MHz, $CDCl_3$) δ (ppm) −127.5. HRMS (DCI-CH_4): calcd for $C_{18}H_{21}O_2F_2$ $[MH]^+$: 307.1510 *m*/*z*, found: 307.1511 *m*/*z*.

*(E)-1-(4-((3,6-Dimethylhepta-2,5-dien-1-yl)oxy)-3-fluorophenyl)-penta-1,4-diyn-3-ol (**47**).* Compound **25** (66 mg, 0.140 mmol, 1.0 equiv.) was dissolved in THF (1.5 mL). At 0 °C under N_2 atmosphere, TBAF (1 M in THF, 183 μL, 0.183 mmol, 1.3 equiv.) was added dropwise. After 30 minutes, a saturated aqueous solution of NH_4Cl was added to quench the reaction mixture. The resulting mixture was extracted with diethyl ether. Combined organic layers were washed with brine and dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude mixture was purified on preparative reversed phase HPLC Waters (XSelect C18, 5 μm (19 × 150 mm) column 70 : 30 to 30 : 70 in 15 minutes H_2O/ACN, 0.6 mL min^{-1}). The dialkynylcarbinol **47** (14 mg, 40%) was isolated as a colorless oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) 7.25–7.17 (m, 2H), 6.91 (t, $J =$ 8.4 Hz, 2H), 5.47 (td, $J = 6.6$, 1.4 Hz, 1H), 5.35 (dd, $J = 7.3$, 2.3 Hz, 1H), 5.09 (tt, $J = 6.8$, 1.5 Hz, 1H), 4.65 (d, $J = 6.6$ Hz, 2H), 2.64 (d, $J = 2.3$ Hz, 1H), 2.36 (d, $J = 7.3$ Hz, 1H), 2.18–2.07 (m, 4H), 1.73 (br s, 3H), 1.67 (br s, 3H), 1.60 (br s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) 152.0 (d, $J = 246.9$ Hz), 148.0 (d, $J = 10.7$ Hz), 142.2, 131.9, 128.5 (d, $J = 3.4$ Hz), 123.6, 119.5 (d, $J = 20.2$ Hz), 118.7, 114.7 (d, $J = 2.7$ Hz), 114.0 (d, $J = 8.5$ Hz), 84.7, 83.7 (d, $J = 2.8$ Hz), 80.8, 73.0, 66.2, 52.5, 39.5, 26.2, 25.7, 17.7, 16.7. ^{19}F NMR (282 MHz, $CDCl_3$) δ (ppm) −133.7. HRMS (DCI-CH_4): calcd for $C_{21}H_{22}O_2F$ $[MH]^-$: 325.1604 *m*/*z*, found: 325.1605 *m*/*z*.

*1-(3-Nonylisoxazol-5-yl)pent-1,4-diyn-3-ol (**48**).* At 0 °C, under N_2 atmosphere the isoxazole 38 (58 mg, 0.135 mmol, 1.0 equiv.) was dissolved into wet THF (1 mL, 2.5% v/v H_2O). TBAF (1 M in THF, 540 μL, 0.540 mmol, 4.0 equiv.) was added dropwise in three portions. After completion of the reaction, a saturated aqueous solution of NH_4Cl was added to quench the reaction. The resulting mixture was extracted with diethyl ether. Combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using a gradient of up to 20% of diethyl ether in pentane. The isoxazole **48** (12 mg, 54%) was isolated as a brown oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 6.35 (s, 1H), 5.36 (dd, $J = 7.8$, 2.4 Hz, 1H), 2.75–2.60 (m, 4H, containing at 2.69 (t, $J = 7.7$ Hz, 2H) and at 2.65 (d, $J = 2.4$ Hz, 1H)), 1.72–1.58 (m, 2H), 1.42–1.20 (m, 12H), 0.96–0.84 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 164.2, 151.8, 108.7, 94.4, 79.3, 74.1, 71.5, 52.1, 31.8, 29.4, 29.2 (*2), 29.1, 28.1, 25.9, 22.7, 14. HRMS (DCI-CH_4): calcd for $C_{17}H_{24}NO_2$ $[MH]^+$: 274.1807 *m*/*z*, found: 274.1796 *m*/*z*.

*1-(1-Nonyl-1H-pyrazol-4-yl)penta-1,4-diyn-3-ol (**49**).* Compound **44** was dissolved in THF (1.5 mL). Under N_2 atmosphere, TBAF (1 M in THF, 573 μL, 0.573 mmol, 1.3 equiv.) was added dropwise at −20 °C. The mixture was warmed to 10 °C over 2.5 h. After completion of the reaction, a saturated aqueous solution of NH_4Cl was added to quench the reaction. The resulting mixture was extracted with diethyl ether. Combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using a gradient of up to 40% of diethyl ether in pentane. The dialkynylcarbinol **49** (51 mg, 42%) was isolated as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.61 (d, $J = 0.7$ Hz, 1H), 7.52 (d, $J = 0.7$ Hz, 1H), 5.34 (dd, $J = 6.4$, 2.3 Hz, 1H), 4.10 (t, $J = 7.1$ Hz, 2H), 3.74 (d, $J =$ 6.4 Hz, 1H), 2.59 (d, $J = 2.3$ Hz, 1H), 1.83 (quint, $J = 7.4$ Hz, 2H), 1.37–1.16 (m, 12H), 0.96–0.85 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 142.0, 132.3, 101.5, 86.7, 81.2, 76.3, 72.5, 52.6, 52.4, 31.8, 30.1, 29.4, 29.2, 29.1, 26.5, 22.6, 14.1. HRMS (DCI-CH_4): calcd for $C_{17}H_{25}N_2O$ $[MH]^+$: 273.1967 *m*/*z*, found: 273.1970 *m*/*z*.

Biological evaluations. HCT-116 (Horizon Discovery), U2OS (ATCC) and their derivatives were grown in DMEM, supplemented with 10% fetal bovine serum, 100 U per mL penicillin and 100 μg mL^{-1} streptomycin (Thermo Fisher Scientific), at 37 °C in a 5% CO_2 humidified incubator. The U2OS derivatives, in which the *HSD17B11* gene has been inactivated by CRISPR/Cas9, have been previously described.[3] Cell viability was analysed as described using sulforhodamine B assays on exponentially growing cells treated for 72 h in complete growth medium.[3] Each point was measured in duplicate and IC_{50} were computed from at least three independent experiments with the GraphPad Prism software using a non-linear regression to a four-parameter logistic curve (variable slope).

Conflicts of interest

There are no conflicts to declare.

Data availability

The data supporting this article have been included as part of the supplementary information (SI). Supplementary information: general synthetic experimental details, characterization data, UPC^2 chromatograms and NMR spectra. See DOI: **https://doi.org/10.1039/d5ra06473b**.

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