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Graphical Abstract

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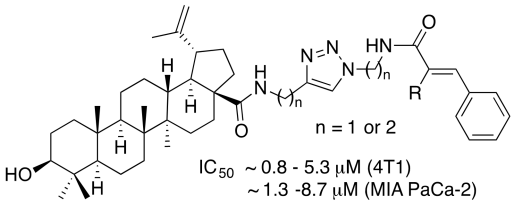

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Synthesis and Cytotoxicity of Baylis-Hillman Template Derived Betulinic Acid-Triazole Conjugates†

Pathi Suman,[a] Amardeep Patel,[a] Lucas Solano,[b] Gayathri Jampana,[a] Zachary S. Gardner,[b§] Crystal M. Holt,[a§] and Subash C. Jonnalagadda.[a,c*]

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ABSTRACT

Several alkynes and azides were prepared starting from betulinic acid and Baylis-Hillman reaction-derived allylic alcohols. These alkynes and azides were then coupled under click cycloaddition conditions to obtain functionalized betulinic acid-triazole conjugates. Similarly, pyrazinyl- and indolylbetulinic acid-triazoles were also prepared employing cycloaddition chemistry. All the synthetic compounds were tested for their cytotoxicity against murine breast cancer (4T1) and human pancreatic cancer (MIA PaCa-2) cell lines. Based on these *in vitro* assays, two series of compounds have been identified as lead compounds for further development.

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§Undergraduate Research Participants

†Dedicated to Professor Deevi Basavaiah on the occasion of his retirement.

Introduction

Pentacyclic triterpenoids such as betulin **1** and betulinic acid **2** (**Figure 1**) are readily found in >200 types of trees.[1] Betulin is abundantly available in nature and can be readily extracted from the bark of birch trees. Various parts of the birch tree including the leaves, bark, and stem have been used in herbal and folk medicine as diuretics as well as for reducing the effects of arthritis and rheumatism.[2] Betulin and related analogs show diverse medicinal activities ranging from anti-cancer, anti-microbial, anti-HIV, and anti-inflammatory properties.[3] While the detailed mechanism of action is not entirely clear, it is generally understood that betulinic acid affects the mitochondrial pathways and increases the caspase-3 activity thereby leading to apoptosis.[4] Betulinic acid is also known to be selective toxic to a variety of cancer cells while the normal cells are typically resistant to this molecule.[5] Recently, betulinic acid was found to exhibit *in vivo* protective effect against dexamethasone induced thymocyte apoptosis in mice.[6] Several recent reports also indicated excellent *in vivo* activity for betulin via the inhibition of NF-κB pathway.[7] In addition to their medicinal effects, these natural products have also found other applications such as their use as anti-feedants,[8] bio-based coatings,[9] solder pastes,[10] and bio-hybrid polymers.[11]

Multicomponent coupling reactions offer ready access to complex and diversely functionalized libraries of compounds and they are valuable tools in drug design and discovery. Baylis-Hillman (BH) reaction involves the coupling of aldehydes or aldimines with activated olefins (acrylates, acrylonitriles, vinylsulfones, etc.) to furnish the allylic alcohols or amines in a one-step transformation.[12] Passerini reaction is an isocyanide based three component coupling reaction used for the preparation of α-acyloxyamides.[13] Click chemistry involves the cycloaddition of azides and alkynes for the preparation of 1,2,3-triazoles.[14] We have been working on the development of novel small molecules[15] as medicinal agents utilizing Baylis-Hillman[16] and Passerini[17] reactions. Previously, we had reported the synthesis of chalcone (**3**), α-acetoxyamide (**4**), and amine (**5**) derivatives of betulin utilizing aldol condensation, Passerini reaction, and reductive amination respectively (**Figure 1**).[3e,18]

Owing to the impressive therapeutic effects as well as the abundant availability of these natural products, we undertook a project involving the development of triazole derivatives of betulinic acid as anti-cancer agents using BH reaction and Click chemistry as the key steps in our synthesis. The synthesis of two precursors (alkyne and azide) required for Click chemistry was envisioned from betulinic acid and BH templates. While there have been multiple reports on click coupling using betulin/betulinic acid and related analogs, so far, limited success has been achieved in terms of identifying potent lead molecule for further development.[19] We hypothesized that molecular hybridization of modestly cytotoxic betulinic acid with the BH reaction-derived and pharmacologically active 1,4-acceptor unit should lead to the compounds with higher potency than the parent betulinic acid for their development as anti-cancer agents. Additionally, the BH template offers multiple avenues for chemical manipulations, which should further assist us in understanding a detailed structure-activity relationship profile for these analogs, once active molecules have been identified.

Results and Discussion

We initiated our synthesis with the preparation of BH reaction derived allylic azide and alkyne motifs (**Scheme 1**). The reaction of benzaldehyde with methyl acrylate in the presence of DABCO yielded the allylic alcohol **8**. The three allylic azides **9a-c** were then obtained from the alcohol **8**. Reaction of **8** with HBr and H_2SO_4 followed by nucleophilic displacement of the resulting allylic bromide with sodium azide resulted in the formation of the azide **9a**. Hydrolysis of **9a** with NaOH and the coupling of the resulting acid with *N*,*N*,*N*'-trimethylethylenediamine in the presence of TBTU and Hünig's base furnished the azide **9b**. Azide **9c** was also obtained from **9a** upon alkaline hydrolysis and coupling with *N*-methylpiperazine (**Scheme 1**).

The two β-azidoethylamide derivatives **9d-e** were prepared with utmost ease starting from the BH alcohol **8**. Acetylation of **8** with acetic anhydride followed by the treatment of the acetate **10** with *N*,*N*,*N*'-trimethylethylenediamine and potassium carbonate in DMF furnished the allylic amine **11**. Alkaline hydrolysis of **11** and the coupling of the resulting acid with 2-azidoethylamine[20] in the presence of HOBt and EDCI produced the azide **9d**. The azide **9e** was obtained from the BH acetate **10** via the displacement with *N*-methylpiperazine followed by hydrolysis and coupling with 2-azidoethylamine. Azide **9f** was obtained via the reaction of cinnamic acid **16** with 2-azidoethylamine (**Scheme 1**).

The alkyne precursors **13a-c** were derived via HOBt, EDCI mediated coupling of propargyl amine with the cinnamic acids **12**, **15**, and **16** respectively (**Scheme 1**).

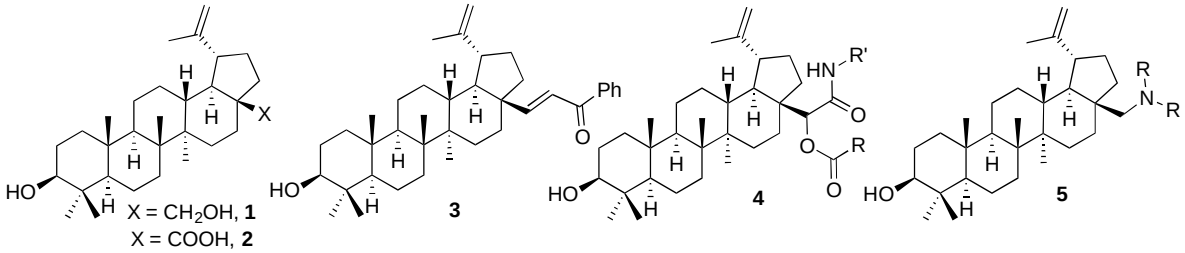
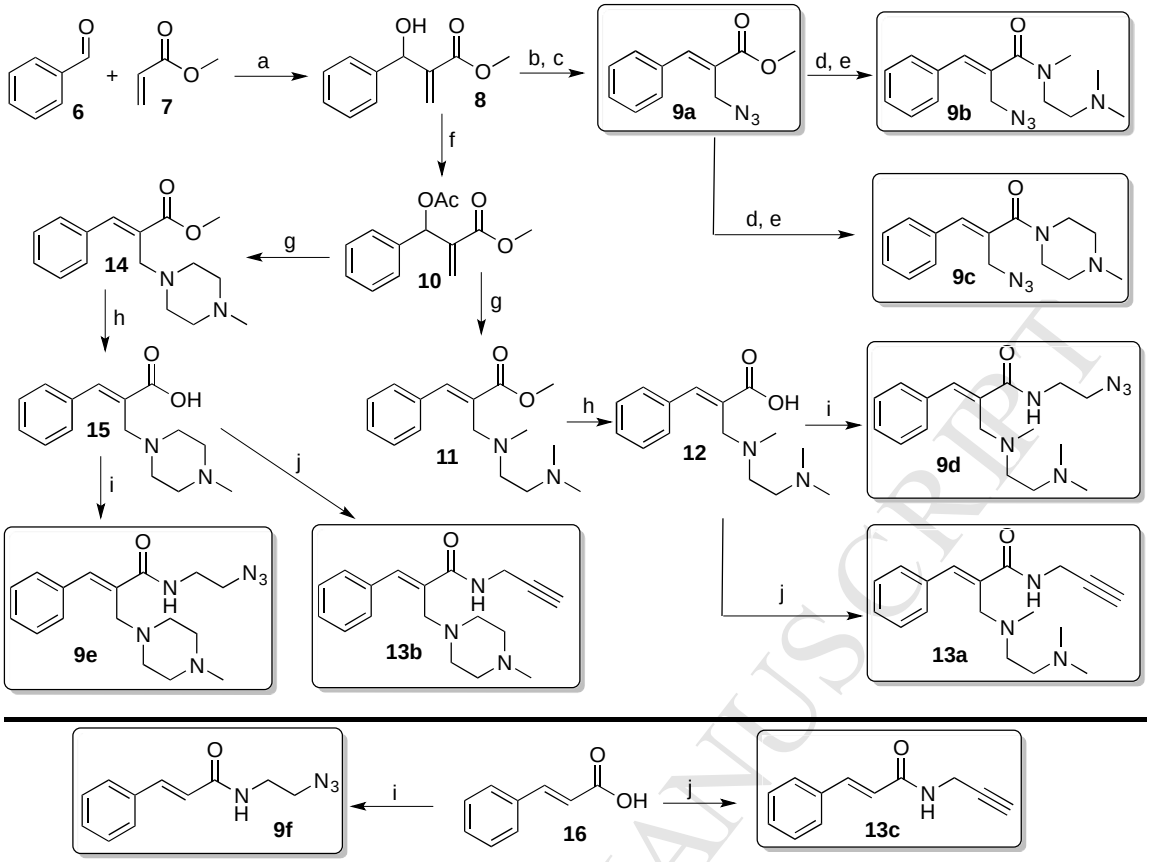


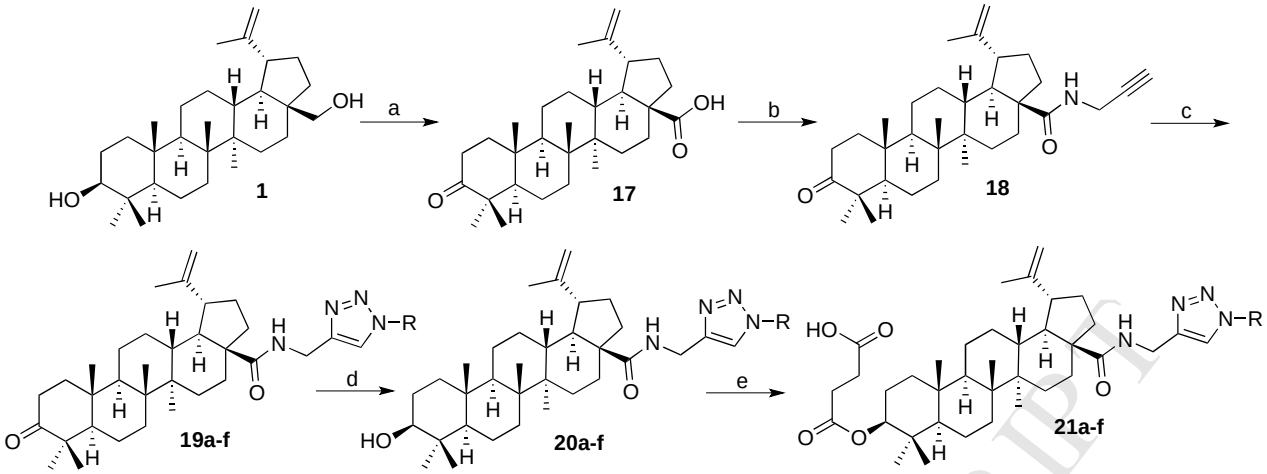
Figure 1: Functionalized Betulin/Betulinic Acid Analogs



Reaction Conditions: (a) DABCO, 25 °C, 14d, 78%; (b) HBr, H_2SO_4, 0-25 °C, 3h, 74%; (c) NaN_3, acetone:H_2O (4:1), 25 °C, 3h, 85%; (d) NaOH, MeOH:THF (1:9), 25 °C, 78%; (e) R_2NH, $^iPr_2NEt$, TBTU, DMF, 0-25 °C, 12-16h, 72-74%; (f) Ac_2O, NEt_3, DMAP, CH_2Cl_2, 25 °C, 2h, 91%; (g) R_2NH, K_2CO_3, DMF, 25 °C, 13-15h, 77-81%; (h) NaOH, MeOH:THF (1:9), 0-25 °C, 8-10h, 71-74%; (i) 2-Azidoethylamine, $^iPr_2NEt$, HOBt, EDCI, CH_2Cl_2, 0-25 °C, 12-16h, 72-74%; (j) Propargyl amine, $^iPr_2NEt$, HOBt, EDCI, CH_2Cl_2, 0-25 °C, 12-16h, 71-76%.

Scheme 1: Preparation of azides **9a-f** and alkynes **13a-c**

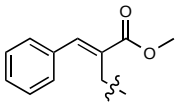
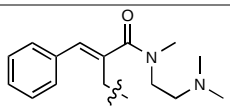
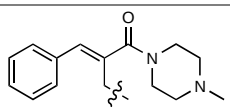
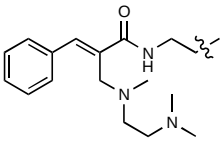
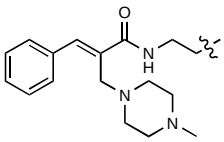
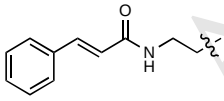
Having prepared the azides **9a-f** and alkynes **13a-c** from BH template, we focused our efforts on the functionalization of betulin for the preparation of click reaction counterparts. Oxidation of betulin **1** with Jones reagent yielded betulonic acid **17**. Reaction of **17** with propargyl amine under peptide coupling conditions using TBTU and Hünig's base resulted in *N*-propargyl betulonamide **18** (**Scheme 2**). The azide motifs **9a-f** (**Scheme 1**) were then utilized for click coupling with **18**. Our initial efforts towards click coupling of methyl α-azidomethylcinnamate **9a** with **18** employing copper iodide were not fruitful and the product triazole **19a** was obtained in trace quantities even after performing the reaction in various solvents or heating the reaction. However, cycloaddition was realized upon using sodium ascorbate and copper sulphate in *t*-butyl alcohol/water as the solvent medium and the corresponding triazole derivative **19a** was obtained in 89% yield (**Entry 1, Table 1**).[21] Reaction of **19a** with sodium borohydride resulted in the reduction of the C_3 ketone to yield the corresponding alcohol **20a**. In an effort towards increasing the hydrophilicity, alcohol **20a** was further converted to the succinic acid hemiester **21a** upon refluxing with succinic anhydride in toluene. Under identical conditions, reaction of the remaining azides **9b-f** with *N*-propargyl betulonamide **18** led to the triazoles **19b-f** in high yield (**Entries 2-6, Table 1**). Treatment of **19b-f** with $NaBH_4$ afforded **20b-f**, which upon succinylation furnished the hemiesters **21b-f** (**Scheme 2**). All the compounds **19-21** were characterized using NMR and mass spectrometric analyses.



Reaction Conditions: (a) Jones reagent, acetone, 0-25 °C, 4h, 75%; (b) Propargyl amine, $^{i}Pr_2NEt$, TBTU, DMF, 0-25 °C, 14h, 73%; (c) **9a-f**, $CuSO_4$, sodium ascorbate, $^{t}BuOH:H_2O$ (1:1), 25 °C, 12-15h, 85-90%; (d) $NaBH_4$, CH_3OH, 0-25 °C, 2-3h, 84-90%; (e) Succinic anhydride, DMAP, toluene, 80 °C, 12-15h, 80-87%.

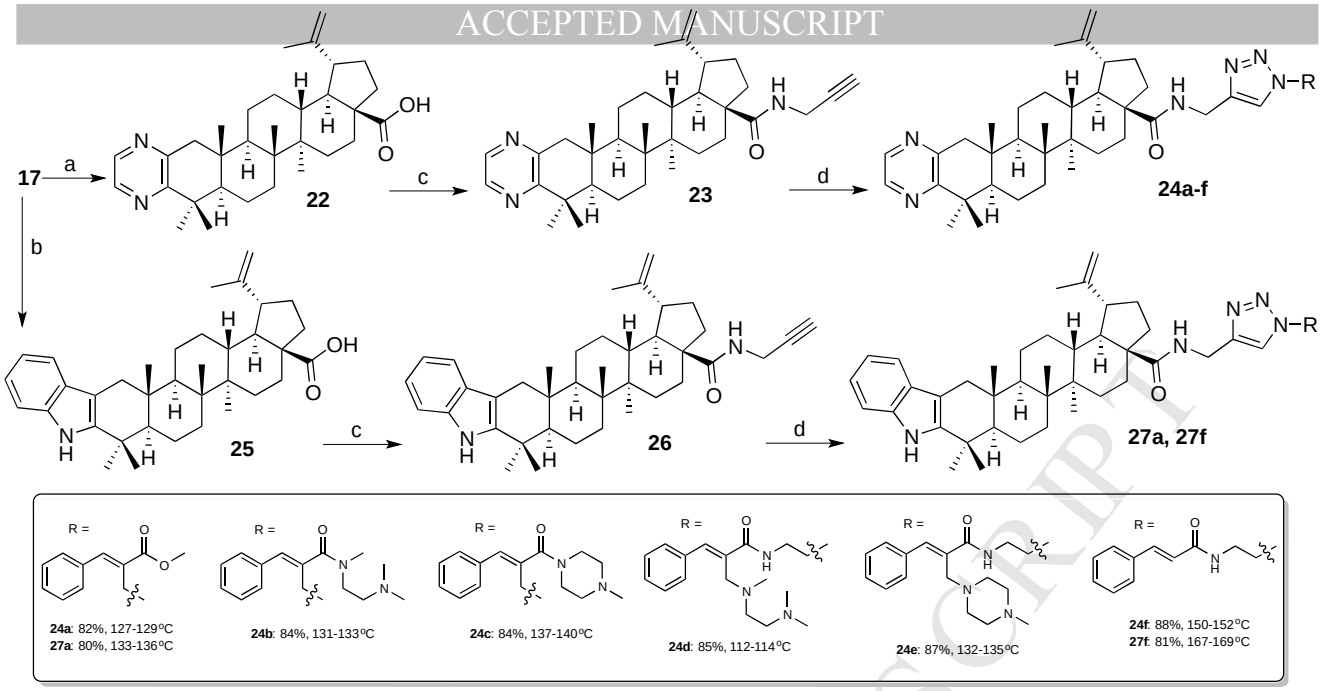
Scheme 2: Coupling of *N*-propargyl betulonamide with azido cinnamates/cinnamamides

Table 1: Preparation of betulin conjugates **19-21**

#	**R**	Compound	Yield (%)	Melting Point (^{o}C)	Compound	Yield (%)	Melting Point (^{o}C)	Compound	Yield (%)	Melting Point (^{o}C)
1		**19a**	89	124-126	**20a**	86	123-125	**21a**	87	122-125
2		**19b**	88	98-101	**20b**	85	118-121	**21b**	80	130-132
3		**19c**	90	134-137	**20c**	88	134-136	**21c**	83	142-145
4		**19d**	85	108-110	**20d**	90	119-122	**21d**	82	114-116
5		**19e**	87	118-120	**20e**	89	130-132	**21e**	84	132-134
6		**19f**	91	139-141	**20f**	90	185-187	**21f**	81	141-144

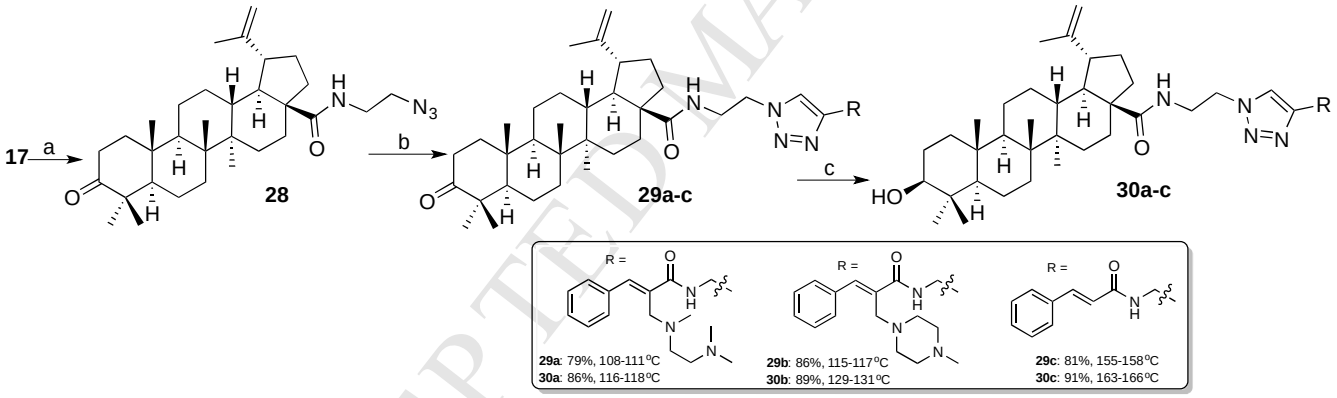
We were able to synthesize pyrazinylbetulinic acid derivative **22**, via the cycloaddition of betulonic acid **17** with ethylenediamine upon refluxing with sulphur and morpholine.[22] Amide coupling of **22** with propargyl amine was accomplished using TBTU and Hünig's base to generate **23**, which was then subjected to cycloaddition with azides **9a-f** under click reaction conditions ($CuSO_4$ and sodium ascorbate). The resulting triazoles **24a-f** were purified by silica gel column chromatography and characterized via spectroscopic techniques (**Scheme 3**).

In an analogous protocol, betulonic acid **17** was converted to the indolylbetulinic acid **25** upon refluxing with phenyl hydrazine in acetic acid under Fischer-Indole synthesis conditions.[22d,23] The reaction of **25** with propargyl amine yielded the *N*-propargyl indolylbetulinamide **26**. Click coupling of **26** with methyl α-azidomethylcinnamate **9a** and *N*-2-azidoethylcinnamamide **9f** yielded triazoles **27a** and **27f** respectively (**Scheme 3**).



Reaction Conditions: (a) Ethylenediamine, Sulfur, Morpholine, reflux, 24h, 71%; (b) Phenylhydrazine, CH_3COOH, reflux, 4h, 45%; (c) Propargyl amine, $^{i}Pr_2NEt$, TBTU, DMF, 0-25 °C, 14-20h, 71-80%; (d) **9a-f**, $CuSO_4$, sodium ascorbate, $^{t}BuOH:H_2O$ (1:1), 25 °C, 12-15h, 80-88%.

Scheme 3: Coupling of fused heterocyclic *N*-propargyl betulinamides with azido cinnamates/cinnamamides



Reaction Conditions: (a) 2-Azidoethylamine, $^{i}Pr_2NEt$, TBTU, DMF, 0-25 °C, 20h, 74%; (b) **13a-c**, $CuSO_4$, sodium ascorbate, $^{t}BuOH:H_2O$ (1:1), 25 °C, 12-15h, 79-86%; (c) $NaBH_4$, CH_3OH, 0-25 °C, 2-3h, 86-91%.

Scheme 4: Coupling of *N*-azidoethyl betulinamide with *N*-alkynylcinnamamides

The triazoles shown in **Schemes 2-3** were obtained upon click coupling of betulin-derived alkynes **18**, **23**, and **26** with Baylis-Hillman motif-derived azides **9a-f**. In order to understand the complete SAR profile of our template, we decided to switch the coupling partners for the click reaction. Accordingly, we chose the BH reaction-derived alkynes (**13a-c**, **Scheme 1**), for coupling with *N*-(2-azidoethyl) betulonamide **28**. The amide **28** was obtained upon coupling betulonic acid **17** with 2-azidoethylamine in the presence of TBTU and *N*,*N*-diisopropylethylamine. It was noticed that an excess of the amine was required for this coupling as the use of molar equivalent of 2-azidoethylamine furnished the unreacted intermediate benzotriazolyl ester of betulonic acid and led to lower yields of the amide **28**. Coupling of **28** with *N*-propargyl α-(dialkylaminomethyl)cinnamamides **13a-b** and *N*-propargyl cinnamamide **13c** under click conditions proceeded smoothly to provide triazoles **29a-c**. Reduction of **29a-c** with sodium borohydride yielded the betulinic acid based triazole derivatives **30a-c** in 86-91% yield (**Scheme 4**).

All the synthesized betulinic acid-triazole conjugates as well as some of the intermediates were evaluated for their general cytotoxicity against murine breast cancer (4T1) and pancreatic cancer (MIA PaCa-2) cell lines. The cells were purchased from ATCC and the assays were performed under standard conditions by seeding the cells in 96 well plates and the cell viability was determined using MTT assay. All the candidate compounds were tested at 50 μM, 12.5 μM, and 1.5 μM concentrations. While betulinic acid showed moderate activity at 12.5 μM (~60% cell death for 4T1 and ~40% cell death for MIA PaCa-2), majority of the betulinic acid-triazole conjugates (eg. **20b-e**, **24d-e**, and **30a-c**, etc.) that were tested showed promising activity at this concentration (>90% cell death for 4T1 and ~80-90% cell death

for MIA PaCa-2). The compounds showing moderate to good cytotoxicity were then selected for determining the IC_{50} values (**Table 2**).

Table 2: *In vitro* cytotoxicity of the BH-template derived betulinic acid-triazole derivatives

#	Compound	4T1 IC_{50} (μM)*	MIA PaCa-2 IC_{50} (μM)*
1	**19a**	NT	NT
2	**19b**	6.93 ± 1.09	9.87 ± 0.79
3	**19c**	7.15 ± 0.18	14.99 ± 2.12
4	**19d**	5.67 ± 0.10	8.11 ± 1.54
5	**19e**	5.17 ± 0.60	5.98 ± 0.99
6	**19f**	NT	NT
7	**20a**	39.75 ± 9.45	NT
8	**20b**	3.97 ± 0.73	2.44 ± 0.36
9	**20c**	4.37 ± 0.43	8.69 ± 0.33
10	**20d**	***2.38 ± 0.45***	***1.36 ± 0.21***
11	**20e**	***2.62 ± 0.24***	***1.64 ± 0.20***
12	**20f**	27.26 ± 12.2	32.50 ± 7.92
13	**21a**	5.26 ± 0.65	47.58 ± 5.51
14	**21b**	7.48 ± 0.59	21.73 ± 5.12
15	**21c**	6.13 ± 0.81	14.44 ± 3.44
16	**21d**	4.13 ± 0.22	9.66 ± 0.51
17	**21e**	7.05 ± 0.53	24.28 ± 3.24
18	**21f**	8.61 ± 2.27	NT
19	**23**	39.33 ± 7.0	26.73 ± 3.70
20	**24a**	NT	NT
21	**24b**	5.14 ± 0.80	8.26 ± 0.91
22	**24c**	17.28 ± 5.00	15.21 ± 1.91
23	**24d**	2.88 ± 0.06	3.87 ± 0.56
24	**24e**	2.88 ± 0.04	4.36 ± 0.44
25	**24f**	13.47 ± 2.10	33.21 ± 2.80
26	**26**	NT	NT
27	**27a**	NT	NT
28	**27f**	NT	NT
29	**28**	NT	NT
30	**29a**	5.39 ± 0.40	5.02 ± 0.47
31	**29b**	4.74 ± 0.93	8.10 ± 2.42
32	**29c**	NT	NT
33	**30a**	***1.49 ± 0.06***	***1.34 ± 0.19***
34	**30b**	5.38 ± 0.22	3.86 ± 0.39
35	**30c**	***0.81 ± 0.03***	3.56 ± 0.38
36	Betulinic acid	6.29 ± 0.96	25.63 ± 3.79

*IC_{50} values reported as average ± SEM

*Minimum of three independent experiments.

NT = Not toxic

Based on the detailed IC_{50} analysis, it was revealed that the C_3 ketone containing betulin analogs (**19a-f, Entries 1-6, Table 2**) showed lower biological activity than the corresponding C_3-alcohol based triazoles **20a-f** (**Entries 7-12**). Further, it was interesting to note that the conversion of C_3-alcohol to the succinic acid hemi ester **21a-f** (**Entries 13-18**) did not improve the biological activity. Compounds **19a-f** and **21a-f** showed comparable activity to that of the parent molecule betulinic acid (**Entry 36**) in both 4T1 and MiaPaCa-2 cells, however, the C_3-alcohol containing analogs **20b-e** (**Entries 8-11**) showed two-fold (4T1) and ~20-fold (MiaPaCa-2) increase in biological activity. While most of the pyrazine and indole containing analogs did not show significant activity, analogs **24d-e** (**Entries 23-24**), which contain the allylic amine moiety (trimethylethylenediamine and piperazine respectively) showed 2-6 fold increase in potency. It was encouraging to note that the betulinic acid derivatives **30a-c** (**Entries 33-35**), which were obtained upon switching coupling partners for the click reaction, showed comparable or better cytotoxicity when compared to their structurally analogous counterparts **20d-f** (**Entries 10-12**).

Based on these findings, we recognize the importance of C_3-alcohol unit (eg. compounds **20** & **30**), and the *N,N,N'*-trimethylethylenediamine motif (eg. compounds **20b, 20d, 24d, 30a**, etc.) for enhancing the biological activity of these molecules. It should also be noted that none of the intermediates tested showed any toxicity, which leads us to believe that the BH motif is also required for the activity. Efforts are currently underway to identify the mechanism of action for the lead derivatives as well as for the identification of potent candidate for further development.

Conclusion

In conclusion, we have prepared betulinic acid-triazole derivatives utilizing Baylis-Hillman reaction and click chemistry as the key protocols in our synthesis. We have also prepared pyrazinyl and indolyl betulinic acid derivatives employing the above protocol. These compounds were tested for their biological efficacy against murine breast cancer cell line (4T1) and human pancreatic cancer cell line (MIA PaCa-2). Based on these *in vitro assays*, we have been able to identify two series of betulin derivatives for further SAR and pre-clinical studies. The ready availability of betulin from natural resources as well as the great chemical diversity afforded by the Baylis-Hillman template imparts significance to this class of compounds for potential development as *anti*-cancer agents.

Experimental Section

General Methods: All operations were carried out under an inert atmosphere of nitrogen. Glassware for all reactions was oven dried at 125 °C and cooled under nitrogen prior to use. Liquid reagents and solvents were introduced by oven-dried syringes or cannulas through septa sealed flasks under a nitrogen atmosphere. THF was distilled from sodium benzophenone ketyl. All other solvents and reagents were purchased and used without further purification. The ^{1}H and ^{13}C NMR spectra were plotted on a Varian-400 spectrometer fitted with a Quad probe.

General amide-coupling procedure A: To a stirred solution of the appropriate acid (1.0 mmol) in dimethylformamide (10.0 mL), was added *N,N*-diisopropylethylamine (2.0 mmol) followed by TBTU (1.1 mmol) at 0 °C and stirred for 30 min. The appropriate amine (1.0 mmol) was then added in one portion and stirred overnight at room temperature. Upon completion (as indicated by TLC), the reaction mixture was quenched by the addition of saturated $NaHCO_3$ and extracted with dichloromethane (2 x 10.0 mL). The combined extracts were washed with cold water (10.0 mL) and brine (10.0 mL). The

organic layer was dried over anhydrous Na_2SO_4, concentrated *in vacuo*, and purified by column chromatography (silica gel, hexanes:ethyl acetate) to obtain pure amides. This procedure was utilized for the preparation of amides **9b-c**, **23**, **26**, and **28**.

General amide-coupling procedure B: *N,N*-diisopropylethylamine (2.0 mmol), HOBt (1.1 mmol), and EDCI (1.1 mmol) were added at 0 °C to a stirred solution of the appropriate acid (1.0 mmol) in dichloromethane (10.0 mL) and the reaction was stirred for 30 min. The appropriate amine (1.0 mmol) was added in one portion and the reaction was stirred overnight at room temperature. After completion of the reaction as indicated by TLC, the reaction mixture was quenched by the addition of saturated $NaHCO_3$ solution and worked up with dichloromethane (2 x 10.0 mL). The combined extracts were washed with brine (10.0 mL), dried over anhydrous Na_2SO_4, concentrated *in vacuo*, and purified by column chromatography (silica gel, hexanes:ethyl acetate) to obtain pure amides in good yields. This procedure was utilized for the preparation of amides **9d-f** and **13a-c**.

Preparation of *N*-(2-*N*,*N*-dimethylaminoethyl) (*E*)-2-azidomethyl-3-phenyl acrylamide, 9b: The reaction of (*E*)-2-(azidomethyl)-3-phenylacrylic acid (1.0 g, 4.9 mmol) with *N,N,N'*-trimethylethylenediamine (602 mg, 5.9 mmol) as per the general amide coupling ***procedure A*** yielded 1.02 g (72%) of **9b** as a pale brown liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.31 – 7.44 (m, 3H), 7.26 – 7.31 (m, 2H), 6.78 (s, 1H), 4.30 (s, 2H), 3.61 (t, *J* = 7.1 Hz, 2H), 3.15 (s, 3H), 2.55 (t, *J* = 7.1 Hz, 2H), 2.28 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) 169.5 134.4, 133.5, 131.6, 128.8, 128.6, 128.4, 49.4, 45.7; ESIMS: m/z calculated for $C_{15}H_{21}N_5O$ $(M+H)^+$ 288.18, found 288.38.

Preparation of (*E*)-2-azidomethyl-1-(4-methylpiperazin-1-yl)-3-phenylprop-2-en-1-one, 9c: The reaction of (*E*)-2-(azidomethyl)-3-phenylacrylic acid (1.0 g, 4.92 mmol) with *N*-methylpiperazine (590 mg, 5.90 mmol) as per the general amide coupling ***procedure A*** furnished 1.04 g (74%) of **9c** as a pale brown liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.24 – 7.41 (m, 5H), 6.69 (s, 1H), 4.26 (s, 2H), 3.61 – 3.80 (m, 4H), 2.37 – 2.50 (m, 4H), 2.29 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) 169.9, 134.3, 134.0, 131.2, 129.0, 128.9, 128.8, 55.0, 49.5, 46.2; ESIMS: m/z calculated for $C_{15}H_{19}N_5O$ $(M+H)^+$ 286.16, found 286.30.

Preparation of *N*-2-azidoethyl (*E*)-2-(*N*-(2-dimethylamino ethyl)-*N*-methylaminomethyl)-3-phenyl acrylamide, 9d: The reaction of **12** (500 mg, 1.90 mmol) with 2-azidoethylamine (180 mg, 2.09 mmol) as per the general amide-coupling ***procedure B*** yielded 460 mg (74%) of **9d** as a pale orange liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 10.10 (s, 1H), 7.96 (s, 1H), 7.21 – 7.41 (m, 5H), 3.49 – 3.53 (m, 4H), 3.39 (s, 2H), 2.43 – 2.51 (m, 2H), 2.34 – 2.42 (m, 2H), 2.24 (s, 6H), 2.14 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) 168.6, 140.1, 136.1, 131.0, 129.2, 128.4, 128.0, 56.8, 54.6, 53.1, 50.8, 45.6, 42.0, 39.7; ESIMS: m/z calculated for $C_{17}H_{26}N_6O$ $(M+H)^+$ 331.22, found 331.35.

Preparation of *N*-(2-azidoethyl) (*E*)-2-(*N*-methylpiperazin-1-ylmethyl)-3-phenyl acrylamide, 9e: The reaction of **15** (250 mg, 0.96 mmol) with 2-azidoethylamine (90 mg, 1.05 mmol) as per the general amide-coupling ***procedure B*** yielded 226 mg, (72%) of **9e** as a pale orange liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 10.04 (s, 1H), 7.92 (s, 1H), 7.18 – 7.36 (m, 5H), 3.50 – 3.56 (m, 2H), 3.45 – 3.49 (m, 2H), 3.39 (s, 2H), 2.33 – 2.68 (m, 8H), 2.25 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) 168.6, 140.7, 135.7, 129.8, 129.2, 128.5, 128.2, 55.3, 54.9, 52.5, 51.2, 46.2, 38.9; ESIMS: m/z calculated for $C_{17}H_{24}N_6O$ $(M+H)^+$ 329.20, found 329.33.

Preparation of Methyl *(E)*-2-(*N*-(2-dimethylaminoethyl)-*N*-methylaminomethyl)-3-phenyl acrylate, 11: *N,N,N'*-Trimethylethylenediamine (521 mg, 5.1 mmol) and K_2CO_3 (883 mg, 6.40 mmol) were added to a stirred solution of **10** (1.0 g, 4.27 mmol) in *N,N*-dimethylformamide (10.0 mL) at room temperature and the reaction mixture was stirred overnight. Upon completion (TLC), the reaction was quenched with cold water and extracted with ethyl acetate (2 x 20.0 mL). The combined organic layers were washed thoroughly with cold water (2 x 10.0 mL), brine (2 x 10.0 mL) and dried over anhydrous Na_2SO_4. The ethyl acetate was concentrated *in vacuo* and purified by column chromatography (silica gel, hexanes: ethyl acetate, 1:4) to obtain **11** as brown liquid (912 mg, 77%). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.80 (s, 1H), 7.57 – 7.61 (m, 2H), 7.29 – 7.41 (m, 3H), 3.82 (s, 3H), 3.39 (s, 2H), 2.48 – 2.54 (m, 2H), 2.37 – 2.44 (m, 2H), 2.21 (s, 6H), 2.18 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) 168.9, 142.6, 135.3, 130.4, 130.2, 128.7, 128.3, 57.2, 55.5, 53.1, 51.9, 45.8, 41.9; ESIMS: m/z calculated for $C_{16}H_{24}N_2O_2$ $(M+H)^+$ 277.19, found 277.38.

Preparation of *(E)*-2-(*N*-(2-dimethylaminoethyl)-*N*-methyl aminomethyl)-3-phenyl acrylic acid, 12: *aq.* NaOH (2.9 mL, 2.5 M, 7.3 mmol) was added to a solution of **11** (1.0 g, 3.6 mmol) in THF:MeOH (9:1, 20.0 mL) at 0 °C and the reaction was stirred overnight at room temperature. Upon completion (TLC), the solution was acidified to pH 6 with 1N HCl. The solution was concentrated *in vacuo* and the resulting slurry was dissolved in isopropyl alcohol to effect the precipitation of sodium chloride. The reaction was then filtered and the filtrate was concentrated *in vacuo* to yield 671 mg (71%) of **12** as pale cream-colored semi-solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.96 (s, 1H), 7.33 – 7.42 (m, 3H), 7.26 – 7.31 (m, 2H), 3.81 (s, 2H), 3.45 (m, 2H), 3.19 (m, 2H), 2.89 (s, 6H), 2.43 (s, 3H); ^{13}C NMR (101 MHz, DMSO-d_6): δ (ppm) 169.5, 142.9, 134.9, 130.4, 129.5, 129.1, 52.9, 52.7, 51.3, 42.6, 41.4; ESIMS: m/z calculated for $C_{15}H_{22}N_2O_2$ $(M+H)^+$ 263.17, found 263.37.

Preparation of *N*-propargyl (*E*)-2-(*N*-(2-dimethylamino ethyl)-*N*-methylaminomethyl)-3-phenyl acrylamide, 13a: The reaction of **12** (430 mg, 1.6 mmol) with propargyl amine (99 mg, 1.8 mmol) as per the general amide-coupling ***procedure B*** yielded 364 mg (72%) of **13a** as a pale orange liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 10.08 (s, 1H), 7.98 (s, 1H), 7.21 – 7.39 (m, 5H), 4.11 (dd, *J* = 2.5, 5.3 Hz, 2H), 3.38 (s, 2H), 2.36 – 2.50 (m, 4H), 2.24 (s, 6H), 2.17 (t, *J* = 2.6 Hz, 1H), 2.14 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) 167.9, 140.3, 136.1, 130.9, 129.2, 128.4, 127.9, 80.9, 70.5, 56.8, 54.6, 52.8, 45.5, 42.1, 29.1; ESIMS: m/z calculated for $C_{18}H_{25}N_3O$ $(M+H)^+$ 300.20, found 300.41.

Preparation of Methyl *(E)*-2-(*N*-methylpiperazin-1-ylmethyl)-3-phenyl acrylate, 14: Procedure similar to that of **11**. The reaction of **10** (1.0 g, 4.3 mmol) with *N*-methylpiperazine (512 mg, 5.1 mmol) and K_2CO_3 (883 mg, 6.4 mmol) provided 943 mg (81%) of **14** as a pale cream liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.84 (s, 1H), 7.63 – 7.68 (m, 2H), 7.32 – 7.41 (m, 3H), 3.81 (s, 3H), 3.35 (s, 2H), 2.31 – 2.63 (m, 8H), 2.26 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) 169.3, 143.6, 135.6, 130.7, 129.9, 129.1, 128.6, 55.5, 53.4, 52.8, 52.3, 46.3; ESIMS: m/z calculated for $C_{16}H_{22}N_2O_2$ $(M+H)^+$ 275.17, found 275.10.

Preparation of *(E)*-2-(*N*-methylpiperazin-1-ylmethyl)-3-phenyl acrylic acid, 15: Procedure similar to that of **12**. The reaction of **14** (1.0 g, 3.6 mmol) and aq. NaOH (2.9 mL, 2.5 M, 7.3 mmol) yielded 710 mg (74%) of **15** as a pale cream-colored solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.02 (s, 1H), 7.38 –

7.42 (m, 3H), 7.30 – 7.32 (m, 2H), 3.66 (s, 2H), 2.95 – 3.10 (m, 8H), 2.69 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) 169.5, 142.9, 134.6, 129.5, 128.8, 128.3, 127.9, 53.2, 52.9, 49.4, 43.4; ESIMS: m/z calculated for $C_{15}H_{20}N_2O_2$ (M^+) 260.15, found 260.80.

Preparation of *N*-propargyl (*E*)-2-(*N*-methylpiperazin-1-ylmethyl)-3-phenyl acrylamide, 13b: The reaction of **15** (210 mg, 0.8 mmol) with propargyl amine (48 mg, 0.9 mmol) as per the general amide-coupling ***procedure B*** yielded 176 mg (71%) of **13b** as a pale orange liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 10.08 (s, 1H), 7.90 (s, 1H), 7.27 – 7.31 (m, 2H), 7.22 – 7.26 (m, 1H), 7.15 – 7.19 (m, 2H), 4.07 (dd, *J* = 2.6, 4.8 Hz, 2H), 3.35 – 3.38 (m, 2H), 2.25 – 2.60 (m, 8H), 2.21 (s, 3H), 2.18 (t, *J* = 2.6 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) 167.9, 140.8, 135.6, 129.4, 129.2, 128.5, 128.2, 80.4, 71.4, 55.3, 54.8, 52.4, 46.2, 29.4; ESIMS: m/z calculated for $C_{18}H_{23}N_3O$ $(M+H)^+$ 298.19, found 298.40.

Preparation of triazole 19a: To a stirred solution of alkyne **18** (450 mg, 0.9 mmol) and azide **9a** (198 mg, 0.9 mmol) in a mixture of *t*-butanol/water (1:1, 8.0 mL), was added $CuSO_4$ (23 mg, 0.1 mmol) and sodium ascorbate (36 mg, 0.2 mmol). The reaction mixture was stirred overnight at room temperature. Upon completion (TLC), the reaction was concentrated *in vacuo* and diluted with water to effect precipitation. The resulting solid was filtered, washed with water, and further purified via column chromatography (silica gel, methanol:dichloromethane, 2:3) to obtain 528 mg (89%) of 1,2,3-triazole **19a** as a white solid. Mp 124 – 126 °C, ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.07 (s, 1H), 7.74 (s, 1H), 7.62 (d, *J* = 7.4 Hz, 2H), 7.39 – 7.46 (m, 3H), 6.36 (t, *J* = 5.2 Hz, 1H), 5.35 (s, 2H), 4.72 (s, 1H), 4.58 (s, 1H), 4.40 – 4.56 (m, 2H), 3.84 (s, 3H), 3.11 (dt, *J* = 4.2, 11.0 Hz, 1H), 2.33 – 2.49 (m, 3H), 0.70 – 2.04 (m, 21H), 1.66 (s, 3H), 1.03 (s, 3H), 0.95 (s, 3H), 0.93 (s, 3H), 0.83 (s, 3H), 0.75 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) 218.4, 176.5, 167.2, 151.1, 146.2, 145.2, 133.7, 130.2, 129.9, 129.2, 125.1, 123.4, 109.6, 55.8, 55.1, 52.8, 50.2, 50.1, 47.5, 47.1, 46.9, 42.6, 40.8, 39.8, 38.4, 37.9, 37.0, 34.8, 34.3, 33.7, 33.6, 31.0, 29.5, 26.8, 25.8, 21.6, 21.2, 19.8, 19.7, 16.1, 15.8, 14.7; ESIMS: m/z calculated for $C_{44}H_{60}N_4O_4$ $(M+H)^+$ 709.47, found 709.55.

Preparation of triazole 19b: Procedure similar to that of **19a**. This compound was prepared by the reaction of alkyne **18** with azide **9b**. Yield: 88%; cream color solid; mp 98 – 101 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.62 (s, 1H), 7.33 – 7.46 (m, 5H), 6.92 (s, 1H), 6.25 (t, *J* = 5.3 Hz, 1H), 5.31 – 5.42 (m, 2H), 4.73 (s, 1H), 4.55 – 4.61 (m, 1H), 4.50 (dd, *J* = 5.5, 15.0 Hz, 1H), 4.44 (dd, *J* = 5.5, 15.2 Hz, 1H), 3.42 – 3.50 (m, 2H), 3.12 (dt, *J* = 4.3, 11.2 Hz, 1H), 3.00 (brs, 3H), 2.33 – 2.52 (m, 5H), 2.24 (brs, 6H), 0.78 – 2.01 (m, 21H), 1.67 (s, 3H), 1.05 (s, 3H), 0.99 (s, 3H), 0.94 (s, 3H), 0.87 (s, 3H), 0.82 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) 218.0, 176.2, 150.8, 145.0, 134.8, 134.0, 130.2, 128.8 (2C), 128.7, 123.2, 109.4, 55.5, 54.9, 50.0, 49.9, 48.5, 47.2, 46.6, 45.6, 42.4, 40.6, 39.6, 38.2, 37.7, 36.8, 34.7, 34.1, 33.6, 33.4, 30.8, 29.6, 29.3, 26.6, 25.6, 21.4, 20.9, 19.6, 19.4, 15.9, 15.6, 14.5; ESIMS: m/z 779.70 [100%, $(M+H)^+$], HRMS-ESI: calculated for $C_{48}H_{70}N_6O_3$ $[M+H]^+$ 779.5582, found 779.5578.

Preparation of triazole 19c: Procedure similar to that of **19a**. This compound was prepared by the reaction of alkyne **18** with azide **9c**. Yield: 90%; cream color solid; mp 134 – 137 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.61 (s, 1H), 7.34 – 7.43 (m, 5H), 6.87 (s, 1H), 6.25 (m, 1H), 5.35 (s, 2H), 4.73 (s, 1H), 4.59 (s, 1H), 4.52 (dd, *J* = 4.0, 16.0 Hz, 1H), 4.42 (dd, *J* = 4.0, 16.0 Hz, 1H), 3.63 (m, 4H), 3.12 (dt, *J* = 4.3, 11.2 Hz, 1H), 2.34 – 2.52 (m, 3H), 2.17 – 2.30 (m, 4H), 2.25 (s, 3H), 0.77 – 1.94 (m, 21H), 1.67 (s, 3H), 1.05 (s, 3H), 1.01 (s, 3H), 0.94 (s, 3H), 0.87 (s, 3H), 0.81 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) 218.4, 176.5, 169.0, 150.9, 145.3, 134.8, 134.1, 129.9, 129.1, 129.0, 128.9, 123.7, 109.6, 55.8, 55.2, 54.9, 50.3, 50.1, 48.8, 47.5, 46.9, 46.2, 42.7, 40.9, 39.8, 38.4, 37.9, 37.1, 34.9, 34.3, 33.8, 33.7, 31.0, 29.6, 26.8, 25.8, 21.6, 21.2, 19.8, 19.7, 16.2, 15.8, 14.8; ESIMS: m/z 777.65 [100%, $(M+H)^+$], HRMS-ESI: calculated for $C_{48}H_{68}N_6O_3$ $[M+Na]^+$ 799.5245, found 799.5239.

Preparation of triazole 19d: Procedure similar to that of **19a**. This compound was prepared by the reaction of alkyne **18** with azide **9d**. Yield: 85%; cream color solid; mp 108 – 110 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 9.89 (brs, 1H), 7.94 (s, 1H), 7.59 (s, 1H), 7.22 – 7.40 (m, 5H), 6.37 (brs, 1H), 4.73 (s, 1H), 4.56 – 4.60 (m, 3H), 4.51 (dd, *J* = 5.4, 15.0 Hz, 1H), 4.44 (dd, *J* = 5.5, 15.0 Hz, 1H), 3.65 – 3.82 (m, 2H), 3.34 (s, 2H), 3.12 (dt, *J* = 4.2, 11.1 Hz, 1H), 2.34 – 2.52 (m, 7H), 2.19 (brs, 3H), 2.07 (s, 6H), 0.82 – 1.97 (m, 21H), 1.67 (s, 3H), 1.05 (s, 3H), 1.01 (s, 3H), 0.94 (s, 3H), 0.90 (s, 3H), 0.84 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) 218.1, 176.4, 168.5, 150.8, 145.0, 140.1, 135.6, 130.5, 128.9, 128.3, 127.9, 122.9, 109.4, 55.9, 55.5, 54.9, 53.8, 52.7, 50.0, 49.9, 49.2, 47.3, 46.7, 44.9, 42.4, 41.6, 40.6, 39.9, 39.6, 38.2, 37.7, 36.9, 34.7, 34.1, 33.6, 33.4, 30.8, 29.6, 29.3, 26.6, 25.6, 21.4, 21.0, 19.7, 19.4, 15.9, 15.6, 14.5; ESIMS: m/z 822.65 [100%, $(M+H)^+$], HRMS-ESI: calculated for $C_{50}H_{75}N_7O_3$ $[M+Na]^+$ 844.5824, found 844.5831.

Preparation of triazole 19e: Procedure similar to that of **19a**. This compound was prepared by the reaction of alkyne **18** with azide **9e**. Yield: 87%; cream color solid; mp 118 – 120 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 9.87 (s, 1H), 7.92 (s, 1H), 7.61 (s, 1H), 7.22 – 7.37 (m, 3H), 7.20 – 7.25 (m, 2H), 6.23 – 6.29 (m, 1H), 4.73 (s, 1H), 4.59 (s, 1H), 4.38 – 4.55 (m, 4H), 3.79 – 3.92 (m, 2H), 3.34 (s, 2H), 3.08 – 3.15 (m, 1H), 2.29 – 2.52 (m, 11H), 2.25 (s, 3H), 0.76 – 1.92 (m, 21H), 1.75 (s, 3H), 1.04 (s, 3H), 1.00 (s, 3H), 0.94 (s, 3H), 0.90 (s, 3H), 0.81 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) 218.3, 176.7, 168.9, 150.9, 145.5, 140.9, 135.4, 129.5, 129.2, 128.5, 128.3, 123.2, 109.7, 55.7, 55.2, 54.9, 54.9, 52.3, 50.2, 50.1, 49.9, 47.5, 46.9, 45.9, 42.7, 40.9, 39.8, 39.4, 38.4, 38.0, 37.1, 35.0, 34.3, 33.8, 33.7, 31.0, 29.6, 26.8, 25.8, 21.6, 21.2, 19.8, 19.7, 16.2, 15.8, 14.8; ESIMS: m/z 820.70 [100%, $(M+H)^+$], HRMS-ESI: calculated for $C_{50}H_{73}N_7O_3$ $[M+H]^+$ 820.5848, found 820.5877.

Preparation of triazole 19f: Procedure similar to that of **19a**. This compound was prepared by the reaction of alkyne **18** with azide **9f**. Yield: 91%; white solid; mp 139 – 141 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.62 (d, *J* = 15.6 Hz, 1H), 7.60 (s, 1H), 7.46 – 7.51 (m, 2H), 7.32 – 7.36 (m, 3H), 6.26 – 6.42 (m, 3H), 4.70 (s, 1H), 4.57 (s, 1H), 4.46 – 4.54 (m, 3H), 4.40 (dd, *J* = 5.7, 15.0 Hz, 1H), 3.85 – 3.94 (m, 2H), 3.12 (dt, *J* = 4.4, 11.1 Hz, 1H), 2.32 – 2.51 (m, 3H), 0.75 – 1.95 (m, 21H), 1.64 (s, 3H), 1.02 (s, 3H), 0.98 (s, 3H), 0.92 (s, 3H), 0.88 (s, 3H), 0.80 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) 218.5, 176.9, 166.7, 150.8, 145.7, 141.7, 134.8, 130.1, 129.0, 128.0, 123.6, 120.3, 109.8, 55.8, 55.1, 50.2, 50.1, 49.9, 47.5, 46.9, 42.7, 40.8, 39.8, 38.4, 37.9, 37.1, 35.0, 34.4, 33.8, 33.6, 31.0, 29.6, 26.8, 25.8, 21.6, 21.2, 19.8, 19.6, 16.2, 15.9, 14.7; ESIMS: m/z 708.55 [100%, $(M+H)^+$], HRMS-ESI: calculated for $C_{44}H_{61}N_5O_3$ $[M+H]^+$ 708.4847, found 708.4833.

Preparation of Alcohol 20a: To a stirred solution of the appropriate ketone **19a** (180 mg, 0.2 mmol) in methanol at 0 °C, was added $NaBH_4$ (14 g, 0.4 mmol), and stirred for 2 h at room

temperature. Upon completion of reaction (as monitored by TLC), the reaction mixture was concentrated *in vacuo*, diluted with water and extracted with ethyl acetate (2 x 10.0 mL). The combined organic extracts were washed with brine (10.0 mL), dried over anhydrous Na_2SO_4, concentrated under vacuum and purified via column chromatography (silica gel, hexane:ethyl acetate, 1:2) to obtain 155 mg (86%) of pure alcohol **20a** as a white solid. Mp 123 – 125 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.06 (s, 1H), 7.72 (s, 1H), 7.57 – 7.64 (m, 2H), 7.39 – 7.46 (m, 3H), 6.49 (m, 1H), 5.33 (s, 2H), 4.70 (s, 1H), 4.56 (s, 1H), 4.50 (dd, *J* = 5.7, 15.0 Hz, 1H), 4.41 (dd, *J* = 5.5, 15.0 Hz, 1H), 3.82 (s, 3H), 3.03 – 3.22 (m, 2H), 2.34 (dt, *J* = 3.5, 12.7 Hz, 1H), 0.59 – 2.02 (m, 24H), 1.64 (s, 3H), 0.91 (s, 3H), 0.90 (s, 3H), 0.72 (s, 3H), 0.70 (s, 3H), 0.69 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) 176.5, 167.2, 151.2, 146.2, 145.2, 133.8, 130.2, 129.9, 129.2, 125.1, 123.3, 109.6, 79.1, 55.8, 55.5, 52.8, 50.8, 50.3, 47.1, 47.0, 42.6, 40.9, 39.0, 38.9, 38.4, 37.9, 37.4, 34.8, 34.5, 33.7, 31.1, 29.6, 28.2, 27.6, 25.8, 21.1, 19.7, 18.5, 16.3, 16.0, 15.6, 14.8; ESIMS: m/z calculated for $C_{44}H_{62}N_4O_4$ $(M+H)^+$ 711.48, found 711.70.

Preparation of 20b: Procedure similar to that of **20a**. Yield: 85%; cream color solid; mp 118 – 121 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.60 (s, 1H), 7.33 – 7.43 (m, 5H), 6.99 (s, 1H), 6.25 – 6.34 (m, 1H), 5.35 (s, 2H), 4.72 (s, 1H), 4.58 (s, 1H), 4.49 (dd, *J* = 5.6, 15.1 Hz, 1H), 4.42 (dd, *J* = 5.6, 15.1 Hz, 1H), 3.61 (brs, 2H), 3.05 – 3.18 (m, 5H), 2.29 – 2.77 (m, 10H), 0.63 – 1.94 (m, 23H), 1.66 (s, 3H), 0.94 (s, 3H), 0.93 (s, 3H), 0.77 (s, 3H), 0.76 (s, 3H), 0.73 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) 176.4, 150.8, 135.1, 133.9, 129.8, 128.84, 128.80, 128.78, 123.3, 109.4, 78.9, 55.6, 55.3, 50.5, 50.1, 48.6, 46.8, 44.9, 44.8, 42.4, 40.7, 38.8, 38.7, 38.2, 37.7, 37.1, 34.8, 34.3, 33.5, 30.8, 29.4, 27.9, 27.4, 25.6, 20.9, 19.4, 18.3, 16.1, 15.8, 15.4, 14.6; ESIMS: m/z 781.70 [100%, $(M+H)^+$], HRMS-ESI: calculated for $C_{48}H_{72}N_6O_3$ $[M+Na]^+$ 803.5558, found 803.5558.

Preparation of 20c: Procedure similar to that of **20a**. Yield: 88%; white solid; mp 134 – 136 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.60 (s, 1H), 7.34 – 7.42 (m, 5H), 6.86 (s, 1H), 6.24 (t, *J* = 5.6 Hz, 1H), 5.34 (s, 2H), 4.73 (s, 1H), 4.58 (s, 1H), 4.52 (dd, *J* = 5.6, 15.1 Hz, 1H), 4.42 (dd, *J* = 5.6, 15.1 Hz, 1H), 3.66 (m, 4H), 3.06 – 3.19 (m, 2H), 2.17 – 2.35 (m, 5H), 2.26 (s, 3H), 0.63 – 1.93 (m, 24H), 1.67 (s, 3H), 0.94 (s, 3H), 0.93 (s, 3H), 0.76 (s, 6H), 0.73 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) 176.3, 168.8, 150.8, 145.1, 134.6, 133.8, 129.6, 128.8, 128.8, 128.7, 123.5, 109.3, 78.8, 55.7, 55.3, 54.7, 50.5, 50.1, 48.5, 46.7, 45.8, 42.4, 40.7, 38.8, 38.7, 38.2, 37.7, 37.1, 34.7, 34.3, 33.5, 30.8, 29.4, 27.9, 27.4, 25.6, 20.9, 19.5, 18.3, 16.1, 15.8, 15.4, 14.6; ESIMS: m/z 779.70 [100%, $(M+H)^+$], HRMS-ESI: calculated for $C_{48}H_{70}N_6O_3$ $[M+Na]^+$ 801.5402, found 801.5443.

Preparation of 20d: Procedure similar to that of **20a**. Yield: 90%; cream color solid; mp 119 – 122 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 9.95 (s, 1H), 7.96 (s, 1H), 7.58 (s, 1H), 7.24 – 7.41 (m, 5H), 6.33 (s, 1H), 4.72 (s, 1H), 4.55 – 4.64 (m, 3H), 4.51 (dd, *J* = 5.5, 15.0 Hz, 1H), 4.43 (dd, *J* = 5.5, 15.0 Hz, 1H), 3.69 – 3.83 (m, 2H), 3.33 (s, 2H), 3.06 – 3.20 (m, 2H), 2.29 – 2.42 (m, 4H), 2.07 (brs, 3H), 2.07 (s, 6H), 0.63 – 1.95 (m, 25H), 1.67 (s, 3H), 0.94 (s, 3H), 0.93 (s, 3H), 0.80 (s, 3H), 0.79 (s, 3H), 0.74 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) 176.4, 168.5, 150.8, 144.9, 140.1, 135.6, 130.5, 129.0, 128.2, 127.9, 122.9, 109.4, 78.9, 56.1, 55.6, 55.3, 54.0, 52.5, 50.6, 50.1, 49.2, 46.8, 45.0, 42.4, 41.7, 40.7, 39.9, 38.8, 38.7, 38.2, 37.7, 37.2, 34.7, 34.3, 33.5, 30.9, 29.4, 27.9, 27.4, 25.6, 20.9, 19.4, 18.2, 16.1, 15.8, 15.4, 14.6; ESIMS: m/z 824.75 [100%, $(M+H)^+$], HRMS-ESI: calculated for $C_{50}H_{77}N_7O_3$ $[M+Na]^+$ 846.5980, found 846.5983.

Preparation of 20e: Procedure similar to that of **20a**. Yield: 89%; cream color solid; mp 130 – 132 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 9.86 (t, *J* = 4.0 Hz, 1H), 7.92 (s, 1H), 7.58 (s, 1H), 7.20 – 7.39 (m, 5H), 6.26 (t, *J* = 5.7 Hz, 1H), 4.73 (s, 1H), 4.58 (s, 1H), 4.46 – 4.56 (m, 3H), 4.40 (dd, *J* = 5.6, 15.0 Hz, 1H), 3.79 – 3.91 (m, 2H), 3.34 (s, 2H), 3.08 – 3.18 (m, 2H), 2.21 – 2.48 (m, 10H), 2.25 (s, 3H), 0.64 – 1.92 (m, 25H), 1.67 (s, 3H), 0.94 (s, 3H), 0.93 (s, 3H), 0.80 (s, 3H), 0.76 (s, 3H), 0.74 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) 176.5, 168.7, 150.8, 145.3, 140.8, 135.2, 129.3, 128.9, 128.3, 128.0, 123.1, 109.4, 78.8, 55.6, 55.3, 54.8, 54.6, 52.1, 50.5, 50.1, 49.7, 46.8, 45.7, 42.4, 40.7, 39.2, 38.8, 38.7, 38.2, 37.8, 37.2, 34.7, 34.3, 33.5, 30.8, 29.4, 27.9, 27.4, 25.6, 20.9, 19.4, 18.2, 16.2, 15.8, 15.4, 14.6; ESIMS: m/z 822.70 [100%, $(M+H)^+$], HRMS-ESI: calculated for $C_{50}H_{75}N_7O_3$ $[M+Na]^+$ 844.5824, found 844.5852.

Preparation of 20f: Procedure similar to that of **20a**. Yield: 90%; gray color solid; mp 185 – 187 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.63 (d, *J* = 15.6 Hz, 1H), 7.60 (s, 1H), 7.45 – 7.53 (m, 2H), 7.33 – 7.60 (m, 3H), 6.38 (d, *J* = 15.6 Hz, 1H), 6.24 – 6.35 (m, 2H), 4.71 (s, 1H), 4.57 (s, 1H), 4.38 – 4.54 (m, 4H), 3.86 – 3.93 (m, 2H), 3.06 – 3.17 (m, 2H), 2.26 – 2.39 (m, 1H), 0.62 – 1.94 (m, 24H), 1.65 (s, 3H), 0.92 (s, 6H), 0.78 (s, 3H), 0.75 (s, 3H), 0.73 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) 176.7, 166.4, 150.7, 145.5, 141.6, 134.6, 129.8, 128.8, 127.8, 123.4, 120.0, 109.4, 78.9, 55.6, 55.3, 50.5, 50.1, 49.7, 46.7, 42.4, 40.7, 39.5, 38.8, 38.7, 38.2, 37.8, 37.1, 34.7, 34.3, 33.4, 30.8, 29.4, 27.9, 27.4, 25.6, 20.9, 19.4, 18.2, 16.1, 15.8, 15.4, 14.6; ESIMS: m/z calculated for $C_{44}H_{63}N_5O_3$ $(M+H)^+$ 710.50, found 710.65.

Preparation of succinic acid hemiester 21a: A stirred solution of alcohol **20a** (110 mg, 0.1 mmol), DMAP (19 mg, 0.1 mmol), and succinic anhydride (31 mg, 0.3 mmol) in toluene (4.0 mL) was refluxed overnight. Upon completion (TLC), the reaction mixture was concentrated *in vacuo*, diluted with water, and extracted with ethyl acetate (2 x 10.0 mL). The combined extracts were washed with brine (10.0 mL), dried over anhydrous Na_2SO_4, concentrated under reduced pressure, and purified using column chromatography (silica gel, hexanes:ethyl acetate, 1:3) to obtain 109 mg (87%) of pure succinic acid hemi ester **21a** as a white solid. Mp 122 – 125 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.07 (s, 1H), 7.73 (s, 1H), 7.58 – 7.63 (m, 2H), 7.41 – 7.47 (m, 3H), 6.71 (t, *J* = 5.9 Hz, 1H), 5.34 (s, 2H), 4.71 (s, 1H), 4.57 (s, 1H), 4.43 – 4.50 (m, 3H), 3.84 (s, 3H), 3.10 (dt, *J* = 4.3, 11.1 Hz, 1H), 2.57 – 2.69 (m, 4H), 2.32 (dt, *J* = 3.6, 12.3 Hz, 1H), 0.65 – 1.98 (m, 23H), 1.66 (s, 3H), 0.92 (s, 3H), 0.80 (s, 3H), 0.78 (s, 3H), 0.75 (s, 3H), 0.68 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) 176.6, 176.3, 171.9, 166.9, 150.9, 146.1, 144.9, 133.5, 130.0, 129.7, 128.9, 124.7, 123.4, 109.3, 81.4, 55.6, 55.5, 52.6, 50.4, 50.1, 46.9, 46.8, 42.4, 40.6, 38.4, 38.1, 37.8, 37.7, 37.0, 34.2, 34.0, 33.3, 30.8, 29.4, 29.3, 29.1, 27.8, 25.5, 23.6, 20.9, 19.4, 18.1, 16.5, 16.1, 15.7, 14.6; ESIMS: m/z 811.65 [100%, $(M+H)^+$], HRMS-ESI: calculated for $C_{48}H_{66}N_4O_7$ $[M+H]^+$ 811.5004, found 811.5038.

Preparation of succinic acid hemiester 21b: Procedure similar to that of **21a**. Yield: 80%; cream color solid; mp 130 – 132 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.60 (s, 1H), 7.33 – 7.43 (m, 5H), 6.99 (s, 1H), 6.29 (m, 1H), 5.33 (s, 2H), 4.72 (s, 1H), 4.58 (s, 1H), 4.39 – 4.50 (m, 3H), 3.55 – 3.70 (m, 2H), 3.07 – 3.18 (m, 1H), 3.05 (brs, 3H), 2.70 (m, 1H), 2.29 – 2.77 (m, 8H), 2.24 – 2.40 (m, 4H), 0.63 – 1.94 (m, 23H), 1.66 (s, 3H), 0.92 (s,

3H), 0.80 (s, 6H), 0.76 (s, 3H), 0.75 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) 176.5, 176.3, 172.6, 150.8, 145.4, 135.1, 133.8, 129.8, 129.7, 128.9, 128.7, 113.9, 109.5, 80.9, 55.6, 55.4, 50.4, 50.1, 48.6, 46.8, 43.8, 42.4, 40.7, 38.3, 38.2, 37.8, 37.7, 37.0, 34.6, 34.2, 33.4, 30.8, 30.1, 30.0, 29.7, 29.4, 27.9, 25.5, 23.6, 20.9, 19.4, 18.1, 16.5, 16.2, 15.8, 14.6; ESIMS: m/z calculated for $C_{52}H_{76}N_6O_6$ $(M+H)^+$ 881.59, found 881.58.

Preparation of succinic acid hemiester 21c: Procedure similar to that of **21a**. Yield: 83%; cream color solid; mp 142 – 145 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.61 (s, 1H), 7.36 – 7.44 (m, 5H), 6.88 (s, 1H), 6.58 (t, *J* = 5.7 Hz, 1H), 5.34 (s, 2H), 4.72 (s, 1H), 4.58 (s, 1H), 4.43 – 4.50 (m, 3H), 3.73 (brs, 4H) 3.12 (dt, *J* = 5.4, 11.0 Hz, 1H), 2.57 – 2.65 (m, 4H), 2.26 – 2.53 (m, 5H), 2.36 (s, 3H), 0.72 – 1.96 (m, 23H), 1.67 (s, 3H), 0.93 (s, 3H), 0.82 (s, 3H), 0.81 (s, 3H), 0.77 (s, 3H), 0.74 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) 176.6, 175.8, 172.3, 168.9, 150.8, 145.4, 135.1, 133.7, 129.1, 128.9, 128.9, 128.7, 123.5, 109.4, 81.1, 55.6, 55.4, 53.8, 50.4, 50.1, 48.6, 46.8, 44.7, 42.4, 40.7, 38.4, 38.1, 37.8, 37.7, 37.0, 34.5, 34.2, 33.4, 30.8, 29.8, 29.6, 29.6, 29.4, 27.9, 25.5, 23.6, 20.9, 19.4, 18.1, 16.5, 16.2, 15.8, 14.6; ESIMS: m/z calculated for $C_{52}H_{74}N_6O_6$ $(M+H)^+$ 879.57, found 879.65.

Preparation of succinic acid hemiester 21d: Procedure similar to that of **21a**. Yield: 82%; white solid; mp 114 – 116 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 9.68 (s, 1H), 7.91 (s, 1H), 7.60 (s, 1H), 7.27 – 7.39 (m, 3H), 7.20 – 7.25 (m, 2H), 6.66 (t, *J* = 5.5 Hz, 1H), 4.72 (s, 1H), 4.58 (s, 1H), 4.40 – 4.57 (m, 5H), 3.73 – 3.85 (m, 2H), 3.34 (s, 2H), 3.12 (dt, *J* = 4.2, 10.8 Hz, 1H), 2.40 – 2.68 (m, 8H), 2.34 (m, 1H), 2.28 (s, 6H), 2.05 (s, 3H), 0.72 – 1.98 (m, 23H), 1.66 (s, 3H), 0.92 (s, 3H), 0.81 (s, 9H), 0.77 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) 176.5 (2C), 172.7, 168.5, 150.8, 145.3, 140.3, 135.5, 130.3, 129.0, 128.3, 127.9, 123.0, 109.4, 80.9, 55.6, 55.4, 55.2, 53.9, 53.5, 53.1, 50.6, 50.5, 50.1, 49.4, 46.7, 44.1, 42.4, 41.4, 40.7, 39.6, 38.4, 38.2, 37.8, 37.7, 37.1, 34.6, 34.2, 33.4, 30.9, 29.4, 27.9, 25.5, 23.7, 20.9, 19.4, 18.1, 16.5, 16.2, 15.8, 14.6; ESIMS: m/z calculated for $C_{54}H_{81}N_7O_6$ $(M+H)^+$ 924.63, found 924.70.

Preparation of succinic acid hemiester 21e: Procedure similar to that of **21a**. Yield: 84%; cream color solid; mp 132 – 134 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.64 (m, 1H), 7.94 (s, 1H), 7.64 (s, 1H), 7.28 – 7.40 (m, 3H), 7.19 – 7.23 (m, 2H), 6.52 (t, *J* = 5.0 Hz, 1H), 4.72 (s, 1H), 4.59 (s, 1H), 4.38 – 4.51 (m, 5H), 3.88 – 3.92 (m, 2H), 3.38 (s, 2H), 3.11 (dt, *J* = 4.4, 11.0 Hz, 1H), 2.40 – 2.76 (m, 10H), 2.44 (s, 3H), 2.33 (m, 3H), 0.71 – 1.95 (m, 23H), 1.67 (s, 3H), 0.93 (s, 3H), 0.81 (s, 6H), 0.79 (s, 3H), 0.75 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 176.7 (2C), 172.6, 168.5, 150.7, 145.7, 141.5, 134.9, 128.9, 128.7, 128.5, 128.3, 123.5, 109.5, 80.9, 55.6, 55.4, 54.2, 53.3, 50.6, 50.4, 50.1, 50.0, 46.8, 44.0, 42.4, 40.7, 39.0, 38.3, 38.2, 37.8, 37.7, 37.1, 34.6, 34.3, 33.4, 30.8, 29.7, 29.4, 27.9, 25.5, 23.6, 20.9, 19.4, 18.1, 16.5, 16.2, 15.8, 14.6; ESIMS: m/z calculated for $C_{54}H_{79}N_7O_6$ $(M+H)^+$ 922.62, found 922.75.

Preparation of succinic acid hemiester 21f: Procedure similar to that of **21a**. Yield: 81%; yellow solid; mp 141 – 144 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.64 (d, *J* = 15.6 Hz, 1H), 7.63 (s, 1H), 7.46 – 7.52 (m, 2H), 7.34 – 7.38 (m, 3H), 6.60 – 6.69 (m, 1H), 6.40 (d, *J* = 15.5 Hz, 1H), 6.26 – 6.34 (m, 1H), 4.70 (s, 1H), 4.57 (s, 1H), 4.39 – 4.54 (m, 5H), 3.80 – 3.97 (m, 2H), 3.09 (dt, *J* = 4.1, 11.0 Hz, 1H), 2.59 – 2.70 (m, 4H), 2.22 – 2.33 (m, 1H), 0.66 – 1.91 (m, 23H), 1.65 (s, 3H), 0.91 (s, 3H), 0.80 (s, 3H), 0.79 (s, 6H), 0.71 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) 176.9 (2C), 172.2, 166.6, 150.7, 145.3, 141.8, 134.5, 129.9, 128.8, 127.9, 123.6, 119.9, 109.5, 81.4, 55.6, 55.4, 50.4, 50.0, 49.8, 46.8, 42.4, 40.7, 39.5, 38.3, 38.1, 37.8, 37.7, 37.0, 34.3, 34.2, 33.3, 30.8, 29.6, 29.3, 27.8, 25.5, 23.6, 20.9, 19.4, 18.1, 16.5, 16.2, 15.7, 14.6; ESIMS: m/z 810.75 [100%, $(M+H)^+$], HRMS-ESI: calculated for $C_{48}H_{67}N_5O_6$ $[M+H]^+$ 832.4984, found 832.5026.

Preparation of *N*-Propargyl pyrazinylbetulinamide 23: The title compound was prepared by the reaction of compound **22** (450 mg, 0.9 mmol) and propargyl amine (60 mg, 1.1 mmol) as per the general amide-coupling ***procedure A*** to yield 387 mg (80%) of **23** as a white solid. Mp 122 – 125 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.38 (s, 1H), 8.25 (s, 1H), 5.77 – 5.89 (m, 1H), 4.74 (s, 1H), 4.60 (s, 1H), 3.93 – 4.10 (m, 2H), 3.11 – 3.16 (m, 1H), 3.01 (d, *J* = 16.6 Hz, 1H), 2.36 – 2.56 (m, 2H), 2.16 – 2.20 (m, 1H), 0.73 – 1.96 (m, 19H), 1.68 (s, 3H), 1.27 (s, 3H), 1.25 (s, 3H), 1.00 (s, 6H), 0.78 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) 176.2, 159.8, 151.0, 150.8, 142.4, 141.6, 109.7, 80.5, 71.2, 55.8, 53.2, 50.3, 49.0, 48.8, 46.8, 42.7, 40.8, 39.7, 38.3, 37.9, 36.9, 33.7, 33.6, 31.7, 31.0, 29.6, 29.2, 25.8, 24.2, 21.7, 20.3, 19.8, 16.3, 15.9, 14.8; ESIMS: m/z calculated for $C_{35}H_{49}N_3O$ $(M+H)^+$ 528.81, found 528.60.

Preparation of triazole 24a: Procedure similar to that of **19a**. This compound was prepared by the reaction of alkyne **23** with azide **9a**. Yield: 82%; white solid; mp 127 – 129 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.32 (s, 1H), 8.20 (s, 1H), 7.98 (s, 1H), 7.68 (s, 1H), 7.49 – 7.60 (m, 2H), 7.45 – 7.29 (m, 3H), 6.30 (brs, 1H), 5.29 (s, 2H), 4.68 (s, 1H), 4.55 (s, 1H), 4.37 – 4.49 (m, 2H), 3.78 (s, 3H), 3.07 (dt, *J* = 4.3, 11.2 Hz, 1H), 2.93 (d, *J* = 16.4 Hz, 1H), 2.30 – 2.43 (m, 2H), 0.61 – 1.93 (m, 19H), 1.62 (s, 3H), 1.20 (s, 3H), 1.15 (s, 3H), 0.91 (s, 3H), 0.73 (s, 3H), 0.66 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 176.5, 167.2, 159.8, 151.1, 150.9, 146.2, 142.5, 141.7 (2C), 133.7 (2C), 130.2, 129.9, 129.2, 125.0, 109.7, 55.9, 53.2, 52.8, 50.3, 49.0, 48.9, 47.1, 46.9, 42.7, 40.8, 39.6, 38.4, 38.0, 36.9, 34.9, 33.7, 33.5, 31.7, 31.1, 29.6, 25.8, 24.2, 21.6, 20.3, 19.8, 16.3, 15.6, 14.8; ESIMS: m/z calculated for $C_{46}H_{60}N_6O_3$ $(M+H)^+$ 745.48, found 745.45.

Preparation of triazole 24b: Procedure similar to that of **19a**. This compound was prepared by the reaction of alkyne **23** with azide **9b**. Yield: 84%; white solid; mp 131 – 133 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.39 (d, *J* = 2.4 Hz, 1H), 8.26 (d, *J* = 2.4 Hz, 1H), 7.63 (s, 1H), 7.29 – 7.48 (m, 5H), 6.95 (brs, 1H), 6.23 – 6.30 (m, 1H), 5.31 – 5.39 (m, 2H), 4.76 (s, 1H), 4.61 (s, 1H), 4.51 (dd, *J* = 5.4, 15.1 Hz, 1H), 4.44 (dd, *J* = 5.6, 15.2 Hz, 1H), 3.39 – 3.54 (m, 2H), 3.13 (dt, *J* = 4.2, 10.9 Hz, 1H), 2.92 – 3.05 (m, 4H), 2.33 – 2.51 (m, 4H), 2.12 – 2.31 (brs, 6H), 0.73 – 1.97 (m, 19H), 1.69 (s, 3H), 1.28 (s, 3H), 1.25 (s, 3H), 0.99 (s, 3H), 0.86 (s, 3H), 0.75 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 176.2, 159.6, 150.8, 150.7, 145.0, 142.2, 141.4 (2C), 134.8, 134.0, 130.2, 128.8, 128.7, 123.2, 109.4, 55.6, 53.0, 50.0, 48.8, 48.6, 48.6, 46.6, 45.6, 42.4, 40.6, 39.4, 38.2, 37.7, 36.7, 34.7, 33.4, 33.3, 31.4, 30.9, 29.4, 25.6, 24.0, 21.4, 20.0, 19.5, 16.0, 15.4, 14.6; ESIMS: m/z calculated for $C_{50}H_{70}N_8O_2$ $(M+H)^+$ 815.57, found 815.30.

Preparation of triazole 24c: Procedure similar to that of **19a**. This compound was prepared by the reaction of alkyne **23** with azide **9c**. Yield: 84%; white solid; mp 137 – 140 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.33 (d, *J* = 2.4 Hz, 1H), 8.20 (d, *J* = 2.4 Hz, 1H), 7.55 (s, 1H), 7.29 – 7.41 (m, 5H), 6.80 (s, 1H), 6.20 - 6.30 (m, 1H), 5.35 (s, 2H), 4.70 (s, 1H), 4.56 (s, 1H), 4.46 (dd, *J* = 5.5, 15.0 Hz, 1H), 4.36 (dd, *J* = 5.5, 15.0 Hz, 1H), 3.60 (brs, 4H), 3.12 (dt, *J* = 4.3, 11.2 Hz, 1H), 3.01 (d, *J* = 16.6 Hz, 1H), 2.05 – 2.39 (m, 9H), 0.64 – 1.89 (m, 19H), 1.63 (s, 3H), 1.22 (s,

3H), 1.19 (s, 3H), 0.93 (s, 3H), 0.78 (s, 3H), 0.69 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) 176.6, 169.0, 159.8, 151.0, 150.9, 145.3, 142.5, 141.7 (2C), 134.8, 134.1, 129.9, 129.0, 128.9, 123.7, 109.7, 55.8, 54.9, 53.2, 50.3, 49.0, 48.9, 48.8, 46.9, 46.2, 42.7, 40.8, 39.6, 38.4, 37.9, 36.9, 34.9, 33.7, 33.5, 31.7, 31.1, 29.6, 25.8, 24.2, 21.6, 20.3, 19.8, 16.3, 15.6, 14.8; ESIMS: m/z 835.75 [100%, $(M+Na)^+$], HRMS-ESI: calculated for $C_{50}H_{68}N_8O_2$ $[M+H]^+$ 813.5538, found 813.5503.

Preparation of triazole 24d: Procedure similar to that of **19a**. This compound was prepared by the reaction of alkyne **23** with azide **9d**. Yield: 85%; white solid; mp 112 – 114 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 9.96 (s, 1H), 8.39 (d, *J* = 2.3 Hz, 1H), 8.26 (d, *J* = 2.4 Hz, 1H), 7.95 (s, 1H), 7.59 (s, 1H), 7.28 – 7.39 (m, 3H), 7.21 – 7.25 (m, 2H), 6.37 (s, 1H), 4.75 (s, 1H), 4.61 (s, 1H), 4.60 – 4.55 (m, 2H), 4.50 (dd, *J* = 5.4, 15.1 Hz, 1H), 4.44 (dd, *J* = 5.4, 15.1 Hz, 1H), 3.82 – 3.65 (m, 2H), 3.33 (s, 2H), 3.13 (dt, *J* = 4.3, 11.2 Hz, 1H), 3.01 (d, *J* = 16.6 Hz, 1H), 2.51 – 2.26 (m, 6H), 2.14 (s, 6H), 2.06 (s, 3H), 0.76 – 1.97 (m, 19H), 1.69 (s, 3H), 1.28 (s, 3H), 1.26 (s, 3H), 0.98 (s, 3H), 0.88 (s, 3H), 0.78 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) 176.4, 168.4, 159.6, 150.8, 150.7, 144.9, 142.2, 141.4, 140.1, 135.6, 130.5, 128.9, 128.2, 127.9, 122.9, 109.4, 56.1, 55.6, 53.9, 53.0, 52.5, 50.0, 49.2, 48.8, 48.6, 46.6, 45.0, 42.4, 41.6, 40.6, 39.9, 39.4, 38.2, 37.7, 36.7, 34.7, 33.4, 33.3, 31.4, 30.9, 29.3, 25.6, 24.0, 21.4, 20.0, 19.5, 16.1, 15.4, 14.7; ESIMS: m/z calculated for $C_{52}H_{75}N_9O_2$ $(M+H)^+$ 858.61, found 858.75.

Preparation of triazole 24e: Procedure similar to that of **19a**. This compound was prepared by the reaction of alkyne **23** with azide **9e**. Yield: 87%; cream color solid; mp 132 – 135 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 9.79 (s, 1H), 8.33 (s, 1H), 8.20 (s, 1H), 7.85 (s, 1H), 7.58 (s, 1H), 7.15 – 7.30 (m, 5H), 6.37 (s, 1H), 4.69 (s, 1H), 4.55 (s, 1H), 4.34 – 4.51 (m, 4H), 3.69 – 3.91 (m, 2H), 3.28 (s, 2H), 3.00 – 3.14 (m, 1H), 2.95 (d, *J* = 16.4 Hz, 1H), 2.14 – 2.52 (m, 13H), 0.68 – 1.93 (m, 19H), 1.63 (s, 3H), 1.21 (s, 3H), 1.20 (s, 3H), 0.92 (s, 3H), 0.79 (s, 3H), 0.72 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) 176.7, 168.9, 159.8, 150.9, 150.8, 145.6, 142.5, 141.7, 141.0, 135.4, 129.4, 129.2, 128.5, 128.3, 123.4, 109.8, 55.8, 54.9, 54.8, 53.2, 52.2, 50.2, 49.9, 48.9, 48.8, 46.9, 45.8, 42.7, 40.8, 39.7, 39.4, 38.4, 38.0, 36.9, 34.9, 33.7, 33.5, 31.7, 31.1, 29.6, 25.8, 24.3, 21.6, 20.3, 19.7, 16.4, 15.6, 14.8; ESIMS: m/z calculated for $C_{52}H_{73}N_9O_2$ $(M+H)^+$ 856.60, found 856.70.

Preparation of triazole 24f: Procedure similar to that of **19a**. This compound was prepared by the reaction of alkyne **23** with azide **9f**. Yield: 88%; white solid; mp 150 – 152 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.39 (s, 1H), 8.26 (s, 1H), 7.63 (d, *J* = 15.6 Hz, 1H), 7.61 (s, 1H), 7.45 – 7.52 (m, 2H), 7.30 – 7.39 (m, 3H), 6.26 – 6.42 (m, 3H), 4.74 (s, 1H), 4.60 (s, 1H), 4.37 – 4.56 (m, 4H), 3.84 – 3.95 (m, 2H), 3.05 – 3.17 (m, 1H), 3.00 (d, *J* = 16.5 Hz, 1H), 2.34 – 2.49 (m, 2H), 0.72 – 1.99 (m, 19H), 1.67 (s, 3H), 1.26 (s, 3H), 1.25 (s, 3H), 0.97 (s, 3H), 0.84 (s, 3H), 0.77 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) 176.9, 166.7, 159.8, 150.9, 150.8, 145.7, 142.5, 141.9, 141.7, 134.8, 130.1, 129.0, 128.1, 123.7, 120.3, 109.8, 55.8, 53.2, 50.2, 49.9, 49.0, 48.8, 46.9, 42.7, 40.8, 39.8, 39.7, 38.4, 38.0, 36.9, 35.0, 33.6, 33.5, 31.7, 31.1, 29.6, 25.8, 24.3, 21.7, 20.2, 19.7, 16.4, 15.7, 14.8; ESIMS: m/z calculated for $C_{46}H_{61}N_7O_2$ $(M+H)^+$ 744.50, found 744.55.

Preparation of *N*-Propargyl indolylbetulinamide 26: The title compound was prepared by the reaction of compound **25** (300 mg, 0.6 mmol) and propargyl amine (37.5 mg, 0.7 mmol) as per the general amide-coupling ***procedure A*** to yield 224 mg (71%) of **26** as a yellow solid. Mp 251 – 254 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 10.64 (s, 1H), 7.98 (s, 1H), 7.26 (d, *J* = 7.7 Hz, 1H), 7.20 (d, *J* = 7.8 Hz, 1H), 6.81 – 6.98 (m, 2H), 4.68 (s, 1H), 4.55 (s, 1H), 3.65 – 3.92 (m, 2H), 2.99 – 3.12 (m, 1H), 2.73 (d, *J* = 15.2 Hz, 1H), 2.50 – 2.63 (m, 1H), 2.10 – 2.18 (m, 1H), 2.03 (d, *J* = 15.1 Hz, 1H), 0.67 – 1.77 (m, 19H), 1.64 (s, 3H), 1.24 (s, 3H), 1.13 (s, 3H), 0.95 (s, 3H), 0.92 (s, 3H), 0.77 (s, 3H); ^{13}C NMR (101 MHz, DMSO-d_6): δ (ppm) 176.1, 151.5, 141.9, 136.9, 128.3, 120.6, 118.4, 117.9, 111.1, 109.9, 105.5, 82.6, 72.5, 55.6, 53.8, 50.3, 49.6, 46.9, 42.6, 41.0, 40.8, 39.6, 38.5, 38.0, 37.6, 34.6, 33.9, 32.7, 31.1, 30.9, 29.6, 28.5, 26.1, 23.3, 21.8, 19.7, 19.5, 16.9, 16.3, 15.0; ESIMS: m/z calculated for $C_{39}H_{52}N_2O$ $(M-H)^+$ 563.40, found 563.50.

Preparation of triazole 27a: Procedure similar to that of **19a**. This compound was prepared by the reaction of alkyne **26** with azide **9a**. Yield: 80%; tan color solid; mp 133 – 136 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.01 (s, 1H), 7.48 – 7.76 (m, 4H), 7.34 – 7.42 (m, 3H), 7.27 – 7.45 (m, 2H), 6.96 – 7.07 (m, 2H), 6.26 (m, 1H), 5.30 (s, 2H), 4.71 (s, 1H), 4.56 (s, 1H), 4.45 – 4.53 (m, 1H), 4.39 (dd, *J* = 5.9, 14.9 Hz, 1H), 3.79 (s, 3H), 3.12 (dt, *J* = 6.2, 12.1 Hz, 1H), 2.74 (d, *J* = 14.9 Hz, 1H), 2.33 – 2.43 (m, 1H), 2.05 (d, *J* = 14.8 Hz, 1H), 0.68 – 1.98 (m, 19H), 1.64 (s, 3H), 1.20 (s, 3H), 1.08 (s, 3H), 0.93 (s, 3H), 0.76 (s, 3H), 0.73 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) 175.3, 165.9, 149.9, 144.9, 143.9, 139.8, 135.1, 132.5, 128.9, 128.7, 127.9, 127.3, 123.8, 122.1, 119.8, 117.8, 116.8, 109.3, 108.4, 105.9, 54.6, 52.2, 51.5, 49.1, 49.0, 48.4, 45.8, 41.4, 39.7, 37.2, 37.2, 36.9, 36.2, 33.8, 33.1, 32.5, 29.8, 29.8, 28.7, 28.4, 24.7, 22.1, 20.4, 18.4, 18.2, 15.3, 14.6, 13.6; ESIMS: m/z 782.85 [100%, $(M+H)^+$]; HRMS-ESI: calculated for $C_{50}H_{63}N_5O_3$ $[M+H]^+$ 782.5004, found 782.4986.

Preparation of triazole 27f: Procedure similar to that of **19a**. This compound was prepared by the reaction of alkyne **26** with azide **9f**. Yield: 81%; tan color solid; mp 167 – 169 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.75 (s, 1H), 7.64 (d, *J* = 15.4 Hz, 1H), 7.61 (s, 1H), 7.44 - 7.54 (m, 2H), 7.33 – 7.41 (m, 4H), 7.28 – 7.32 (m, 1H), 7.00 – 7.13 (m, 2H), 6.38 (d, *J* = 15.7 Hz, 1H), 6.29 – 6.36 (m, 1H), 6.20 – 6.28 (m, 1H), 4.75 (s, 1H), 4.61 (s, 1H), 4.37 – 4.57 (m, 4H), 3.87 – 3.96 (m, 2H), 3.05 – 3.20 (m, 1H), 2.80 (d, *J* = 15.1 Hz, 1H), 2.33 – 2.50 (m, 1H), 2.11 (d, *J* = 15.1 Hz, 1H), 0.76 – 1.96 (m, 19H), 1.68 (s, 3H), 1.26 (s, 3H), 1.17 (s, 3H), 0.99 (s, 3H), 0.85 (s, 3H), 0.83 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) 177.0, 166.7, 150.9, 145.7, 141.9, 141.2, 136.4, 134.8, 130.1, 129.1, 128.5, 128.1, 123.6, 121.1, 120.2, 119.0, 118.1, 110.6, 109.9, 107.0, 55.9, 53.5, 50.3, 49.9, 49.6, 47.0, 42.7, 41.0, 39.8, 38.5, 38.2, 37.5, 35.0, 34.4, 33.8, 33.7, 31.0, 29.7, 25.9, 23.4, 21.7, 19.6, 19.4, 16.6, 15.9, 14.9; ESIMS: m/z calculated for $C_{50}H_{64}N_6O_2$ $(M+Na)^+$ 803.50, found 803.55.

Preparation of *N*-2-azidoethyl betulonamide 28: The title compound was prepared by the reaction of betulonic acid **17** (850 mg, 1.87 mmol) and 2-azidoethylamine (241 mg, 2.80 mmol) using the general amide-coupling ***procedure A*** to furnish the amide **28** (722 mg, 74%) as a white solid. Mp 82 – 84 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.94 (s, 1H), 4.72 (s, 1H), 4.58 (s, 1H), 3.32 – 3.48 (m, 4H), 3.03 – 3.15 (m, 1H), 2.35 – 2.49 (m, 3H), 0.81 – 1.95 (m, 21H), 1.66 (s, 3H), 1.05 (s, 3H), 1.00 (s, 3H), 0.96 (s, 6H), 0.91 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 218.4, 176.7, 150.9, 109.7, 55.9, 55.2, 51.4, 50.2, 50.2, 47.5, 46.9, 42.7, 40.9, 39.8, 38.9, 38.4, 38.0, 37.1, 34.4, 33.9, 31.0, 29.6, 26.8, 25.8, 21.7, 21.2, 19.8, 19.7, 16.2, 16.1, 14.8; ESIMS: m/z calculated for $C_{32}H_{50}N_4O_2$ $(M-H)^+$ 521.39, found 521.20.

Preparation of triazole 29a: Procedure similar to that of **19a**. This compound was prepared by the reaction of azide **28** with alkyne **13a**. Yield: 79%; off white solid; mp 108 – 111 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.86 (s, 1H), 7.61 (s, 1H), 7.20 – 7.40 (m, 5H), 6.40 (brs, 1H), 4.73 (s, 1H), 4.53 – 4.61 (m, 3H), 4.35 – 4.50 (m, 2H), 3.69 – 3.79 (m, 2H), 3.41 (s, 2H), 3.07 (m, 1H), 2.27 – 2.63 (m, 12H), 2.14 (s, 3H), 0.83 – 1.99 (m, 22H), 1.66 (s, 3H), 1.04 (s, 3H), 1.00 (s, 3H), 0.96 (s, 3H), 0.94 (s, 3H), 0.91 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) 218.1, 176.9, 168.3, 150.7, 145.7, 139.5, 135.6, 131.3, 128.9, 128.3, 127.8, 123.4, 109.4, 56.1, 55.6, 54.9, 53.3, 53.1, 49.9, 49.8, 47.3, 46.5, 44.9, 42.4, 41.8, 40.7, 39.6, 39.3, 38.2, 37.6, 36.9, 35.3, 34.1, 33.7, 33.4, 30.8, 29.6, 29.4, 26.6, 25.6, 21.5, 20.9, 19.6, 19.4, 15.9, 15.9, 14.5; ESIMS: m/z 822.60 [100%, $(M+H)^+$]; HRMS-ESI: calculated for $C_{50}H_{75}N_7O_3$ $[M+H]^+$ 822.6004, found 822.6025.

Preparation of triazole 29b: Procedure similar to that of **19a**. This compound was prepared by the reaction of azide **28** with alkyne **13b**. Yield: 86%; cream color solid; mp 115 – 117 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 10.23 (m, 1H), 7.94 (s, 1H), 7.60 (s, 1H), 7.29 – 7.37 (m, 3H), 7.21 – 7.25 (m, 2H), 6.05 (t, *J* = 5.7 Hz, 1H), 4.73 (s, 1H), 4.59 (s, 2H), 4.57 (s, 1H), 4.38 – 4.52 (m, 2H), 3.78 (q, *J* = 5.7 Hz, 2H), 3.41 (s, 2H), 3.07 (dt, *J* = 4.3, 11.2 Hz, 1H), 2.31 – 2.62 (m, 10H), 3.69 (s, 3H), 0.87 – 1.66 (m, 22H), 1.66 (s, 3H), 1.04 (s, 3H), 1.00 (s, 3H), 0.95 (s, 6H), 0.91 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) 218.1, 176.9, 168.2, 150.6, 145.3, 140.4, 135.3, 129.5, 128.9, 128.3, 128.0, 122.9, 109.5, 55.6, 54.9, 54.8, 54.6, 52.1, 49.9, 49.9, 49.6, 47.3, 46.5, 45.7, 42.4, 40.6, 39.6, 39.1, 38.2, 37.6, 36.9, 35.0, 34.1, 33.6, 33.4, 30.7, 29.4, 26.6, 25.6, 21.4, 20.9, 19.6, 19.4, 15.9, 15.9, 14.5; ESIMS: m/z 820.60 [100%, $(M+H)^+$]; HRMS-ESI: calculated for $C_{50}H_{73}N_7O_3$ $[M+H]^+$ 820.5848, found 820.5855.

Preparation of triazole 29c: Procedure similar to that of **19a**. This compound was prepared by the reaction of azide **28** with alkyne **13c**. Yield: 81%; white solid; mp 155 – 158 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.62 (d, *J* = 15.9 Hz, 1H), 7.60 (s, 1H), 7.44 – 7.51 (m, 2H), 7.31 – 7.39 (m, 3H), 6.55 – 6.66 (m, 1H), 6.43 (d, *J* = 15.6 Hz, 1H), 6.12 – 6.20 (m, 1H), 4.71 (s, 1H), 4.62 (d, *J* = 5.5 Hz, 2H), 4.57 (s, 1H), 4.39 – 4.53 (m, 2H), 3.68 – 3.80 (m, 2H), 2.97 – 3.09 (m, 1H), 2.29 – 2.53 (m, 3H), 0.82 – 1.90 (m, 21H), 1.64 (s, 3H), 1.03 (s, 3H), 0.99 (s, 3H), 0.93 (s, 3H), 0.92 (s, 3H), 0.90 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) 218.5, 177.2, 166.4, 150.8, 145.2, 141.6, 134.8, 130.1, 129.0, 128.0, 123.5, 120.5, 109.8, 55.8, 55.2, 50.2, 50.1, 49.9, 47.5, 46.8, 42.7, 40.9, 39.8, 39.4, 38.4, 37.8, 37.1, 35.3, 34.4, 33.9, 33.6, 30.9, 29.6, 26.8, 25.8, 21.7, 21.2, 19.8, 19.6, 16.2, 16.2, 14.7; HRMS-ESI: calculated for $C_{44}H_{61}N_5O_3$ $[M+H]^+$ 708.4847, found 708.4840.

Preparation of 30a: Procedure similar to that of **20a**. Yield: 86%; pale yellow solid; mp 116 – 118 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 10.21 (brs, 1H), 7.92 (s, 1H), 7.61 (s, 1H), 7.33 – 7.43 (m, 2H), 7.28 – 7.32 (m, 1H), 7.19 – 7.25 (m, 2H), 6.21 (brs, 1H), 4.73 (s, 1H), 4.58 (s, 1H), 4.53 – 4.57 (m, 2H), 4.33 – 4.51 (m, 2H), 3.74 (q, *J* = 5.5 Hz, 2H), 3.38 (s, 2H), 3.16 (dd, *J* = 5.0, 11.2 Hz, 1H), 3.07 (dt, *J* = 3.7, 11.2 Hz, 1H), 2.36 – 2.51 (m, 5H), 2.25 (brs, 6H), 2.12 (s, 3H), 0.64 – 1.91 (m, 24H), 1.66 (s, 3H), 0.94 (s, 3H), 0.93 (s, 3H), 0.91 (s, 3H), 0.80 (s, 3H), 0.73 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) 176.9, 168.2, 150.8, 145.9, 139.7, 135.7, 130.9, 128.9, 128.2, 127.8, 123.2, 109.4, 78.8, 56.2, 55.6, 55.4, 53.8, 52.8, 50.6, 50.0, 49.6, 46.6, 45.1, 42.4, 41.8, 40.7, 39.2, 38.8, 38.7, 38.2, 37.5, 37.2, 35.3, 34.4, 33.4, 30.8, 29.6, 29.4, 27.9, 27.4, 25.6, 20.9, 19.4, 18.3, 16.1, 15.4, 14.7; ESIMS: m/z 824.75 [100%, $(M+H)^+$]; HRMS-ESI: calculated for $C_{50}H_{77}N_7O_3$ $[M+Na]^+$ 846.5980, found 846.5954.

Preparation of 30b: Procedure similar to that of **20a**. Yield: 89%; pale orange solid; mp 129 – 131 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 10.22 (t, *J* = 5.3 Hz, 1H), 7.95 (s, 1H), 7.60 (s, 1H), 7.33 – 7.37 (m, 2H), 7.28 – 7.31 (m, 1H), 7.21 – 7.24 (m, 2H), 6.00 – 6.10 (m, 1H), 4.73 (s, 1H), 4.56 – 4.60 (m, 3H), 4.39 – 4.52 (m, 2H), 3.77 (q, *J* = 5.7 Hz, 2H), 3.42 (s, 2H), 3.16 (dd, *J* = 5.0, 11.2 Hz, 1H), 3.06 (dt, *J* = 3.8, 11.1 Hz, 1H), 2.24 – 2.61 (m, 10H), 2.29 (s, 3H), 0.65 – 1.92 (m, 23H), 1.66 (s, 3H), 0.94 (s, 6H), 0.90 (s, 3H), 0.80 (s, 3H), 0.74 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) 176.9, 168.1, 150.6, 145.2, 140.5, 135.3, 129.4, 128.9, 128.3, 128.0, 122.9, 109.5, 78.8, 55.7, 55.4, 54.7, 54.6, 51.9, 50.6, 49.9, 49.6, 46.6, 45.6, 42.4, 40.7, 39.1, 38.8, 38.7, 38.2, 37.6, 37.2, 35.0, 34.4, 33.4, 30.8, 29.6, 29.4, 27.9, 27.4, 25.6, 20.9, 19.4, 18.3, 16.1, 15.4, 14.6; ESIMS: m/z 822.80 [100%, $(M+H)^+$]; HRMS-ESI: calculated for $C_{50}H_{75}N_7O_3$ $[M+Na]^+$ 844.5824, found 844.5885.

Preparation of 30c: Procedure similar to that of **20a**. Yield: 91%; white solid; mp 163 – 166 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.63 (d, *J* = 15.6 Hz, 1H), 7.59 (s, 1H), 7.46 – 7.50 (m, 2H), 7.33 – 7.39 (m, 3H), 6.50 (brs, 1H), 6.41 (d, *J* = 15.6 Hz, 1H), 6.10 (brs, 1H), 4.72 (s, 1H), 4.62 (d, *J* = 5.8 Hz, 2H), 4.57 (s, 1H), 4.37 – 4.52 (m, 2H), 3.76 (q, *J* = 5.6 Hz, 2H), 3.11 – 3.20 (m, 1H), 3.04 (dt, *J* = 4.0, 12.0 Hz, 1H), 2.42 (dt, *J* = 3.6, 12.7 Hz, 1H), 0.60 – 1.89 (m, 24H), 1.64 (s, 3H), 0.93 (s, 3H), 0.92 (s, 3H), 0.89 (s, 3H), 0.79 (s, 3H), 0.73 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ (ppm) 177.0, 166.2, 150.6, 144.9, 141.3, 134.6, 129.8, 128.8, 127.8, 123.2, 120.4, 109.5, 78.9, 55.6, 55.3, 50.6, 49.9, 49.7, 46.6, 42.4, 40.7, 39.2, 38.8, 38.7, 38.2, 37.6, 37.2, 34.9, 34.4, 33.4, 30.8, 29.4, 28.0, 27.4, 25.5, 20.9, 19.4, 18.3, 16.1, 15.4, 14.6; ESIMS: m/z 710.65 [100%, $(M+H)^+$]; HRMS-ESI: calculated for $C_{44}H_{63}N_5O_3$ $[M+Na]^+$ 732.4823, found 732.4836.

Cell Viability Assay: Human pancreatic cancer MIAPaCa-2 cells were purchased from ATCC. Cells were maintained in D-MEM supplemented with 10% FBS, 2.5% horse serum, and 1% Penicillin Streptomycin in a humidified atmosphere of 5% CO_2 at 37 °C. Murine breast cancer 4T1 cells were purchased from ATCC. Cells were maintained in RPMI-1640 supplemented with 10% FBS and 1% Penicillin Streptomycin in a humidified atmosphere of 5% CO_2 at 37 °C. Cells were seeded in 96 well plates at a density of 5 x 10^4 cells/mL, 100µL/well incubated for 18-24 hours, then exposed to compounds starting at a concentration of 50 µM and serial diluted. Compounds were added in duplicate and exposed for 72 hours. Each IC_{50} was reported as an average of a minimum of three trials. Compounds were dissolved in DMSO at a concentration of 50 mM and diluted into the appropriate media 1:1000. The final concentration of DMSO was kept below 0.1%. Furthermore, DMSO was added as a negative control. Cellular viability was determined using MTT (3-(4, 5-dimethylthiazolyl-2)-2, 5-diphenyltetrazolium bromide). MTT was dissolved in 1X PBS solution (5 mg/mL) and 10 µL was added to each well. After 4 hours of incubation, cells were lysed with 100 µL of a SDS (sodium dodecyl sulfate) solution (100 mg/mL of 0.01 N HCl) and incubated for an additional 4 hours. The absorbance of each well was then measured using a microplate reader at 570 nm. Control wells absorbance was defined as 100% viability and all of the tested compounds were expressed as percentage relative to the control.

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Supplementary Data

Supplementary data associated with this article can be found in the online version, at XXX.

References

1. (a) Jager, S.; Trojan, H.; Kopp, T.; Laszczyk, M. N.; Scheffler, A. *Molecules* **2009**, *14*, 2016-2031. (b) Hayek, E. W. H.; Jordis, U.; Moche, W.; Sauter, F. *Phytochem.* **1989**, *28*, 2229-2242.
2. (a) Jain, A.; Srivastava, S. K. *Indian J. Pharm. Sci*. **1984**, *46*, 161-162. (b) Batta, A. K.; Rangaswami, S. *Phytochem.* **1973**, *12*, 214-16.
3. For general reviews refer:
(a) Zhang, D. M.; Xu, H. G.; Wang, L.; Li, Y. J.; Sun, P. H.; Wu, X. M.; Wang, G. J.; Chen, W. M.; Ye, W. C. *Med. Res. Rev.* **2015**, *35*, 1127-1155.
(b) Seyed, M. A.; Jantan, I.; Vijayaraghavan, K.; Nasir, S.; Bukhari, A. *Chem. Biol. Drug Design* **2015**, *87*, 517-536.
(c) Lee, S. Y.; Kim, H. H.; Park, S. U.; *EXCLI J.* **2015**, *14*, 199-203.
(d) Periasamy, G.; Teketelew, G.; Gebrelibanos, M.; Sintayehu, B.; Gebrehiwot, M.; Karim, A.; Geremedhin, G. *Arch. Appl. Sci. Res.* **2014**, *6*, 47-58.
(e) Jonnalagadda, S. C.; Corsello, M. A.; Sleet, C. E. *Anti-Cancer Agents Med. Chem.* **2013**, *13*, 1477-1499.
(f) Mullauer F. B.; Kessler J. H.; Medema J. P. *Anti Cancer Drugs* **2010**, *21*, 215-227.
(g) Fulda, S. *Int. J. Mol. Sci*. **2008**, *9*, 1096-1107.
(h) Sami, A.; Taru, M.; Salme, K.; Jari, Y. K. *Eur. J. Pharmaceutical Sci.* **2006**, *29*, 1-13.
(i) Tolstikov, G. A.; Flekhter, O. B.; Shultz, E. E.; Baltina, L. A.; Tolstikov, A. G. *Chem. Sus. Dev.* **2005**, *13*, 1-29.
(j) Yu, D.; Wild, C. T.; Martin, D. E.; Morris-Natschke, S. L.; Chen, C-H.; Allaway, G. P.; Lee, K-H. *Exp. Op. Invest. Drugs.* **2005**, *14*, 681-693.
(k) Yogeeswari, P.; Sriram, D. *Curr. Med. Chem.* **2005**, *12*, 657-666.
4. (a) Fulda, S.; Kroemer, G. *Drug Discovery Today* **2009**, *14*, 885-890.
(b) Schmidt, M. L.; Kuzmanoff, K. L.; Ling-Indeck, L.; Pezzuto, J. M. *Eur. J. Cancer* **1997**, *33*, 2007–2010.
(c) Pisha, E.; Chai, H.; Lee, I. S.; Chagwedera, T. E.; Farnsworth, N. R.; Cordell, G. A.; Beecher, C. W. W.; Fong, H. H. S.; Kinghorn, A. D.; Brown, D. M.; Wani, M. C.; Wall, M. E.; Hieken, T. J.; Das Gupta, T. K.; Pezzuto, J. M. *Nature Med.* **1995,** *1*, 1046–1051.
5. Zuco, V.; Supino, R.; Righetti, S. C.; Cleris, L.; Marchesi, E.; Gambacorti-Passerini, C.; Formelli, F. *Cancer Lett.* **2002**, *175*, 17–25.
6. Yi, J.; Zhu, R.; Wu, J.; Wu, J.; Xia, W.; Zhu, L.; Jiang, W.; Xiang, S.; Tan, Z. *Pharmacological Rep.* **2016**, *68*, 95-100.
7. (a) Zhao, H.; Zheng, Q.; Hu, X.; Shen, H.; Li, F. *Life Sci.* **2016**, *144*, 185-193.
(b) Zhao, H.; Liu, Z.; Liu, W.; Han, X.; Zhao, M. *Intl. Immunopharmacol.* **2016**, *30*, 50-56.
8. (a) Lugemwa, F. N.; Huang, F. Y.; Bentley, M. D.; Mendel, M. J.; Alford, A. R. *J. Agri. Food Chem.* **1990**, *38*, 493-496.
(b) Miles, D. H.; Tunsuwan, K.; Chittawong, V.; Hedin, P. A.; Kokpol, U. *J. Agri. Food Chem.* **1994**, *42*, 1561-1562.
(c) Huang, F. Y.; Chung, B. Y.; Bentley, M. D.; Alford, A. R. *J. Agri. Food Chem.* **1995**, *43*, 2513-2516.
9. Auclair, N.; Kaboorani, A.; Riedl, B.; Landry, V. *Industrial Crops and Prod.* **2015**, *76*, 530-537.
10. Gorbunova, M. N.; Krainova, G. F.; Tolmacheva, I. A.; Grishko, V. V. *Russ. J. Appl. Chem.* **2012**, *85*, 1137-1141.
11. (a) Zhao, J.; Schlaad, H.; Weidner, S.; Antonietti, M. *Polym. Chem.* **2012**, *3*, 1763-1768.
(b) Jeromenok, J.; Bohlmann, W.; Antonietti, M.; Weber, J. *Macromol. Rapid Commun.* **2011**, *32*, 1846-1851.
12. For general reviews refer:
(a) Basavaiah, D.; Reddy, B. S.; Badsara, S. S. *Chem. Rev.* **2010**, *110*, 5447–5674.
(b) Declerck, V.; Martinez, J.; Lamaty F. *Chem. Rev*. **2009**, *109*, 1-48.
(c) Basavaiah, D.; Rao, A. J.; Satyanarayana, T. *Chem. Rev.* **2003**, *103*, 811-891.
13. For general reviews refer:
(a) Banfi, L.; Riva, R. *Org. Reactions* **2005**, *65*, 1-141.
(b) Domling, A.; Ugi, I. *Angew Chem. Int. Ed.* **2000**, *39*, 3168-3210.
14. For general reviews refer:
(a) Kacprzak, K.; Skiera, I.; Piasecka, M.; Paryzek, Z. *Chem. Rev.* **2016**, *116*, 5689-5743.
(b) Tiwari, V. K.; Mishra, B. B.; Mishra, K. B.; Mishra, N.; Singh, A. S.; Chen, X. *Chem. Rev.* **2016**, *116*, 3086-3240.
(c) Alonso, F.; Moglie, Y.; Radivoy, G. *Acc. Chem. Res.* **2015**, *48*, 2516-2528.
(d) Kolb, H. C.; Finn, M. G.; Sharpless, K. B. *Angew. Chem. Int. Ed*. **2001**, *40*, 2004-2021.
15. (a) Alam, M. A.; Arora, K.; Gurrapu, S.; Jonnalagadda, S. K.; Nelson, G. L.; Kiprof, P.; Jonnalagadda, S. C.; Mereddy, V. R. *Tetrahedron*. **2016**, *72*, 3795-3801.
(b) Suman, P.; Patel, B. P.; Kasibotla, A. V.; Solano, L. N.; Jonnalagadda, S. C. *J. Organomet. Chem.* **2015**, *798*, 125-131.
(c) Kumar, J. S.; Alam, M. A.; Gurrapu, S.; Nelson, G. L.; Williams, M.; Corsello, M. A.; Johnson, J. L.; Jonnalagadda, S. C.; Mereddy. V. R. *J. Het. Chem.* **2013**, *50*, 814-820.
(d) Gunasekera, D. S.; Gerold, D. A.; Aalderks, N. A.; Jonnalagadda, S. C.; Kiprof, P.; Zhdankin, V. V.; Reddy, M. V. R. *Tetrahedron* **2007**, *63*, 9401-9405.
(e) Reddy, V. J.; Chandra, J. S.; Reddy, M. V. R. *Org. Biomol. Chem.* **2007**, *5*, 889-891.
(f) Ramachandran, P. V.; Prabhudas, B.; Chandra, J. S.; Reddy, M. V. R.; Brown, H. C. *Tetrahedron Lett.* **2004**, *45*, 1011-1013.
16. (a) Tekkam, S.; Alam, M. A.; Just, M. J.; Johnson, J. L.; Jonnalagadda, S. C.; Mereddy, V. R. *Anti-Cancer Agents in Med. Chem*. **2013**, *13*, 1514-1530.
(b) Kumar, J. S.; Bashian, C. M.; Corsello, M. A.; Jonnalagadda, S. C.; Mereddy, V. R. *Tetrahedron Lett.* **2010**, *51*, 4482-4485;
(c) Jonnalagadda, S. C.; Verga, S. R.; Patel, P. D.; Reddy, A. V.; Tekkam, S.; Scott, P. M.; Mereddy, V. R. *Appl. Organomet. Chem.* **2010**, *24*, 294-300.
17. (a) Kumar, J. S.; Jonnalagadda, S. C.; Mereddy, V. R. *Tetrahedron Lett.* **2010**, *51*, 779-782.
(b) Jonnalagadda, S. C.; Cruz, J.; Connell, R. J.; Scott, P.; Mereddy, V. R. *Tetrahedron Lett.* **2009**, *50*, 4314-4317.
18. Gurrapu, S.; Walsh, W. J.; Brooks, J. M.; Jonnalagadda, S. C.; Mereddy, V. R. *Nat. Prod., Ind. J.* **2012**, *8*, 115-120.
19. (a) Xiao, S.; Wang, Q.; Si, L.; Zhou, X.; Zhang, Y.; Zhang, L.; Zhou, D. *Eur. J. Med. Chem.* **2016**, *124*, 1-9.
(b) Spivak, A. Y.; Gubaidullin, R. R.; Galimshina, Z. R.; Nedopekina, D. A.; Odinokov, V. N. *Tetrahedron* **2016**, *72*, 1249-1256.
(c) Khan, I.; Guru, S. K.; Rath, S. K.; Chintakindi, P. K.; Singh, B.; Koul, S.; Bhushan, S.; Sangwan, P. L. *Eur. J. Med. Chem.* **2016**, *108*, 104-116.

(d) Bhunia, D.; Pallavi, P. M. C.; Bonam, S. R.; Reddy, S. A.; Verma, Y.; Halmuthur, M. S. K. *Arch. Pharm. Chem. Life Sci.* **2015**, *348*, 689-703.
(e) Chakraborty, B.; Dutta, D.; Mukherjee, S.; Das, S.; Maiti, N. C.; Das, P.; Chowdhury, C. *Eur. J. Med. Chem.* **2015**, *102*, 93-105.
(f) Thi, T. A. D.; Tuyet, N. T. K.; The, C. P.; Nguyen, H. T.; Thi, C. B.; Phuong, H. T.; Boi, L. V.; Nguyen, T. V.; D'hooghe, M. *Tetrahedron Lett.* **2015**, *56*, 218-224.
(g) Shi, W.; Tang, N.; Yan, W-D. *J. Asian Nat. Prod. Res.* **2015**, *17*, 159-169.
(h) Bori, I. D.; Hung, H. Y.; Qian, K.; Chen, C. H.; Morris-Natschke, S. L.; Lee, K. H. *Tetrahedron Lett.* **2012**, *53*, 1987-1989.
(i) Csuk, R.; Barthel, A.; Sczepek, R.; Siewert, B.; Schwarz, S. *Arch. Pharm. Chem. Life Sci.* **2011**, *344*, 37-49.

20. Beld, J.; Cang, H.; Burkart, M. D. *Angew. Chem. Int. Ed.* **2014**, *53*, 14456-14461.
21. Suman, P.; Srikanth, D.; Rajukumar, K.; Murthy, T. R.; Dayakar, Ch.; Kishor, K.; Addlagatta, A.; Kalivendi, S. V.; Raju, B. C. *Eur. J. Med. Chem.* **2015**, *90*, 603-619.
22. (a) Vik, M.; Micolova, P.; Urban, M.; Kvasnica, M.; Saman, D.; Saren, J. *J. Radioanal. Nucl. Chem.* **2016**, *308*, 733-739.
(b) Soural, M.; Hodon, J.; Dickinson, N. J.; Sidova, V.; Gurska, S.; Dzubak, P.; Hajduch, M.; Sarek, J.; Urban, M. *Bioconjugate Chem.* **2015**, *26*, 2563-2570.
(c) Zhang, H.; Wang, Y.; Zhu, P.; Liu, J.; Xu, S.; Yao, H.; Jiang, J.; Ye, W.; Wu, X.; Xu, J. *Eur. J. Med. Chem.* **2015**, *97*, 235-244.
(d) Havikko, R.; Nasereddin, A.; Sacerdoti-Sierra, N.; Kopelyanskiy, D.; Alakurtti, S.; Tikka, M.; Jaffe, C. L.; Yli-Kauhluoma, J. *MedChemCommun*, **2014**, *5*, 445-451.
(e) Xu, J.; Li, Z.; Luo, J.; Yang, F.; Liu, T.; Liu, M.; Qiu, W-W.; Tang, J. *J. Med. Chem.* **2012**, *55*, 3122-3134.
(f) Urban, M.; Sarek, J.; Kvasnica, M.; Tislerova, I.; Hajduch, M. *J. Nat. Prod.* **2007**, *70*, 526-532.

23. (a) Kazakova, O. B.; Khusutdinova, E. F.; Suponitskii, K. Y. *J. Str. Chem.* **2011**, *52*, 1030-1032.
(b) Kumar, V.; Rani, N.; Aggarwal, P.; Sanna, V. K.; Singh, A. T.; Jaggi, M.; Joshi, N.; Sharma, P. K.; Irchhaiya, R.; Burman, A. C. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 5058-5062.
(c) Mukherjee, R.; Srivastava, S. K.; Siddiqui, M. J. A.; Jaggi, M.; Singh, A. T.; Vardhan, A.; Singh, M. K.; Rajendran, P.; Jajoo, H. K.; Burman, A. C.; Kumar, V.; Rani, N.; Agarwal, S. K. *PCT Int. Appl.* (**2006**), WO2006085334 A2 20060817.