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LETTERS

Design, synthesis and Structure-Activity Relationship of novel Phenolic based Pyrimidine hybrids from Cashew Nut Shell Liquid (CNSL) components as potential antitumor agents

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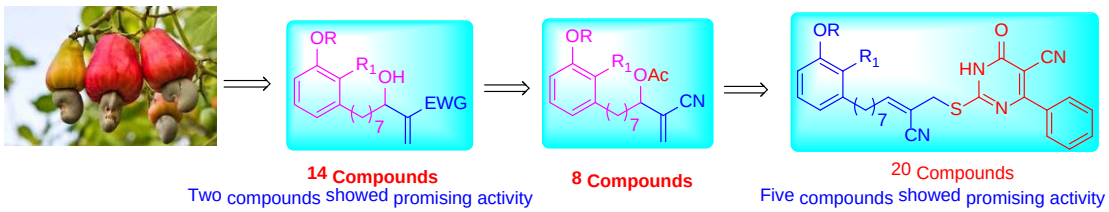
ABSTRACT



Herein we describe a simple method for the synthesis of Baylis-Hillman adducts and their acetates by utilizing inexpensively available cashew nut shell liquid (CNSL) natural resource. Furthermore, by using a molecular hybridization approach, a series of novel pyrimidine scaffolds (**15a-15t**) were synthesized by utilizing Baylis-Hillman acetate derivatives from cashew nut shell liquid (CNSL). All the newly synthesized compounds were screened for their *in vitro* antitumor activity. Baylis-Hillman compounds **5b** and **5h** showed promising anticancer activity against MCF-7. Among pyrimidine derivatives, compounds **15i**, **15j** and **15l** showed promising activity against HEP-G2, whereas compounds **15j**, **15k**, **15l** and **15m** showed promising activity against MCF-7. In addition, compound **15m** showed significant activity against K562 when compared with the standard. The structure-activity relationship (SAR) analysis suggests that the length of the carbon chain of phenyl ring played an important role in the potency of activity.

Keywords: Cashew nut shell liquid, Baylis-Hillman adducts, pyrimidine derivatives, Anti-cancer activity

INTRODUCTION

Investigation of new chemical entities for the treatment of cancer is an emerging area in drug discovery. Cancer is one of the fatal causes of death globally both in the developed and developing countries.[1] Cancer is the second leading cause of death and the number of new cases is increasing mainly due to environmental prospects.[2] The World Health Organization (WHO) stated approximately seven million people deceased from cancer per year and it is estimated that 12 million deaths could occur due to cancer in 2030.[3] Nature has been an essential source of new drug candidates since ancient times and a large number of the anticancer agents approved are either natural product resources or their analogues.[4] Therefore, natural products represent an inspiring resource of drug leads for the designing of new pharmaceuticals with the improved medicinal profile. Hence, there is an urgent need to search for some newer, safer and more effective anticancer agents to improve both life expectancy and quality of a patient's life.

The development of environmentally benign and sustainable methodologies for high value-added chemicals from renewable natural resources has received great interest in various fields of synthetic organic community in both academic and industrial

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research due to recent economic and public health burden views.[5,6] Among various renewable resources, cashew nut shell liquid (CNSL), low-cost agricultural byproduct and waste in cashew processing industry, is one of the most commonly used renewable resources.[6] The Food and Agricultural Organization reported that large amounts of cashew nut shell liquid (CNSL), over 0.3 million tons per year, are produced in Asia, Africa, and South America, especially in Brazil, which is a waste and non-edible natural resource.[7] However, disposal of these industrial feedstock waste to the soil or landfill causes huge environmental problems. To reach these global targets, development of low-cost impact technologies for the utilization of CNSL has become increasingly urgent.

Generally, CNSL contains phenolic derivatives with meta-substituted saturated/unsaturated aliphatic long chain. The major components in CNSL are anacardic acid, cardanol, cardol and 2-methylcardol (Figure 1), in which their composition dependson the basis of the mode of extraction.[8] CNSL liquid is classified into two types: natural CNSL and technical CNSL. Natural CNSL is obtained by solvent extraction method or cold method, which contains mainly anacardic acid (60-65%), cardanol (10%), cardol (15-20%) and smaller amounts of 2-methyl cardol.[9] However, technical CNSL obtained through roasting or hot oil process contains cardanol as the main component generated via decarboxylation of anacardic acid. The proportion of CNSL components is cardanol (60-65%), cardol (15-20%) and a smaller amount of methyl cardol (Figure 1).[10]

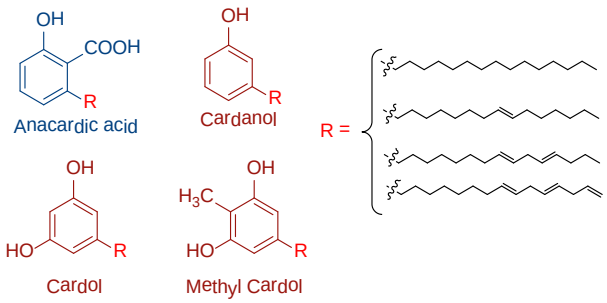


Figure 1. Components of CNSL.

CNSL based components have wide applications in industry as raw material for the fine chemical process, epoxyresins, pesticides, varnishes, adhesives, bio-based polymers, lamination, automobile and as an additive in the surface coating as well as key precursors in pharmaceutical applications.[11] CNSL constituents cardanol and anacardic acid derivatives play a diverse role in the field of medicinal chemistry due to its various biological activities, such as antitumor,[12a] insecticidal,[12b] enzyme inhibitor,[12c] antioxidant,[12d] antibacterial,[12e] antifungal,[12f] and larvicide activity.[12g] The chemical components of CNSL have free phenolic OH groups and double bonds on the side chain attached to a phenolic ring susceptible to chemical modification.[13] The literature describes many selective chemical modifications on CNSL components, including alkylation, acylation, allylation, hydrogenation, nitration, halogenation, epoxidation, amination, and cylcocarbonylation.[14] The mixture plays a major role in organic synthesis and it is being used as a building block for the academic and industrial research, and it replaces phenol in many reactions with better results due to its low-cost availability, biodegradability, and renewable natural material.[15] Therefore, based on this versatile chemical structure, much attention has been drawn towards CNSL.

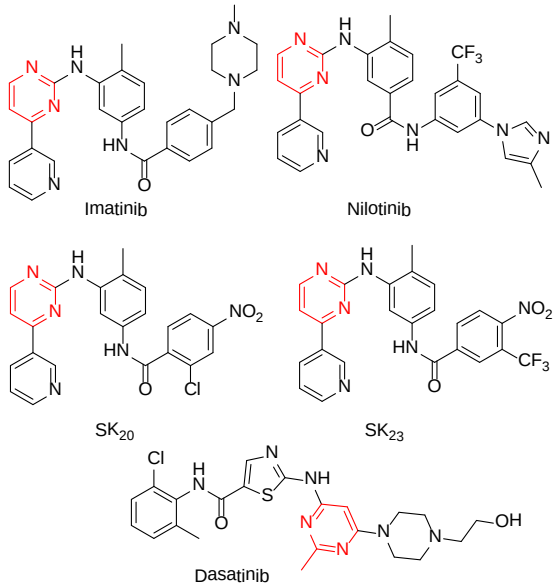


Figure 2. Representative biologically active pyrimidine derivatives.

On the other hand, the structural diversity and biological importance of nitrogen containing heterocycles, including pyrimidine, piperidine, triazole, peptide, and tetrazole have made them attractive targets for synthesis over they ears because they are found in many natural products with biological importance and they have been intensively used as a versatile scaffolds for drug discovery.[16] Amongst the numerous scaffolds, pyrimidine and their derivatives have received much attention in various fields of synthetic organic chemistry that can be renewed into useful molecules.[17] The pyrimidine scaffold is constituent of a large number of medicines (Figure 2) and can display a broad spectrum of interesting pharmacological and physiological activities, including antiviral,[18a] antibacterial,[18b] antifungal,[18c] anti-filarial,[18d] antioxidant,[18e] anthelmintic,[18f] anticancer,[18g] anti-HIV,[18h] antimalarial,[18i] and antitubercular[18j] activities. For example Imatinib is a pyrimidine scaffold known as a tyrosine kinase inhibitor and isl icensed for the treatment of patients with chronic myeloid leukemia and gastrointestinal stromal tumors.[19] Although many synthetic methods have been developed for the preparation of pyrimidine scaffolds, the development of novel synthetic methodsis in great progress.

Morita-Baylis-Hillman reaction is a powerful C-C bond forming method for generating highly functionalized molecules in an atom-economical manner from an activated alkene and a carbonyl compound under the influence of suitable catalyst such as tertiary amine or phosphine.[20] Baylis-Hillman adducts holding versatile functionalities i.e. alkene, hydroxyl, and an electron withdrawing functional group in close proximity are valuable structural motifs for diverse organic reactions and transformations.[20] These adducts have also been used as

valuable synthons for the architecture of representative natural products, unnatural products, useful heterocycles and bioactive molecules.[21] Recently, various promising functionalized molecular frameworks derived from Baylis-Hillman reaction and their acetates displayed good biological profile.[22]

To the best of our knowledge, no report has yet explored the Baylis-Hillman reaction of cardanol and anacardic acid. On this basis, we found valuable to develop new chemical entities for new drug design utilizing cashew nut shell liquid (CNSL). In continuation of our ongoing efforts endowed with the discovery of potential chemotherapeutic agents,[23] we investigated facile route for the synthesis of novel Baylis-Hillman adducts and their acetates from aldehydes derived from inexpensive cardanol and anacardic acid. Further, based on the concept of molecular hybridization and taken into account the Imatinib molecular framework in the treatment of cancer, we report herein the synthesis of novel pyrimidine probes by using Baylis-Hillman acetates derived from cardanol and anacardic acid.

RESULTS AND DISCUSSION

Synthesis of Baylis-Hillman adducts and acetates from CNSL

Initially, the required cardanol aldehyde (2) was synthesized from cardanol ene-mixture (**1**), which was isolated from commercially available cashew nut shell liquid (CNSL) by vacuum distillation according to the reported method.[24] Next, cardanol ene-mixture (**1**) was subjected to ozone treatment in the presence of ethyl acetate at -78 ^{o}C for 3 h, followed by reduced with Zn in acetic acid furnished cardanol aldehyde (2, C7-CHO) in 78% yield.[25] Cardanol aldehyde (**2**) was alkylated using alkyl halides such as methyl iodide, propyl bromide, butyl bromide, pentyl bromide and hexyl bromide in presence of K_2CO_3 in acetone to provide the corresponding alkylated cardanol aldehydes (**3a-3e**) in 83-90% yield (Scheme 1). Anacardic acid ene-mixture (**6**) was obtained from cashew nut by solvent extraction according to the reported procedure.[26] After that, the methylated anacardic acid aldehyde (**8**, C7-CHO) was achieved by the same method used to furnish cardanol aldehyde (**2**) as outlined in Scheme 2.[25]

Initial investigations led to the selection of cardanol aldehyde (**2**) and acrylonitrile (**4a**) as model substrates for optimization of reaction conditions and the results are outlined in Table 1. To select a favorable reaction conditions, we initiated our study by testing the applicability of the catalyst (DABCO, 10 mol%) with a variety of solvents at room temperature. From this screening, we obtained an excellent yield of BH adduct (**5a**) with the reaction performed without any additional solvent at room temperature after 12 h. Therefore, an initial reaction was executed using THF:H_2O (1:1) with acrylonitrile and DABCO (10 mol%) as a catalyst and, the desired product could be obtained in 80% yield at room temperature after 12 h (entry 1). When the reaction was performed using water as a co-solvent with dioxane (1:1) the desired product could be obtained in 90% yield (entry 2). No product was detected when the reaction was run in dioxane, THF, CH_2Cl_2, $CHCl_3$, CH_3CN, MeOH, and EtOH. Only the starting material was recovered from the reaction after 24 h. Under similar conditions, the reaction was tested with high boiling solvents such as H_2O, DMSO, and DMF to give good yields (70-85%). Interestingly, the complete starting material conversion was observed and BH adduct yield could be improved up to 90% when the reaction was performed without any additional solvent at room temperature, which was chosen as standard reaction condition (entry 13). It should be noted that without a catalyst, no reaction proceeded at all (entry 14). Subsequently, after this optimization, several alkyl substituted cardanol aldehydes (**3a-3e**) and methyl anacardic acid aldehyde (**8**) could be produced into the corresponding BH adducts (**5b-5f** and **9a**) in good yields (Scheme 1 & 2, Table 2).

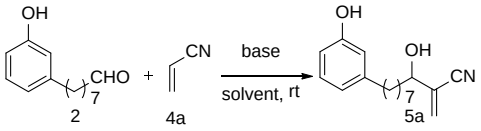


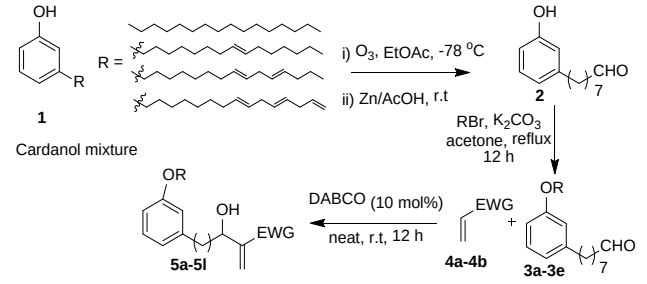
Table 1. Optimization of the reaction conditions.[a]

Entry	Solvent	Base	Time (h)	Yield (%)[b]
1	THF:H_2O(1:1)	DABCO	24	80
2	Dioxane:H_2O(1:1)	DABCO	24	90
3	THF	DABCO	24	-[c]
4	Dioxane	DABCO	24	-
5	MeOH	DABCO	24	-
6	CH_2Cl_2	DABCO	24	-
7	CH_3CN	DABCO	24	-
8	EtOH	DABCO	24	-
9	$CHCl_3$	DABCO	24	-
10	H_2O	DABCO	24	70
11	DMSO	DABCO	24	85
12	DMF	DABCO	24	80
13	Neat	DABCO	12	90
14	Neat	-	12	-

[a]Reaction conditions: aldehyde **2** (1.0 mmol), acrylonitrile **4a**(1.5 mmol) and DABCO(10 mol%), [b]isolated yield, [c]no reaction.

Further, several cardanol aldehydes (**2**, **3a-3e**) and methyl anacardic acid aldehyde (**8**) were explored with butyl acrylate (**4b**) and DABCO as a catalyst under solvent-free conditions. The cardanol aldehyde (**2**) furnished BH adduct (**5g**) in good yield. In contrast, alkylated aldehydes (**3a-3e**) showed low reactivity towards butyl acrylate (less than 50% conversion). A probable reason could be due to the electronic effect of the alkyl chain on the phenyl ring. To overcome this problem, several modifications were attempted, including prolonged reaction time up to 24 h, the amount of butyl acrylate increased 1.5 to 3 equivalents with respect to aldehyde and PEG(1 mL) as an additive. These modifications made possible to obtain the corresponding BH adducts (**5h-5l**, **9b**) in good yields (Scheme 1 & 2, Table 2).

To investigate the scalability of the method, 1.0 g of methyl cardanol aldehyde (**3a**) was used to react with acrylonitrile (**4a**) under standard reaction conditions that provided the BH adduct (**5b**) in good yield (85%).

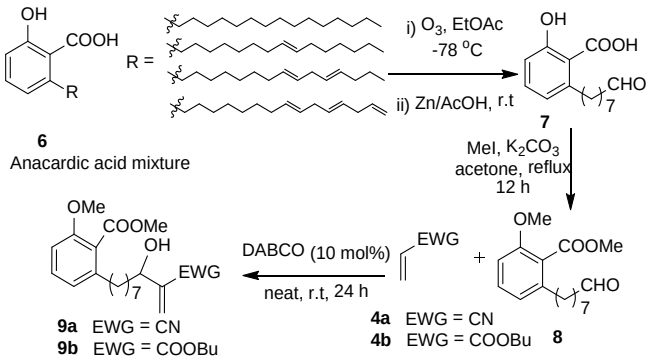


5a R = H, EWG = CN
5b R = Me, EWG = CN
5c R = Propyl, EWG = CN
5d R = Butyl, EWG = CN
5e R = Pentyl, EWG = CN
5f R = Hexyl, EWG = CN
5g R = H, EWG = COOBu
5h R = Me, EWG = COOBu
5i R = Propyl, EWG = COOBu
5j R = Butyl, EWG = COOBu
5k R = Pentyl, EWG = COOBu
5l R = Hexyl, EWG = COOBu

4a EWG = CN
4b EWG = COOBu

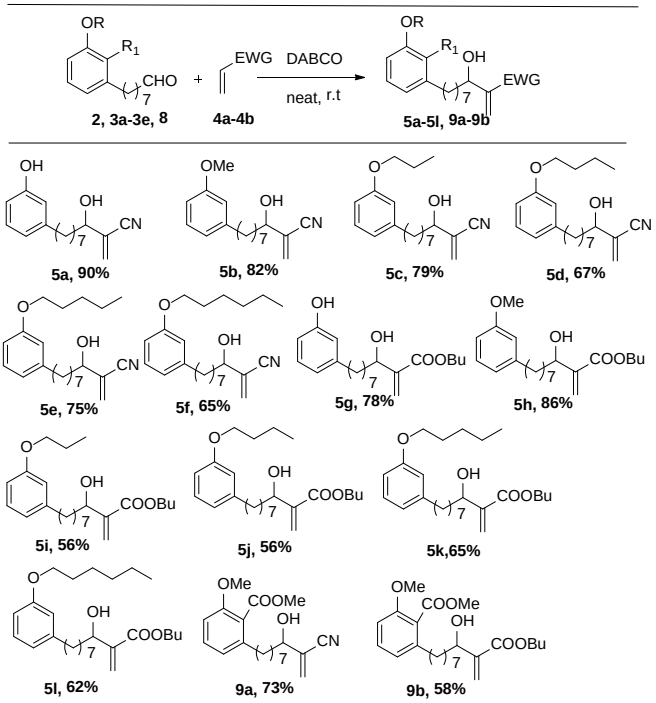
2 R = H; **3a** R= Me,
3b R = Propyl; **3c** R= Butyl
3d R= Pentyl; **3e** R=Hexyl

Scheme 1. Synthesis of Baylis-Hillman adducts from cardanol.



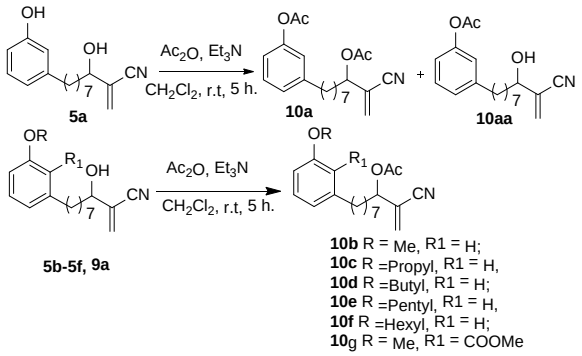
Scheme 2. Synthesis of Baylis-Hillman adducts from anacardic acid.

Table 2. Scope and limitations for various Baylis-Hillman adducts.[a]



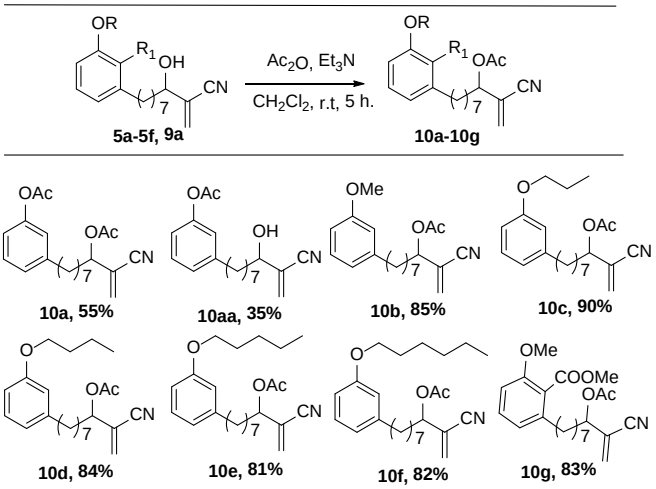
[a]Reaction conditions: aldehyde (2.0 mmol), alkene (3.0 mmol) and DABCO (10 mol%).

The obtained nitrile BH adducts derived from cardanol and anacardic acid derivatives were easily converted into acetates as shown in Scheme 3 and Table 3. All nitrile BH adducts (**5b-5f**, **9a**) except **5a** were acetylated with acetic anhydride in the presence of triethylamine in CH_2Cl_2 to give the corresponding acetylated compounds (**10b-10g**) as the sole product in excellent yields, whereas in the case of compound **5a** both phenolic and allylic hydroxyl groups could be acetylated. All the synthesized BH adducts and their acetates were well characterized by spectroscopic analysis and further screened for their *in vitro* antitumor activity.

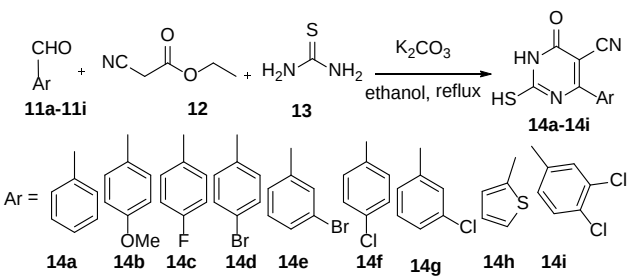


Scheme 3. Synthesis of Baylis-Hillman acetates.

Table 3. Scope and limitations for various Baylis-Hillman acetates.[a]



[a]Reactionconditions: BH adduct (1.0 mmol), Et_3N (2.0 mmol), Ac_2O (2.0 mmol) and CH_2Cl_2 (10 mL).

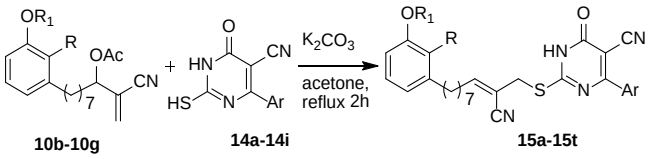


Scheme 4. Synthesis of thiopyrimidine derivatives.

Synthesis of phenolic based pyrimidine derivatives from Baylis-Hillman acetates

Having succeeded in synthesizing Baylis-Hillman alcohols and acetates from cardanol and anacardic acid, we further synthesized phenolic based pyrimidine derivatives. The synthetic strategy for the proposed target phenolic based pyrimidine hybrid scaffolds (**15a-15t**) is outlined in Scheme 5.

At this stage, the aryl-2-sulfanyl-1,6-dihydropyrimidine-5-carbonitriles (**14a-14i**) could be prepared according to the reported procedure as depicted in Scheme 4.[27] Cyclisation of aldehydes (**11a-11i**), ethyl cyanoacetate (**12**), and thiourea (**13**) in ethanol as solvent, in the presence of potassium carbonate at reflux temperature for 5 h, furnished the corresponding aryl-2-sulfanyl-1,6-dihydropyrimidine-5-carbonitriles (**14a-14i**) in good yields (Scheme 4). The obtained Baylis-Hillman acetates (**10b-10g**) were treated with various aryl-2-sulfanyl-1,6-dihydropyrimidine-5-carbonitriles (**14a-14i**) using K_2CO_3 in acetone at 40 ^oC for 2 h, to provide (E)-2-((2-cyano-10-(3-methoxyphenyl)dec-2-en-1-yl)thio)-6-oxo-4-phenyl-1,6-dihydropyrimidine-5-carbonitriles (**15a-15t**) in good yields (Scheme 5 and Table 4).

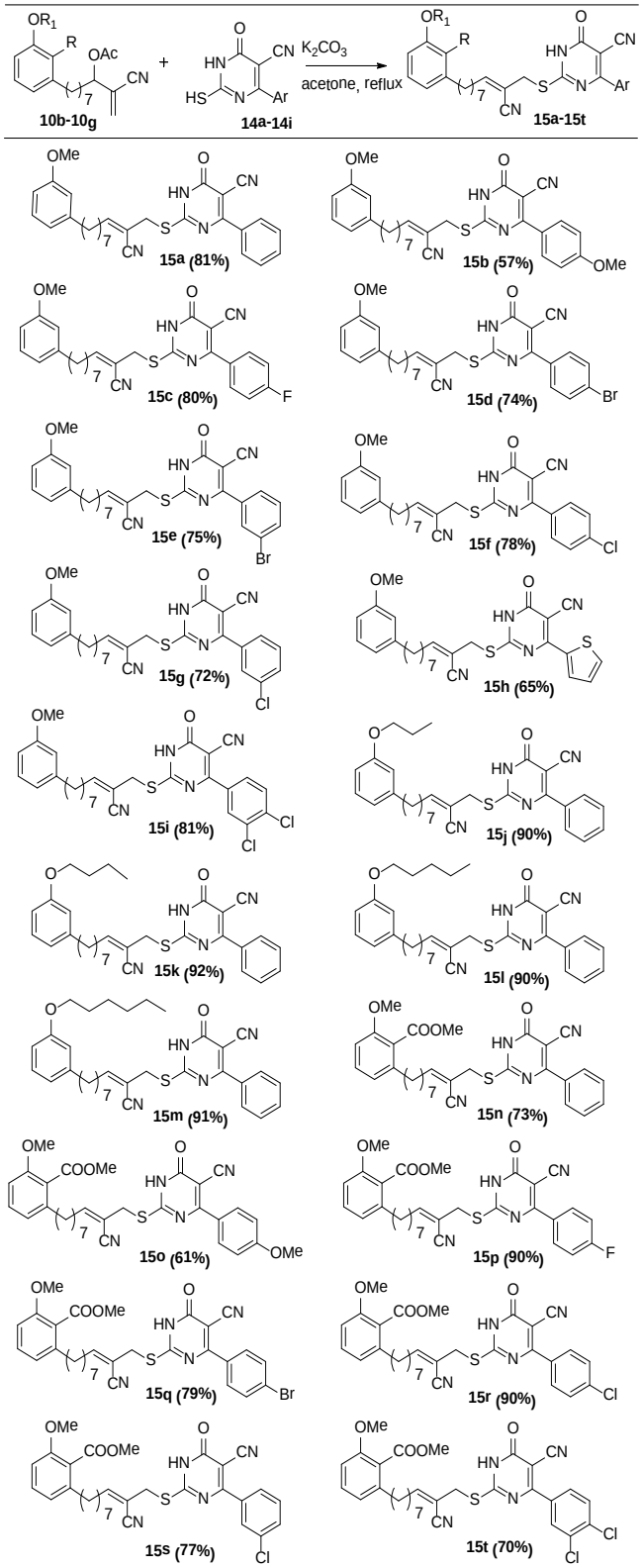


R1 = Me, Propyl, Butyl, Pentyl, Hexyl; R = H, COOMe; Ar = Ph, 4-OMe-C_6H_4, 4-F-C_6H_4, 4-Br-C_6H_4, 3-Br-C_6H_4, 4-Cl-C_6H_4, 3-Cl-C_6H_4, 2-thienyl, 3,4-di-Cl-C_6H_3

Scheme 5. Synthesis of phenolic based pyrimidine derivatives.

We optimized the reaction conditions with Baylis-Hillman acetate (**10b**) and aryl-2-sulfanyl-1,6-dihydropyrimidine-5-carbonitrile (**14a**) as a model substrate for this conversion using various bases such as piperidine, pyridine, trimethylamine, K_2CO_3. The findings suggested that K_2CO_3 was one of the best choice for this conversion. This reaction did not proceed in the absence of a base. Different solvent systems such as DMF, THF, CH_2Cl_2, CH_3CN, acetone, ethanol and toluene could be examined to facilitate this reaction, but only acetone provided excellent results, emerging as one of the best solvents for this conversion. The synthesis of target compounds in excellent yields (81%) was standarized in presence of K_2CO_3 as base and acetone as a solvent at 40 ^oC for 1 h. Other Baylis-Hillman acetates (**10b-10g**) were reacted with different aryl-2-sulfanyl-1,6-dihydropyrimidine-5-carbonitriles (**14a-14i**) to obtain the desired products in good to excellent yields (Table 4).Both electron-donating (OMe) and electron-withdrawing (F, Cl, Br) groups in phenyl ring of pyrimidine scaffolds could be executed under the standard conditions, leading to corresponding products. This revealed that pyrimidine substrates bearing electron donating groups provided milder yields (**15b** and **15o**) and pyrimidine substrates bearing a halogen atom (F, Cl, or Br) on phenyl ring gave the desired products in good yields (**15c-15g**, **15i** and **15p-15t**). The effect of various alkoxy groups (methyl, propyl, butyl, and hexyl) of the benzene ring in the BH acetate (**15j-15m**) suggested that diverse alkoxy groups could deliver the desired products, with superior yields for those with the longest length of alkoxy chain (methyl to Hexyl).

Table 4. Scope and limitations for phenolic based pyrimidine derivatives[a]



[a]Reaction conditions: BH acetate (1.0 mmol), thiopyrimidine (1.0 mmol), K_2CO_3 (1.0 mmol) and acetone (15 mL).

Biological activity

The anticancer activities of the above newly synthesized Baylis-Hillman derivatives and phenolic-based pyrimidine hybrid compounds were screened *in vitro*for their cytotoxic effects against four human cancer cell lines MCF-7 (breast cancer), PC-03 (prostate cancer), HEP G2 (liver cancer) and K562 (leukaemia cancer) by using the SRB and MTT assay methods.[28] GI_{50} is the concentration of drug to cause a 50% reduction in the proliferation of cancer cells. Table 5 and 6 shows the values of growth inhibition of 50% (GI_{50}) of all evaluated cells for synthesized hybrid molecules at 48 hours.

Antitumor activity of Baylis-Hillman adducts and acetates

The results in Table 5 revealed that target Baylis-Hillman compounds **5b** and **5h** showed promising activity, whereas remaining compounds showed moderate to low activity against tested cell lines. Compounds **5a-5f**, **9a**, **10aa**, all the BH adducts bear nitrile functionality at the double bond (Table 2). Compound **5b** having methoxy functionality on the phenyl ring showed promising selective anticancer activity against MCF-7 with the GI_{50} value 19.86 μM and no activity against PC-03, HEP-G2 and K562 (Table 4). Compounds **5g-5l** and **9b**, all the BH adducts possess ester functionality at the double bond (Table 2). Compound **5h**, having methoxy functionality in the phenyl ring, showed promising activity against MCF-7 (with GI_{50} of 19.72 μM) and moderate activity against HEP G2 (with GI_{50} of 30.34 μM), while weak activity against PC-03 (97.93 μM) and K562 (69.87 μM) (Table 5). When Baylis-Hillman adducts were converted into corresponding acetates, their activity decreased. Baylis-Hillman acetates (**10a-10g**) possess nitrile functionality at the double bond (Table 3). The results indicated that presence of alkyl groups on the phenyl ring cancel the activity. Compounds **10a**, **10b**, and **10g** displayed moderate activity, while the remaining compounds **10c-10f** showed no activity against the tested cells .

Previous studies also showed that anacardic acid obtained from cashew nuts have antiproliferative activity against prostate cancer cells (TAN) and isobenzofurans designed from anacardic acids show activity against HL-60 cells leukemia, SF295 glioblastome and, MDA-MB435 melanome,[29] demonstrating the promising anticancer activity of these compounds.

Antitumor activity of phenolic based pyrimidine derivatives

Our results (Table 6) showed that target phenolic based hybrid compounds were active against all tested cell lines. Among them, compounds **15i**, **15j**, and **15l** showed promising activity against HEP-G2 with the GI_{50} value of 6.17, 2.87 and 4.56 μM respectively, whereas compounds **15j**, **15k**, **15l**, and **15m** showed promising activity against MCF-7 with the GI_{50} value of 8.51, 8.64, 8.66 and 5.02 μM respectively. Moreover, compound **15m** showed equipotent activity with the GI_{50} value of 0.25 μM and compound **15j** showed good activity with the GI_{50} value of 12.86 μM against K562, as compared to the standard doxorubicin (0.04 to 0.25 μM).

The structure-activity relationship (SAR) analysis indicates that the presence of the methoxy group at the phenyl ring of BH acetate moiety compounds **15a-15i** showed moderate activity (Table 4 &6). Subsequently, we investigated the effects of methoxy and halogen atoms on the phenyl ring of pyrimidine scaffold, in order to identify some more potent inhibitors.

Table 5. In vitro anticancer activity of Baylis-Hillman derivatives.

Com. no	MCF-7 GI_{50} (μM)	PC-03 GI_{50} (μM)	HEP G2 GI_{50} (μM)	K562 GI_{50} (μM)
5a	>100	>100	98.76±0.76	>100
5b	19.86±0.11	>100	>100	>100
5c	91.42±0.69	>100	>100	>100
5d	84.98±0.63	91.05±0.39	>100	97.45±0.19
5e	76.56±0.13	90.24±0.12	>100	>100
5f	78.31±0.56	65.17±0.11	>100	80.66±0.11
5g	73.17±0.90	>100	>100	82.76±0.06
5h	19.72±0.56	97.93±0.72	30.34±0.14	69.87±0.40
5i	71.69±0.64	>100	69.14±0.33	62.60±0.66
5j	>100	>100	>100	>100
5k	>100	>100	>100	>100
5l	>100	>100	>100	>100
9a	75.26±0.71	63.68±0.50	>100	91.30±0.05
9b	59.44±0.78	62.54±0.25	61.82±0.46	99.73±0.12
10a	67.14 ±0.11	>100	81.13±0.52	72.04±0.13
10aa	85.6±0.152	>100	>100	>100
10b	63.74±0.12	78.92±0.21	97.13±0.68	72.18±0.11
10c	>100	>100	>100	>100
10d	>100	>100	>100	>100
10e	>100	>100	>100	>100
10f	>100	>100	>100	>100
10g	>100	>100	64.52±0.41	62.53±0.08
[a]	0.07±0.02	0.6±0.02	0.47±0.03	0.25±0.08

[a]Doxorubicin is the positive control

Keeping the methoxy group (**15a-15i**) at the phenyl ring of BH acetate moiety but with the presence of methoxyl, halogen groups (F, Cl, and Br) and 2-thienyl on the phenyl ring of pyrimidine scaffold (**15a-15i**) had no significant influence on the activity. Compounds **15a-15h** showed good to moderate activity against all tested cells with GI_{50} values in the range of 15.95-249.21 μM. In contrast, compound **15i** bearing two chlorine atoms at 3,4 position of the phenyl ring of pyrimidine moiety, showed promising activity against HEP G2 (6.17 μM), and moderate activity against MCF-7 (25.41 μM) and PC-03 (24.98 μM), while less activity against K562 (170.11 μM).

Interestingly, the methyl group on the phenyl ring of BH acetate when replaced by propyl, butyl, pentyl and hexyl groups (**15j-15m**) in absence of any substitution on the phenyl ring of pyrimidine scaffold confer an increased activity. Compound **15j** bearing propyl group on phenyl ring showed promising activity against MCF-7 (8.51μM) and HEP-G2 (2.87μM), while moderate activity against PC-03 (23.71 μM) and good activity against K562 (12.86 μM). Compound **15k** having butyl group on phenyl ring showed promising activity against MCF-7 (8.64 μM), and moderate activity against for PC-03 (36.17 μM), HEP-G2 (15.24 μM) and K562 (24.45 μM). Compound **15l** having pentyl group on phenyl ring showed promising activity against MCF-7 (8.66 μM) and HEP-G2 (4.56 μM), whereas it showed

moderate activity against PC-03 (22.62 μM) and K562 (24.62 μM). It can be verified that compound **15m** having hexyl group on phenyl ring showed substantial activity for K562 (0.25 μM) and promising activity against MCF-7 (5.02 μM), however, showed moderate activity against PC-03 (18.36 μM) and HEP-G2 (22.42 μM). These findings clearly indicate that the compound **15m** was the most potent compound. Thus, the length of the carbon chain of phenyl ring played an important role for the activity (Table 6).

Table 6.*In vitro* anticancer activity data of compounds **15a-15t**

Comp. no	MCF-7 GI_{50} (μM)	PC-03 GI_{50}(μM)	HEP G2 GI_{50}(μM)	K562 GI_{50}(μM)
15a	26.64±0.33	71.19±0.29	28.15±0.20	>100
15b	30.41±0.40	25.67±1.32	>100	>100
15c	27.13±0.45	25.40±0.39	23.73±0.88	>100
15d	58.22±0.31	25.70±0.43	78.81±0.96	24.49±0.06
15e	16.12±0.41	26.14±0.89	35.35±3.14	24.28±0.55
15f	31.28±0.21	25.95±0.46	19.01±0.32	>100
15g	27.34±0.45	26.23±0.67	58.60±0.52	23.99±0.12
15h	24.24±0.30	24.00±0.27	15.95±0.16	24.59±0.22
15i	25.41±0.90	24.98±0.51	**6.17**±0.31	>100
15j	**8.51**±0.45	23.71±0.65	**2.87**±0.47	12.86±0.42
15k	**8.64**±0.33	36.17±0.82	15.24±0.62	24.45±0.18
15l	**8.66**±0.44	22.62±0.42	**4.56**±0.68	24.62±0.10
15m	**5.02**±0.23	18.36±0.56	22.42±1.13	**0.25**±0.06
15n	26.25±0.51	>100	30.72±2.21	>100
15o	22.21±0.37	24.34±0.43	24.79±0.39	>100
15p	27.02±0.32	29.58±0.37	25.06±0.94	35.44±0.09
15q	22.28±0.43	25.17±2.10	14.04±0.27	25.95±0.61
15r	28.58±0.51	25.40±0.72	45.10±0.44	>100
15s	>100	>100	>100	>100
15t	27.02±0.42	51.03±2.3	28.21±0.74	35.44±0.13
[a]	0.07±0.02	0.6±0.02	0.47±0.03	0.25±0.08

[a]Doxorubicin is the positive control.

The **Figure 3**summarizes the *in vitro*antitumor activity of main componds found in this study.

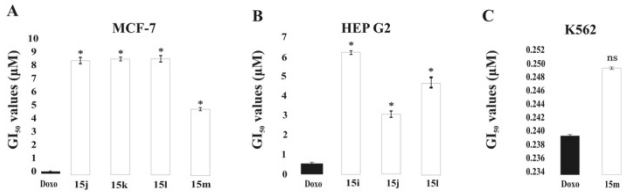


Figure 3:*In vitro* anticancer activity of compounds15i-15m.The bar graphs show the concentration in μM of each compound required for 50% inhibition (GI_{50}) of MCF-7, HEP G2 and K562 cell lines compared to Doxorubicin (positive control). **Note: ***p<0.05 was considered as significant and ns (no significant).

Further modifications including compounds bearing methoxy group and methyl ester (COOMe) groups (**15n-15t**) on the phenyl ring of BH acetate and the presence of methoxy group and halogen groups (F, Cl and Br) on the phenyl ring of pyrimidine scaffold had no much influence on the anticancer activity against all tested cell lines, while compound **15s** having chlorine at meta position of phenyl ring of pyrimidine scaffold led to dramatically decreasing the activity. Compounds **15n-15t** showed moderate to small activities towards all tested cell lines with GI_{50} values in the range of 14.04->250 μM (Table 6).

EXPERIMENTAL

General remarks

All reagents were analytical grade and used without further purification. Chromatographic purification was performed on silica gel (Merck, 100-200 mesh) and analytical thin layer chromatography (TLC) on silica gel 60-F_{254}. ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were measured with a Bruker Avance DPXT-300 spectrometer with $CDCl_3$ and DMSO-d_6 as solvents and recorded in ppm relative to internal tetramethylsilane standard (TMS). The ^{1}H NMR spectra are reported as follows: ppm (multiplicity, coupling constant J/Hz, number of protons). Multiplicity is abbreviated as follows: s (singlet), d (doublet), dd (doublet of doublets), t (triplet), m (multiplet). Coupling constants (*J*) are quoted in Hertz and recorded to the nearest 0.1 Hz. High-resolution mass spectroscopy (HRMS) was performed on a UFLC Shimadzu LC-20AD apparatus, with and IES-Q-QTOF-microTOF III detector (Bruker Daltonics) in chemical ionization positive ion mode (m/z 120-1200). The samples were prepared with 0.1 g/mL (methanol/ water 7:3) and injected 1μL, using elution gradient water (phase A) and acetonitrile (phase B), both with acetic acid 1%, isocratic method 50% and the running time of 3 min. The infrared spectra were recorded on a FT-IR spectrometer and reported as wavenumbers (cm^{-1}).

General experimental procedure for the synthesis of Baylis-Hillman adducts (5a-5l, 9a-9b)

Several substituted aldehydes (**2, 3a-3e, 8**) (2 mmol), activated olefin (**4a-4b**) (3 mmol) and DABCO (10 mol% with respect to aldehyde) were mixed well and allowed to stir at room temperature until reaction is completed (reaction monitored by the TLC).(In case of aldehydes **3a-3e**, **8** with butyl acrylate **4b** showed less reactivity. Then reaction time was increased to 12-24 h, butyl acrylate **4b** (6 mmol) and PEG (1 mL) as additive). After completion, the reaction mixture was diluted with water (15 mL) and extracted with ethyl acetate (3x20 mL). The combined organic layers were dried over sodium sulphate, filtered, concentrated under vacuum to give the crude product. The product was purified by silica gel column chromatography using ethyl acetate:hexane as eluent (2:8), providing corresponding BH adducts (**5a-5l**, **9a-9b)** in good yield as colorless liquids.

3-Hydroxy-10-(3-hydroxyphenyl)-2-methylenedecanenitrile (5a): Colorless liquid; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.14-7.07 (m, 1H), 6.73-6.69 (m, 1H), 6.65-6.61 (m, 2H), 5.97-5.96 (m, 1H), 5.96-5.95 (m, 1H), 5.66 (s, 1H), 4.24-4.16 (m, 1H), 2.52 (t, *J* = 7.3 Hz, 2H), 1.94 (s, 1H), 1.74-1.50 (m, 4H), 1.34-1.22 (m, 8H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 165.2, 155.5, 144.6, 130.0, 129.3, 126.7, 120.7, 115.3, 112.5, 72.3, 35.6, 35.5, 30.9, 29.0, 28.9, 28.8, 24.8; IR (neat): 3386, 3039, 2927, 2854, 2229, 1589,

1485, 1458, 1269, 1234, 1157, 948 cm^{-1}; HRMS-ESI (*m/z*): Calcd for $C_{17}H_{24}NO_2$: 274.1807 $[M+H]^+$; found. 274.1813.

3-Hydroxy-10-(3-methoxyphenyl)-2-methylenedecanenitrile (5b): Colorless liquid; ^1H NMR (300 MHz, $CDCl_3$): δ 7.23-7.16 (m, 1H), 6.77 (d, *J* = 7.6 Hz, 1H), 6.74-6.70 (m, 2H), 6.00-5.96 (m, 2H), 4.23 (t, *J* = 6.7 Hz, 1H), 3.79 (s, 3H), 2.57 (t, *J* = 7.3 Hz, 2H), 1.77-1.55 (m, 4H), 1.42-1.28 (m, 8H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.4, 144.3, 129.6, 129.0, 126.9, 120.7, 116.9, 114.1, 110.7, 72.2, 55.0, 35.8, 35.5, 31.1, 29.1, 29.0(2), 24.9; IR (neat): 3459, 2997, 2931, 2854, 2225, 1600, 1585, 1488, 1465, 1454, 1434, 1315, 1261, 1180, 1045, 948 cm^{-1}; HRMS-ESI (*m/z*): Calcd for $C_{18}H_{26}NO_2$: 288.1964 $[M+H]^+$; found. 288.1950.

3-Hydroxy-2-methylene-10-(3-propoxyphenyl)decanenitrile (5c): Colorless liquid; ^1H NMR (300 MHz, $CDCl_3$): δ 7.21-7.14 (m, 1H), 6.78-6.69 (m, 3H), 5.99-5.95 (m, 2H), 4.25-4.19 (q, *J* = 5.7 Hz, 1H), 3.91 (t, *J* = 6.5 Hz, 2H), 2.57 (t, *J* = 7.4 Hz, 2H), 2.13 (d, *J* = 5.1 Hz, 1H), 1.86-1.56 (m, 6H), 1.43-1.28 (m, 8H), 1.03 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.0, 144.3, 129.6, 129.0, 126.9, 120.6, 116.9, 114.7, 111.3, 72.3, 69.3, 35.9, 35.6, 31.2, 29.2, 29.0, 24.9, 22.5, 10.5; IR (neat): 3471, 3031, 2958, 2931, 2854, 2225, 1600, 1581, 1485, 1450, 1392, 1261, 1157, 1049, 948 cm^{-1}; HRMS-ESI (*m/z*): Calcd for $C_{20}H_{30}NO_2$: 316.2277 $[M+H]^+$; found. 316.2272.

10-(3-Butoxyphenyl)-3-hydroxy-2-methylenedecanenitrile (5d): Colorless liquid; ^1H NMR (300 MHz, $CDCl_3$): δ 7.22-7.14 (m, 1H), 6.78-6.69 (m, 3H), 6.00-5.95 (m, 2H), 4.26-4.17 (m, 1H), 3.95 (t, *J* = 6.4 Hz, 2H), 2.57 (t, *J* = 7.4 Hz, 2H), 2.30-2.20 (m, 1H), 1.82-1.69 (m, 4H), 1.66-1.57 (m, 2H), 1.55-1.44 (m, 2H), 1.40-1.27 (m, 8H), 0.98 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ159.0, 144.3, 129.7, 129.0, 126.9, 120.6, 117.0, 114.7, 111.3, 72.2, 67.4, 35.8, 35.5, 31.3, 31.2, 29.2, 29.0, 24.9, 19.2, 13.8; IR (neat): 3463, 3031, 2931, 2854, 2225, 1600, 1581, 1488, 1450, 1392, 1311, 1257, 1157, 1068, 1029, 945 cm^{-1}; HRMS-ESI (*m/z*): Calcd for $C_{21}H_{32}NO_2$: 330.2433 $[M+H]^+$; found. 330.2429.

3-Hydroxy-2-methylene-10-(3-(pentyloxy)phenyl)decanenitrile (5e): Colorless liquid; ^1H NMR (300 MHz, $CDCl_3$): δ 7.21-7.14 (m, 1H), 6.77-6.69 (m, 3H), 5.99-5.95 (m, 2H), 4.26-4.18 (q, *J* = 5.2 Hz, 1H), 3.94 (t, *J* = 6.5 Hz, 2H), 2.56 (t, *J* = 7.4 Hz, 2H), 2.10 (d, *J* = 5.2 Hz, 1H), 1.83-1.55 (m, 6H), 1.49-1.26 (m, 12H), 0.93 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.0, 144.3, 129.6, 129.0, 126.9, 120.6, 116.9, 114.7, 111.3, 72.3, 67.8, 35.9, 35.6, 31.2, 29.2, 29.0, 28.9, 28.1, 24.9, 22.4, 13.9; IR (neat): 3456, 3031, 2931, 2854, 2225, 1600, 1581, 1488, 1465, 1450, 1392, 1284, 1261, 1157, 1076, 1053, 1033, 945 cm^{-1}; HRMS-ESI (*m/z*): Calcd for $C_{22}H_{34}NO_2$: 344.2590 $[M+H]^+$; found. 344.2590.

10-(3-(Hexyloxy)phenyl)-3-hydroxy-2-methylenedecanenitrile (5f): Colorless liquid; ^1H NMR (300 MHz, $CDCl_3$): δ 7.21-7.13 (m, 1H), 6.77-6.66 (m, 3H), 5.99-5.95 (m, 2H), 4.25-4.17 (m, 1H), 3.94 (t, *J* = 6.5 Hz, 2H), 2.56 (t, *J* = 7.6 Hz, 2H), 2.17-2.11 (m, 1H), 1.83-1.54 (m, 6H), 1.50-1.22 (m, 14H), 0.91 (t, *J* = 6.7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.1, 144.3, 129.7, 129.1, 126.9, 120.6, 117.0, 114.8, 111.4, 72.3, 67.8, 35.9, 35.6, 31.6, 31.2, 29.3, 29.1, 25.7, 25.0, 22.6, 14.0; IR (neat): 3459, 3031, 2927, 2854, 2225, 1600, 1581, 1488, 1465, 1450, 1392, 1311, 1261, 1157, 1045, 948 cm^{-1}; HRMS-ESI (*m/z*): Calcd for $C_{23}H_{36}NO_2$: 358.2746 $[M+H]^+$; found. 358.2733.

Butyl 3-hydroxy-10-(3-hydroxyphenyl)-2-methylenedecanoate (5g): Colorless liquid; ^1H NMR (300 MHz, $CDCl_3$): δ 7.16-7.09 (m, 1H), 6.73 (d, *J* = 7.3 Hz, 1H), 6.67-6.62 (m, 2H), 6.21 (s, 1H), 5.77 (s, 1H), 5.22 (brs, 1H), 4.43-4.34 (m, 1H), 4.18 (t, *J* = 6.5 Hz, 2H), 2.67 (brs, 1H), 2.54 (t, *J* = 7.3 Hz, 2H), 1.72-1.53 (m, 6H), 1.48-1.22 (m, 10H), 0.95 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.8, 155.7, 144.6, 142.4, 129.2, 124.8, 120.5, 115.3, 112.5, 71.8, 64.8, 36.1, 35.6, 31.0, 30.5, 28.9, 25.6, 19.1, 13.6; IR (neat): 3390, 2927, 2854, 1697, 1623, 1589, 1485, 1458, 1272, 1157, 1095, 1064, 952 cm^{-1}; HRMS-ESI (*m/z*): Calcd for $C_{21}H_{32}O_4Na$: 371.2198 $[M+Na]^+$; found. 371.2186.

Butyl 3-hydroxy-10-(3-methoxyphenyl)-2-methylenedecanoate (5h): Colorless liquid; ^1H NMR (300 MHz, $CDCl_3$): δ 7.22-7.15 (m, 1H), 6.79-6.69 (m, 3H), 6.20 (s, 1H), 5.76 (s, 1H), 4.40-4.33 (q, *J* = 6.5 Hz, 1H), 4.18 (t, *J* = 6.5 Hz, 2H), 3.79 (s, 3H), 2.60-2.53 (m, 3H), 1.72-1.55 (m, 8H), 1.48-1.26 (m, 8H), 0.95 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.6, 159.5, 144.5, 142.7, 129.1, 124.5, 120.8, 114.1, 110.7, 71.8, 64.6, 55.0, 36.2, 35.9, 31.3, 30.5, 29.4, 29.3, 29.2, 25.8, 13.6; IR (neat): 3444, 2927, 2854, 1712, 1600, 1585, 1488, 1458, 1434, 1261, 1153, 1099, 1045, 952 cm^{-1}; HRMS-ESI (*m/z*): Calcd for $C_{22}H_{34}O_4Na$: 385.2355 $[M+Na]^+$; found: 385.2342.

Butyl 3-hydroxy-2-methylene-10-(3-propoxyphenyl)decanoate (5i): Colorless liquid; ^1H NMR (300 MHz, $CDCl_3$): δ 7.20-7.13 (m, 1H), 6.77-6.68 (m, 3H), 6.20 (s, 1H), 5.76 (s, 1H), 4.40-4.34 (q, *J* = 6.2 Hz, 1H), 4.18 (t, *J* = 6.5 Hz, 2H), 3.90 (t, *J* = 6.5 Hz, 2H), 2.61 (d, *J* = 6.2 Hz, 1H), 2.56 (t, *J* = 7.6 Hz, 2H), 1.86-1.74 (m, 2H), 1.72-1.55 (m, 6H), 1.48-1.26 (m, 10H), 1.03 (t, *J* = 7.4 Hz, 3H), 0.95 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.6, 159.0, 144.3, 142.6, 129.0, 124.5, 120.5, 114.7, 111.3, 71.7, 69.2, 64.6, 36.1, 35.9, 31.2, 30.5, 29.3, 29.2, 25.7, 22.6, 19.1, 13.5, 10.4; IR (neat): 3494, 2958, 2931, 2854, 1712, 1600, 1581, 1450, 1392, 1261, 1157, 1064, 952 cm^{-1}; HRMS-ESI (*m/z*): Calcd for $C_{24}H_{38}O_4Na$: 413.2688 $[M+Na]^+$; found: 413.2667.

Butyl 10-(3-butoxyphenyl)-3-hydroxy-2-methylenedecanoate (5j): Colorless liquid; ^1H NMR (300 MHz, $CDCl_3$): δ 7.20-7.12 (m, 1H), 6.77-6.67 (m, 3H), 6.21 (s, 1H), 5.76 (s, 1H), 4.41-4.34 (q, *J* = 6.7 Hz, 1H), 4.18 (t, *J* = 6.5 Hz, 2H), 3.94 (t, *J* = 6.4 Hz, 2H), 2.61 (d, *J* = 6.7 Hz, 1H), 2.56 (t, *J* = 7.6 Hz, 2H), 1.81-1.56 (m, 8H), 1.54-1.26 (m, 12H), 1.02-0.91 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ166.6, 159.1, 144.4, 129.0, 124.5, 120.6, 114.7, 111.3, 71.8, 67.4, 64.6, 36.2, 35.9, 31.3, 31.3, 30.5, 29.34, 29.3, 29.2, 25.8, 19.2, 19.1, 13.8, 13.6; IR (neat): 3467, 3031, 2958, 2858, 1712, 1627, 1600, 1581, 1485, 1458, 1392, 1261, 1157, 1068, 1029, 952 cm^{-1}; HRMS-ESI (*m/z*): Calcd for $C_{25}H_{41}O_4$: 405.3005 $[M+H]^+$; found: 405.2996.

Butyl 3-hydroxy-2-methylene-10-(3-(pentyloxy)phenyl)decanoate (5k): Colorless liquid; ^1H NMR (300 MHz, $CDCl_3$): δ 7.21-7.13 (m, 1H), 6.80-6.68 (m, 3H),

6.21 (s, 1H), 5.76 (s, 1H), 4.43-4.34 (m, 1H), 4.18 (t, *J* = 6.5 Hz, 2H), 3.93 (t, *J* = 6.5 Hz, 2H), 2.62 (d, *J* = 6.7 Hz, 1H), 2.56 (t, *J* = 7.3 Hz, 2H), 1.84-1.56 (m, 8H), 1.50-1.28 (m, 14H), 1.03-0.90 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.6, 159.1, 144.4, 142.7, 129.0, 124.5, 120.6, 114.7, 111.3, 71.8, 67.7, 64.6, 36.2, 35.9, 31.3, 30.5, 29.4, 29.3, 29.2, 29.0, 28.2, 25.8, 22.4, 19.1, 13.9, 13.6; IR (neat): 3490, 3031, 2954, 2931, 2858, 1712, 1600, 1581, 1488, 1465, 1392, 1261, 1157, 1056, 1033, 952 cm^{-1}; HRMS-ESI (*m/z*): Calcd for $C_{26}H_{43}O_4$: 419.3161 $[M+H]^+$; found: 419.3164.

Butyl 10-(3-(hexyloxy)phenyl)-3-hydroxy-2-methylenedecanoate (5l): Colorless liquid; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.20-7.13 (m, 1H), 6.77-6.67 (m, 3H), 6.21 (s, 1H), 5.76 (s, 1H), 4.41-4.34 (q, *J* = 6.4 Hz, 1H), 4.18 (t, *J* = 6.5 Hz, 2H), 3.94 (t, *J* = 6.4 Hz, 2H), 2.63 (d, *J* = 6.4 Hz, 1H), 2.56 (t, *J* = 7.7 Hz, 2H), 1.83-1.54 (m, 8H), 1.51-1.26 (m, 16H), 0.98-0.88 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.6, 159.1, 144.4, 142.7, 129.0, 124.5, 120.6, 114.7, 111.3, 71.8, 67.7, 64.6, 36.2, 35.9, 31.5, 31.3, 30.5, 29.4, 29.3, 29.28, 29.2, 25.8, 25.7, 22.5, 19.1, 13.9, 13.6; IR (neat): 3421, 2954, 2927, 2854, 1712, 1600, 1581, 1488, 1461, 1392, 1261, 1157, 1064, 952 cm^{-1}; HRMS-ESI (*m/z*): Calcd for $C_{27}H_{45}O_4$: 433.3318 $[M+H]^+$; found: 433.3318.

Methyl 2-(9-cyano-8-hydroxydec-9-enyl)-6-methoxybenzoate (9a): Colorless liquid; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.26 (t, *J* = 8.1 Hz, 1H), 6.81 (d, *J* = 7.6 Hz, 1H), 6.76 (d, *J* = 8.1 Hz, 1H), 5.98 (s, 1H), 5.96 (s, 1H), 4.22 (t, *J* = 6.4 Hz, 1H), 3.90 (s, 3H), 3.81 (s, 3H), 2.53 (t, *J* = 7.7 Hz, 2H), 1.79-1.50 (m, 4H), 1.45-1.24 (m, 8H); ^{13}C NMR (75 MHz, $CDCl_3$): δ169.0, 156.1, 141.1, 130.2, 129.6, 129.5, 126.9, 121.4, 117.0, 108.3, 72.1, 55.8, 52.1, 35.5, 33.3, 30.8, 29.1, 29.0, 28.9, 24.8; IR (neat): 3471, 3000, 2931, 2854, 2225, 1731, 1585, 1469, 1434, 1269, 1188, 1110, 1072, 952 cm^{-1}; HRMS-ESI (*m/z*): Calcd for $C_{20}H_{27}NO_4Na$: 368.1838 $[M+Na]^+$; found: 368.1846.

Methyl 2-(9-(butoxycarbonyl)-8-hydroxydec-9-enyl)-6-methoxybenzoate (9b): Colorless liquid; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.30-7.23 (m, 1H), 6.81 (d, *J* = 7.6 Hz, 1H), 6.75 (d, *J* = 8.3 Hz, 1H), 6.20 (s, 1H), 5.76 (s, 1H), 4.41-4.33 (m, 1H), 4.17 (t, *J* = 6.5 Hz, 2H), 3.89 (s, 3H), 3.81 (s, 3H), 2.60 (d, *J* = 7.3 Hz, 1H), 2.52 (t, *J* = 7.7 Hz, 2H), 1.72-1.52 (m, 6H), 1.47-1.25 (m, 10H), 0.94 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.8, 166.6, 156.1, 142.7, 141.2, 130.1, 124.4, 121.42, 121.4, 108.3, 71.6, 64.6, 55.7, 52.0, 36.2, 33.3, 31.0, 30.5, 29.3, 29.23, 29.2, 25.7, 19.1, 13.6; IR (neat): 3513, 2931, 2858, 1731, 1716, 1627, 1585, 1469, 1434, 1396, 1269, 1164, 1110, 1087, 956 cm^{-1}; HRMS-ESI (*m/z*): Calcd for $C_{24}H_{37}O_6$: 421.2590 $[M+H]^+$; found: 421.2592.

General experimental procedure for the synthesis of Baylis-Hillman acetates (10a-10g)

To a well stirred solution of Baylis-Hilmann adduct (**5a-5f**, **9a**) (1 mmol) in dichloromethane (10 mL) was added Et_3N (2 mmol) at 0 ^{o}C under N_2 atmosphere, then the reaction mixture was stirred for about 15 min. Acetic anhydride (2 mmol) was added slowly at the same temperature and allowed to stir at room temperature until complete consumption of starting material as monitored by the TLC. After completion, the reaction mixture was diluted with water (10 ml) and extracted with dichloromethane (2x15 mL), then separated the layers and dried over Na_2SO_4, filtered and concentrated under reduced. The crude product was submitted to silica gel column chromatography using ethyl acetate:hexane as eluent (1:9), providing the corresponding BH acetates (**10a-10g**) as a colorless liquid. The synthesized BH acetates were characterized by spectroscopic techniques.

3-(8-Acetoxy-9-cyanodec-9-enyl)phenyl acetate (10a): Colorless liquid; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.24-7.20 (m, 1H), 7.00 (d, *J* = 7.8 Hz, 1H), 6.88-6.83 (m, 2H), 5.99 (s, 1H), 5.93 (s, 1H), 5.21 (t, *J* = 7.0 Hz, 1H), 2.56 (t, *J* = 7.4 Hz, 2H), 2.25 (s, 3H), 2.06 (s, 3H), 1.80-1.66 (m, 2H), 1.62-1.51 (m, 2H), 1.31-1.21 (m, 8H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.8, 169.5, 150.5, 144.4, 132.5, 129.0, 125.8, 122.7, 121.3, 118.6, 116.1, 73.1, 35.5, 32.7, 30.9, 29.0, 28.9, 28.8, 24.7, 21.0, 20.8; IR (neat): 2931, 2858, 2225, 1766, 1747, 1612, 1585, 1485, 1442, 1369, 1211, 1118, 1018, 952 cm^{-1}; HRMS-ESI (*m/z*): Calcd for $C_{21}H_{28}NO_4$: 358.2018 $[M+H]^+$; found: 358.2016.

3-(9-Cyano-8-hydroxydec-9-enyl)phenyl acetate (10aa): Colorless liquid; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.24-7.20 (m, 1H), 7.00 (d, *J* = 7.7 Hz, 1H), 6.87-6.83 (m, 2H), 5.95-5.92 (m, 2H), 4.20-4.15 (m, 1H), 2.56 (t, *J* = 7.6 Hz, 2H), 2.25 (s, 3H), 1.80 (brs, 1H), 1.70-1.51 (m, 4H), 1.34-1.21 (m, 8H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.7, 150.5, 144.4, 129.7, 129.6, 129.0, 126.9, 125.9, 121.3, 118.6, 72.1, 35.5, 30.9, 29.0, 28.9, 28.8, 24.8, 21.1; IR (neat): 3463, 2927, 2854, 2225, 1766, 1739, 1612, 1585, 1485, 1446, 1369, 1211, 1141, 1014, 948 cm^{-1}; HRMS-ESI (*m/z*): Calcd for $C_{19}H_{26}NO_3$: 316.1913 $[M+H]^+$; found: 316.1912.

2-Cyano-10-(3-methoxyphenyl)dec-1-en-3-yl acetate (10b): Colorless liquid; ^{1}H NMR (300 MHz, $CDCl_3$): δ7.22-7.16 (m, 1H), 6.79-6.70 (m, 3H), 6.03 (s, 1H), 5.97 (s, 1H), 5.25 (t, *J* = 6.8 Hz, 1H), 3.79 (s, 3H), 2.57 (t, *J* = 7.6 Hz, 2H), 2.10 (s, 3H), 1.84-1.70 (m, 2H), 1.64-1.54 (m, 2H), 1.36-1.26 (m, 8H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.8, 159.5, 144.3, 132.5, 129.1, 122.8, 120.7, 116.1, 114.1, 110.7, 73.2, 55.0, 35.8, 32.7, 31.2, 29.1, 29.0, 28.9, 24.7, 20.9; IR (neat): 2931, 2854, 2225, 1747, 1600, 1585, 1488, 1458, 1434, 1373, 1261, 1230, 1153, 1045, 1029, 956 cm^{-1}; HRMS-ESI (*m/z*): Calcd for $C_{20}H_{28}NO_3$: 330.2069 $[M+H]^+$; found: 330.2065.

2-Cyano-10-(3-propoxyphenyl)dec-1-en-3-yl acetate (10c): Colorless liquid; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.21-7.12 (m, 1H), 6.77-6.64 (m, 3H), 6.03 (s, 1H), 5.97 (s, 1H), 5.25 (t, *J* = 6.8 Hz, 1H), 3.90 (t, *J* = 6.5 Hz, 2H), 2.56 (t, *J* = 7.6 Hz, 2H), 2.10 (s, 3H), 1.86-1.70 (m, 4H), 1.63-1.54 (m, 2H), 1.35-1.21 (m, 8H), 1.03 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.8, 159.0, 144.2, 132.5, 129.0, 122.8, 120.5, 116.1, 114.7, 111.3, 73.1, 69.2, 35.8, 32.7, 31.1, 29.1, 29.0, 28.9, 24.7, 22.5, 20.8, 10.4; IR (neat): 3031, 2931, 2854, 2225, 1747, 1600, 1581, 1488, 1450, 1373, 1261, 1230, 1157, 1049, 1026 cm^{-1}; HRMS-ESI (*m/z*): Calcd for $C_{22}H_{32}NO_3$: 358.2382 $[M+H]^+$; found: 358.2380.

10-(3-Butoxyphenyl)-2-cyanodec-1-en-3-yl acetate (10d): Colorless liquid; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.20-7.13 (m,

1H), 6.77-6.58 (m, 3H), 6.03 (s, 1H), 5.97 (s, 1H), 5.26 (t, *J* = 6.7 Hz, 1H), 3.95 (t, *J* = 6.4 Hz, 2H), 2.56 (t, *J* = 7.3 Hz, 2H), 2.10 (s, 3H), 1.83-1.71 (m, 4H), 1.65-1.56 (m, 2H), 1.53-1.45 (m, 2H), 1.38-1.26 (m, 8H), 0.97 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): *δ*169.8, 159.1, 144.2, 132.5, 129.0, 122.8, 120.5, 116.1, 114.7, 111.3, 73.2, 67.4, 35.9, 32.7, 31.3, 31.2, 29.1, 29.0, 28.9, 24.7, 20.8, 19.2, 13.8; IR (neat): 3031, 2858, 2225, 1747, 1600, 1581, 1488, 1450, 1373, 1257, 1230, 1157, 1064, 1026, 956 cm^{-1}; HRMS-ESI (*m/z*): Calcd for $C_{23}H_{34}NO_3$: 372.2539 $[M+H]^+$; found: 372.2538.

2-Cyano-10-(3-(pentyloxy)phenyl)dec-1-en-3-yl acetate (10e): Colorless liquid; ^{1}H NMR (300 MHz, $CDCl_3$): *δ* 7.21-7.14 (m, 1H), 6.77-6.68 (m, 3H), 6.03 (s, 1H), 5.97 (s, 1H), 5.25 (t, *J* = 6.8 Hz, 1H), 3.94 (t, *J* = 6.5 Hz, 2H), 2.56 (t, *J* = 7.4 Hz, 2H), 2.10 (s, 3H), 1.83-1.72 (m, 4H), 1.65-1.56 (m, 2H), 1.49-1.38 (m, 4H), 1.36-1.28 (m, 8H), 0.93 (t, *J* = 7.01 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): *δ* 169.8, 159.1, 144.2, 132.5, 129.0, 122.8, 120.5, 116.1, 114.7, 111.3, 73.2, 67.7, 35.9, 32.7, 31.2, 29.1, 29.0, 28.99, 28.9, 28.1, 24.7, 22.4, 20.8, 13.9; IR (neat): 3031, 2931, 2858, 2225, 1747, 1600, 1581, 1488, 1461, 1450, 1373, 1257, 1230, 1157, 1049, 1026, 952 cm^{-1}; HRMS-ESI (*m/z*): Calcd for $C_{24}H_{36}NO_3$: 386.2695 $[M+H]^+$; found: 386.2694.

2-Cyano-10-(3-(hexyloxy)phenyl)dec-1-en-3-yl acetate (10f): Colorless liquid; ^{1}H NMR (300 MHz, $CDCl_3$): *δ* 7.13-7.05 (m, 1H), 6.70-6.58 (m, 3H), 5.95 (s, 1H), 5.89 (s, 1H), 5.18 (t, *J* = 6.7 Hz, 1H), 3.86 (t, *J* = 6.4 Hz, 2H), 2.49 (t, *J* = 7.6 Hz, 2H), 2.02 (s, 3H), 1.77-1.62 (m, 4H), 1.58-1.47 (m, 2H), 1.44-1.34 (m, 2H), 1.31-1.19 (m, 12H), 0.83 (t, *J* = 6.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): *δ*169.8, 159.1, 144.2, 132.5, 129.0, 122.8, 120.5, 116.1, 114.7, 111.3, 73.2, 67.7, 35.9, 32.7, 31.5, 31.2, 29.2, 29.1, 29.0, 28.9, 25.7, 24.7, 22.5, 20.8, 13.9; IR (neat): 2931, 2858, 2225, 1747, 1600, 1581, 1488, 1450, 1373, 1257, 1230, 1157, 1026, 952 cm^{-1}; HRMS-ESI (*m/z*): Calcd for $C_{25}H_{38}NO_3$: 400.2852 $[M+H]^+$; found: 400.2834.

Methyl 2-(8-acetoxy-9-cyanodec-9-enyl)-6-methoxybenzoate (10g): Colorless liquid; ^{1}H NMR (300 MHz, $CDCl_3$): *δ*7.26 (t, *J* = 8.3, 7.6 Hz, 1H), 6.81 (d, *J* = 7.6 Hz, 1H), 6.76 (d, *J* = 8.3 Hz, 1H), 6.03 (s, 1H), 5.97 (s, 1H), 5.25 (t, *J* = 7.1 Hz, 1H), 3.90 (s, 3H), 3.81 (s, 3H), 2.53 (t, *J* = 7.6 Hz, 2H), 2.10 (s, 3H), 1.84-1.70 (m, 2H), 1.62-1.51 (m, 2H), 1.36-1.22 (m, 8H); ^{13}C NMR (75 MHz, $CDCl_3$): *δ*169.8, 168.9, 156.2, 141.1, 132.5, 130.2, 130.1, 122.8, 121.4, 116.1, 108.4, 73.2, 55.8, 52.1, 33.3, 32.8, 30.9, 29.2, 29.1, 28.9, 24.8, 20.9; IR (neat): 3004, 2931, 2858, 2225, 1731, 1585, 1469, 1434, 1373, 1265, 1230, 1110, 1072, 1026, 960 cm^{-1}; HRMS-ESI (*m/z*): Calcd for $C_{22}H_{29}NO_5Na$: 410.1943 $[M+Na]^+$; found: 410.1940.

General procedure for the synthesis of 6-oxo-4-substituted aryl-2-sulfanyl-1,6-dihydropyrimidine-5-carbonitrile (14a-14i)

A mixture with equimolar amounts of various aromatic aldehydes (**11a-11i)** (10 mmol), ethyl cyanoacetate (**12)** (10 mmol), thiourea (**13)** (10 mmol) and potassium carbonate (10 mmol) in absolute ethanol (25 mL) was gently heated under reflux temperature for 5 h. The completion of the reaction was monitored by TLC, upon completion a solid precipitated. The reaction mixture was poured in ice water and stirred until clear solution was formed. Then the mixture was neutralized with glacial acetic acid to precipitate out the product, which was gently washed with water. The product was isolated and recrystallized from ethanol. The spectroscopic and analytical data of all the synthesized compounds were in good agreement with those reported in the literature.[27]

General procedure for the synthesis of (E)-2-(2-Cyano-10-(3-methoxyphenyl)dec-2-enylthio)-6-oxo-4-phenyl-1,6-dihydropyrimidine-5-carbonitrile (15a-15t)

Potassium carbonate (1 mmol) was added to a well stirred solution of aryl-2-sulfanyl-1,6-dihydropyrimidine-5-carbonitrile (**14a-14i**) (1 mmol) in dry acetone (15 mL) at room temperature under nitrogen atmosphere and reaction mixture was stirred for 15 min at that temperature. Then Baylis-Hillman acetate (**10b-10g**) (1 mmol) in acetone (5 mL) was added slowly and the mixture was allowed to stir at reflux temperature for 2 h. Completion of the reaction was monitored by TLC. Following the completion of reaction, solvent was removed under reduced pressure, residue was diluted with water (15 mL) and extracted with ethyl acetate (2x25 mL). The combined organic layers were dried over sodium sulphate, filtered, concentrated under vacuum to give the crude product that was purified by silica gel column chromatography using ethyl acetate:hexane (3:7) as eluent, providing corresponding (*E*)-2-(2-Cyano-10-(3-methoxyphenyl)dec-2-enylthio)-6-oxo-4-phenyl-1,6-dihydropyrimidine-5-carbonitrile products (**15a-15t)** in good yields.

(E)-2-(2-Cyano-10-(3-methoxyphenyl)dec-2-enylthio)-6-oxo-4-phenyl-1,6-dihydropyrimidine-5-carbonitrile (15a): Sticky colorless liquid; ^{1}H NMR (300 MHz, $CDCl_3$): *δ* 7.94 (d, *J* = 7.0 Hz, 2H), 7.55-7.40 (m, 3H), 7.18 (t, *J* = 8.3 Hz, 1H), 6.79-6.69 (m, 3H), 6.47-6.39 (m, 1H), 4.10-4.00 (m, 2H), 3.78 (s, 3H), 2.55 (t, *J* = 7.3 Hz, 2H), 2.31-2.10 (m, 2H), 1.62-1.49 (m, 2H), 1.34-1.10 (m, 8H); ^{13}C NMR (75 MHz, $CDCl_3$): *δ*168.4, 159.5, 152.3, 144.3, 135.1, 131.9, 129.1, 128.9, 128.58, 128.5, 120.8, 116.3, 114.28, 114.2, 110.8, 110.7, 109.7, 102.3, 55.1, 35.9, 33.6, 31.5, 31.1, 29.0, 28.9, 28.8, 28.0; IR (neat): 2927, 2854, 2217, 1689, 1662, 1581, 1535, 1469, 1438, 1377, 1296, 1257, 1153, 1041, 1002 cm^{-1}; HRMS-ESI (*m/z*): Calcd for $C_{29}H_{31}N_4O_2S$: 499.2168$[M+H]^+$; found: 499.2187 .

(E)-2-(2-Cyano-10-(3-methoxyphenyl)dec-2-enylthio)-4-(4-methoxyphenyl)-6-oxo-1,6-dihydropyrimidine-5-carbonitrile (15b): Sticky light yellow liquid; ^{1}H NMR (300 MHz, $CDCl_3$): *δ* 8.01 (d, *J* = 8.7 Hz, 2H), 7.17 (t, *J* = 7.7 Hz, 1H), 6.93 (d, *J* = 8.7 Hz, 2H), 6.78-6.69 (m, 3H), 6.45 (t, *J* = 7.6 Hz, 1H), 4.13-4.03 (m, 2H), 3.84 (s, 3H), 3.78 (s, 3H), 2.54 (t, *J* = 7.6 Hz, 2H), 2.34-2.15 (m, 2H), 1.63-1.50 (m, 2H), 1.35-1.15 (m, 8H); ^{13}C NMR (75 MHz, $CDCl_3$): *δ* 167.2, 164.3, 162.8, 159.5, 152.3, 144.3, 131.1, 129.1, 127.0, 120.7, 116.2, 114.2, 114.1, 113.9, 110.79, 110.7, 109.6, 91.6, 55.4, 55.0, 35.8, 33.5, 31.5, 31.1, 29.1, 29.0, 28.8, 28.0; IR (neat): 3432, 2927, 2854, 2217, 1650, 1604, 1539, 1508, 1469, 1377, 1303, 1261, 1176, 1153, 1029, 999, 914, 840, 783 cm^{-1}; HRMS-ESI (*m/z*): Calcd for $C_{30}H_{33}N_4O_3S$: 529.2273 $[M+H]^+$; found: 529.2282.

(E)-2-(2-Cyano-10-(3-methoxyphenyl)dec-2-enylthio)-4-(4-fluorophenyl)-6-oxo-1,6-dihydropyrimidine-5-carbonitrile (15c): Sticky colorless liquid; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.85 (t, J = 8.4 Hz, 2H), 7.17 (t, J = 8.0 Hz, 1H), 7.02 (t, J = 8.4 Hz, 2H), 6.78-6.69 (m, 3H), 6.37 (t, J = 7.4 Hz, 1H), 5.37 (brs, 1H), 3.94 (s, 2H), 3.78 (s, 3H), 2.55 (t, J = 7.6 Hz, 2H), 2.29-2.01 (m, 2H), 1.65-1.51 (m, 2H), 1.37-1.12 (m, 8H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.6, 166.7, 166.2, 162.9, 159.5, 152.0, 144.3, 131.3, 131.1, 131.0, 129.1, 120.8, 116.9, 116.4, 115.7, 115.4, 114.1, 110.7, 110.0, 91.8, 55.0, 35.8, 33.6, 31.5, 31.1, 29.1, 29.0, 28.9, 28.1; IR (neat): 3440, 2927, 2854, 2217, 1662, 1604, 1539, 1512, 1485, 1469, 1380, 1303, 1257, 1242, 1157, 1103, 1045, 1006, 867, 837, 783 cm^{-1}; HRMS-ESI (*m/z*): Calcd for $C_{29}H_{30}FN_4O_2S$: 517.2074 $[M+H]^+$; found: 517.2074.

(E)-4-(4-Bromophenyl)-2-(2-cyano-10-(3-methoxyphenyl)dec-2-enylthio)-6-oxo-1,6-dihydropyrimidine-5-carbonitrile (15d): Sticky light yellow liquid; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.66 (d, J = 8.3 Hz, 2H), 7.45 (d, J = 8.3 Hz, 2H), 7.17 (t, J = 7.6 Hz, 1H), 6.78-6.68 (m, 3H), 6.40-6.30 (m, 1H), 4.90 (brs, 1H), 3.98-3.78 (m, 2H), 3.77 (s, 3H), 2.54 (t, J = 7.6 Hz, 2H), 2.28-2.06 (m, 2H), 1.62-1.49 (m, 2H), 1.30-1.08 (m, 8H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.2, 166.7, 166.6, 159.4, 151.9, 144.3, 134.0, 131.6, 130.1, 130.0, 129.0, 120.7, 117.1, 116.4, 114.1, 110.7, 110.0, 91.7, 55.0, 35.8, 33.8, 31.5, 31.1, 29.0, 28.9, 28.1; IR (neat): 3429, 2927, 2854, 2217, 1666, 1585, 1539, 1469, 1396, 1377, 1307, 1299, 1257, 1153, 1114, 1072, 1045, 1006, 860, 837, 802, 790, 694 cm^{-1}; HRMS-ESI (*m/z*): Calcd for $C_{29}H_{30}BrN_4O_2S$: 577.1273 $[M+H]^+$; found: 577.1266.

(E)-4-(3-Bromophenyl)-2-(2-cyano-10-(3-methoxyphenyl)dec-2-enylthio)-6-oxo-1,6-dihydropyrimidine-5-carbonitrile (15e): Sticky light yellow liquid; ^{1}H NMR (300 MHz, $CDCl_3$): δ7.83 (s, 1H), 7.72 (d, J = 7.8 Hz, 1H), 7.51 (d, J = 7.8 Hz, 1H), 7.22-7.13 (m, 2H), 6.77-6.68 (m, 3H), 6.37 (t, J = 7.6 Hz, 1H), 4.45 (brs, 1H), 3.89 (s, 2H), 3.77 (s, 3H), 2.54 (t, J = 7.6 Hz, 2H), 2.28-2.07 (m, 2H), 1.60-1.49 (m, 2H), 1.30-1.12 (m, 8H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.9, 168.6, 166.2, 159.4, 151.9, 144.3, 137.2, 134.2, 131.4, 129.9, 129.1, 127.2, 122.5, 120.8, 116.9, 116.5, 114.1, 110.7, 110.2, 91.9, 55.1, 35.9, 33.8, 31.6, 31.2, 29.1, 29.0, 28.9, 28.1; IR (neat): 3421, 2927, 2854, 2217, 1677, 1539, 1485, 1465, 1377, 1303, 1257, 1211, 1153, 1076, 1045, 1010, 883, 783, 694 cm^{-1}; HRMS-ESI (*m/z*): Calcd for $C_{29}H_{30}BrN_4O_2S$: 577.1273 $[M+H]^+$; found: 577.1244.

(E)-4-(4-Chlorophenyl)-2-((2-cyano-10-(3-methoxyphenyl)dec-2-en-1-yl)thio)-6-oxo-1,6-dihydropyrimidine-5-carbonitrile (15f): Sticky colorless liquid;^{1}H NMR (300 MHz, $CDCl_3$): δ 7.81 (d, J = 7.6 Hz, 2H), 7.35 (d, J = 7.6 Hz, 2H), 7.17 (t, J = 7.7 Hz, 1H), 6.78-6.67 (m, 3H), 6.37 (t, J = 7.7 Hz, 1H), 4.99 (brs, 1H), 3.97 (s, 2H), 3.78 (s, 3H), 2.55 (t, J = 7.6 Hz, 2H), 2.30-2.08 (m, 2H), 1.63-1.49 (m, 2H), 1.34-1.12 (m, 8H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.7, 159.4, 152.5, 144.3, 138.1, 133.4, 130.1, 129.1, 128.7, 120.8, 116.3, 114.1, 110.7, 109.8, 55.0, 35.8, 33.7, 31.5, 31.1, 29.0, 28.9, 28.1; IR (neat): 3429, 2927, 2854, 2217, 1658, 1593, 1539, 1488, 1400, 1377, 1307, 1292, 1257, 1153, 1091, 1045, 1002, 840, 783 cm^{-1}; HRMS-ESI (*m/z*): Calcd for $C_{29}H_{30}ClN_4O_2S$: 533.1778 $[M+H]^+$; found: 533.1807.

(E)-4-(3-Chlorophenyl)-2-(2-cyano-10-(3-methoxyphenyl)dec-2-enylthio)-6-oxo-1,6-dihydropyrimidine-5-carbonitrile (15g): Sticky colorless liquid; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.69-7.61 (m, 2H), 7.35-7.28 (m, 1H), 7.25-7.11 (m, 2H), 6.75-6.65 (m, 3H), 6.34 (t, J = 7.6 Hz, 1H), 5.46 (brs, 1H), 3.87 (s, 2H), 3.75 (s, 3H), 2.51 (t, J = 7.4 Hz, 2H), 2.25-2.01 (m, 2H), 1.59-1.47 (m, 2H), 1.31-1.06 (m, 8H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.8, 168.6, 166.2, 159.4, 151.9, 144.3, 137.0, 134.3, 131.2, 129.6, 129.0, 128.5, 126.7, 120.7, 116.9, 116.5, 114.1, 110.7, 110.1, 91.9, 55.0, 35.8, 33.7, 31.5, 31.2, 29.0, 28.9, 28.1; IR (neat): 3467, 2927, 2854, 2217, 1677, 1581, 1539, 1485, 1469, 1377, 1303, 1257, 1211, 1153, 1045, 1010, 891, 783 cm^{-1}; HRMS-ESI (*m/z*): Calcd for $C_{29}H_{30}ClN_4O_2S$: 533.1778 $[M+H]^+$; found: 533.1773.

(E)-2-(2-Cyano-10-(3-methoxyphenyl)dec-2-enylthio)-6-oxo-4-(thiophen-2-yl)-1,6-dihydropyrimidine-5-carbonitrile (15h): Sticky colorless liquid; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.28 (d, J = 3.6 Hz, 1H), 7.57 (d, J = 4.6 Hz, 1H), 7.17 (t, J = 7.6 Hz, 1H), 7.09 (t, J = 4.6 Hz, 3.6 Hz, 1H), 6.77-6.66 (m, 3H), 6.58 (t, J = 7.4 Hz, 1H), 5.85 (brs, 1H), 4.07-3.93 (m, 2H), 3.78 (s, 3H), 2.53 (t, J = 7.8 Hz, 2H), 2.36-2.21 (m, 2H), 1.62-1.49 (m, 2H), 1.40-1.16 (m, 8H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 165.3, 165.1, 159.5, 159.4, 152.0, 144.3, 139.5, 133.6, 132.2, 129.3, 129.1, 120.7, 116.3, 116.2, 114.1, 110.7, 109.8, 88.1, 55.0, 35.8, 33.3, 31.5, 31.1, 29.1, 29.0, 28.9, 28.1; IR (neat): 3429, 2927, 2854, 2217, 1666, 1581, 1546, 1527, 1469, 1415, 1388, 1346, 1288, 1257, 1149, 1114, 1045, 983, 864, 779, 725 cm^{-1}; HRMS-ESI (*m/z*): Calcd for $C_{27}H_{29}N_4O_2S_2$: 505.1732 $[M+H]^+$; found: 505.1767.

(E)-2-(2-Cyano-10-(3-methoxyphenyl)dec-2-enylthio)-4-(3,4-dichlorophenyl)-6-oxo-1,6-dihydropyrimidine-5-carbonitrile (15i): Sticky light yellow liquid; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.88-7.85 (m, 1H), 7.70 (d, J = 8.4 Hz, 1H), 7.43 (d, J = 8.4 Hz, 1H), 7.17 (t, J = 7.7 Hz, 1H), 6.78-6.68 (m, 3H), 6.39 (t, J = 7.4 Hz, 1H), 4.07 (brs, 1H), 3.95 (s, 2H), 3.77 (s, 3H), 2.54 (t, J = 7.4 Hz, 2H), 2.31-2.11 (m, 2H), 1.63-1.51 (m, 2H), 1.36-1.15 (m, 8H); ^{13}C NMR (75 MHz, $CDCl_3$): δ168.3, 165.2, 159.4, 152.1, 144.2, 135.9, 134.7, 132.8, 130.7, 130.3, 129.0, 127.6, 120.6, 116.4, 116.3, 114.0, 110.6, 109.9, 92.1, 55.0, 35.8, 33.7, 31.5, 31.1, 28.9, 28.8, 28.0 cm^{-1}; HRMS-ESI (*m/z*): Calcd for $C_{29}H_{29}Cl_2N_4O_2S$: 567.1467 $[M+H]^+$; found: 567.1391.

(E)-2-(2-Cyano-10-(3-propoxyphenyl)dec-2-enylthio)-6-oxo-4-phenyl-1,6-dihydropyrimidine-5-carbonitrile (15j): Sticky colorless liquid; ^{1}H NMR (300 MHz, $CDCl_3$): δ7.77-7.67 (m, 2H), 7.39-7.32 (m, 1H), 7.31-7.22 (m, 2H), 7.14 (t, J = 7.7 Hz, 1H), 6.75-6.65 (m, 3H), 6.32 (t, J = 7.6 Hz, 1H), 5.11 (brs, 1H), 3.93-3.91 (m, 4H), 2.52 (t, J = 7.7 Hz, 2H), 2.22-2.04 (m, 2H), 1.84-1.71 (sex, J = 7.1, 6.8 Hz, 2H), 1.60-1.47 (m, 2H), 1.27-1.07 (m, 8H), 1.01 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.7, 169.1, 167.8, 159.1, 151.7, 144.2, 135.5, 131.1, 129.0, 128.6, 128.3, 120.6, 118.0, 116.6, 114.7, 111.3, 110.2, 91.3, 69.3, 35.9, 33.6, 31.5, 31.2, 29.0, 28.9, 28.1, 22.6, 10.5; IR (neat): 2927, 2854, 2217, 1670, 1581, 1539, 1473, 1438, 1315, 1296, 1257, 1157, 1002, 860, 767, 694, 675 cm^{-1};

HRMS-ESI (*m/z*): Calcd for $C_{31}H_{35}N_4O_2S$: 527.2481 $[M+H]^+$; found: 527.2482.

(E)-2-(10-(3-Butoxyphenyl)-2-cyanodec-2-enylthio)-6-oxo-4-phenyl-1,6-dihydropyrimidine-5-carbonitrile (15k): Sticky colorless liquid; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.81 (d, J = 7.4 Hz, 2H), 7.41 (d, J = 7.3 Hz, 1H), 7.34 (t, J = 7.4, 7.3 Hz, 2H), 7.16 (t, J = 7.3 Hz, 1H), 6.76-6.67 (m, 3H), 6.36 (t, J = 7.6 Hz, 1H), 5.49 (brs, 1H), 3.98-3.88 (m, 4H), 2.53 (t, J = 7.7 Hz, 2H), 2.25-2.07 (m, 2H), 1.80-1.69 (m, 2H), 1.61-1.42 (m, 4H), 1.26-1.10 (m, 8H), 0.96 (t, J = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.2, 168.0, 167.9, 159.0, 151.9, 144.2, 135.3, 131.3, 129.0, 128.7, 128.3, 120.5, 116.5, 114.8, 114.7, 111.3, 110.0, 92.0, 67.4, 35.8, 33.6, 31.5, 31.3, 31.2, 29.0, 28.98, 28.9, 28.0, 19.2, 13.8; IR (neat): 2927, 2854, 2217, 1666, 1562, 1535, 1481, 1469, 1299, 1253, 1157, 1006 cm^{-1}; HRMS-ESI (*m/z*): Calcd for $C_{32}H_{37}N_4O_2S$: 541.2637 $[M+H]^+$; found: 541.2665.

(E)-2-(2-Cyano-10-(3-(pentyloxy)phenyl)dec-2-enylthio)-6-oxo-4-phenyl-1,6 dihydropyrimidine-5-carbonitrile (15l): Sticky colorless liquid;^{1}H NMR (300 MHz, $CDCl_3$): δ 7.79 (d, J = 7.7 Hz, 2H), 7.40 (d, J = 7.0 Hz, 1H), 7.32 (t, J = 7.7, 7.0 Hz, 2H), 7.15 (t, J = 7.6 Hz, 1H), 6.75-6.67 (m, 3H), 6.35 (t, J = 7.6 Hz, 1H), 4.15 (brs, 1H), 3.97-3.87 (m, 4H), 2.53 (t, J = 7.6 Hz, 2H), 2.25-2.04 (m, 2H), 1.81-1.72 (quin, J = 6.8 Hz, 2H), 1.61-1.50 (m, 2H), 1.48-1.33 (m, 4H), 1.29-1.12 (m, 8H), 0.91 (t, J = 6.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.1, 168.1, 167.9, 159.1, 151.7, 144.2, 135.6, 135.5, 131.1, 129.0, 128.6, 128.3, 120.5, 116.6, 114.7, 111.3, 110.2, 91.4, 67.7, 35.9, 33.6, 31.4, 31.2, 29.0, 28.9, 28.17, 28.1, 22.4, 19.4, 13.9; IR (neat): 3371, 2927, 2854, 2217, 1674, 1581, 1535, 1473, 1438, 1380, 1315, 1299, 1257, 1157, 1018, 771, 694 cm^{-1}; HRMS-ESI (*m/z*): Calcd for $C_{33}H_{39}N_4O_2S$: 555.2794 $[M+H]^+$; found: 555.2793.

(E)-2-(2-Cyano-10-(3-(hexyloxy)phenyl)dec-2-enylthio)-6-oxo-4-phenyl-1,6-dihydropyrimidine-5-carbonitrile (15m): Sticky colorless liquid; ^{1}H NMR (300 MHz, $CDCl_3$): δ7.90 (d, J = 7.4 Hz, 2H), 7.52-7.32 (m, 3H), 7.16 (t, J = 7.4 Hz, 1H), 6.76-6.68 (m, 3H), 6.39 (t, J = 7.6 Hz, 1H), 4.06-3.98 (m, 2H), 3.93 (t, J = 6.4 Hz, 2H), 3.54 (brs, 1H), 2.54 (t, J = 7.6 Hz, 2H), 2.30-2.10 (m, 2H), 1.81-1.71 (quin, J = 6.4 Hz, 2H), 1.61-1.51 (m, 2H), 1.49-1.41 (m, 2H), 1.37-1.31 (m, 4H), 1.28-1.11 (m, 8H), 0.89 (t, J = 6.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.1, 167.4, 167.0, 159.0, 152.0, 144.2, 135.2, 131.5, 129.0, 128.7, 128.4, 120.5, 116.5, 116.4, 114.7, 111.3, 109.9, 92.4, 67.7, 35.8, 33.6, 31.5, 31.3, 31.2, 29.2, 29.0, 28.9, 28.0, 25.6, 22.5, 13.9; IR (neat): 2927, 2854, 2217, 1666, 1581, 1539, 1473, 1438, 1377, 1296, 1253, 1157, 1006, 767, 694 cm^{-1}; HRMS-ESI (*m/z*): Calcd for $C_{34}H_{41}N_4O_2S$: 569.2950 $[M+H]^+$; found: 569.2984.

(E)-Methyl 2-(9-cyano-10-(5-cyano-6-oxo-4-phenyl-1,6-dihydropyrimidin-2-ylthio)dec-8-enyl)-6-methoxybenzoate (15n): Sticky colorless liquid; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.97 (d, J = 7.1 Hz, 2H), 7.59-7.44 (m, 3H), 7.26 (t, J = 7.7 Hz, 1H), 6.80 (d, J = 7.7 Hz, 1H), 6.76 (d, J = 8.3 Hz, 1H), 6.53-6.41 (m, 1H), 5.91 (brs, 1H), 4.15-4.04 (m, 2H), 3.89 (s, 3H), 3.80 (s, 3H), 2.51 (t, J = 7.7 Hz, 2H), 2.34-2.11 (m, 2H), 1.60-1.47 (m, 2H), 1.33-1.13 (m, 8H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.0, 168.9, 168.4, 164.4, 156.2, 152.5, 141.0, 134.8, 132.1, 130.2, 129.0, 128.9, 128.6, 128.5, 121.4, 116.1, 109.6, 108.4, 101.0, 55.8, 52.1, 33.6, 33.3, 31.5, 30.9, 29.1, 28.9, 28.7, 27.9; IR (neat): 2927, 2854, 2221, 1728, 1693, 1662, 1581, 1535, 1469, 1434, 1377, 1265, 1110, 1072, 1002, 767, 698 cm^{-1}; HRMS-ESI (*m/z*): Calcd for $C_{31}H_{33}N_4O_4S$: 557.2223 $[M+H]^+$; found: 557.2258.

(E)-Methyl 2-(9-cyano-10-(5-cyano-4-(4-methoxyphenyl)-6-oxo-1,6-dihydropyrimidin-2-ylthio)dec-8-enyl)-6-methoxybenzoate (15o): Colorless liquid; ^{1}H NMR (300 MHz, $CDCl_3$): δ8.03 (d, J = 8.7 Hz, 2H), 7.25 (t, J = 8.1 Hz, 1H), 6.95 (d, J = 8.7 Hz, 2H), 6.79 (d, J = 7.6 Hz, 1H), 6.75 (d, J = 8.1 Hz, 1H), 6.46 (t, J = 7.7 Hz, 1H), 4.10-4.03 (m, 2H), 3.89 (s, 3H), 3.85 (s, 3H), 3.79 (s, 3H), 2.50 (t, J = 7.6 Hz, 2H), 2.34-2.08 (m, 2H), 1.61-1.46 (m, 2H), 1.33-1.13 (m, 8H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.9, 167.2, 163.9, 162.9, 156.1, 152.3, 141.0, 131.1, 130.2, 126.9, 123.3, 121.4, 116.1, 115.8, 113.9, 109.6, 108.3, 91.8, 55.8, 55.4, 52.1, 33.4, 33.3, 31.5, 30.8, 29.1, 28.9, 28.7, 28.0; IR (neat): 2931, 2854, 2217, 1728, 1689, 1654, 1604, 1539, 1469, 1377, 1307, 1261, 1180, 1110, 1072, 1026, 999, 840, 783 cm^{-1}; HRMS-ESI (*m/z*): Calcd for $C_{32}H_{35}N_4O_5S$: 587.2328 $[M+H]^+$; found: 587.2322.

(E)-Methyl 2-(9-cyano-10-(5-cyano-4-(4-fluorophenyl)-6-oxo-1,6-dihydropyrimidin-2-ylthio)dec-8-enyl)-6-methoxybenzoate (15p): Sticky colorless liquid; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.87-7.78 (m, 2H), 7.22 (t, J = 7.8 Hz, 1H), 7.01 (t, J = 8.4 Hz, 2H), 6.76 (d, J = 7.7 Hz, 1H), 6.72 (d, J = 8.3 Hz, 1H), 6.34 (t, J = 7.7 Hz, 1H), 5.57 (brs, 1H), 3.99-3.89 (m, 2H), 3.86 (s, 3H), 3.77 (s, 3H), 2.48 (t, J = 7.7 Hz, 2H), 2.25-2.06 (m, 2H), 1.55-1.43 (m, 2H), 1.30-1.08 (m, 8H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.0, 168.2, 167.9, 166.6, 162.9, 156.2, 151.9, 141.0, 131.1, 131.0, 130.2, 123.3, 121.4, 117.0, 116.4, 115.6, 115.3, 110.0, 108.3, 91.6, 55.8, 52.1, 33.6, 33.3, 31.4, 30.8, 29.1, 28.9, 28.7, 28.0; IR (neat): 3452, 2931, 2854, 2217, 1731, 1689, 1600, 1581, 1539, 1508, 1469, 1373, 1307, 1265, 1242, 1141, 1087, 1072, 1060, 1006, 914, 848 cm^{-1}; HRMS-ESI (*m/z*): Calcd for $C_{31}H_{32}FN_4O_4S$: 575.2128 $[M+H]^+$; found: 575.2136.

(E)-Methyl 2-(10-(4-(4-bromophenyl)-5-cyano-6-oxo-1,6-dihydropyrimidin-2-ylthio)-9-cyanodec-8-enyl)-6-methoxybenzoate (15q): Sticky light yellow liquid; ^{1}H NMR (300 MHz, $CDCl_3$): δ7.79 (d, J = 8.3 Hz, 2H), 7.57 (d, J = 8.3 Hz, 2H), 7.25 (t, J = 7.7 Hz, 1H), 6.79 (d, J = 7.7 Hz, 1H), 6.75 (d, J = 8.3 Hz, 1H), 6.40 (t, J = 7.6 Hz, 1H), 4.07-3.99 (m, 2H), 3.89 (s, 3H), 3.80 (s, 3H), 2.51 (t, J = 7.6 Hz, 2H), 2.32-2.11 (m, 2H), 1.60-1.47 (m, 2H), 1.33-1.15 (m, 8H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.0, 167.2, 167.0, 165.2, 156.2, 152.4, 141.0, 133.7, 131.8, 130.3, 130.2, 126.9, 123.3, 121.4, 116.2, 115.5, 109.7, 108.3, 93.1, 55.8, 52.1, 33.6, 33.3, 31.5, 31.5, 29.1, 28.9, 28.7, 28.0; IR (neat): 3436, 2927, 2854, 2217, 1728, 1693, 1662, 1585, 1535, 1469, 1299, 1265, 1110, 1072, 1006, 837, 771 cm^{-1}; HRMS-ESI (*m/z*): Calcd for $C_{31}H_{32}BrN_4O_4S$: 635.1328 $[M+H]^+$; found: 635.1330.

(E)-Methyl 2-(10-(4-(4-chlorophenyl)-5-cyano-6-oxo-1,6-dihydropyrimidin-2-ylthio)-9-cyanodec-8-enyl)-6-methoxybenzoate (15r): Sticky light yellow liquid; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.86 (d, J = 8.4 Hz, 2H), 7.39 (d, J = 8.4

Hz, 2H), 7.25 (t, *J* = 7.8 Hz, 1H), 6.79 (d, *J* = 7.8 Hz, 1H), 6.75 (d, *J* = 8.3 Hz, 1H), 6.40 (t, *J* = 7.6 Hz, 1H), 4.07-3.99 (m, 2H), 3.89 (s, 3H), 3.79 (s, 3H), 2.51 (t, *J* = 7.6 Hz, 2H), 2.32-2.12 (m, 2H), 1.59-1.47 (m, 2H), 1.33-1.15 (m, 8H); ^{13}C NMR (75 MHz, $CDCl_3$): *δ* 169.0, 166.9, 166.1, 165.4, 156.2, 152.4, 141.1, 138.3, 133.3, 130.3, 128.9, 123.3, 121.4, 118.6, 116.3, 115.7, 109.8, 108.4, 93.1, 55.8, 52.2. 33.7, 33.3, 31.6, 30.9, 29.2, 28.9, 28.8, 28.1; IR (neat): 3440, 2931, 2854, 2217, 1728, 1693, 1662, 1581, 1539, 1469, 1377, 1307, 1265, 1110, 1091, 1083, 1002, 840, 786 cm^{-1}; HRMS-ESI (*m/z*): Calcd for $C_{31}H_{32}ClN_4O_4S$: 591.1833 $[M+H]^+$; found: 591.1828.

(E)-methyl 2-(10-(4-(3-chlorophenyl)-5-cyano-6-oxo-1,6-dihydropyrimidin-2-ylthio)-9-cyanodec-8-enyl)-6-methoxybenzoate (15s): Sticky colorless liquid; ^{1}H NMR (300 MHz, $CDCl_3$): *δ*7.71-7.63 (m, 2H), 7.39-7.31 (m, 1H), 7.28-7.18 (m, 2H), 6.78 (d, *J* = 7.8 Hz, 1H), 6.74 (d, *J* = 8.3 Hz, 1H), 6.35 (t, *J* = 7.7 Hz, 1H), 5.59 (brs, 1H), 3.95-3.83 (m, 5H), 3.78 (s, 3H), 2.49 (t, *J* = 7.6 Hz, 2H), 2.26-2.07 (m, 2H), 1.57-1.44 (m, 2H), 1.27-1.10 (m, 8H); ^{13}C NMR (75 MHz, $CDCl_3$): *δ* 169.5, 169.0, 167.5, 166.2, 156.1, 151.7, 143.1, 141.0, 134.3, 130.2, 129.7, 128.4, 126.6, 123.2, 121.4, 120.9, 116.5, 115.8, 110.3, 108.3, 91.5, 55.8, 52.1, 33.8, 33.3, 31.5, 30.9, 29.1, 28.9, 28.8, 28.0; IR (neat): 3429, 2927, 2854, 2217, 1728, 1647, 1581, 1539, 1469, 1380, 1303, 1265, 1207, 1161, 1110, 1072, 1010, 891, 790 cm^{-1}; HRMS-ESI (*m/z*): Calcd for $C_{31}H_{32}ClN_4O_4S$: 591.1833 $[M+H]^+$; found: 591.1835

(E)-Methyl 2-(9-cyano-10-(5-cyano-4-(3,4-dichlorophenyl)-6-oxo-1,6-dihydropyrimidin-2-ylthio)dec-8-enyl)-6-methoxybenzoate (15t): Sticky colorless liquid; ^{1}H NMR (300 MHz, $CDCl_3$): *δ* 7.83 (s, 1H), 7.66 (d, *J* = 8.3 Hz, 1H), 7.40 (d, *J* = 8.3 Hz, 1H), 7.24 (t, *J* = 8.1 Hz, 1H), 6.79 (d, *J* = 7.7 Hz, 1H), 6.74 (d, *J* = 8.1 Hz, 1H), 6.37 (t, *J* = 7.6 Hz, 1H), 4.27 (brs, 1H), 3.97-3.86 (m, 5H), 3.79 (s, 3H), 2.50 (t, *J* = 7.6 Hz, 2H), 2.30-2.08 (m, 2H), 1.59-1.46 (m, 2H), 1.33-1.11 (m, 8H); ^{13}C NMR (75 MHz, $CDCl_3$): *δ*169.0, 168.5, 168.0, 164.4, 155.5, 150.3, 140.3, 136.1, 133.9, 131.8, 129.8, 129.7, 127.3, 122.8, 120.8, 117.2, 116.1, 110.5, 107.8, 90.8, 55.2, 51.4, 32.8, 32.6, 30.8, 30.3, 28.5, 28.3, 28.1, 27.5 cm^{-1}; HRMS-ESI (*m/z*): Calcd for $C_{31}H_{31}Cl_2N_4O_4S$: 625.1443 $[M+H]^+$; found: 625.1446.

Conclusion

We have described a convenient and efficient protocol for the synthesis of novel Baylis-Hillman adducts and their acetates in fine yields under solvent-free conditions from inexpensive CNSL constituents and, evaluated for anticancer activity. The novelty of this protocol is mainly related to the use of CNSL components as starting materials for Baylis-Hillman adducts. Compounds **5b** and **5h** bearing methoxy functionality in the phenyl ring showed promising activity against MCF-7. Furthermore, we have described the synthesis, biological activity and structure-activity relationship of a series of twenty novel phenolic based pyrimidine derivatives. Baylis-Hillman adducts derived from CNSL renewable natural resources were employed as key precursors in the synthesis of these pyrimidine derivatives. Compounds **15i**, **15j** and **15l** showed promising activity against HEP-G2 with the GI_{50} value of 6.17, 2.87 and 4.56 μM respectively, whereas compounds **15j**, **15k**, **15l** and **15m** showed promising activity against MCF-7 with the GI_{50} value of 8.51, 8.64, 8.66 and 5.02 μM respectively. Compound **15m** showed high activity against K562 cell line with the GI_{50} value of 0.25 μM being similar to standard control. These results illustrated that alkyl substitutions on the aromatic ring areimportant for maintaining the antitumor activity. Our structure activity relationship (SAR) study around these scaffolds suggests thatnew antitumor agents with an improved biological profilecan be prepared for developing new clinical candidates.

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Supplementary Information

General experimental procedures, characterization details of **2-3**, **7-8**, and ^{1}H and ^{13}CNMR spectra of all synthesized compounds.

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