Bioorganic & Medicinal Chemistry Letters 22 (2012) 2251–2256

Contents lists available at SciVerse ScienceDirect

Bioorganic & Medicinal Chemistry Letters

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

One pot synthesis and anticancer activity of dimeric phloroglucinols ☆

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ARTICLE INFO

Article history:
Received 22 October 2011
Revised 5 January 2012
Accepted 24 January 2012
Available online 31 January 2012

Keywords:
Phloroglucinol
Anticancer
Dimeric
Cytotoxic
2,4-Diacetyl phloroglucinol

ABSTRACT

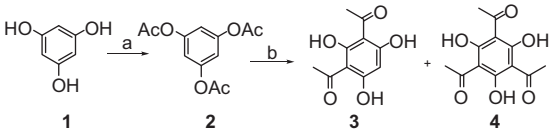
A series of dimeric phloroglucinol compounds were synthesized in a single step using commercially available phloroglucinol and methanesulfonic acid. Based on the reported anticancer activity of plant derived dimeric phloroglucinols, these synthesized compounds were evaluated for their in vitro anti-proliferative activities against various cancer cell lines. Several compounds demonstrated in vitro cytotoxic effects across a wide array of tumor cell types. The compound **29** with pyridin-3-yl group on linker methylene and two diisovaleryl phloroglucinol moieties was found to be the most active in all the five cancer cell lines having a low IC_{50} of 5.5 μM in colon cancer cell lines (HCT116).

Cancer is a fatal disease and a leading cause of death worldwide with projected 12 million deaths in 2030.[1] Several classes of anticancer drugs have been developed and many of them are of natural origin. Natural products have been the mainstay of cancer chemotherapy for the past 30 years.[2] However, most of the currently used anticancer drugs cause undesirable side effects due to lack of tumor specificity and multidrug resistance. Therefore the search for potent, safe and selective anticancer compounds is crucial for new drug development in cancer research. Natural products, due to their structural diversity, provide excellent templates for the construction of novel compounds.[2]

Naturally occurring dimeric phloroglucinol compounds have shown a diverse range of biological activities including anticancer activity.[3] Dimeric phloroglucinols comprise compounds having two phloroglucinol units joined either through a methylene linkage or by the formation of a chroman ring. Several dimeric phloroglucinol derivatives such as mallotojaponin, mallotochromene, mallotorin and mallotophenone have been isolated from *Mallotus japonicus* and evaluated for anticancer activity in various cancer cell lines.[4a–e] Mallotojaponin was found to be active in all the cancer cell lines, it inhibited tumor promoter-enhanced phospholipid metabolism in cultured cells, and also suppressed the promoting effect of 12-*O*-tetradecanoylphorbol-13-acetate on skin tumor formation in mice.[5,6] Several monomeric acylphloroglucinol derivatives from *Garcinia cowa* and *Hypericum prolificum* have also exhibited potent anticancer activity.[7,8]

As a part of our continuing efforts to synthesize naturally occurring phloroglucinol compounds and analogs to explore their biological potential,[9–12] herein, we report a novel synthesis of diacyl phloroglucinols and one pot synthesis of dimeric phloroglucinol compounds containing various functionalities by varying substitution at the methylene bridge. All the synthesized compounds were tested for their in vitro anti-proliferative activities against various cancer cell lines.

Earlier reported methods for synthesis of monomeric acylated phloroglucinol units require toxic catalysts such as $AlCl_3$,[9] $ZnCl_2$,[13] BF_3-etherate,[14] and toxic solvent nitrobenzene.[9] Some reports used BF_3-etherate as a solvent for the reactions.[14] Purification of final product required distillation of high boiling nitrobenzene. In this letter we report a simple and greener method for the synthesis of diacyl phloroglucinols and dimeric phloroglucinols using environment friendly methanesulfonic acid (MSA). Initially, solid catalysts such as basic alumina[15] and perchloric acid-silica[16] were



Scheme 1. Reagents and conditions: (a) Acetic anhydride, pyridine; (b) CH_3SO_2OH, 80 °C, 30 min.

☆ NIPER Communication Number 487.

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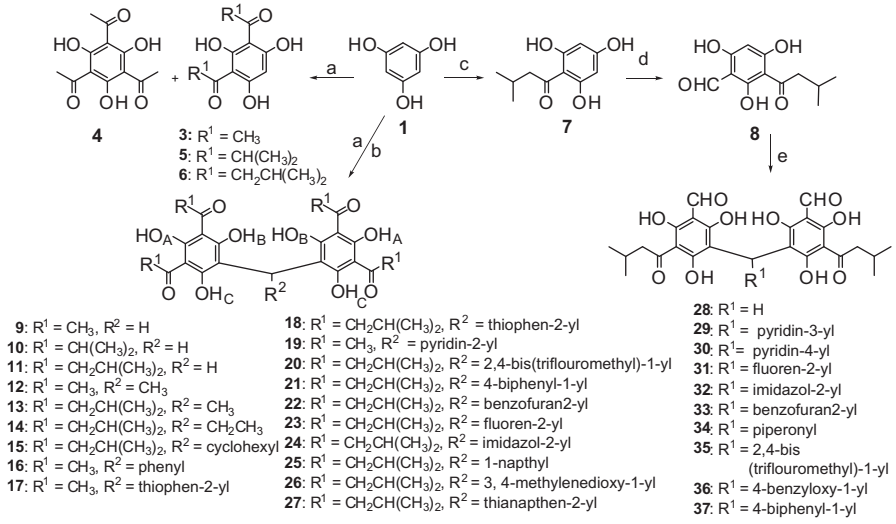
doi:10.1016/j.bmcl.2012.01.089

Table 1
Reaction conditions for synthesis of 2,4-diacetylphloroglucinol (DAPG)

Catalyst	Reaction conditions	Yield[a] (%)
4 mol equiv MSA	3 mol equiv Ac_2O, THF, 80 °C, 0.5 h	0
4 mol equiv MSA	3 mol equiv Ac_2O, Methanol, 80 °C, 0.5 h	0
3 mol. equiv MSA and 1 mol equiv acetic acid	3 mol equiv Ac_2O, 80 °C, 0.5 h	94
3 mol equiv MSA	3 mol equiv Ac_2O, 80 °C, 0.5 h	90
3 mol equiv MSA	2 mol equiv Ac_2O, 80 °C, 0.5 h	64
3 mol equiv MSA	3 mol equiv CH_3COCl, 80 °C, 0.5 h	92
3 mol equiv HCl	3 mol equiv Ac_2O, 80 °C, 0.5 h	0
3 mol equiv CH_3COOH	4 mol equiv Ac_2O, 80 °C, 0.5 h	0
3 mol equiv $HClO_4$	4 mol equiv Ac_2O, 80 °C, 0.5 h	0
3 mol equiv TFA	4 mol equiv Ac_2O, 80 °C, 0.5 h	50
3 mol equiv H_2SO_4	4 mol equiv Ac_2O, 80 °C, 0.5 h	0
3 mol equiv HBr/Acetic acid	4 mol equiv Ac_2O, 80 °C, 0.5 h	94
MSA/Alumina	4 mol equiv Ac_2O,80 °C, 0.5 h	0
MSA/Graphite	3 mol equiv CH_3COOH, 80 °C, 0.5 h	0
10 mol% of MSA and 1 mol equiv acetic acid	3 mol equiv Ac_2O, MW 700 W, 5 min	0
20 mol% of MSA and 1 mol equiv acetic acid	3 mol equiv Ac_2O, MW 700 W, 1 min	65
30 mol% of MSA and 1 mol equiv acetic acid	3 mol equiv Ac_2O, MW 700 W, 1 min	88

[a] Isolated yields after crystallization.



Scheme 2. Reagents and conditions: (a) RCOCl, CH_3SO_2OH, 80 °C, 30 min/RCOCl, CH_3SO_2OH, MW, 1 min, 700 W, (b) R-CHO, 15 min, (c) $AlCl_3$, isovaleryl chloride, $PhNO_2$, 1.5 h, (d) DMF, $POCl_3$, EtOAc, 1 h, (e) CH_3SO_2OH, R-CHO, 80 °C, 15 min.

employed for direct Friedel–Crafts C-acylation of phloroglucinol (**1**) using acetic anhydride as an acylating agent. Several variations with the amount of catalyst, temperature and solvent mostly gave 1,3,5-tri-*O*-acetyl phloroglucinol (**2**) and phloroacetophenone[9] as major and minor products, respectively. We have found that methanesulphonic acid (MSA), an environment friendly bronsted acid can also be used to synthesize the target compound through Fries rearrangement of 1,3,5-tri-*O*-acetyl phloroglucinol. First, 1,3,5-tri-*O*-acetyl phloroglucinol was reacted with 8 mol equiv of MSA at 80 °C for 30 min to yield a mixture of 2,4-diacetyl phloroglucinol (DAPG) (**3**) and 2,4,6-triacetyl phloroglucinol (**4**) in 8:2 ratio (Scheme 1).

Further, we have optimized the reaction in a single step for direct acylation of phloroglucinol (**1**) by varying the amount of MSA and acetic anhydride. Use of MSA less than 3 mol equiv resulted in an incomplete reaction. Use of solvent such as methanol or THF did not yield the desired products. The direct acylation of phloroglucinol (**1**) with 3 mol equiv of MSA, and 3 mol equiv Ac_2O at 80 °C for 0.5 h in neat condition gave 2,4-diacetylphloroglucinol (**3**) and 2,4,6-triacetyl phloroglucinol (**4**) in 8:2 ratio with 90% yield (Table 1). In order to minimize the formation of (**4**), we reduced the amount of acetic anhydride to 2 mol equiv, but it resulted incomplete reaction and low yield of the product. Finally addition of 1 mol equiv of acetic acid along with 3 mol equiv MSA and 3 mol equiv Ac_2O at 80 °C for 0.5 h in neat condition gave DAPG (**3**) and 2,4,6-triacetyl phloroglucinol (**4**) in 95:5 ratio with 94% yield (Table 1). We also tried different bronsted acids like CH_3COOH, HCl, H_2SO_4, HBr in acetic acid, and HCOOH with acetic anhydride at 80 °C to observe the outcome of the reaction, except HBr in acetic acid none of the acid catalysts gave the desired products. MSA adsorbed on alumina or graphite with Ac_2O at 80 °C also failed to yield the desired product. The reaction conditions for synthesis of DAPG were optimized further to limit the use of MSA from stoichiometric to catalytic amount using microwave irradiation. Initially reaction of phloroglucinol (**1**) with 10 mol % of MSA, 1 mol equiv acetic acid and 3 mol equiv of acetic anhydride at 700 W power for 5 min showed incomplete reaction and a mixture of products. Increasing the concentration of MSA from 10 to 30 mol% gave the desired DAPG (**3**) and **4** in 9:1 ratio with 88% yield (Table 1). This improved synthetic methodology using microwave heating as well as conventional heating was applied for synthesis of various diacyl derivatives using different acyl chlorides and anhydrides (Scheme 2). Reaction of diisobutyryl and diisovaleryl chloride with phloroglucinol (**1**) under similar reaction conditions gave

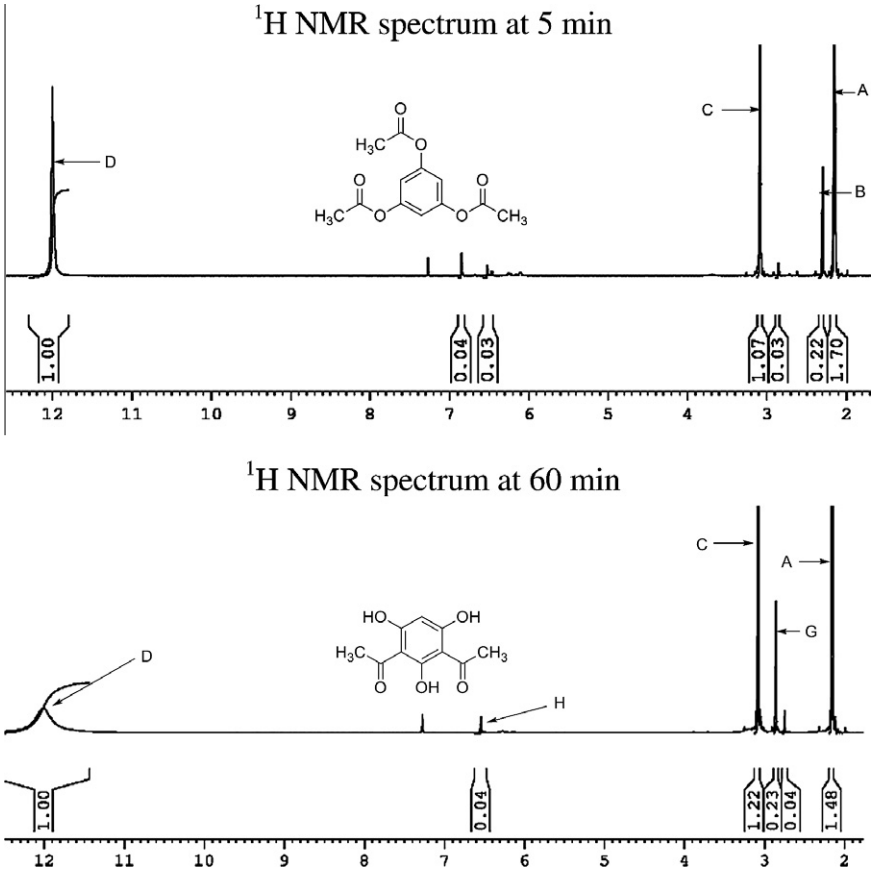


Figure 1. A = CH_3 of acetic acid, B = CH_3 of tri-*O*-acetyl phloroglucinol, C = CH_3 of MSA, D = OH of MSA, G = CH_3 of 2,4-diacetyl phloroglucinol (DAPG), H = Aromatic proton of DAPG.

Table 2
Cytotoxicity of dimeric phloroglucinol derivatives against various human cancer cell lines[a]

Compd	ACHN	Panc1	Calu1	H460	HCT116	Compd	ACHN	Panc1	Calu1	H460	HCT116
3	44	0	0	25	0	**21**	59	54	52	54	55
5	33	0	15	22	0	**22**	7	0	56	37	20
6	30	0	0	46	55	**23**	17	18	0	15	0
8	52	50	59	58	57	**24**	0	0	11	15	0
9	46	22	39	0	8	**25**	6	17	15	26	0
10	30	12	16	25	6	**26**	67	69	62	63	60
11	35	0	7	3	1	**27**	54	59	54	54	65
12	19	0	38	0	3	**28**	35	15	29	0	9
13	11	0	12	12	25	**29**	71	67	66	68	69
14	0	0	10	10	22	**30**	21	5	17	0	0
15	14	0	18	29	0	**31**	50	57	58	54	52
16	29	0	47	29	0	**32**	38	0	0	22	18
17	57	64	0	54	55	**33**	6	0	2	5	11
18	50	60	62	54	57	**34**	53	55	54	51	50
19	12	0	24	0	11	**35**	0	0	6	5	14
20	57	60	65	64	61	**36**	44	6	30	49	48
Gemcitabine (500 nM)	77	83	74	81	86	**37**	0	0	0	28	5

[a] The values given in the table is % death of cancer cells at 10 μm concentration, ACHN, renal cancer; Panc1, pancreatic cancer; Calu1, lung cancer, H460, non-small cell lung cancer; HCT116, colon cancer.

2,4-diisobutyryl phloroglucinol (**5**)[14] and 2,4-diisovaleryl phloroglucinol (**6**)[14] in 93% and 95% yield. No triisovaleryl or triisobutyryl phloroglucinol was formed in conventional as well as microwave heating. Steric hindrance due to bulky isovaleryl and isobutyryl groups may have provided the selectivity. In case of conventional heating, reaction of the bulky acyl chlorides required more time compared to short chain acyl chlorides. Bronsted acids were studied for Friedel–Crafts C versus O-acylation of phenols. Direct Friedel–Crafts C-acylation has been reported with strong bronsted acids.[17] Phloroglucinol nucleus is electron rich, therefore MSA catalyzed acylation of phloroglucinol (**1**) may proceed either by direct Friedel–Crafts C-acylation or through Fries rearrangement of the intermediate *O*-acetyl derivatives (**2**) or both the mechanisms operating simultaneously (Fig. S1, Supplementary data). Reaction of 3 mol equiv of MSA and 3 mol equiv Ac_2O at room temperature for 1 h gave 1,3,5-tri-*O*-acetyl phloroglucinol (**2**) and phloroacetophenone as major and minor products, respectively. This interesting observation showed that the minor product phloroacetophenone could be formed from direct Friedel–Crafts C-acylation. Hence, 1D NMR spectroscopy was employed to elucidate the

reaction mechanism for formation of diacetyl phloroglucinol derivatives. Acetylation of phloroglucinol (**1**) was done as discussed above and NMR spectra were recorded at different time intervals starting from 5 min of the reaction till the completion of the reaction. The ^{1}HNMR spectrum at 5 min showed CH_3 protons at δ 2.3 indicating the presence of intermediate 1,3,5-tri-*O*-acetyl phloroglucinol (**2**) (Fig. 1). As the reaction progressed, the intermediate slowly converted to DAPG (**3**), NMR spectra at 60 min showed CH_3 protons at δ 2.85 indicating the complete transformation into the DAPG (**3**) (Fig. 1). The ^{13}C NMR spectra at 5 and 60 min showed the characteristic ester and ketone carbonyl signals at 169.03 and 203.40, respectively.

These experiments concluded that the 2,4-diacetylphloroglucinol was formed through Fries migration (Figs. S2–S4, see Supplementary data).

3-Formyl phloroisovalerophenone moiety required for synthesis of dimeric phloroglucinol compounds (**28–37**) was synthesized in two steps.[9] The Friedel–Crafts acylation of phloroglucinol (**1**) using isovaleryl chloride resulted in formation of phloroisovalerophenone (**7**) in 70% yield. Treatment of **7** with Vilsmeier–Haack reagent ($POCl_3$, DMF) in ethyl acetate resulted in formation of 3-formyl phloroisovalerophenone (**8**) in 70% yield.

The synthetic methodology described for DAPG using conventional heating was extended for the synthesis of naturally occurring dimeric phloroglucinol derivatives. We envisaged that the acidic hydrogen of the diacyl phloroglucinol derivatives could be trapped with aldehyde molecules to form the bioactive dimeric phloroglucinol in a single step. Synthesis of **9**[17] was started with reaction of phloroglucinol (**1**), with 3 mol equiv MSA, 1 mol equiv acetic acid and 3 mol equiv Ac_2O at 80 °C for 0.5 h. After consumption of phloroglucinol in the reaction mixture, linker aldehyde was added to the reaction mixture and allowed to stir for another 15 min. TLC analysis in 50% ethyl acetate in hexane showed formation of the desired dimeric phloroglucinol. Similarly, other naturally occurring dimeric phloroglucinols with isovaleryl, isobutyryl and 3-formyl phloroisovalerophenone moieties viz. methylene-*bis*-(3,5-di-isobutanoyl-2,4,6-trihydroxybenzene) (**10**), methylene-*bis*-(3,5-di-isopentanoyl-2,4,6-trihydroxybenzene) (**11**), methylene-*bis*-(3-formyl-5-isopentanoyl-2,4,6-trihydroxybenzene) (**28**) and other dimeric phloroglucinols (**12–27** and **29–36**) were synthesized by varying the substitution on aromatic ring (changing acyl functionalities) and at methylene bridge (by using different aldehydes viz. saturated, aromatic and heteroaromatic) in a key condensation step as shown in Scheme 2. This methodology has wide applicability for one pot synthesis of naturally occurring dimeric phloroglucinol derivatives joined through the methylene linkage. The structures of synthesized compounds are shown in Scheme 2. The diacyl dimeric phloroglucinol compounds could be easily purified by crystallization. The dimers with formyl functionality were purified by RP-C_{18} silica gel column chromatography. All the compounds were characterized by IR, MS, ^{1}H NMR and ^{13}C NMR spectral data.

The single dose in vitro cytotoxicity screening assays of the analogs were carried out at 10 μM concentration. The human tumor cell line panel included non-small cell lung, colon, pancreas, and renal cancer cell lines. From the preliminary results (Table 2) dimeric phloroglucinols containing formyl substituents on the aromatic moiety exhibited good growth inhibition properties. The ten most active compounds from the preliminary screening were subsequently evaluated in four dose–response studies for their in vitro cytotoxic effects on growth parameters against each of human tumor cell lines. The dose response curves were created by plotting cytotoxic effect against the log 10 of the drug concentration for each cell line. IC_{50} values are presented in Table 3. Structure–activity relationship study was established by varying the aromatic and heteroaromatic substituents on linker methylene carbon and the acyl groups on aromatic phloroglucinol moieties containing two formyl groups. Monomeric diacyl phloroglucinol derivatives (**3, 5** and **6**) showed weak activity in the initial screening, while formyl phloroisovalerophenone (**8**) was active in all the cancer cell lines. Dimeric phloroglucinol nucleus with diisovaleryl, diisobutyryl, diacetyl and formyl-isovaleryl functionality (**9–11**) and **28** on the aromatic nuclei and devoid of substitution at methylene bridge were found weakly active in all the cancer cell lines. Next, different alkyl, aromatic, heteroaromatic were introduced on the linker methylene bridge. Results indicate that ten compounds (**8**, **17**, **18**, **20**, **21**, **26**, **27**, **29**, **31** and **34**) were active in all the five cancer cell lines. Moreover, the compounds were not toxic to normal cell lines (MCF10A, normal breast epithelium cell line). Among the ten active compounds **26** and **29** showed highest activity in all the cancer cell lines. Compound **29** with pyridin-3-yl group on linker methylene and two diisovaleryl phloroglucinol moieties was found to be the most active in all the five cancer cell lines having a lowest IC_{50} of 5.5 μM in colon cancer cell lines (HCT116). Compounds (**12–14**) possessing small alkyl substituents on linker methylene carbon were inactive or less active as compared to compounds with bulky aromatic substituents. Replacing acyl functionality with formyl group resulted in increased activity as observed in **8, 29** and **34**. This SAR study suggested the basic pharmacophore responsible for activity would be a dimeric phloroglucinol nucleus with long chain acyl (isovaleryl) and formyl substituents and linker methylene carbon substituted with bulky aromatic groups.

Table 3
IC_{50} values of selected diacyl and dimeric phloroglucinol derivatives in μM concentration

Compd	Cancer cell lines (IC_{50} value)[a]					
	ACHN	Panc1	Calu1	H460	HCT116	MCF10A[b]
8	8.9	8.5	9.1	9.4	9.7	>27.3
17	9.2	9.4	9.7	8.9	9.9	>30
18	>10	8.5	8.9	9.1	8.9	>30
20	8.8	8.3	8.5	8.6	9.2	27.6
21	8.9	9.1	7.9	8.3	8.6	>26.3
26	6.7	7.2	6.5	6.6	7.1	>30
27	9.9	9.8	9.5	9.7	9.8	>30
29	5.7	6.1	6.3	5.8	5.5	>30
31	9.9	9.6	8.8	9.2	9.4	26.2
34	8.9	8.8	9.2	8.6	9.5	25.9
Gemcitabine	0.48	0.11	0.52	0.23	0.32	>10

[a] The IC_{50} values, defined as the drug concentration at which 50% of cells are viable, were calculated from the respective logarithmic cytotoxicity curves of the different cancer cells.
[b] MCF10A: normal breast epithelium cells.

In conclusion, a novel one pot synthesis has been developed for diacyl and dimeric phloroglucinol derivatives starting from commercially available phloroglucinol and biodegradable methanesulfonic acid catalyst. Twenty five novel dimeric phloroglucinols have been synthesized and screened for in vitro anticancer activity in various cell lines. The long chain acyl (isovaleryl) and formyl substituents and linker methylene carbon substituted with bulky aromatic group were found essential for anticancer activity. This new synthetic method could be applicable to bulk scale synthesis of variety of new diacyl and dimeric phloroglucinol derivatives. The active compound (**29**) could be used as a lead molecule for further development of new anticancer therapeutic molecules.

Acknowledgment

Authors are thankful to Director, NIPER for support.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2012.01.089.

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General method for synthesis of diacyl and dimeric phloroglucinols using conventional heating: The mixture of phloroglucinol (**1**, 1 mmol), acid anhydride/acyl chloride (3 mmol), acetic acid (1 mmol) and methanesulfonic acid (3 mmol) was heated for 30 min at 80 °C. On cooling, water was added and the reaction mixture and was extracted with ethyl acetate. Crude diacyl phloroglucinol derivative were crystallised from methanol. In case of synthesis of dimeric phloroglucinol, after 30 min, the linker aldehyde was added to the reaction mixture and the reaction was continued for further 15 min. After completion of reaction (TLC), water was added to the reaction mixture and extracted with ethyl acetate. Organic layer was dried over sodium sulphate and the solvent was removed under vacuum and the crude product was purified by crystallisation from methanol. *General method for synthesis of diacyl phloroglucinol derivative using microwave (IFB, model: 30SC2 with functions to control heating) heating:* The mixture of phloroglucinol (**1**, 1 mmol), acid anhydride/acyl chloride (3 mmol), acetic acid (1 mmol) and methanesulfonic acid (30 mol %) was irradiated in microwave oven for 1 min. The reaction workup is similar to the conventional heating method. The yields are reported less than 50% as two equivalents of monomeric starting material produce 1 equiv of dimeric product. *Cell proliferation assay (CCK-8 assay):* All the cancer cells, Panc1, ACHN, H460, Calu1, HCT116, and MCF10A were obtained from the American Type Culture Collection (ATCC, Manassas, VA). Cells were maintained in Dulbecco's Modified Eagle Medium (DMEM, Sigma St. Louis, MO), supplemented with 10% fetal bovine serum Gibco (Paisley, Scotland), 100 U/ml penicillin (Sigma, St. Louis, MO) and 100-mg/ml streptomycin (Sigma St. Louis, MO). The cells were grown in 75-cm^2 culture flasks kept in a humidified (37 °C, 5% CO_2) incubator, and passaged on reaching 80% confluence. The assay is based on the reduction of water-soluble tetrazolium salt (WST-8; [2-(2-methoxy-4-nitrophenyl)-3-(4-nitrophenyl)-5-(2,4-disulfophenyl)]-2*H*-tetrazolium mono sodium salt) by dehydrogenase enzyme of live cells to give a yellow coloured product (formazan). 5×10^3 cells were seeded per well in a 96 well tissue culture grade plate and the plate was kept overnight at 37 °C in 5% CO_2 incubator. After overnight incubation, cells were treated with different concentrations of compounds/standard. An equal concentration of vehicle (DMSO-never exceeding 0.1%) was used as a control. At 48 h after treatment, aliquots of 5 μl of CCK-8 reagent were added to each well and incubated for 4 h at 37 °C. After appropriate incubation, the absorbance was measured on Tecan Sapphire multi-fluorescence micro-plate reader (Tecan, Germany, GmbH) at a wavelength of 450 nm corrected to 650 nm and normalized to controls. DMSO treated control cells were considered to have a cell viability of 100%. The average number of viable cells at different compound/standard concentrations was expressed as a percentage of the control.

Methyl-methylene-bis-(3,5-diacetyl-2,4,6-trihydroxybenzene) (**12**): Yield: 32%; yellow solid; mp 206–208 °C; UV ($CHCl_3$): λ_{max} ($\log\varepsilon$) 276 (4.37), 341 (3.92); IR (KBr): ν_{max} 3168, 1618, 1579, 1476, 1419, 1364, 1263, 1185, 1115, 1024 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 17.65 (s, 2H, 2× OH_C), 16.25 (s, 2H, 2× OH_B), 10.71 (br s, 1H, OH_A), 10.22 (br s, 1H, OH_A), 4.80 (q, J = 7.2 Hz, 1H), 2.76 (s, 6H), 2.73 (s, 6H), 1.79 (d, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 206.0, 205.7, 171.2, 168.2, 166.2, 108.9, 105.7, 104.6, 34.0, 32.9, 24.2, 17.6; CIMS: m/z 447 $[M+1]^+$, 237 $[M-C_{10}H_{10}O_5]$; analysis for $C_{22}H_{22}O_{10}$ (446.1), calcd, C, 59.19; H, 4.97; found, C, 59.10; H, 5.04. *Methyl-methylene-bis-(3,5-di-isopentanoyl-2,4,6-trihydroxybenzene)* **(13)**: Yield: 37%; yellow sticky mass; UV ($CHCl_3$): λ_{max} ($\log\varepsilon$) 285 (4.49), 340 (4.15); IR (Neat): ν_{max} 3403, 2949, 1615, 1581, 1459, 1399, 1459, 1399, 1195, 1044 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 17.94 (br s, 2H, 2× OH_C), 16.46 (s, 2H, 2× OH_B), 10.70 (br s, 1H, OH_A), 10.22 (br s, 1H, OH_A), 4.80 (q, J = 7.2 Hz, 1H), 3.05 (d, J = 6.5 Hz, 8H), 2.27 (m, 4H), 1.79 (d, J = 7.2 Hz, 3H), 1.00 (d, J = 6.4 Hz, 24H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 208.5, 208.0, 171.2, 167.2, 163.1, 109.2, 105.7, 104.7, 53.9, 52.9, 25.7, 23.3, 17.7; CIMS: m/z 321$[M-C_{10}H_{10}O_5]$; analysis for $C_{34}H_{46}O_{10}$ (614.3), calcd, C, 66.43; H, 7.54; found, C, 66.52; H, 7.49. *Ethyl-methylene-bis-(3,5-di-isopentanoyl-2,4,6-trihydroxybenzene)* **(14)**: Yield: 41%; yellow oil; UV ($CHCl_3$): λ_{max} ($\log\varepsilon$) 285 (4.48), 337 (4.13); IR (Neat): ν_{max} 3199, 2960, 2873, 1616, 1584, 1466, 1367, 1367, 1301, 1200, 1047 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 18.00 (s, 1H, OH_C), 17.76 (s, 1H, OH_C), 16.45 (s, 2H, 2× OH_B), 10.87 (s, 1H, OH_A), 10.06 (s, 1H, OH_A), 4.44 (t, J = 7.7 Hz, 1H), 3.06 (d, J = 6.5 Hz, 8H), 2.27 (m, 6H), 1.00 (d, J = 6.4 Hz, 24H), 0.87 (t, J = 7.2 Hz, 3H, overlapped); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 208.7, 208.1, 171.2, 169.6, 166.1, 107.9, 105.7, 104.6, 53.9, 52.9, 32.7, 25.7, 24.3, 23.3, 12.8; CIMS: m/z 335$[M-C_{10}H_{10}O_5]$; analysis for $C_{35}H_{48}O_{10}$ (628.3), calcd, C, 66.86; H, 7.69; found, C, 66.70; H, 7.82. *Cyclohexyl-methylene-bis-(3,5-di-isopentanoyl-2,4,6-trihydroxybenzene)* **(15)**: Yield: 33%; reddish brown solid; mp 158–160 °C; UV ($CHCl_3$): λ_{max} ($\log\varepsilon$) 282 (4.49), 341 (3.90); IR (KBr): ν_{max} 3199, 2957, 2930, 1618, 1579, 1467, 1365, 1300, 1197, 1052 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 18.04 (s, 1H, OH_C), 17.74 (s, 1H, OH_C), 16.46 (s, 1H, OH_B), 16.42 (s, 1H, OH_B), 10.96 (s, 1H, OH_A), 10.07 (s, 1H, OH_A), 4.17 (d, J = 10.8 Hz, 1H), 3.01 (br s, 8H), 2.82 (m, 1H), 2.27 (m, 4H), 1.74–1.52 (m, 6H), 1.00 (d, J = 5.7 Hz, 24H), 0.80–0.74 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 208.2, 208.0, 171.1, 169.1, 163.3, 166.4, 166.0, 107.4, 107.1, 105.6, 104.5, 53.9, 53.0, 43.8, 37.5, 36.6, 32.9, 30.3, 26.8, 26.6, 25.9, 25.7, 23.3; CIMS: m/z 683 $[M+1]^+$, 389 $[M-C_{10}H_{10}O_5]$; analysis for $C_{39}H_{54}O_{10}$ (682.4), calcd, C, 68.60; H, 7.97; found, C, 68.49; H, 8.06. *Phenyl-methylene-bis-(3,5-diacetyl-2,4,6-trihydroxybenzene)* **(16)**: Yield: 30%; cream colored solid; mp 109–111 °C; UV ($CHCl_3$): λ_{max} ($\log\varepsilon$) 272 (4.22), 339 (3.39); IR (KBr): ν_{max} 2925, 2676, 2562, 1688, 1603, 1584, 1455, 1424, 1327, 1292, 1180, 1128, 1073, 1027 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 17.65 (s, 2H, 2× OH_C), 16.37 (s, 2H, 2× OH_B), 10.21 (s, 2H, 2× OH_A), 7.30–7.23 (m, 3H), 7.10 (d, J = 7.3 Hz, 2H), 6.17 (s, 1H), 2.78 (s, 6H), 2.72 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 205.9, 205.6, 171.6, 169.2, 166.6, 137.5, 128.9, 127.1, 127.0, 106.5, 105.8, 104.9, 34.0, 33.7, 32.9, 30.2; CIMS: m/z 299 $[M-C_{10}H_{10}O_5]$; analysis for $C_{27}H_{24}O_{10}$ (508.1), calcd, C, 63.78; H, 4.76; found, C, 63.64; H, 4.65. *Thiophen-2-yl-methylene-bis-(3,5-diacetyl-2,4,6-trihydroxybenzene)* **(17)**: Yield: 42%; yellowish green solid; mp 178–180 °C; UV ($CHCl_3$): λ_{max} ($\log\varepsilon$) 272 (4.29), 334 (3.65); IR (KBr): ν_{max} 3179, 1616, 1579, 1481, 1409, 1365, 1262, 1186, 1116; ^1H NMR ($CDCl_3$, 300 MHz): δ 17.80 (s, 2H, 2× OH_C), 16.39 (s, 2H, 2× OH_B), 10.32 (s, 2H, 2× OH_A), 7.19 (d, J = 5.0 Hz, 1H), 6.91 (t, J = 4.0 Hz, 1H), 6.70 (s, 1H), 6.26 (s, 1H), 2.78 (s, 6H), 2.73 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 206.0, 205.7, 171.8, 169.2, 166.3, 142.9, 127.0, 125.4, 124.9, 106.9, 106.8, 105.4, 34.0, 32.8, 31.1; CIMS: m/z 305 $[M-C_{10}H_{10}O_5]$; analysis for $C_{25}H_{22}O_{10}S$ (514.1), calcd, C, 58.36; H, 4.31; S, 6.23; found, C, 58.22; H, 4.44; S, 6.11.*Thiophen-2-yl-methylene-bis-(3,5-di-isopentanoyl-2,4,6-trihydroxybenzene)* **(18)**: Yield: 51%; dark yellow solid; mp 170–172 °C; UV ($CHCl_3$): λ_{max} ($\log\varepsilon$) 286 (4.56), 340 (3.99); IR (KBr): ν_{max} 3172, 2958, 2870, 1615, 1577, 1470, 1434, 1202, 1169, 1128, 1067 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 18.06 (s, 2H, 2× OH_C), 16.60 (s, 2H, 2× OH_B), 10.33 (s, 2H, 2× OH_A), 7.19 (d, J = 5.1 Hz, 1H), 6.92 (dd, J = 3.6, 5.0 Hz, 1H), 6.70 (t, J = 1.6 Hz, 1H), 6.25 (s, 1H), 3.05 (d, J = 6.1 Hz, 8H), 2.27 (m, 4H), 1.00 (d, J = 4.9 Hz, 24 H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 207.9, 207.6, 171.3, 168.9, 165.4, 142.8, 126.4, 124.9, 124.3, 106.6, 105.2, 104.3, 53.3, 52.3, 31.2, 25.2, 23.3; CIMS: m/z 390 $[M-C_{10}H_{10}O_5]$; analysis for $C_{37}H_{46}O_{10}S$ (682.3), calcd, C, 65.08; H, 6.79; S, 4.70; found, C, 65.19; H, 6.87; S, 4.59. *Pyridin-2-yl-methylene-bis-(3,5-diacetyl-2,4,6-trihydroxybenzene)* (**19**): Yield: 44%; brown solid; mp 230–232 °C; UV ($CHCl_3$): λ_{max} ($\log\varepsilon$) 276 (4.32), 339 (3.53); IR (KBr): ν_{max} 3096, 2933, 1610, 1454, 1360, 1294, 1219, 1117, 1028 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz): δ 17.09 (s, 1H, O*H*), 8.82 (d, J = 5.3 Hz, 1H), 8.56 (br s, 1H), 8.00 (s, 1H), 7.84 (d, J = 7.9 Hz, 1H), 6.94 (s, 1H), 2.86 (s, 6H), 2.81 (s, 6H); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 204.1, 172.7, 160.1, 145.2, 143.1, 125.2, 124.0, 106.0, 33.4, 32.8; CIMS: m/z 510 $[M+1]^+$, 300 $[M-C_{10}H_{10}O_5]$; analysis for $C_{26}H_{23}NO_{10}$ (509.1), calcd, C, 61.30; H, 4.55; N, 2.75; found, C, 61.21; H, 4.39; N, 2.60. *2,4-bis-(triflouromethyl)-1-yl-methylene-bis-(3,5-di-isopentanoyl-2,4,6-trihydroxybenzene)* **(20)**: Yield: 40%; yellow crystals, mp 211–213 °C, ^1H NMR ($CDCl_3$, 300 MHz): δ7.93 (s, 1H), 7.75 (d, J = 8.1 Hz, 1H), 7.48 (d, J = 8.1 Hz, 1H), 6.59 (s, 1H), 2.99–3.07 (Overlapped signals, 8H), 2.26 (m, 4H) , 0.99 (d, J = 6.6 Hz, 24H) ^{13}C NMR ($CDCl_3$, 75 MHz): δ 208.4, 208.1, 207.5, 207.2, 171.6, 168.5, 166.1, 165.6, 142.2, 130.2, 130.00, 129.7, 129.3, 129.08, 128.8, 128.4, 126.1, 125.7, 124.9, 122.4, 122.1, 106.7, 105.7, 104.9, 53.9, 53.5, 52.9, 30.1, 25.6, 23.2 ; MALDI-TOF: m/z 812.02. *4-Biphenyl-1-yl-methylene-bis-(3,5-di-isopentanoyl-2,4,6-trihydroxybenzene)* (**21**): Yield: 43%; yellow crystals, mp 227–229 °C, ^1H NMR ($CDCl_3$, 300 MHz): δ 17.95 (br s, 2H, 2× OH_C), 16.57 (s, 2H, 2× OH_B), 10.32 (br s, 2H, 2× OH_A), 7.57 (d, J = 7.3 Hz, 2H), 7.49 (d, J = 8.1 Hz, 2H), 7.40 (t, 2H), 7.30 (d, J = 7.2 Hz, 1H), 7.15 (d, J = 8.0 Hz, 2H), 6.18 (s, 1H), 3.03 (d, J = 12 Hz, 8H), 2.27 (m, 4H), 0.99 (d, J = 5.5 Hz, 24 H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 208.4, 208.2, 171.6, 169.4, 166.2, 141.1, 139.8, 136.8, 129.3, 127.7, 127.6, 127.5, 106.7, 105.8, 104.9, 53.8, 52.9, 33.7, 25.7, 23.3; MALDI-TOF: m/z 751.47. calcd, C, 71.79; H, 6.96; found, C, 71.75.; H, 6.94. *Benzofuran-2-yl-methylene-bis-(3,5-di-isopentanoyl-2,4,6-trihydroxybenzene)* **(22)**: Yield: 41%; yellow crystals, mp 186–188 °C, IR (KBr): ν_{max} 3435, 2958, 1614, 1580, 1466, 1301, 1199, 1108, ^1H NMR ($CDCl_3$, 300 MHz): δ 17.95 (br s, 2H, 2× OH_C), 16.57 (s, 2H, 2× OH_B), 10.32 (br s, 2H, 2× OH_A), 7.48 (d, 1H), 7.33 (d, 1H), 7.16–7.21 (m, 2H), 6.42 (s, 1H), 6.17 (s, 1H), 2.92 (d, J = 12 Hz, 8H), 2.28 (m, 4H), 0.98 (d, J = 5.5 Hz, 24 H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 208.4, 208.2, 172.1, 169.2, 165.8, 155.4, 129.0, 125.5, 124.2, 123.6, 120.9, 111.4, 110.1, 105.7, 105.4, 53.8, 52.7, 37.3, 25.4, 23.3; MALDI-TOF: m/z 717.4. *Flourene-2-yl-methylene-bis-(3,5-di-isopentanoyl-2,4,6-trihydroxybenzene* **(23)**: Yield: 40%; yellow crystals, mp 204–206 °C; ^1H NMR ($CDCl_3$, 300 MHz): δ 17.95 (br s, 2H, 2× OH_C), 16.60 (s, 2H, 2× OH_B), 10.32 (br s, 2H, 2× OH_A), 7.72 (d, J = 7.2 Hz, 1H), 7.66 (d, J = 7.8 Hz, 1H), 7.49 (d, J = 7.2, 1H), 7.32–7.25 (m, 3H), 7.11 (d, J = 8.1, 1H), 6.24 (s, 1H), 3.81 (s, 2H), 3.06 (d,

J = 10.6 Hz, 8H), 2.28 (m, 4H), 0.99 (d, *J* = 6.7 Hz, 24 H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 208.4, 208.2, 171.6, 169.5, 166.2, 144.0, 143.8, 141.9, 140.7, 136.3, 127.3, 127.1, 125.8, 125.5, 123.7, 120.3, 120.2, 107.0, 105.8, 104.9, 53.9, 52.9, 37.5, 34.1, 25.7, 23.3; calculated *m*/*z* for $C_{46}H_{52}O_{10}$ (764.36), found CIMS: *m*/*z* 471 [M−$C_{16}H_{21}O_5$]. calcd, C, 72.23; H, 6.85 found, C, 72.28; H, 6.79. *Imidazole-2-yl-methylene-bis-(3,5-di-isopentanoyl-2,4,6-trihydroxy benzene)* **(24)**: Yield: 41%; white solid; mp 222–224 °C UV ($CHCl_3$): λ_{max} (log ε) 280 (4.51), 340 (3.72); IR (Neat): ν_{max} 3435, 2957, 1614, 1416, 1124, 917 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 16.81 (s, 2H, 2× O*H*$_C$), 15.31 (s, 2H, 2× O*H*$_B$), 7.18 (s, 2H), 7.02 (s, 1H), 3.38 (d, *J* = 8.7 Hz, 2H), 3.11 (d, *J* = 8.7 Hz, 2H), 2.69 (d, *J* = 7.8 Hz, 2H), 2.36 (d, *J* = 9.6 Hz, 2H), 2.15 (m, 2H), 2.19 (m, 2H), 0.95 (d, *J* = 6.7 Hz, 24 H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 208.1, 206.4 174.4, 174.1, 170.3, 152.2, 118.3, 107.1, 104.6, 102.8, 53.3, 53.09, 27..07, 26.2, 25.8, 23.6, 23.4, 23.2, 23.1; MALDI-TOF: *m*/*z* 667.6. calcd, C, 64.85; H, 6.95; N, 4.20; found, C, 64.78; H, 6.86; N, 4.25. *1-Napthyl-methylene-bis-(3,5-di-isopentanoyl-2,4,6-trihydroxy benzene)* **(25)**: Yield: 35%; brown crystals; mp 255–256 °C ^{1}H NMR ($CDCl_3$, 300 MHz): δ 16.40 (s, 2H, 2× O*H*$_C$), 10.42 (s, 2H, 2× O*H*$_A$), 7.86 (d, *J* = 8.1 Hz, 1H), 7.80 (d, *J* = 8.1 Hz, 1H), 7.60–7.77 (m, 2H), 7.56 (d, *J* = 8.7 Hz, 1H), 7.44–7.28 (aromatic protons, 3H), 6.56 (s, 1H), 3.04 (d, *J* = 10.6 Hz, 8H), 2.27 (m, 4H), 0.98 (d, *J* = 6.3 Hz, 24 H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 208.2, 171.1, 137.1, 135.8, 134.7, 133.3, 132.1, 129.7, 129.0, 128.8, 127.5, 126.6, 126.1, 125.6, 125.4, 123.4, 105.3, 53.5, 32.9, 25.7, 23.3, calculated *m*/*z* for $C_{43}H_{50}O_{10}$ (726.34), found CIMS: *m*/*z* 727.3 *3,4-methylenedioxy-1-yl-methylene-bis-(3,5-di-isopentanoyl-2,4,6-trihydroxybenzene)* **(26)**: Yield: 41%; yellow solid; mp 186–188 °C ^{1}H NMR ($CDCl_3$, 300 MHz): δ 17.9 (br s, 2H, 2× O*H*$_C$), 16.56 (s, 2H, 2× O*H*$_B$), 10.24 (br s, 2H, 2× O*H*$_A$), 6.71 (d, *J* = 8.1 Hz, 1H), 6.58 (s, 1H), 6.55 (d, *J* = 8.7 Hz, 1H), 6.07 (s, 1H), 5.94 (s, 1H), 3.04 (d, *J* = 14.4 Hz, 8H), 2.26 (m, 4H), 0.99 (d, *J* = 6.5 Hz, 24 H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 208.4, 208.1, 171.5, 169.3, 166.1, 148.5, 146.6, 131.4, 119.9, 108.4, 107.9, 106.7, 105.7, 104.8, 101.6, 53.8, 52.8, 33.6, 25.7, 23.3, MALDI-TOF: *m*/*z* 720.471. *Thianapthene-2-yl-methylene-bis-(3,5-di-isopentanoyl-2,4,6-trihydroxybenzene)* (**27**): Yield: 43%; yellow crystals; mp 172–174 °C ^{1}H NMR ($CDCl_3$, 300 MHz): δ 16.48 (s, 2H, 2× O*H*$_B$), 10.24 (br s, 1H, O*H*$_A$), 9.88 (br s, 1H, O*H*$_A$), 7.83 (d, *J* = 7.1 Hz, 1H), 7.17–7.35 (Overlapped signals, 3H), 7.06 (s, 1H), 6.16 (s, 1H), 3.05 (d, *J* = 10.6 Hz, 8H), 2.27 (m, 4H), 0.98 (d, *J* = 6.7 Hz, 24 H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 208.3, 171.4, 168.9, 141.05, 138.7, 132.0, 124.9, 124.6, 123.5, 121.9, 106.8, 105.6, 104.9, 53.8, 53.0, 31.0, 25.7, 23.3; calculated *m*/*z* for $C_{41}H_{48}O_{10}S$ (732.88), found CIMS: *m*/*z*; 732.3. calcd, C, 67.19; H, 6.60; found, C, 67.23; H, 6.58.

General experimental procedures for compound 29–37

The mixture of 3-formyl phloroisovalerophenone (**8**) (1 mmol), methanesulfonic acid (3 mmol) and aldehyde (0.5 mmol) in was heated at 80 °C for 30 min. After completion of reaction (TLC), water was added to the reaction mixture and extracted with ethyl acetate. Organic layer was dried over sodium sulphate and the solvent was removed under vacuum and the crude product was purified by reverse phase silica gel column chromatography using methanol: water as eluent.

Pyridine-3-yl-methylene-bis-(3-isopentanoyl-5-formyl-2,4,6-trihydroxybenzene) (**29**): Yield: 44%; yellow solid; mp 156–157 °C; UV $CHCl_3$): λ_{max} (log ε) 268 (3.40); IR (KBr): ν_{max} 3470, 2930, 1630, 1545, 1470, 1366, 1302, 1045 cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz): δ 9.90 (s, 2H), 8.48 (d, *J* = 5.4 Hz, 1H), 8.27 (s, 1H), 7.69 (d, *J* = 7.5 Hz, 1H), 7.54 (t, *J* = 4.8 Hz, 1H), 6.56 (s, 1H), 2.88 (d, *J* = 5.4 Hz, 4H), 2.10 (m, 2H), 0.83 (d, *J* = 6.6 Hz, 12H); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 209.0, 207.0, 194.9, 192.1, 173.6, 171.4, 146.2, 142.0, 140.0, 127.9, 107.8, 103.1, 53.9, 32.0, 26.9, 23.5; Calcd *m*/*z* for $C_{30}H_{31}NO_{10}$ (565.57): found CIMS: *m*/*z* 566.1, analysis for $C_{30}H_{31}NO_{10}$ C, 67.71; H, 5.52; N, 2.48. Found: C, 67.62; H, 5.56; N, 2.43. *Pyridine-4-yl-methylene-bis-(3-isopentanoyl-5-formyl-2,4,6-trihydroxybenzene)* **(30)**: Yield: 40%; yellow solid; mp 158–159 °C ^{1}H NMR (CD_3OD, 300 MHz): δ 9.89 (s, 2H), 8.38 (d, *J* = 5.3 Hz, 2H), 7.78 (d, *J* = 5.3 Hz, 2H), 2.86 (d, *J* = 5.4 Hz, 4H), 2.14 (m, 2H), 0.87 (d, *J* = 6.6 Hz, 12H); ^{13}C NMR (CD_3OD, 75 MHz): δ 206.9, 194.9, 191.8, 173.4, 164.4, 145.3, 126.1, 108.3, 53.9, 34.6, 31.1, 26.6, 23.5; calculated *m*/*z* for $C_{30}H_{31}NO_{10}$ (565.57), found CIMS: *m*/*z* 566.0. calcd, C, 63.71; H, 5.52; N, 2.48; found, C, 63.77; H, 5.49; N, 2.43. *Flourene-2-yl-methylene-bis-(3-isopentanoyl-5-formyl-2,4,6-trihydroxybenzene)* (**31**): Yield: 41%; yellow solid; mp 216–218 °C IR (Neat): ν_{max} 3369, 1618, 1404, 1344, 1275, 1261, 1126, 1053 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 17.90 (br s, 2H, 2× O*H*), 14.68 (s, 2H, 2× O*H*), 10.16 (s, 1H) 7.72 (d, *J* = 7.2 Hz, 1H), 7.66 (d, *J* = 7.8 Hz, 1H), 7.49 (d, *J* = 7.2, 1H), 7.32–7.25 (m, 3H), 7.11 (d, *J* = 8.1, 1H), 6.20 (s, 1H), 3.82 (s, 2H), 3.03 (d, *J* = 5.7 Hz, 4H), 2.26 (m, 2H), 1.00 (d, *J* = 6.3 Hz, 12 H), ^{13}C NMR ($CDCl_3$, 75 MHz): 208.11, 194.0, 171.4, 169.5, 166.1, 144.2, 143.8, 141.7, 140.9, 135.4, 127.3, 127.2, 125.7, 125.5, 123.6, 120.3, 107.3, 106.4 105.7, 104.4, 52.6, 37.5, 33.4, 32.4, 30.2, 25.6, 23.3; MALDI-TOF: *m*/*z* 652.08. calcd, C, 69.93; H, 5.56; found, C, 69.87; H, 5.45. *Imidazole-2-yl-methylene-bis-(3-isopentanoyl-5-formyl-2,4,6-trihydroxybenzene)* (**32**): Yield: 43%; white solid; IR (Neat): ν_{max} 3431, 2919, 1614, 1404, 1275, 1260, 1109 cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz): δ 16.05 (br s, 1H, O*H*$_C$), 15.92 (s, 1H, O*H*$_C$), 15.12 (s, 1H, O*H*$_B$), 13.68 (br s, 1H, O*H*$_A$), 13.46 (s, 1H, O*H*$_A$), 9.94 (s, 2H), 7.47 (s, 2H), 6.55 (s, 1H), 2.93 (d, *J* = 5.7 Hz, 4H), 2.15 (m, 2H), 0.92 (d, *J* = 6.3 Hz, 12H), ^{13}C NMR (DMSO-d_6, 75 MHz): δ 207.0, 204.9, 193.6, 190.2, 173.3, 171.7, 170.4, 167.3, 148.8, 119.0, 106.5, 104.3, 101.3, 51.9, 25.7, 25.1, 22.9; MALDI-TOF: *m*/*z* 555.13. calcd, C, 60.64; H, 5.45; N, 5.05; found, C, 60.61; H, 5.36; N, 4.96. *Benzofuran-2-yl-methylene-bis-(3-isopentanoyl-5-formyl-2,4,6-trihydroxybenzene)* (**33**): Yield: 39%; cream colored solid; IR (Neat): ν_{max} 3369, 2958, 2869, 1620, 1275, 1454, 1425, 1187, 1123 cm^{-1}; ^{1}H NMR (CD_3OD, 300 MHz): δ 10.04 (s, 2H) 7.38 (d, 1H), 7.29 (d, 1H), 7.08 (m, 2H), 6.55 (s, 1H), 6.29 (s, 1H), 2.94 (d, *J* = 5.7 Hz, 4H), 2.18 (m, 2H), 0.93 (d, *J* = 6.3 Hz, 12 H); ^{13}C NMR (CD_3OD, 75 MHz): δ 205.2, 192.4, 171.0, 168.7, 168.1, 157.3, 154.2, 128.0, 122.1, 121.7, 119.1, 113.0, 109.4, 105.0, 104.0, 101.5, 51.5, 28.5, 24.3, 21.02; MALDI-TOF: *m*/*z* 621.36 (M+NH_3). calcd, C, 65.56; H, 5.33; found, C, 65.63; H, 5.39. *3,4-Methylenedioxy-1-yl-methylene-bis-(3-isopentanoyl-5-formyl-2,4,6-trihydroxybenzene)* (**34**): Yield: 46%; yellow solid; mp 190–192 °C; UV ($CHCl_3$): λ_{max} (log ε) 282 (4.53), 340 (3.95); IR (KBr): ν_{max} 3429, 2924, 1620, 1487, 1422, 1122, 1041 ^{1}H NMR (CD_3OD, 300 MHz): δ 10.16 (s, 2H), 6.72 (d, *J* = 7.8 Hz, 1H), 6.57 (s, 1H), 6.55 (d, *J* = 7.8 Hz, 1H), 6.03 (s, 1H), 5.94 (s, 2H), 3.08–2.99 (m, 4H), 2.21 (m, 2H), 0.97 (d, *J* = 6.6 Hz, 12H); ^{13}C NMR (CD_3OD, 75 MHz) δ 206.2, 194.5, 170.1, 168.3, 167.8, 148.8, 146.3, 120.3, 111.3, 110.6, 109.4, 108.3, 101.7, 53.5, 32.6, 26.9, 26.7, 23.2; calculated *m*/*z* for $C_{38}H_{47}NO_{10}$ (608), found CIMS: *m*/*z* 609.2. calcd, C, 63.15; H, 5.30; found, C, 63.20; H, 5.36. *2,4-bis-(triflouromethyl)-1-yl-methylene-bis-(3-isopentanoyl-5-formyl-2,4,6-trihydroxybenzene)* (**35**): Yield: 35% cream colour solid; mp 162–164 °C ^{1}H NMR (CD_3OD, 300 MHz): δ 9.98 (s, 2H), 7.88 (s, 1H), 7.78 (d, *J* = 8.4 Hz, 1H), 7.61 (d, *J* = 8.4 Hz, 1H), 6.84 (s, 1H), 2.96 (d, *J* = 6.6, 4H), 2.15–2.24 (m, 2H), 0.94 (d, *J* = 6.6 Hz, 12H); ^{13}C NMR (CD_3OD, 75 MHz): δ 205.6 191.2, 170.0, 167.4, 165.3, 130.7, 127.1, 125.0, 124.7, 122.6, 121.4, 121.1, 107.4, 104.1, 103.1, 51.7, 31.1, 24.1, 20.9; calculated *m*/*z* for $C_{33}H_{30}F_6O_{10}$ (700.58), found CIMS: *m*/*z* 701.4. *4-Benzyloxy-1-yl-methylene-bis-(3-isopentanoyl-5-formyl-2,4,6-trihydroxybenzene)* (**36**): Yield: 33%; cream colour soild; mp 195–197 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ17.84 (br s, 2H, 2× O*H*$_C$), 14.6 (s, 2H, 2× O*H*$_B$), 10.16 (s, 2H), 9.63 (s, 2H, 2× O*H*$_A$), 7.42–7.30 (m, 5H), 7.00 (d, *J* = 8.7 Hz, 2H), 6.89 (d, *J* = 8.7 Hz, 2H), 6.06 (s, 1H), 5.04 (s, 2H), 3.05–2.96 (m, 4H), 2.22–2.31 (m, 2H), 1.00 (d, *J* = 6.6 Hz, 12H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 208.11, 194.0, 171.4, 169.4, 166.0, 158.0, 137.4, 129.1, 128.7, 128.5, 128.2, 128.0, 115.3, 107.2, 105.6, 104.3, 70.6, 53.9, 52.6, 32.5, 25.6, 23.3; calculated *m*/*z* for $C_{38}H_{38}O_{11}$ (670.24) found CIMS: *m*/*z* 671.20. calcd, C, 68.05; H, 5.71; found, C, 68.11; H, 5.66.

4-Biphenyl-1-yl-methylene-bis-(3-isopentanoyl-5-formyl-2,4,6-trihydroxybenzene) (**37**): Yield: 35%; white solid; mp 247–249 °C; ^{1}H NMR (CD_3OD, 300 MHz): δ 10.01 (s, 2H), 7.55 (d, *J* = 7.5 Hz, 2H), 7.45 (d, *J* = 7.8 Hz, 2H), 7.36 (t, *J* = 7.2 Hz, 2H), 7.26 (d, *J* = 7.2 Hz, 1H), 7.12 (d, *J* = 7.2 Hz, 2H), 6.55 (s, 1H), 2.96 (d, *J* = 6.0 Hz, 4H), 2.15–2.23 (m, 2H), 0.95 (d, *J* = 6.0 Hz, 12H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 207.7,193.7,174.2, 171.5, 142.9, 139.7, 130, 128.6, 128.4, 128.1, 127.9, 110.3, 106.6, 105.9, 54.0, 33.4, 27.0, 23.5; calculated *m*/*z* for $C_{37}H_{36}O_{10}$ (640.23), found CIMS: *m*/*z* 403.4 [M−$C_{12}H_{13}O_5$]. calcd, C, 69.36; H, 5.66; found, C, 69.42; H, 5.60.