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Graphical Abstract

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Facile TMSOI Catalysed Stereoselective Synthesis of 2-Methylene Selanyl-4-Chromanols and *Anti*-Cancer Activity

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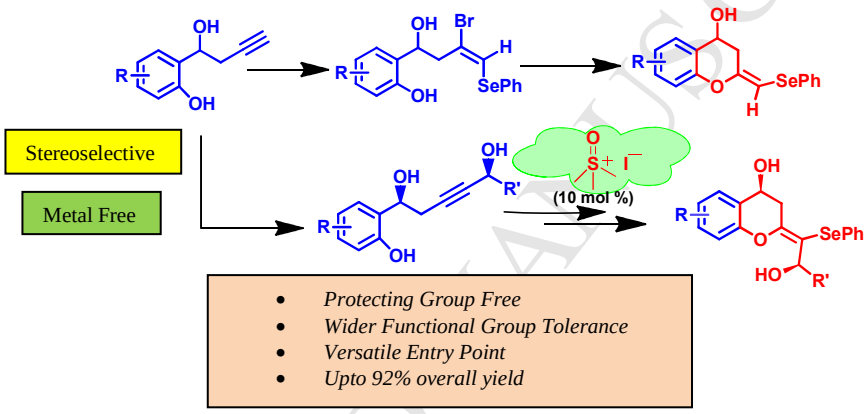

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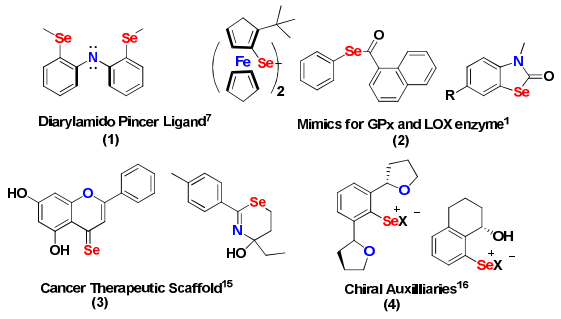
ABSTRACT

In the present study, a catalytic synthesis of 2-methylene selanyl-4-chromanols has been described. The manuscript highlights a facile Trimethylsulphoxonium iodide (TMSOI) catalysed intramolecular *6-exo-trig* coupling reaction in metal-free environment. The reaction exhibits satisfactory yields in presence of multiple free -hydroxyl groups. A stereoselectivegeneration of *syn*-3-hex-yne-1,5diols has been explored. The relative stereochemistry has been confirmed by single-crystal X-ray of crystalline-selanyl-chromanols. To determine the anticancer efficacy of the synthesized compounds, cell viability assay using MTT was performed against MCF-7 breast cancer cell line. Notably, Compound **9j**(IC_{50} =3.157 µmol) was found to exhibit potent cytotoxic activity. Compounds **9a** and **9e** also showed activity with IC_{50} values of 31.60±4.012 and 36.797±2.72 µmol respectively highlighting the potential of the synthesized compounds as novel lead molecules for future development of potent *anti*-cancer therapeutics

Introduction

Selenium has been element of prime importance for human health to Organic Synthesis. Interestingly, appropriately designed modern organoselenium molecules have shown impressive responses in apoptosis and cell cycle analysis studies and thus have been already identified as important *anti*-cancer agents.[1]Thus an urge to find newer organoselenium derivatives along with creation of innovative methodologies certainly demand for attention.[2] Recent studies on selenium compounds have shown to possess *anti*-cancer activitywithselective reactivity towards specific tumor cells. Trials for biomimetic designing of such peptides have been limited.[3] The latest developments of Pincer selenium ligands has also been very inspiring which opens up a new direction of selenium research.[4] Ring annulations encapsulating an organoselenium backbone at metal free conditions have not been explored to satisfactory levels.[5] The interesting point lies with the fact that such organoseleniums can easily be removed employing oxidative elimination [6]or even can be replaced with facile nucleophilic protocols.[7] Surprisingly, only few catalytic approaches have been designed to develop functionalized organoselenium compounds.[8] Thus,metal freecatalytic approaches towards development of these crucial organoselenium compounds requires immediate attention.

Concurrently, flavonoids and chromanoids constitute a huge class of biologically active natural benzopyrans and they have high commercial demand today.[9] Amongst this huge group, 2H-chromene derivatives and 2-methylene chromanols categorically embrace an important member of this set, not only because of their pronounced biological and pharmaceutical activity but also of interesting structural outlay(Fig-1).[10-14]



Scheme 1 Potent organoselenium molecules

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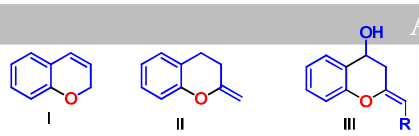


Figure 1 2H- chromene(I), 2-methylenechroman(II), 2-methylenechroman-4-ol(III)

The 2H- chromenesthusact as vital building blocks in natural product synthesis.[17-19]It was anticipated that selenium tagged with such chromanoid moieties may prove important molecules of medical interest.

The celebrated ylideTrimethylsulfoxonium Iodide (TMSOI) also known for the Corey - Chaykovsky reaction[20], has been known as a methylene transfer and cyclopropanating reagent, albeit to the best of our knowledge, there is no report which recognizes TMSOI as an effective reagent for ring annulation. Herein, we report a facile metal free TMSOI catalysed protection group free synthesis of 2-Methylene selanyl 4-chromanols via an interesting *6-exo-trig*ring annulation employing a seleno functionalization of alkynes. A stereoselective synthesis of *syn*-1,5 diols has been encountered and explored (**Scheme 2**). In the latter part, the study also reveals notable *anti*-cancer properties against MCF-7 breast cancer cell line by these molecules.

Retro-synthetically it was envisaged that a two way approach would be a preferred trajectory towards developing such moieties. The first one being a facile catalytic halogen exchange of the vinyl selenium bromide followed by a concomitant phenoxide induced ring closure (Path A) or a metal assisted intramolecular6-*exo-trig*annulation to an activated vinyl-selenium bromides towards the access of these selanylchromanols (Path-B) **(Figure-2)**, Path-A would be the preferred 6-*exo-trig* coupling.

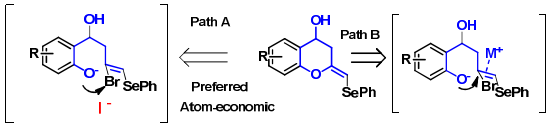
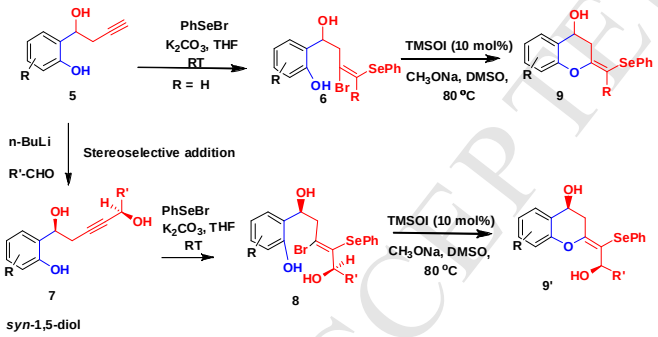
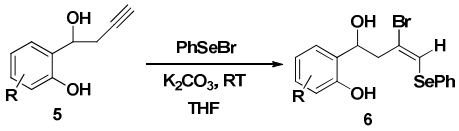


Figure 2 Retrosynthetic Perspective

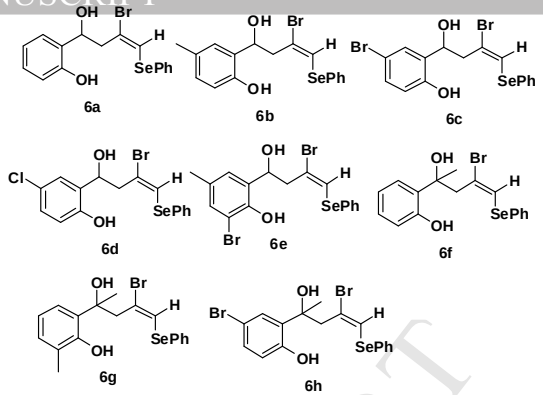


Scheme 2 Synthesis of 2-methylene-selanyl-4-chromanols

At the outset, 2-(1-hydroxybut-3-yn-1-yl) phenol (**5**) was chosen as model substrate to check our hypothesis. The 2-(1-hydroxybut-3-yn-1-yl) phenol (**5**) was transformed into the corresponding organoselenium bromide, (*E*)-2-(3-bromo-1-hydroxy-4-(phenylselanyl)but-3-en-1-yl) phenol **(6)** in a simple reaction using phenylseleniumbromide and potassium carbonate as a base. The selenylated phenol was screened through a various catalytic systems in different experimental conditions as stated in **Table 1.**



Scheme 3 Seleno functionalization of 2-(1-hydroxybut-3-yn-1-yl) phenol



To our delight, a combination of trimethylsulphoxonium iodide (TMSOI, 10 mol%) and (*E*)-2-(3-bromo-1-hydroxy-4-(phenylselanyl) but-3-en-1-yl)phenols **(6)** delivered the cyclized (*E*)-2-((phenylselanyl)methylene)chroman-4-ols (**9**) in excellent yields at room temperature in shorter time span.

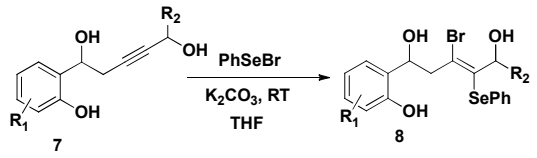
Screening of various bases, iodides and solvents puts up an impression that, CH_3ONa and DMSO to be the best combination for the reaction. No protection of the benzylic alcohol is necessary for this transformation. TMSOI as catalyst is concluded to deliver the best yields.

Table 1: (*E*)-2-(3-bromo-1-hydroxy-4-(phenylselanyl)but-3-en-1-yl)phenol(6)(1 mmol) as a model substrate, variation with bases, catalysts and solvents

Entry No:	Base (1 mmol)	Solvent (10 ml)	Catalyst (10 mol%)	%Yield
1	Cs_2CO_3	Acetone	Absent	NR
2	Cs_2CO_3	DMSO	Absent	55
3	K_2CO_3	DMSO	Absent	50
4	Cs_2CO_3	THF	TMSOI	28
5	Cs_2CO_3	MeCN	TMSOI	30
6	**CH_3ONa**	**DMSO**	**TMSOI**	**90**
7	^{t}BuOK	DMSO	TMSOI	72
8	LiOH	DMSO	TMSOI	NR
9	CH_3ONa	DMSO	NH_4I	Trace
10	CH_3ONa	THF	KI	55
11	CH_3ONa	DMSO	CsI	32
12	CH_3ONa	DMSO	AgI	20
13	CH_3ONa	DMSO	LiI	22
14	CH_3ONa	DMSO	KI	60
15	No Base	DMSO	Absent	NR
16	CH_3ONa	DMSO	NaI	45
17	CH_3ONa	DMF	TMSOI	60
18	CS_2CO_3	Acetone	TMSOI	12
19	K_2CO_3	Acetone	TMSOI	30
20	CH_3ONa	DMSO	$[PPh_3Me]^+I^-$	NR
21	CH_3ONa	DMSO	$[PPh_3Et]^+I^-$	NR
22	^{t}BuONa	THF	TMSOI	45
23	^{t}BuONa	THF	MeI	NR

Encouraged by these results, the scope was then explored with a variety of Phenylselanyl-but-3-en-1-yl phenols as shown in **Table 3**. As expected tertiary-alcohols (**9g**, **9h**, **9k**) exhibited moderate yields, presumably due to a larger separation of the alkenylselenyl bromide from

the phenoxide end. Trials with different iodides clearly manifested TMSOI to be the best of the lot.



8a : R_1 = -H, R_2 = -CH_3, **8b:** R_1 = -H, R_2 = -Ph,

Scheme 4 Seleno functionalization of *syn*-3-hex-yne-1,5diols

Concurrently with these studies, an interesting observation hinged upon our attention. In order to increase the substrate scope further, it was felt to test the efficacy of our methodology with an additional alcoholic substitution. With this apprehension, synthesis of the alcohols **9i**, (*R*/*S*,*E*)-2-((*R*)-2-hydroxy-1-(phenylselanyl)propylidene)chroman-4-ol)and **9j**,(*R*/*S*,*E*)-2-((*R*)-2-hydroxy-2-phenyl-1-(phenylselanyl) ethylidene) chroman-4-ol was attempted.

It was surprisingly noticed that hydroxylation of the alkynes (2- hydroxy-but-3-1-yn-1-yl phenol & acetaldehyde (**Scheme – 5)** with n-BuLi, delivered only one stereoisomer as the sole product. Repeated trials with other similar alkynes (**Table-2:7a**, **7b**, **7c**, **7d**, **7e**) interestingly delivered onto the similar results. The NOE experiments were not very convincing and the relative stereochemistry could not be confined at this point. The diols didn't deliver single crystals during routine trials in different solvents. However, the single crystals were achieved asbromo-selanyl derivatives which finally confirmed the relative stereochemistry as *syn*-1,5-diol. No trace of the relative *trans*- stereochemistry was found.

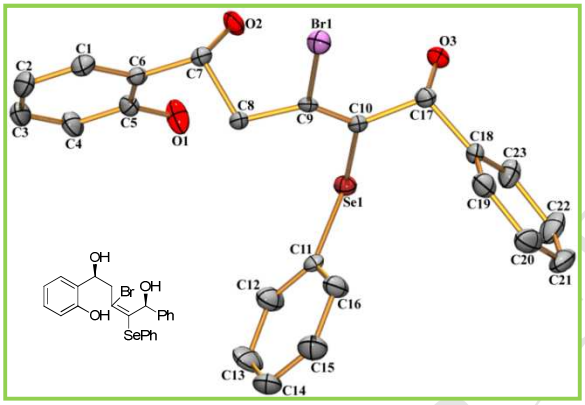
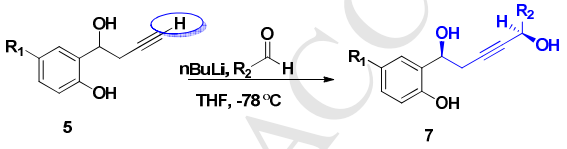


Figure 3 ORTEP view and atom numbering scheme of complex (**1**) ((1*S*,5*S*)/(1*R*/5*R*), *E*)-3-bromo-5-(2-hydroxyphenyl)-1-phenyl-2-(phenylselanyl)pent-2-ene-1,5-diol**(8b).**The displacement thermal ellipsoids are drawn at 30% probability level. (**CCDC No. 1517795**)

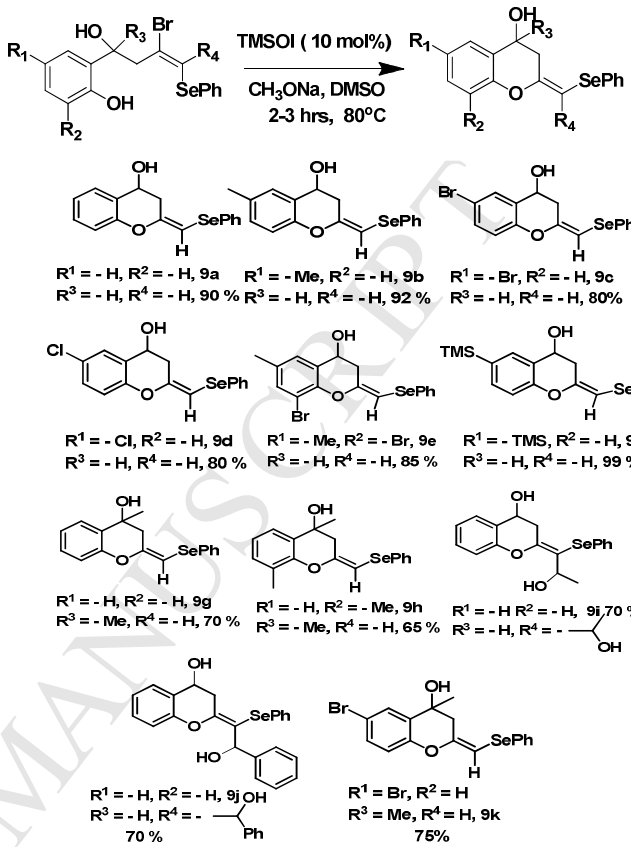


Scheme 5 Hydroxylation of Alkynes

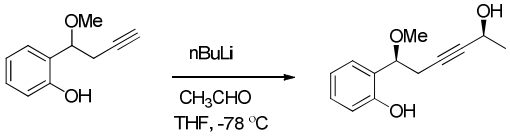
Table- 2 Substrates Scope on Hydroxylation of Alkynes

Entry	Product	R_1	R_2	Yield [%]
1	**7a**	H	Me	85
2	**7b**	H	Ph	88
3	**7c**	H	CH_2-CH_3	82
4	**7d**	Cl	CH_2-CH_3	86
5	**7e**	H	*p*-Me-C_6H_4	85

Table3 Substrate Scope of 2-Methylene-selanyl-4-chromanols



It was also observed that the aromatic alkynes (2-(1-methoxybut-3-yn-1-yl)phenol) with protected benzylic groups delivered single diastereomer after the reaction.



Mechanistically, it is apprehended that it is the presence of enforced coordination caused by the lithium cation which delivers a facile BurgiDunitz trajectory[21] with a fast supply of the electrophilic carbonyl to the alkynyl anion. This may also ensure an adequate overlap between the HOMO (sp) and LUMO (π*) orbitals.**(Figure 4)** Finally the preferred *syn*-stereoelectronic arrangement arising out of this lithium coordinated chelation control in the product diol which delivers such product selectivity.

To the best of our information, there has been no such report of stereoselective generation of *syn*-1,5-diols.

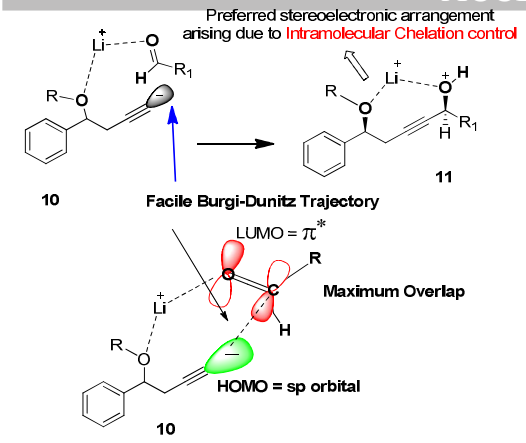


Figure 4 Mechanistic Postulation of the diol generation

Coming back to our original assignment, it was overwhelming to discover that((1*S*,5*S*)/(1*R*,5*R*),*E*)-3-bromo-1-(2-hydroxyphenyl)-4 (phenylselanyl)hex-3-ene-1,5-diol (**8a**) and ((1*S*,5*S*)/(1*R*/5*R*),*E*)-3-bromo-5-(2-hydroxyphenyl)-1-phenyl-2-(phenylselanyl)pent-2-ene-1,5-diol (**8b**) delivered (*S*/*R*,*E*)-2-((*R*)-2-hydroxy-1-(phenylselanyl) propylidene) chroman-4-ol(**9i**) and (*S*/*R*,*E*)-2-((*R*)-2-hydroxy-2-phenyl-1-(phenylselanyl)ethylidene) chroman-4-ol(**9j**) in excellent yields in 2-3 hrs. It was over whelming to explore that the cyclisation occurs with the presence of two unprotected alcoholic groups.

The reaction mechanism of these unprecedented catalyticreactions has not been unequivocally established.But a plausible mechanism on the basis of literature survey is exemplified in (**Figure 5**). It is perceived that the alkenyl-bromide exchange of seleno-alkene (**A**) with iodide in presenceof TMSOI followed by a phenoxy aided nucleophilic displacement of vinylic iodide delivers the ring annulated Chromenols.

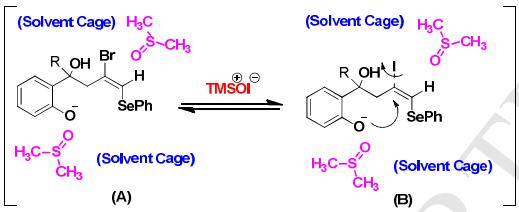


Figure 5 Plausible Reaction Mechanism

DMSO has been found the best solvent for the reaction. Carrying out the reaction in other solvents delivered reduced yields. This points out towards the predominant characters of DMSO solvent cage in this reaction. It is manifested that the DMSO-cage helps in vinyl-halogen-exchange in presence of the co-catalyst TMSOI which accelerates the reaction. The solvent polarity and the microscopic reaction cage of DMSO facilitate the reaction.

Trials with oxidizing agents like thiosulphates did not enhance the rate of reaction, clearly, manifesting the absence of any oxidative insertion playing out in the reaction mechanism. Using of the radical quenchers like TEMPO didn't inhibit the reaction at all, thus, ruling out the probability of radical mediated transformations. We believe that the presence of TMSOI in the solvent cage of polar DMSO, provide rapid halogen interchange which facilitates the ring annulation towards this transformation. No trace of 7-*endo* ring annulation was encountered.

Determination of cell viability using MTT assay is an economic, convenient, rapid and preliminary inference step for accessing the cytotoxic potential of a compound. The percentage calculation of viable cell populations is based on the mitochondrial dehydrogenase activity measurement at 595 nm. The novel formulations **9a**, **9e** and **9j** were screened for their *anti*-cancer efficacy against breast cancer cell line MCF-7. **Figure 6** shows the % cell viability of the cell line upon treatment with **9a**, **9e** and **9j** formulations. All the samples viz. **9a**, **9e** and **9j** show potent cytotoxic effect against MCF-7 cells. **9j** is the most toxic as it causes 46% cell death as compared to control at a concentration of 5µmol due to presence of two *syn*-alcoholic -OH group. From the graph, theIC_{50} values were calculated to be 31.60±4.012 and 36.797±2.72 µmol for **9a** and **9e** respectively.

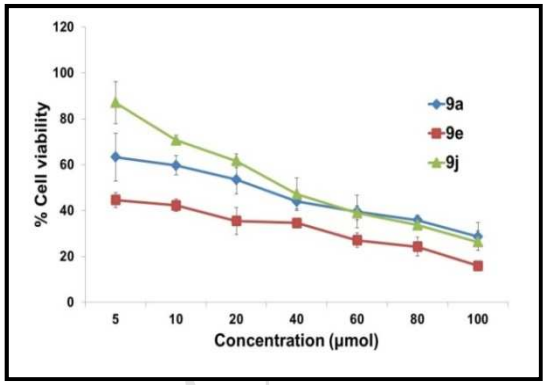


Figure 6 Graph showing in-vitro dose dependent cytotoxic activity of the prepared formulations (**9a**,**9e**&**9j**) against MCF-7 breast cancer cell line

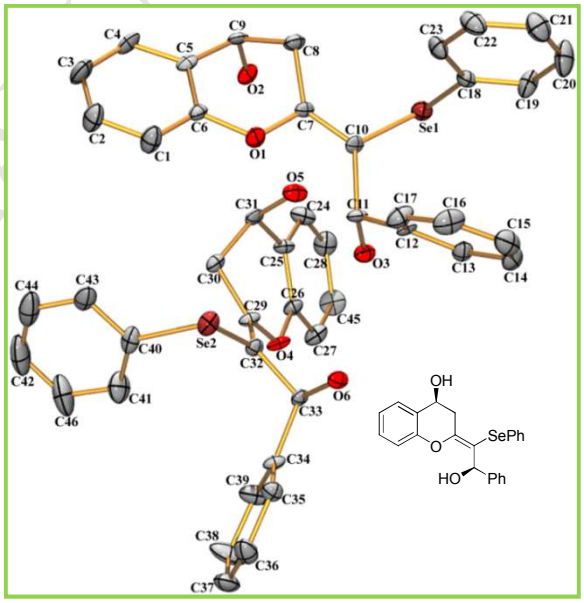


Figure 7ORTEP view and atom numbering scheme of complex (**2**)(*S*/*R*,*E*)-2-((*R*/*S*)-2-hydroxy-2-phenyl-1 (phenylselanyl)ethylidene)chroman-4-ol **(9j).** The displacement thermal ellipsoids are drawn at 30% probability level. (**CCDC No. 1528577**)

CONCLUSIONS

The report describes a metal-free catalytic 6-*exo*-trig coupling approach towards generation of 2-methylene selanyl-4-chromanols which are important motifs for pharmaceutical interest and also efficient building blocks for natural product synthesis. TMSOI acts as a trustworthy catalyst in such ring annulation works impressively well with a wider substrate scope and yields with appreciable stereocontrol. Concurrently, it also highlights the stereoselective generation of *syn*-3-hex-yne-1,5-diols proceeding through a noteworthy supply of incoming aldehyde to alkyne anion maintaining a preferred Burgi-Dunitz trajectory. The relative *syn*- stereochemistry has been supported using single-crystal X-ray studies. To our best information, this report is the first synthesis of such 2-methylene selanyl-4-chromanols as well as the stereoselective generation of *syn*-3-hex-yne-1,5diols. The selanyl-chromanols have

exhibited potent *anti*-cancer activity against MCF-7 breast cancer cell line. Thus, synthesis and characterisation of proper stereochemistry of these novel selenium molecules with potent *anti*-oxidant activity may act synergetically with existing drugs and revolutionise cancer therapy.

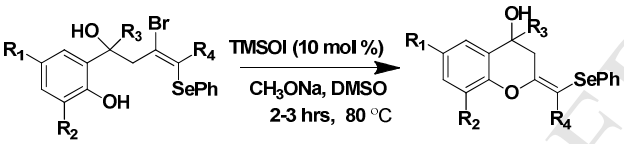
EXPERIMENTAL

Materials & Methods

All reactions were performed under nitrogen atmosphere using oven dried glass wires. All solvents are used after drying with agent. THF was first dried over potassium carbonate then by metallic sodium with benzophenone and used after prusiant blue colour appears. DMSO was distilled over calcium hydride under reduced pressure. Phenylselenium Bromide (PhSeBr) was purchased from Sigma Aldrich chemicals and all others reagent from Across, Sigma Aldrich, HIMEDIA, SRL& used without further purification. Anhydrous sodium sulphate was used for drying reaction mixture after aqueous workup.

TLC was performed with .25mm coated commercial silica gel plates (E-Merck, DC-kiesel gel 60 F_{254}) and stain by Iodine, vanillin solution. Chromatographic separation was done by using (200-400mesh) silica gel. ^{1}H &^{13}C NMR spectra were recorded on a Bruker (400MHz, 100 MHz respectively). NMR chemical shift values are reported in (δppm). TMS taken as internal slandered for ^{1}H the residual signal for $CDCl_3$ taken as 7.28 ppm & for ^{13}C 77.00ppm. ^{1}H spectral data reported as δ (multiplicity, Coupling constant, integration).Multiplicity reported as follows, *s*=singlet, *d*=doublet, *t*=triplet, *q*=quartet, *m*=multiplet, *dd*=doublet of a doublet. HRMS (High resolution Mass Spectra) was measured in a QTOF I (quadrupolehexapole-TOF) mass spectrometer with an orthogonal Z-spray-electrospray interface on micro (YA-263) mass spectrometer. IR spectra were recorded by using Perkin-Elmer spectrum-2 spectrometer using thin film deposit on NaCl& absorption frequency reported in cm^{-1}. Melting point of solid samples was monitored on Yanaco Melting Point Apparatus SP-500.

General Procedure **(A)** for (*E*)-2-((phenylselanyl)methylene) chroman-4-ols:



In all reactions, the reaction flask was flame dried and cooled under Nitrogen. All reactions were carried out under Nitrogen atmosphere.

To a solution of compound **6& 8**(1mmol) in dry DMSO (1.2 ml / 100 mg), a solution of CH_3ONa (1mmol) in DMSO was added slowly at room temperature. The colour of reaction mixture changed from yellow to wine-red. After the colour change, it was followed by addition of catalytic amount TMSOI (10 mol%), then heated at 80°C followed by monitoring of the reaction by TLC. The reaction was quenched by saturated NH_4Cl solution followed by extraction with EtOAc (Volume mentioned). The combined organic layer was washed with brine and dried over anhydrous Na_2SO_4 and concentrated under vaccuo. Purification by flash column chromatography delivered the required chromanols(**9a – 9k**) using Hexane/EtOAc as eluent**.**

(*E*)-2-((phenylselanyl)methylene)chroman-4-ol (9a): This reaction was performed according to general procedure A. To a stirred solution of (*E*)-2-(3-bromo-1-hydroxy-4-(phenylselanyl)but-3-en-1-yl)phenol **6a** (50 mg, 0.12 mmol) in dry DMSO (6 ml), CH_3ONa (6.7 mg, 0.12mmol) and TMSOI (10 mol %) was added. The reaction mixture was stirred for 4 hrs at room temperature. The reaction was quenched with saturated NH_4Cl & extracted with EtOAc (3 x 3ml). The organic layer was washed with saturated brine solution, dried over anhydrous sodium sulphate& concentrated under vaccuo. The mixture was purified using in silica gel chromatography under flash conditions to deliver (*E*)-2-((phenylselanyl)methylene)chroman-4-ol, **9a** (36mg,0.108mmol, 90 %) as yellow liquid. The solvent combination used was (Hexane :EtOAc = 93 : 7). R_f= 0.6 (30:70 = EtOAc:Hexane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 - 7.55 (dd, *J*= 8 Hz,1.6 Hz, 2H), 7.37 - 7.32 (m, 2H), 7.31 - 7.26 (m, 3H), 7.08 - 7.04 (t, *J*= 6.4 Hz, 2H), 5.65 (s, 1H), 4.8 (d, *J*= 4 Hz, 1H), 2.84 (d, *J*= 4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.1, 146.7, 131.8, 130.9, 130.1, 129.1, 128.4, 126.9, 124.3, 122.1, 116.7, 96.9, 64.3, 36.1; ^{77}Se δ 304.7 ; IR(neat filmNaCl): 3620,2150,1450,1235,1180,1030,739,708 ; HRMS (ESI) calc'd for $C_{16}H_{14}O_2Se$: $[M+Na]^+$: 341.0057, Found 341.0054.

(*E*)-6-methyl-2-((phenylselanyl)methylene)chroman-4-ol (9b): To a stirred solution of (*E*)-2-(3-bromo-1-hydroxy-4-(phenylselanyl)but-3-en-1-yl)-4-methylphenol **(6b)** (70 mg, 0.169 mmol)) in dry DMSO, CH_3ONa (9 mg, 0.169 mmol), TMSOI (10mol%) was added. The reaction mixture was stirred for 4 hrs at room temperature.The reaction was quenched with saturated NH_4Cl & extracted with EtOAc(3 x 3 ml). The organic layer was washed with brine, dried over anhydrous sodium sulphate& concentrated. The mixture was purified by silica column using Hexane:EtOAc [94:6], to give (*E*)-6-methyl-2-((phenylselanyl)methylene)chroman-4-ol, **9b** (52 mg, 0.156 mmol, 92%) as yellow liquid. R_f= 0.7 (30:70 = EtOAc:Hexane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 - 7.54 (m, 2H), 7.31 - 7.24 (m, 4H), 7.15 (s, 1H), 7.15 - 7.09 (m, 1H), 6.95 (d, *J*= 8.4 Hz, 1H), 5.61 (s, 1H), 4.81 - 4.78 (t, *J*= 4.4 Hz, 1H), 2.82 - 2.80 (t, *J*= 1.6, 2H), 2.32 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.9, 147.1, 131.7, 131.6, 131, 130.6, 129.1, 128.6, 126.8, 123.9, 116.4, 96.3, 64.3, 36.2, 20.5; IR(neat film NaCl): 3620,2940,2150,1446,1239,1182,1027,741,705; HRMS (ESI) calc'd for $C_{17}H_{16}O_2Se$ $[M+Na]^+$: 355.0208, found 355.0211.

(*E*)-6-bromo-2-((phenylselanyl)methylene)chroman-4-ol (9c): To a solution of compound **6c** (*E*)-4-bromo-2-(3-bromo-1-hydroxy-4-(phenylselanyl)but-3-en-1-yl)phenol (80 mg, 0.167mmol) in dry DMSO (1ml), CH_3ONa (9mg, 0.167mmol) and TMSOI (10mol%) was added. The reaction was stirred for 4hrs and monitored by TLC. The reaction was quenched with saturated NH_4Cl & extracted with EtOAc (3 x 5). The organic layer was washed with brine, dried over anhydrous sodium sulphate& concentrated. The mixture was purified by silica column using [94:6] Hexane:EtOAc to give (*E*)-6-bromo-2-((phenylselanyl)methylene)chroman-4-ol, 9c (53mg, 0.134mmol, 80%) as yellow liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 - 7.55 (m, 2H), 7.50 (d, *J*= 2.4 Hz, 1H), 7.38-7.41 (dd, *J*= 8.8 Hz,2.4 Hz, 1H), 7.28-7.31 (t, *J*= 4.4 Hz, 3H), 6.95 (d, *J*= 8.8 Hz, 1H), 5.67 (s, 1H), 4.82 - 4.80 (t, *J*= 4.4 Hz, 1H), 2.86 - 2.75 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.5, 147.4,134.2,133.4,132.3,131.9,128.5,127.8,123.5,119.9,115.7,99.3,65.4, 37.36;IR(neatfilmNaCl):3623,2150,1452,1236,1178,1075,1030,736,710; HRMS (ESI) calc'd for $C_{16}H_{13}BrO_2Se$: $[M+Na]^+$: 418.9162, Found 418.9159.

(*E*)-6-chloro-2-((phenylselanyl)methylene)chroman-4-ol (9d): To a solution of **6d** (*E*)-2-(3-bromo-1-hydroxy-4-(phenylselanyl)but-3-en-1-yl)-4-chlorophenol (65 mg, 0.15mmol) in dry DMSO(0.7 ml), CH_3ONa (8mg, 0.15 mmol)and TMSOI (10 mol%) was added. After stirring for 4hrs, this was monitored by TLC. The reaction was quenched with saturated NH_4Cl & extracted with EtOAc (3 x 5 ml). The organic layer was washed with brine, dried over anhydrous sodium sulphate& concentrated. The mixture was purified by silica column using [94:6] Hexane:EtOAc in petroleum ether to give (*E*)-6-chloro-2-((phenylselanyl)methylene)chroman-4-ol, **9d** (42 mg, 0.12mmol, 80%) as yellow liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 - 7.54 (m, 2H), 7.348 (d, *J*= 2.8 Hz, 1H), 7.32 - 7.27 (m, 3H), 7.25 - 7.23 (m, 1H), 6.98 (d, *J*= 8.4 Hz, 1H), 5.65 (s, 1H), 4.79 (s, 1H), 2.85 - 2.74 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.5, 146.2, 131.9, 130.5, 129.8, 129.2, 128.8, 127.9, 127, 126.9, 125.9, 118, 97.5, 63.9, 35.9; IR(neat film NaCl); 3620,2147,1453,1234,1176,1075,1030,729,713; HRMS (ESI) calc'd for $C_{16}H_{13}ClO_2Se$: $[M+Na]^+$: 374.9667, Found 374.9669.

(*E*)-8-bromo-6-methyl-2-((phenylselanyl)methylene)chroman-4-ol (9e): The compound **6e** (*E*)-2-bromo-6-(3-bromo-1-hydroxy-4-(phenylselanyl)but-3-en-1-yl)-4-methylphenol (85mg, 0.173mmol) was taken in dry DMSO(1 ml) in two necked round bottom flask under nitrogen atmosphere. CH_3ONa (9.3mg, 0.173 mmol)and TMSOI (10 mol%) was added to it. The resulting mixture was stirred for 3-4hrs and monitored by TLC. After completion, reaction mixture was quenched by saturated NH_4Cl and extracted by EtOAc (3 x 5 ml), washed by brine solution. The organic layer was collected and dried over anhydrous Na_2SO_4 powder and concentrated under reduced pressure. The mass was purified by flash column chromatography using [94:6] Hexane:EtOAc in petroleum ether to give (*E*)-8-bromo-6-methyl-2-((phenylselanyl)

methylene)chroman-4-ol, **9e** (61 mg, 0.15 mmol, 85%) as a yellow liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 - 7.57 (m, 2H), 7.36 (d, *J*= 1.6 Hz, 1H), 7.32 - 7.27 (m, 3H), 7.10 (d, *J*= 1.6 Hz, 1H), 5.73 (s, 1H), 4.78-4.80 (t, *J*= 4.4 Hz, 1H), 2.81 (d, *J*= 4.8 Hz, 2H), 2.30 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.5, 145.1, 133.9, 132.4, 132, 129.1, 127.9, 126.9, 125.2, 110, 99, 64.3, 35.6, 20.2; IR(neat film NaCl): 3620,2940,2150,1446,1239,1182,1027,1070,726,694; HRMS(ESI) calc'd for $C_{17}H_{15}BrO_2Se$: $[M+Na]^+$: 432.9318, Found 432.9316.

(*E*)-2-((phenylselanyl)methylene)-6-(trimethylsilyl)chroman-4-ol (9f): The compound **9d**, (*E*)-6-chloro-2-((phenylselanyl)methylene)chroman-4-ol(30 mg, 0.085mmol) was taken in dry THF. Hexamethyldisilazane (1.5 eqv.) was added to it. The resulting mixture was refluxed for 3-4hrs. After completion, reaction mixture was quenched by water and extracted by EtOAc (3 x 5 ml), washed by brine solution. The organic layer was collected and dried over anhydrous Na_2SO_4 powder and concentrated under reduced pressure. The mass was purified by flash column chromatography using [97:3] Hexane:EtOAc to give (*E*)-2-((phenylselanyl)methylene)-6-(trimethylsilyl)chroman-4-ol, **9f** (32.8 mg, 0.084 mmol, 99%) as a yellow liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 - 7.54 (m, 2H), 7.32 - 7.25 (m, 4H), 7.21- 7.18 (dd, *J*= 8.4 Hz, 2.4 Hz, 1H), 6.94 (d, *J*= 8.8 Hz, 1H), 5.57 (s, 1H), 4.84 - 4.81 (m, 1H), 2.83 - 2.27 (dd, *J*= 14 Hz,4.4 Hz, 1H), 2.70 - 2.64 (m, 1H), 0.23 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.5, 146.2, 131.9, 130.5, 129.8, 129.2, 128.8, 127.9, 127, 126.9, 125.9, 118, 97.5, 63.9, 35.9, 0.16; IR(neat film NaCl): 3620,2150,1450,1235,1180,1030,810,743,712;HRMS (ESI) calc'd for $C_{19}H_{22}O_2SeSi$ [M]+ : 390.0554, Found 390.0531.

(*E*)-4-methyl-2-((phenylselanyl)methylene)chroman-4-ol (9g): To a stirred solution of **6f** (*E*)-2-(4-bromo-2-hydroxy-5-(phenylselanyl)pent-4-en-2-yl)phenol (100 mg, 0.242 mmol)) in dry DMSO (1.2 ml), CH_3ONa (13mg, 0.242 mmol)and TMSOI (10 mol%) was added. The reaction mixture was stirred for 4 hrs at room temperature. The reaction was quenched with saturated NH_4Cl & extracted with EtOAc (3 x 5 ml). The organic layer was washed with brine, dried over anhydrous sodium sulphate& concentrated. The mixture was purified by silica column using [94:6] Hexane: EtOAc in petroleum ether to give (*E*)-4-methyl-2-((phenylselanyl)methylene)chroman-4-ol, **9g** (56 mg, 0.169mmol, 70%) as a green liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 - 7.51 (m, 3H), 7.32 - 7.24 (m, 4H), 7.07 - 7.03 (m, 2H), 5.61 (s, 1H), 2.77 (s, 2H), 2.38 (s, 1H), 1.60 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.1, 148.3, 131.7, 130.9, 129.4, 129.2, 129, 128.8, 126.9, 124.8, 122.3, 116.6, 95.6, 67.6,42.9,28.11;IR(neatfilmNaCl):3670,2920,2155,1235,1457,1175,1040 ,716,689 ; HRMS (ESI) calc'd for $C_{17}H_{16}O_2Se$: $[M+Na]^+$: 355.0213, found 355.0216.

(*E*)-4,8-dimethyl-2-((phenylselanyl)methylene)chroman-4-ol (9h): To a solution of **6g**, (*E*)-2-(4-bromo-2-hydroxy-5-(phenylselanyl)pent-4-en-2-yl)-6-methylphenol (90 mg, 0.211mmol) in dry DMSO (1ml), CH_3ONa (12 mg, 0.211mmol) and TMSOI (10 mol%) was added. The reaction mixture was stirred for 4 hrs at room temperature. The reaction was quenched with saturated NH_4Cl & extracted with EtOAc (3 x 5 ml). The organic layer was washed with brine, dried over anhydrous sodium sulphate& concentrated. The mixture was purified by silica column using [94:6] Hexane: EtOAc to give (*E*)-4,8-dimethyl-2-((phenylselanyl)methylene) chroman-4-ol, **9h** (47mg, 0.137 mmol, 65%) as green liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.30 (s, 1H), 7.49 - 7.31 (m, 5H), 7.05 - 7.03 (m, 1H), 6.94 - 6.91 (dd, *J*= 8 Hz,1.2 Hz, 1H), 6.75 - 6.71 (t, *J*= 7.6 Hz, 1H), 5.60 (s, 1H), 3.92 (s, 1H), 3.18 - 3.04 (q, *J*= 14.8 Hz, 2H), 2.21 (s, 3H), 1.73 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.1, 148.3, 135.1, 132, 131.7, 131.2, 130, 129.4, 127.9, 124.9, 120.3, 80.6, 46.9, 30.3, 17.6; IR(neat film NaCl): 3670,2942,2920,2155,1235,1457,1175,1040,743,710 ; HRMS (ESI) calc'd for $C_{18}H_{18}O_2Se$: $[M+Na]^+$: 369.0370, found 369.0372.

(*S,E*)-2-((*R*)-2-hydroxy-1-(phenylselanyl)propylidene)chroman-4-ol (9i): To a solution of compound **8a**, (1*S*,5*S*,*E*)-3-bromo-1-(2-hydroxyphenyl)-4-(phenylselanyl)hex-3-ene-1,5-diol (140 mg, 0.316mmol) in dry DMSO (1.5ml), CH_3ONa (17 mg, 0.211 mmol)and TMSOI (10 mol%) was added. The reaction mixture was stirred for 4 hrs at room temperature. The reaction was quenched with saturated NH_4Cl & extracted with EtOAc (3 x 5 ml). The organic layer was washed with brine, dried over anhydrous sodium sulphate& concentrated. The mixture was purified by silica column using [85:15] Hexane: EtOAc to give (*E*)-2-(2-hydroxy-1-(phenylselanyl)propylidene)chroman-4-ol, **9i** (80 mg, 0.221 mmol, 70 %) as a yellowish white solid.R_f = 0.5 (50:50 = EtOAc:Hexane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 - 7.44 (m, 2H), 7.44 - 7.18 (m, 5H), 7.07 - 7.03 (m, 2H), 5.39 - 5.34 (q, *J*= 6.4 Hz, 1H), 4.80 - 4.78 (t, *J*= 4.8 Hz, 1H), 3.53 - 3.48 (m, 1H), 2.93 - 2.89 (m, 1H), 1.34 (d, *J*= 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.8, 151.7, 132.5, 129.9, 129.2, 129, 128.1, 126.1, 124.3, 122.46, 119.7, 117.5,116.3,65.07,64.08,34.7,23.06;IR(neatfilmNaCl):3630,2923,1460,1240,1183,1073,729,685; HRMS (ESI) calc'd for $C_{18}H_{18}O_3Se$: $[M+Na]^+$: 385.0319, found 385.0317; M.P. 75-77°C.

(*S,E*)-2-((*R*)-2-hydroxy-2-phenyl-1-(phenylselanyl)ethylidene)chroman-4-ol (9j): To a mixture of **8b**, (1*S*,5*S*,*E*)-3-bromo-5-(2-hydroxyphenyl)-1-phenyl-2-(phenylselanyl)pent-2-ene-1,5-diol (120mg, 0.237mmol) in DMSO (1.5ml), CH_3ONa (13 mg, 0.237mmol)and TMSOI (10 mol%) was added. The reaction mixture was stirred for 4 hrs at room temperature. The reaction was quenched with saturated NH_4Cl & extracted with EtOAc (3 x 5 ml). The organic layer was washed with brine, dried over anhydrous sodium sulphate& concentrated. The mixture was purified by silica column using [83:17] Hexane: EtOAc to give (*E*)-2-(2-hydroxy-2-phenyl-1-(phenylselanyl)ethylidene)chroman-4-ol, **9j** (71mg, 0.165mmol, 70%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (d, *J*= 7.6 Hz, 2H), 7.36 - 7.24 (m, 6H), 7.15 - 6.47 (m, 4H), 6.47 (s, 1H), 4.81 - 4.79 (m, 1H), 3.49 - 3.44 (m, 1H), 2.96 - 2.91 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.4, 151.7, 142.8, 132.2, 130, 129.5, 129, 128.1, 128, 127.1, 126.2, 125.6, 124.4, 122.6, 116.5, 116.4, 69.5, 63.9, 34.6; IR (Neat Film NaCl) 2923, 1605, 1457, 1230, 1189, 1020, 735, 700cm^{-1}; HRMS (ESI) calc'd for $C_{23}H_{20}O_3Se$ [M]$^+$: 424.0578, found 424.0616; M.P. 146-147°C, Yellowish white solid.

(*E*)-6-bromo-4-methyl-2-((phenylselanyl)methylene)chroman-4-ol (9k): To a solution of **6h**, (*E*)-4-bromo-2-(4-bromo-2-hydroxy-5-(phenylselanyl)pent-4-en-2-yl)phenol (140mg, 0.285mmol)) in DMSO (1.5ml), CH_3ONa (16mg, 0.285mmol) and TMSOI (10 mol%) was added. The reaction mixture was stirred for 4 hrs at room temperature. The reaction was quenched with saturated NH_4Cl & extracted with EtOAc (3 x 5 ml). The organic layer was washed with brine, dried over anhydrous sodium sulphate& concentrated. The mixture was purified by silica column using [94:6] Hexane: EtOAc to give (*E*)-6-bromo-4-methyl-2-((phenylselanyl)methylene)chroman-4-ol**,** **9k** (88mg, 0.213mmol, 75%) as a brownish liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (d, *J*= 2.4 Hz, 1H), 7.56 - 7.54 (m, 2H), 7.37 - 7.27 (m, 4H), 6.92 (d, *J*= 8.4 Hz, 1H), 5.6 (s, 1H), 2.77 (d, J= 0.4 Hz, 2H), 1.58 - 1.56 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.1, 147.3, 132.08, 131.8, 131.09, 130.6, 129.1, 127.7, 126.9, 118.3, 114.5, 96.5, 67.4, 42.5, 28.1; IR(neat film NaCl): 3640,2985,1610,1450,1235,1180,1070,1020,731,716; HRMS (ESI) calc'd for $C_{17}H_{15}BrO_2Se$: $[M+Na]^+$: 432.9318, Found 432.9320.

Experimental Procedures (B) for the synthesis of (*E*)-2-(3-bromo-1-hydroxy-4-(phenylselanyl) but-3-en-1-yl)phenols:

The compound **6**&**8** was prepared from **5**&**7** (1.2mmol) was dissolved in dry THF and K_2CO_3 (1.2 mmol) and PhSeBr (1.2 mmol) were added at room temperature. The reaction was stirred for 2-3hrs which was monitored by TLC. The reaction mixture has then quenched with saturated NH_4Cl. Mixture was extracted with ethyl acetate (3 x 5 ml) and dried over Na_2SO_4 and concentrated. The mixture was subjected to column chromatography over silica gel.

(*E*)-2-(3-bromo-1-hydroxy-4-(phenylselanyl) but-3-en-1-yl)phenol (6a): The compound **6a** was prepared according to procedure **B**. 2-(1-hydroxybut-3-yn-1-yl)phenol, **5a** (200mg, 1.2mmol) was dissolved in dry THF and K_2CO_3 (165.6 mg, 1.2 mmol) and PhSeBr (283 mg, 1.2mmol) to give 6a, (*E*)-2-(3-bromo-1-hydroxy-4-(phenylselanyl) but-3-en-1-yl)phenol (382mg, 0.96mmol, 80%) as a yellow liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 - 7.54 (m, 2H), 7.21 - 7.17 (m, 3H), 6.92 - 6.87 (m, 2H), 6.85 - 6.81 (m, 1H), 6.65 (s, 1H), 5.24 - 5.20 (m, 1H), 3.25 - 3.19 (q, *J*= 14.4 Hz, 1H), 2.76 - 2.71 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.4, 133.8, 131.8, 129.7, 129.2, 128.4, 128.3, 127.2, 126.3, 120, 117.2, 109.6, 73.9, 42.3 ; ^{77}Se(104 MHz, $CDCl_3$) δ 450.5 ; IR(neat

film NaCl): 3630,3610,3000,1460,1075,728,715; HRMS (ESI) calc'd for $C_{16}H_{15}BrO_2Se$: $[M+Na]^+$: 420.9318, Found 420.9316.

(*E*)-2-(3-bromo-1-hydroxy-4-(phenylselanyl)but-3-en-1-yl)-4-methylphenol (6b):The compound **6b** was prepared from **5b** according to procedure **B**. 2-(1-hydroxybut-3-yn-1-yl)-4-methylphenol, **5b** (150mg, 0.85mmol) was dissolved in dry THF(2 ml) and K_2CO_3 (117 mg, 0.85 mmol) and PhSeBr (200 mg, 0.85mmol) were added to the reaction mixture at room temperature afforded 6b, (*E*)-2-(3-bromo-1-hydroxy-4-(phenylselanyl)but-3-en-1-yl)-4-methylphenol (308mg, 0.748mmol, 88%) as a yellow liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (s, 1H), 7.57 - 7.55 (m, 2H), 7.37 - 7.35 (m, 3H), 6.99 - 6.97 (d, *J*= 8 Hz, 1H), 6.78 (d, *J*= 8 Hz, 1H), 6.7 (d, *J*= 1.6 Hz, 1H), 6.638 (s, 1H), 5.19 - 5.15 (m, 1H), 3.24 - 3.20 (m, 1H), 2.74 - 2.69 (dd, *J*= 14.4 Hz, 4Hz, 1H), 2.25 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.1, 133.8, 131.9, 129.7, 129.6, 129, 128.4, 128.2, 127.5, 125.8, 117, 109.4, 74.1, 42.3, 20.5; IR(neat film NaCl): 3630,3610,3000,2923,1456,732,717;HRMS (ESI) calc'd for $C_{17}H_{17}BrO_2Se$ $[M]^+$: 411.9577, Found 411.9574.

(*E*)-4-bromo-2-(3-bromo-1-hydroxy-4-(phenylselanyl)but-3-en-1-yl)phenol (6c): The Compound **6c** was prepared by the reaction of **5c**, (4-bromo-2-(1-hydroxybut-3-yn-1-yl)phenol (150mg, 0.622 mmol) in dry THF (1.5ml) and K_2CO_3 (86mg, 0.622 mmol) and PhSeBr (147 mg, 0.622mmol) at room temperature to give **6c,** (*E*)-4-bromo-2-(3-bromo-1-hydroxy-4-(phenylselanyl)but-3-en-1-yl)phenol (255 mg, 0.534 mmol, 86 %) as a yellow liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.43 - 8.30 (m, 1H), 7.54 - 7.52 (m, 2H), 7.35 (s, 3H), 7.29 - 7.23 (d, *J*= 8.8 Hz, 1H), 7.02 (d, *J*= 6 Hz, 1H), 6.72 (d, *J*= 8.8 Hz, 1 H), 6.58 (s, 1H), 5.14 - 5.12 (m,1H), 3.74 (s, 1H), 3.18 - 3.12 (q, *J*= 13.6 Hz, 1H), 2.69-2.74 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.9, 135.3, 133.2, 133, 131.27, 131.2, 129.9, 129.6, 120.2, 113.2, 111, 69.4, 43.4; IR(neat film NaCl): 3630,3610,3000,1460,1075,728,707; HRMS (ESI) calc'd for $C_{16}H_{14}Br_2O_2Se$: $[M+Na]^+$: 498.8423, Found 498.8425.

(*E*)-2-(3-bromo-1-hydroxy-4-(phenylselanyl)but-3-en-1-yl)-4-chlorophenol (6d): Prepared according to general procedure B as a yellow liquid; 227 mg (86%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (s, 1H), 7.56 - 7.54 (q, *J*= 2 Hz, 2H), 7.39 - 7.36 (m, 3H), 7.14 - 7.12 (m, 1H), 6.87 (d, *J*= 2.4 Hz, 1H), 6.80 (d, *J*= 8.4 Hz, 1H), 6.65 (s, 1H), 5.169 (m, 1H), 3.21 - 3.15 (q, *J*= 14.4 Hz, 9.6 Hz, 1H), 2.76 - 2.71 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.2, 133.8, 131.2, 129.7, 128.9, 128.6, 127.8, 127.1, 126.7, 124.4, 118.7, 109.6, 73.7, 42.1; IR(neat film NaCl): 3630,3610,3000,1460,1075,1090,725,708; HRMS (ESI) calc'd for $C_{16}H_{14}BrClO_2Se$: $[M+Na]^+$: 454.8929, Found 454.8932.

(*E*)-2-bromo-6-(3-bromo-1-hydroxy-4-(phenylselanyl)but-3-en-1-yl)-4-methylphenol (6e):Prepared according to general procedure B as a colourless liquid; 237 mg (88%).^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 - 7.52 (m, 2H), 7.36 - 7.33 (m, 3H), 7.23 (d, *J*= 1.6 Hz, 1H), 6.81 (d, *J*= 2 Hz, 1H), 6.62 (s, 1H), 5.20 - 5.17 (q, *J*= 9.2 Hz, 1H), 3.18 - 3.12 (q, *J*= 14.4 Hz, 1H), 2.76 - 2.72 (dd, *J*= 14.4 Hz, 4.4 Hz, 1H), 2.24 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.4, 133.6, 131.9, 131.7, 130.6, 129.5, 128.3, 128.1, 127.9, 127.1, 110.1, 109.4, 72.4, 41.9, 20.1; IR(neat film NaCl): 3630,3610,3000,2923,1460,1075,738,704; HRMS (ESI) calc'd for $C_{17}H_{16}Br_2O_2Se$ [M]+ : 489.8682, Found 489.8713.

(*E*)-2-(4-bromo-2-hydroxy-5-(phenylselanyl)pent-4-en-2-yl)phenol (6f):Prepared according to general procedure B as a greenish liquid; yield 294 mg (71%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.19 (s, 1H), 7.52 - 7.50 (m, 2H), 7.38 - 7.30 (m, 3H), 7.21 - 7.17 (m, 1H), 7.11 - 7.09 (m, 1H), 6.88 - 6.84 (m, 2H), 6.68 (s, 1H), 4.07 (s, 1H), 3.18 (d, *J*= 14.4 Hz, 1H), 3.06 (d, *J*= 14.8 Hz, 1H), 1.76 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.8, 133.8, 130.6, 129.8, 129.24, 129.23, 128.7, 128, 126, 119.6, 117.8, 110.8, 79.1, 45.5, 28.3; IR(neat film NaCl): 3630,3610,3000,2920,1460,1075,723,695;HRMS (ESI) calc'd for $C_{17}H_{17}BrO_2Se$: $[M+Na]^+$: 434.9475, Found 434.9477.

(*E*)-2-(4-bromo-2-hydroxy-5-(phenylselanyl)pent-4-en-2-yl)-6-methylphenol (6g):Prepared according to general procedure B as a liquid; yield 161 mg (72%).^{1}H NMR (400 MHz, $CDCl_3$) δ 9.30 (s, 1H), 7.49 - 7.31 (m, 5H), 7.05 - 7.03 (m, 1H), 6.94 - 6.91 (dd, *J*= 8 Hz, 1.2 Hz, 1H), 6.75 - 6.71 (t, *J*= 7.6 Hz, 1H), 6.65 (s, 1H), 3.92 (s, 1H), 3.18 - 3.04 (q, *J*= 38.4 Hz, 14.8 Hz, 2H), 2.21 (s, 3H), 1.73 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.4, 135.1, 132, 131.7, 131.2, 130, 129.4, 127.9, 124.9, 120.3, 112.3, 80.6, 46.9, 30.3, 17.6; IR(neat film NaCl): 3630,3610,3000,2940,2921,1460,1075,735,700;HRMS (ESI) calc'd for $C_{18}H_{19}BrO_2Se$: $[M+Na]^+$: 448.9631, Found 448.9633.

(1*S*,5*S*,*E*)/(1*R*,5*R*,*E*)-3-bromo-1-(2-hydroxyphenyl)-4-(phenylselanyl)hex-3-ene-1,5-diol (8a):Prepared according to general procedure B. To a solution of 7a, (1*S*,5*S*)-1-(2-hydroxyphenyl)hex-3-yne-1,5-diol (250mg, 1.21 mmol) in dry THF (3 ml), K_2CO_3(167 mg, 1.21 mmol) and PhSeBr (285mg, 1.21mmol) was added at room temperature to obtain 8a, (470mg, 1.06mmol, 88%) as a yellowish white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 - 7.35 (m, 2H), 7.26 - 7.16 (m, 4H), 6.96 - 6.94 (dd, *J*= 7.6 Hz, 1.6 Hz, 1H), 6.86 - 6.80 (m, 2H), 5.26 - 5.23 (q, *J*= 8.8 Hz, 1H), 5.06 - 5.02 (m, 1H), 3.79 - 3.73 (q, *J*= 14.4 Hz, 1H), 3.22 - 3.17 (m, 1H) , 1.27 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.5, 137.4, 131.1, 130.06, 130, 129.9, 129.5, 129.4, 129.2, 128.7, 127.8, 127.6, 127.1, 126.8, 126.3, 125.7, 119.7, 117.2, 113.9,74,71.8,31.8,22.1;IR(neatfilmNaCl):3630,3610,3000,2920,2150,1457,1075,732,710; HRMS (ESI) calc'd for $C_{18}H_{19}BrO_3Se$: $[M+Na]^+$: 464.9580, Found 464.9578; M.P. 74-76°C.

(1*S*,5*S*,*E*)/(1*R*,5*R*,*E*)-3-bromo-5-(2-hydroxyphenyl)-1-phenyl-2-(phenylselanyl)pent-2-ene-1,5-diol (8b): Prepared according to general procedure B. (1*S*,5*S*)-5-(2-hydroxyphenyl)-1-phenylpent-2-yne-1,5-diol, 7b (200mg, 0.74 mmol) in dry THF, , K_2CO_3(103mg, 0.74mmol) and PhSeBr(176mg, 0.74mmol) to afford **8b** (300mg, 0.59mmol, 80%) as a yellowish white solid.^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (s, 1H), 7.37 - 7.08 (m, 11H), 6.97 - 6.76 (m, 3H), 6.24 (s, 1H), 5.32 - 5.29 (m, 1H), 3.78 - 3.67 (m, 1H), 3.41 (s, 1H), 3.24 - 3.19 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.4, 140.6, 131.06, 130.1, 129.8, 129.3, 129.2, 128.5, 128.3, 127.7, 127.1, 126.9, 125.9, 119.8, 117.1, 76.1, 73.8, 48.4; IR(neat film NaCl): 3630,3610,3000,2923,2150,1459,1076,738,705; HRMS (ESI) calc'd for $C_{23}H_{21}BrO_3Se$ $[M]^+$: 503.9839, Found 503.9808; M.P. 148-150°C.

(Z)-4-bromo-2-(4-bromo-2-hydroxy-5-(phenylselanyl)pent-4-en-2-yl)phenol(6h): To a solution of **5h**, 4-bromo-2-(2-hydroxypent-4-yn-2-yl)phenol (100mg, 0.392mmol) in dry THF, K_2CO_3(54mg, 0.392mmol) and PhSeBr(92.5mg, 0.392mmol) to obtain **6h** (*E*)-4-bromo-2-(4-bromo-2-hydroxy-5-(phenylselanyl)pent-4-en-2-yl)phenol (144mg, .294mmol, 75%) as a liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.15 (s, 1H), 7.50 - 7.47 (m, 2H), 7.38 - 7.35 (m, 3H), 7.27 - 7.24 (dd, *J*= 8.8 Hz, 2.4 Hz, 1H), 7.17 (d, *J*= 2.4 Hz, 1H), 6.75 - 6.72 (m, 2H), 4.03 (s, 1H), 3.13 - 3.01 (q, J= 32.4 Hz, 2H), 1.72 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.9, 133.6, 131.8, 130.9, 129.9, 129.7, 128.6, 127.6, 119.6, 111.3, 78.8,45.2,28.4;IR(neatfilmNaCl):3630,3610,3000,2920,1460,1075,735,700;HRMS (ESI) calc'd for $C_{17}H_{16}Br_2O_2Se$: $[M+Na]^+$: 512.8580, Found 512.8583.

General methods (C) for the synthesis of substituted (1*S*,5*S*/*1R,5R*)-1-(2-hydroxyphenyl)hex-3-yne-1,5-diols :

To a solution of **6** in dry THF, n-BuLi (3eqv.) was added in -78°C dropwise. The temperature of the reaction medium was increased slowly from -78°C to -55°C. After 1hr the solution of corresponding aldehydes (1eqv.) in THF was added dropwise with vigorous stirring. After 3hrs of stirred the resulting reaction mixture was quenched with saturated solution of NH_4Cl and extracted by EtOAc (3 x 5 ml). The organic layer was washed with brine, dried over anhydrous sodium sulphate& concentrated. The mixture was purified by silica column using [70:30] Hexane:EtOAc to give **7**.

(1*S*,5*S*/ *1R,5R*)-1-(2-hydroxyphenyl)hex-3-yne-1,5-diol (7a):The synthesis of compound **7a** is synthesize using the method C, and is a yellowish white solid (85%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.16 - 7.12 (m, 1H), 7.05 (d, J= 8 Hz, 1H), 6.85 - 6.82 (m, 2H), 5.56 (s, 1H), 5.01 - 4.98 (q, J= 8 Hz, 1H), 4.49 - 4.45 (m, 1H), 2.77 - 2.62 (m, 2H), 1.40 - 1.38 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.6, 128.9, 127, 126.4, 119.9, 116.7, 84.2, 80.9, 72.4, 58.2, 27.9, 24.1; IR(neat film NaCl): 3620,3600,2923,2147,1460; HRMS (ESI) calc'd for $C_{12}H_{14}O_3$:$[M+Na]^+$: 229.0841, Found 229.0843; M.P. 81-83°C.

(1*S*,5*S*/*1R,5R*)-5-(2-hydroxyphenyl)-1-phenylpent-2-yne-1,5-diol (7b): The synthesis of compound **7b** is following the method C which was explained in details in above, which is yellowish white solid (88%). ^{1}H

NMR (400 MHz, $CDCl_3$) δ 8.14 (d, *J*= 6.8 Hz, 1H), 7.49 - 7.45 (m, 2H), 7.39 - 7.31 (m, 3H), 7.19 - 7.16 (t, *J*= 7.6 Hz, 1H), 7.0 (d, *J*= 7.6 Hz, 1H), 6.86 - 6.82 (m, 2H), 5.43 (s, 1H), 5.02 - 4.99 (m, 1H), 2.87 - 2.69 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.9, 140.3, 129.1, 128.56, 128.50, 127.6, 127.1, 126.58, 126.53, 125.6, 119.9, 117.1, 83.4, 82.4, 73.2, 64.5, 28.2; IR(neat film NaCl): 3620, 3600,2920,2150,1460;HRMS (ESI) calc'd for $C_{17}H_{16}O_3$:$[M+Na]^+$: 291.0997, Found 291.0994; M.P. 143-146°C.

(1*S*,5*S*/ *1R*,5*R*)-1-(2-hydroxyphenyl)hept-3-yne-1,5-diol (7c):
The synthesis of compound **7c** is following the method C which was explained in details in above, which is yellowish white solid (82%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.48 (s, 1H), 7.16 - 7.12 (m, 1H), 7.05 (d, *J*= 7.6 Hz, 1H), 6.85 - 6.82 (m, 2H), 5.01 - 4.98 (m, 1H), 4.29 - 4.26 (m, 1H), 2.79 - 2.64 (m, 2H), 1.70 - 1.62 (m, 2H), 0.96 - 0.92 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.1, 130.47, 128.6, 128, 121.4, 118.2, 84.6, 83.3, 74, 65.2, 32.1, 29.5, 10.9; IR(neat film NaCl): 3620,2960,2920,2152,1453;HRMS (ESI) calc'd for $C_{13}H_{16}O_3$:$[M+Na]^+$: 243.0997, Found 243.0968; M.P. 78-80°C.

(1*S*,5*S*/*1R*,5*R*)-1-(5-chloro-2-hydroxyphenyl)hept-3-yne-1,5-diol (7d):
The synthesis of compound **7d** is following the method C which was explained in details in above, which is yellowish solid (86%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.11 - 7.09 (m, 1H), 7.03 - 7.02 (t, *J*= 1.2 Hz, 1H), 6.77 (d, *J*= 8.4 Hz, 1H), 4.96 - 4.93 (m, 1H), 4.31 - 4.28 (m, 1H), 2.78 - 2.64 (m, 2H), 1.70 - 1.65 (m, 2H), 0.97 - 0.93 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.4, 128.7, 127.6, 126.8, 124.4, 118.2, 83. 5, 81.2, 72.2, 63.8, 30.7, 27.9, 9.3; IR(neat film NaCl): 3620,2960,2920,2154,1451,1091; HRMS (ESI) calc'd for $C_{13}H_{15}ClO_3$: $[M+Na]^+$: 277.0607, Found 277.0610; M.P. 89-90°C.

(1*S*,5*S*/*1R*,5*R*)-5-(2-hydroxyphenyl)-1-(p-tolyl)pent-2-yne-1,5-diol (7e):The synthesis of compound **7e** is following the method C which was explained in details in above, which is a yellow solid (85%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 - 7.33 (m, 3H), 7.19 - 7.14 (m, 3H), 7.00 (d, *J*= 7.6 , 1H), 6.99 - 6.82 (m, 2H), 5.38 (s, 1H), 5.31 (s, 1H), 5.01 - 4.98 (m, 1H), 4.66 (s, 1H), 2.86 - 2.68 (m, 2H), 2.36 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155, 138.1, 137.5, 129.2, 128.4, 127.6, 127.1, 126.9, 126.5, 119.8, 117.1, 83.2, 82.6, 73.2, 64.3, 28.2, 21; IR(neat film NaCl): 3620, 3600,2920,2940,2150,1460; HRMS (ESI) calc'd for $C_{18}H_{18}O_3$: $[M+Na]^+$: 305.1154, Found 305.1152; M.P. 142-144°C.

General procedure (D) for synthesis of substituted 2-(2-hydroxypent-4-yn-2-yl)phenols: The compound **5** was synthesized from **4**. To a stirred solution of Zn-dust (1.2 eqv) in dry THF (10 ml (in 1 gm)), Propargyl bromide (1.2 eqv) was added. The reaction mixture was stirred for 1-2 hrs at room temperature. The colour of reaction of mixture was changed to white, which indicates the formation of Grignard reagent. Then, 1-(2-hydroxyphenyl)ethanone (1 eqv) in THF (6 ml) was added to the reaction mixture. The reaction was stirred for 16 hrs and monitored by TLC. The reaction was quenched with saturated NH_4Cl & extracted with EtOAc(3X3 ml). The organic layer was washed with brine, dried over anhydrous sodium sulphate& concentrated. The mixture was purified by silica column chromatography.

2-bromo-6-(1-hydroxybut-3-yn-1-yl)-4-methylphenol(5e):
Preparedaccording to general procedure D as a liquid; yield 75%.^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 (d, *J*= 1.2 Hz, 1H), 7.00 (s, 1H), 5.03-5.06 (m, 1H), 2.72-2.74 (m, 2H), 2.25 (d, *J*= 13.6 Hz, 3H), 2.12-2.13 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ147.7, 131.97, 130.8, 130.8, 127.6, 123.2, 110.4, 80.2, 71.2, 70.9, 27.5, 20.4.

2-(2-hydroxypent-4-yn-2-yl)phenol (5f): Prepared according to general procedure D as a yellow liquid; yield 549 mg (85%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.93 (s, 1H), 7.18-7.22 (m, 1H), 7.08-7.10 (m, 1H), 6.84-6.91 (m, 2H), 3.46 (d, *J*= 2 Hz, 1H), 2.94-2.99 (dd, *J*= 16.8 Hz, 2.4 Hz, 1H), 2.68-2.73 (dd, *J*= 16.8 Hz, 2.8 Hz, 1H), 1.75 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.9, 130.8, 129.7, 127.2, 121.1, 119.2, 81.1, 77.8, 73.9, 34.4, 29.08; IR(neat film NaCl): 3620,3300,2925,2150,1457.

2-(2-hydroxypent-4-yn-2-yl)-6-methylphenol (5g): Prepared according to general procedure D as a liquid; yield 664 mg (75%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.98 (d, *J*= 16.8 Hz, 1H), 7.07-7.10 (m, 2H), 6.93-7.01 (m,1H), 6.94 (d, *J*= 7.6 Hz, 1H), 6.75-6.79 (m, 2H), 5.65 (s, 1H), 5.02-5.04 (m, 1H), 3.25 (s, 1H), 2.68-3.25 (m, 2H), 2.26 (s, 3H), 1.75 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ153.0, 137.5, 130.4,128.6, 126.1, 118.0, 79.7, 76.1, 72.32, 32.9, 27.5, 20.6;IR(neat film NaCl): 3617,3400,2940,2918,2150,1456.

ANTICANCER ACTIVITY:

3-(4,5-dimethylthiazozyl)-2,5-diphenyl tetrazolium bromide (MTT), Dulbecco's modified Eagle's medium (DMEM), fetal bovine serum (FBS), Antibiotic solution (penicillin-streptomycin) were all obtained from Hi-Media (Mumbai, India). 96 well flat bottomed plates were purchased from Tarsons, India. To test the cytotoxic effect of the samples, cell viability study was done with the conventional MTT reduction assay on MCF-7 breast cancer cell line. Briefly, the cells were seeded in 96-well plates at the density of 3000 cells/well in 200µL of DMEM supplemented with 10% FBS and 1% penicillin-streptomycin solution and incubated for 24 h in an incubator containing 5% CO_2 at 37 °C. After 24 h of seeding, the existing media was removed and replaced by fresh media along with various concentrations of the samples (5, 10, 20, 40, 60, 80 and 100µmol) and incubated for 24 h at 37 °C, 5% CO2. To detect the cell viability, MTT working solution was prepared from a stock solution of 5 mg/mL in growth medium without FBS to the final working concentration of 0.8 mg/mL. 100µL of MTT solution was added and incubated. After 4 h of incubation, the MTT solution was discarded followed by addition of 100µL of DMSO solvent to each well under dark and incubated for of 15 min. The optical density of the formazan product was read at 595nm in a microplate reader (PerkinElmer, Waltham, MA, U.S.A.).

CRYSTALLOGRAPHIC ANALYSIS:

Single crystal X-ray diffraction intensity data of the title complexes (**8b**) and (**9j**) were collected at 150(2)K and 273(2)K respectively using a Bruker APEX-II CCD diffractometer equipped with graphite monochromatedM_oK_α radiation (λ=0.71073Å). Data reduction was carried out using the program Bruker SAINT. An absorption correction based on multi-scan method was applied. Successive attempts to crystallize the sample gave crystals of both complexes that were brittle needles and were difficult to cut. The best crystal possible that was finally selected for data collection gave diffuse diffraction spots, indicating the crystal has a large mosaic spread. As a result of this, a few of the diffraction spots were overlapping and the integration of these spots could not be carried out properly by the processing software. A small portion of the reflections collected were therefore rejected on the basis that they were measured incorrectly. Despite this the title structures were refined using the possible data, which is adequate to give a precise structure. The structures were solved by direct methods and refined by the full-matrix least-square technique on F^2 using the programs SHELXS97 and SHELXL97 respectively. All calculations were carried out using WinGX system Ver-1.64 and PLATON. The hydrogen atoms were located from difference Fourier map and treated as riding. A summary of crystal data and relevant refinement parameters are given in supporting information.

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Supplementary Material

Supplementary material that may be helpful in the review process should be prepared and provided as a separate electronic file. That file can then be transformed into PDF format and submitted along with the manuscript and graphic files to the appropriate editorial office.