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Design, Synthesis, *in vitro* and *in vivo* Evaluation of (*Z*)-3,4,5-Trimethoxystyryl Benzenesulfonamides/Sulfonates as Highly Potent Tubulin Polymerization Inhibitors

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Abstract: Newer therapeutics can be developed in drug discovery by adopting the strategy of scaffold hopping of the privileged scaffolds from known bioactive compounds. This strategy has been widely employed in drug discovery process. Structure based docking studies illustrates the basic underlying concepts, which have been carried out, reveal interactions of sulfonamide group and hydrophobic interactions are crucial. Based on this strategy over 60 synthetic analogues were synthesized and evaluated for their cytotoxicity against the NCI panel of sixty human cancer cell lines, majority of these compounds exhibited promising cytotoxicity with GI_{50} values ranging between 18-50 nM, among them compounds **7a** and **9a** were found to be potent. Similar results were obtained against three human cancer cell lines with IC_{50}values ranging between 0.04-3.0 µM. Further studies aimed at elucidating the mechanism of action of these new analogues revealed that they inhibited the *in vitro* tubulin polymerization and disorganized the microtubule assembly in HeLa and MCF-7cancer cells. The lead compounds **7a** and **9a** displayed notable *in vivo* antitumor activity in HeLa tumor xenograft model. Our studies resulted in the identification of a scaffold that can target tubulin polymerization having significant potential towards the development of new antitumor drugs.

Introduction

The aggregation of α- and β-tubulins to form microtubules and its disassembly, generally known as microtubule dynamics, constitutes a vital process that aids in the proper functioning and division of eukaryotic cells.[1-3] The pivotal role of microtubule dynamics in mediating cell division makes it an attractive target for the design of cancer chemotherapeutics. A number of natural and manmade molecules that cause mitotic arrest by disrupting the microtubule dynamics are known. They are generally classified into microtubule stabilizers (e.g., paclitaxel)[4] and microtubule destabilizers such as vinca alkaloids,[5,6] colchicine (**1**)[7] and combretastain A-4 (**2a**)[8] (Figure 1). The latter inhibits the polymerization of tubulin by interacting at the colchicine-binding site.[9] The potent activity and the simple chemical structure has made it a popular starting point for the design of new anticancer agents.[10] A water soluble pro-drug (CA-4P, **2b**) that is currently undergoing phase I/II clinical trials is a notable and closely related CA-4 analogue.[11] Numerous synthetic derivatives and analogues of **2a** have been developed in the recent past to address various drawbacks such as unstable nature of the olefinic unit, poor solubility and toxicity.

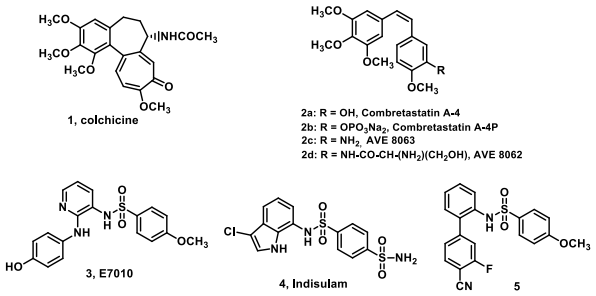


Figure 1. Novel combretastatin-sulfonamide (sulfonate) conjugates designed for the present study.

The beneficial influence of sulfonamide substituents on the anticancer potential of designed compounds have been demonstrated earlier.[12,13] The antitubulin agents such as E7010 (3),[14] E7070 (indisulam, 4),[15] and the biarylsulfonamide 5 [16] constitute a few illustrative examples that are pertinent to the present work. The sulfonamide moiety is easy to install as well as it generally imparts stability and crystallinity to the attached pharmacophore. Our approach of hybridizing two pharmacophoric units to design improved anticancer agents has led to the development of a variety of potent, small molecule tubulin binders.[17] In this context, we surmised that the anchoring of sulfonamide groups on the combretastain scaffold may improve its general anticancer potential and stability. The

docking process involves two basic steps: prediction of the ligand conformation as well as its position and orientation within the sites and assessment of the binding affinity, the binding modes of these compounds are discussed.[18-19] Considering this fact, a collection library of combretastatin-sulfonamide (and sulfonate) conjugates were designed as depicted in Figure 2. The trimethoxyphenyl ring of CA-4 has not been tinkered as it has shown to be essential for the biological activity. Attachment of the sulfonamide/sulfonate groups on the remaining aryl ring would result in **6, 7, 8** and **9**, whereas the fictionalization of the olefinic unit with *N*-sulfonyl carboxamide groups would afford compounds 10 and 11 (Figure 2). This study, therefore, is aimed at the synthesis of combretastatin-sulfonamide (and sulfonate) conjugates and later the antiproliferative activity. The cytotoxicity depicted in this article has been previously described in patent 3076DEL2014 (PCT/IN2015/050148).[20] Further, tubulin-binding potential and the *in vivo* antitumor activity of the designed compounds were examined. It is noteworthy to mention that most all the compounds exhibited excellent antiproliferative activity and two representative compounds (**7a** and **9a**) displayed promising *in vivo* activity against HeLa tumor in mice.

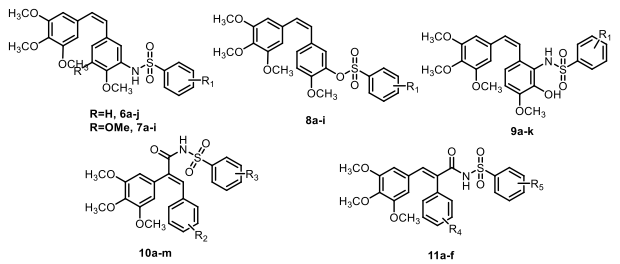


Figure 2: Novel combretastatin-sulfonamide (sulfonate) conjugates designed for the present study.

Design of newer tubulin inhibitors based on pharmacophore features.

Pharmacophore may be defined as a set of key chemical features contributing to biological activity of a compound. Based on the strategy of scaffold hoping of the privileged scaffolds from known bioactive compounds, new therapeutics can be developed and has been widely employed in drug discovery.[21-22] Trimethoxy phenyl and tropolone methyl ester rings of colchicine are essential features contributing to the binding of colchicine. Specifically, the keto group on the tropolone ring has been known to exhibit interactions with binding site residues.[23] The hydroxyl and methoxy groups on the second phenyl ring of CA-4 is known to exhibit interactions with colchicine binding site similar to functional groups on tropolone of colchicines.[24] Olefinic bond is known to be important in maintaining the compound in the right configuration and its modification is reported to reduce the activity of CA-4 analogues.[25] Pharmacophore of sulfonamide focused libraries (including E7010) targeting tubulin have been evaluated in an array-based structure and gene expression relationship study. The study revealed N-(2-aminophenyl sulfoniamide moiety as the key pharmacophore.[26-27] Novel series of tubulin inhibitors including key pharmacophore features from E7010 and CA-4 were designed and synthesized (Figure 1).[28] Previous studies enabled to rationalize the key pharmacophore elements from a diverse set of colchicine site inhibitors, which included a hydrogen bond acceptor, two hydrophobic centers and a planar group.Trimethoxystyryl series has an additional hydrogen bond donor and a hydrophobic feature. Trimethoxystyryl series has been designed to test the optimal position to add phenylsulfonalamide moiety and the synthesized analogues are divided into the following four groups (Figure 3):

(i) Sulfonamide phenyl moiety at *meta* position of ring B of CA-4 (**6a-j, 7a-i** series),

(ii) Replace 'NH' of sulfonylamide moiety with a 'O' from group 1 (**8a-8i**series),

(iii) Sulfonamide phenyl moiety at *ortho* position of ring B of CA-4 (**9a-9k**) and

(iv) Sulfonamide phenyl moiety on the olefinic bond (**10a-m, 11a-f** series).

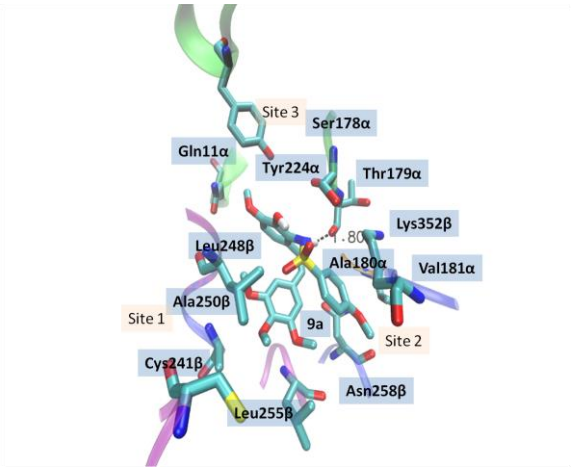


Figure 3. Compound **9a** docked into the αβ interface of tubulin (1SA0). Residues within 3.5 A of ligands are shown. Site 1 binds with trimethoxy phenyl moiety (backbone is coloured in magenta), Site 2 is occupied by 4-methoxy phenyl moiety (backbone is shown in blue) and site 3 involves 3,4-substituted phenyl moiety (backbone is shown in blue) and site 3 involves 3,4-substituted phenyl moiety (backbone is shown in green). H-bonding interaction with Thr179α is represented by a dotted line.

Molecular docking analysis.

Docking studies were performed to understand binding modes of trimethoxystyryl benzene series. Following observations are based on binding mode predicted by docking. Trimethoxy phenyl binds in a pocket surrounded by residues Leu255β, Leu248β and Ala250β (site 1, Figure 3). Where These studies also suggest the water mediated hydrogen bonding interactions between Leu248β and Ala250β and the methoxy groups, and this observation, however needs further investigation. Predicted binding mode revealed the presence of a olefin bond which plays a key role in maintaining the compounds in 'cis' conformation, consistent with prior observations. Addition of a bulky group onto this bond thus weakens the activity of group 4 series. The amino group from sulfonyl amido group acts as H-bond donor to Thr179α. The H-bonding interaction of colchicine binding site inhibitors with Thr179α, has been widely discussed in literature. Lack of H-bond donor in this position explains the difference in activities of group 3 series versus group 1 and 2. Methoxy phenyl occupies a pocket formed by Ala180α, Val181α,

Lys352β and Asn258β (site 2, Figure 3). Mutational studies established equivalent residue (Lys350β) as one of the key interacting residues.[29,30] Where as 4-methoxy of phenyl exhibited hydrophobic interactions with side chains of Val 181 and Met b259 and is consistent with the pharmacophore discussed previously. The residues Gln11α and Tyr224α are within 3.5 Å of 3-hydroxy, 4-methoxy phenyl moiety (site 3, Figure 3). The 3-hydroxy and 4-methoxy phenyl moiety represents novel hydrophobic feature among colchicine inhibitors that target novel binding pocket (site 3, Figure 3). Mutational studies of Gln11α and Tyr224α could be interesting to further establish this new binding pocket. Extending or replacing 4-methoxy with hydrogen bond donors for the trimethoxystyryl series, could also contribute to favorable interactions in this binding site and the predicted docking model agrees well with the earlier experimental studies.[33,34] However, some experimental studies will further establish crucial roles played by various residues and encourage structure-based optimization of suggested leads. The docking studies also reveal there is ample scope for further optimization of the trimethoxystyryl series.

Results and Discussion

Chemistry

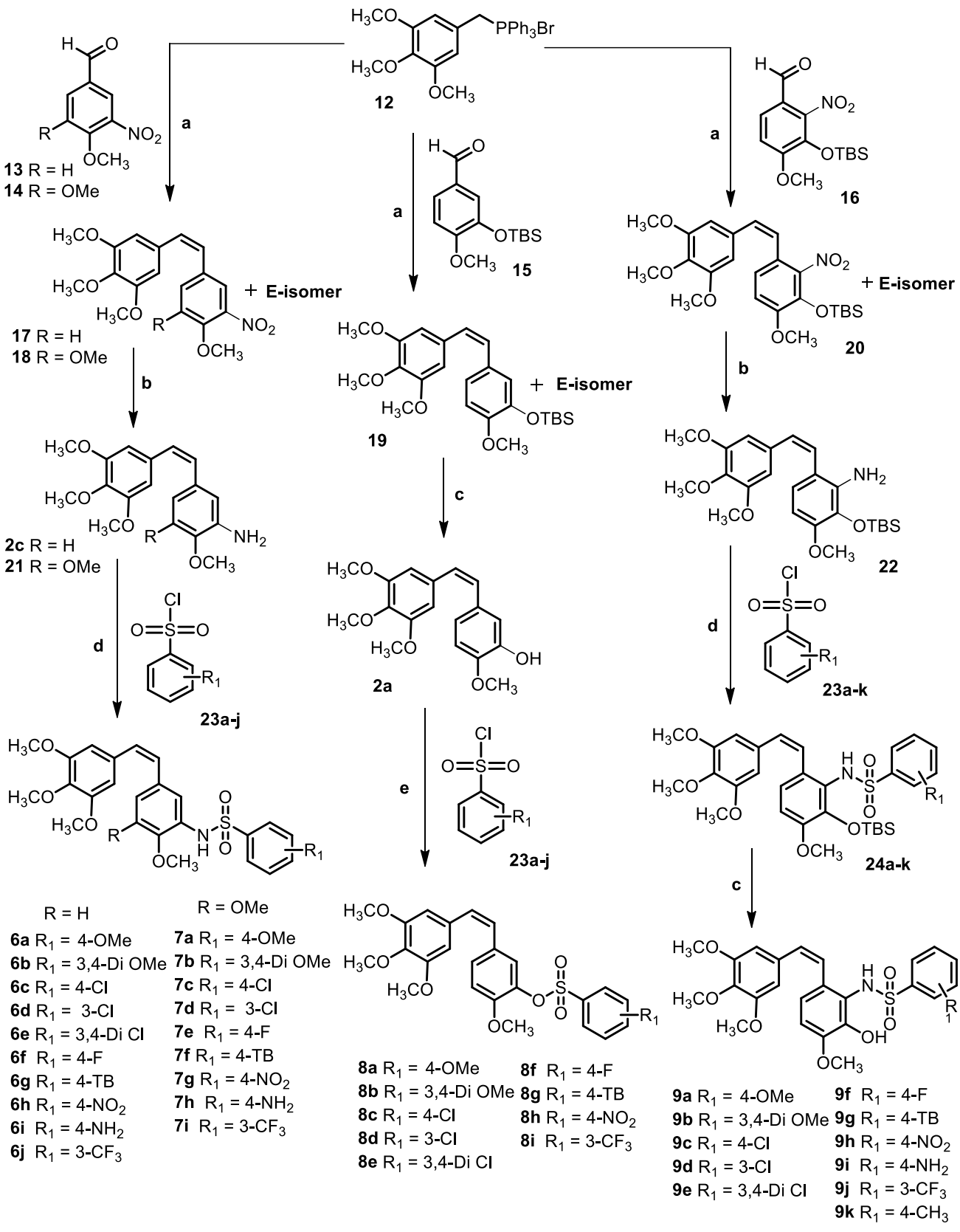
Compounds (**6a**-j, **7a**-i) and (**9a**-k) were prepared by coupling of properly substituted (Z)-(3,4,5-trimethoxystyryl)anilines (**2c, 21** and **22**) with various commercially available substituted benzenesulfonyl chlorides (**23a-k**) in a 1:4 (v/v) mixture of pyridine in anhydrous dichloromethane13 and (Z)-3-styrylphenyl benzenesulfonates (**8a-i**) prepared by the reaction of combretastatin (**2a**) with the similar benzenesulfonyl chlorides by using dichloromethane as a solvent in the presence of triethylamine with outstanding yields. The intermediate compounds **2a, 2c, 21** and **22** were obtained by the reduction and deprotection of their respective nitro, hydroxyl stilbene derivatives (17-20), which were synthesized by double bond forming Wittig reaction between the suitable benzaldehydes (**13-16**) with 3,4,5-trimethoxybenzyl triphenylphosphonium bromide (**12**) in presence of sodium hydride in anhydrous dichloromethane, afforded a mixture (1:1, v/v) of nitro Z-stilbenes (**17-20**) and E-stilbenes as depicted in Scheme 1 and these isomers have been separated by column chromatography. The compounds (10a-m and 11a-f) have been achieved by the formation of amide bond between the stilbene-acrylic acids (**27a-f** and **31a-**c) with a variety of substituted benzene sulfonamides (**28a-f** and **32a-c**) by using EDCI/DMAP.39 Wherein, the intermediates were prepared in good yield by the Claisen–Schmidt condensation of different phenyl acetic acids with appropriate benzaldehydes.

Biological studies

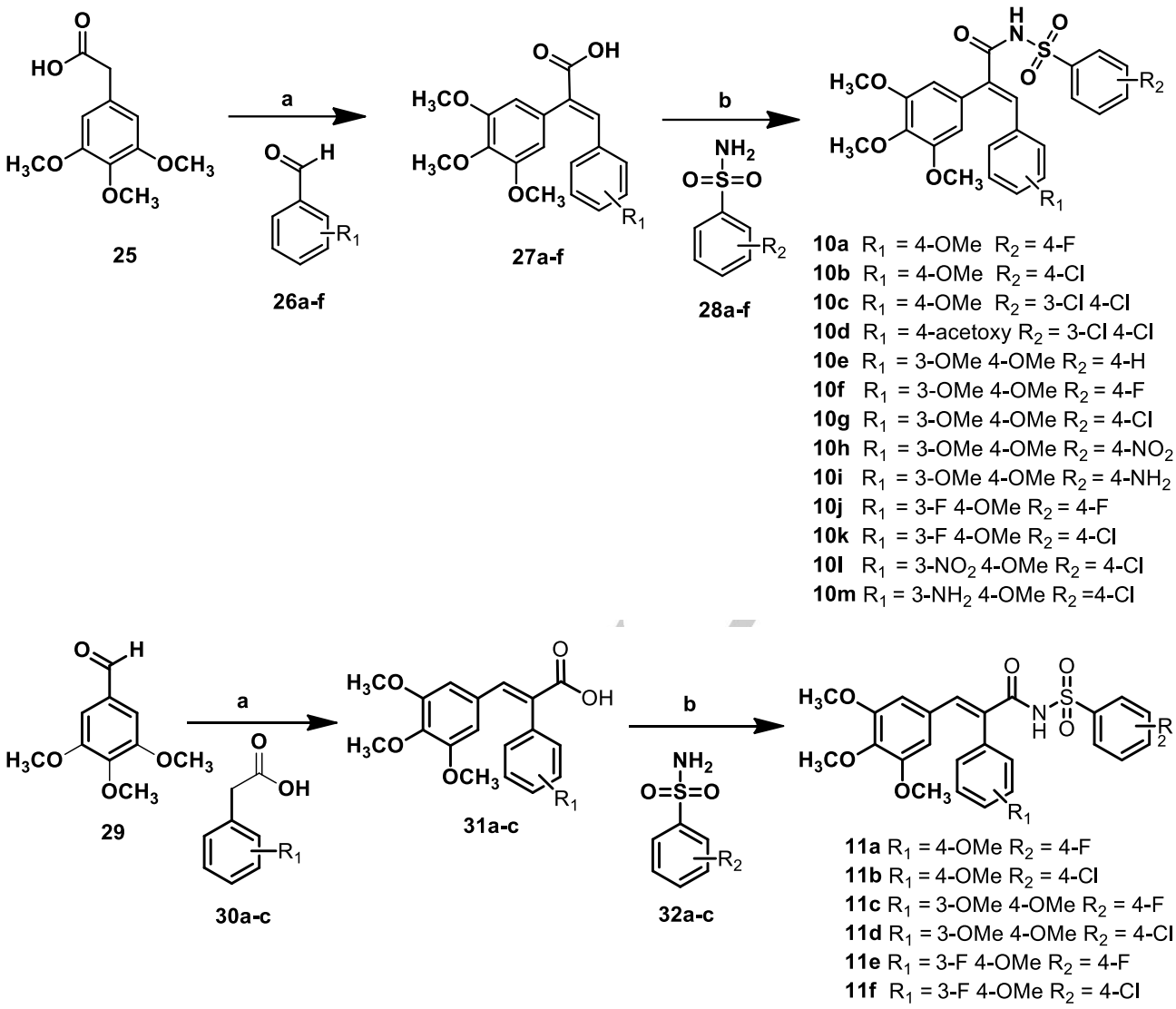
The synthesized derivatives (Z)-N-(3-styrylphenyl)benzene sulfonamides/sulfonates (**6a-j, 7a-i, 8a-i, 9a-k, 10a-m** and **11a-f**) have been evaluated for their cytotoxicity against a panel of sixty human tumor cell lines accomplished from different types of nine cancer cell lines (leukemia, non-small cell lung cancer, colon cancer, CNS cancer, melanoma, ovarian cancer, renal cancer, prostate cancer and breast cancer) as per the NCI protocol. Over sixty compounds, eighteen (**6a–c, 7a-d, 7f, 7g-i, 9a-c 9f-i** and **9k**) were selected for the preliminary screening at a single dose concentration (10 μM) which exhibited significant mean growth inhibition. Eleven compounds were further evaluated in the secondary screening at five dose concentrations with 10-fold dilutions which displayed remarkable antiproliferative efficacy on most of the NCI cell lines. The primary objective of the present study was to develop new combretastatin sulfonamides bearing the key pharmacophore such as E7010 and CA-4. In addition, the SAR studies disclosed that the sulfonamide group situated between two aromatic rings (B, C rings) need to be eternal as a basic design accompanied by a methoxy group at the *para*-position as observed in E7010 which is crucial for maximum cytotoxicity.

The SAR studies have been examined for these diverse combrestatin sulfonamide analogs. In particular, the aryl sulphanamide has been attached on B-ring and *cis*- double bond. Mostly B-ring linked sulphonamides (**6a-j**, **7a-i**, **8a-l** and **9a-k**) exhibited remarkable antiproliferative activity as compared to the double bond linked sulphonamides (**10a-m** and **11a-f**). Specifically, the compound **7a** and **9a** possess broad spectrum of cytotoxicity within nanomolar range against most of cell lines with GI50 values below 0.05 μM, wherein, eight different types of tumor cell lines displayed GI50 values below 0.03 μM and relatively twenty five cell lines showed GI_{50} values less than 0.04 μM. This is reliable with pharmacophore studies and docking. In detail, the compound **7a** demonstrated remarkable cytotoxicity against HL-60 (TB), K-562, SR (leukemia), NCI-H552 (lung), HCC-2998, HCT-116 (colon), SF-539, SNB-75 (CNS), MDA-MB-435 (melanoma), SK-OV-3 (ovarian), A498 (renal) and MCF-7 (breast) cancer cell lines with GI_{50} values of 0.02, 0.03, 0.03, 0.02, 0.04, 0.02, 0.02, 0.02, 0.04, 0.02 and 0.03 μM, respectively. In similar cell lines, compound **9a** exhibited GI_{50} values of 0.02, 0.03, 0.03, 0.02, 0.03, 0.03, 0.02, 0.02, 0.03, 0.02 and 0.04 μM, respectively. Moreover, the other compounds with methyl and fluoro substituents at the *para*-position of C-ring showed significant activity in the sub-micromolar range against all the tested cell lines. However, the addition of one methoxy group in the C ring decreased the cytotoxicity. Furthermore, the presence of electron withdrawing substituents like nitro and trifluoromethyl groups at the *para*-position of the sulfonamide system resulted in the decrease in cytotoxicity. These observations suggest that by replacing the electron donating by withdrawing groups on the C-ring showed a reduction in the antiproliferative activities.

Further, all of the compounds (**6a-j, 7a-i, 8a-i, 9a-k**, **10 a-m** and **11a-f**) of this series were evaluated for their antiproliferative activities against three human cancer cells such as A549 (lung), MCF-7 (breast) and HeLa (cervical) and the results to this regard are summarized in Table 2. Interestingly, similar to the NCI screening results, the compounds (Figure 2) possessing a methoxy group at *para*-position of C ring showed superior cytotoxicity with IC_{50} values ranging between 0.04 to 3 μM. Correspondingly, the compounds **7a** and **9a** showed significant cytotoxicity with respective IC_{50} values of 0.057 μM and 0.078 μM in MCF7 cell line. These compounds were quite promising in cervical cancer cell line (HeLa) with respective IC_{50} values of 0.044 μM and 0.047 μM. Based on these promising results, we selected the HeLa cell line for further *in vivo* experiments.



Scheme 1. Reagents and conditions: (a) NaH, dry CH_2Cl_2, 0 °C to rt, 12 h; (b) Zn, HCO_2NH_4, MeOH, rt, 4 h; (c) TBAF (1M in THF), THF 0 °C, 2 h (d) Pyridine, 0-5 °C, 4 h; (e) TEA, CH_2Cl_2, 0-5 °C, 4 h.



Scheme 2 & 3. Reagents and conditions:(a) AC_2O, NaOH, 140 °C; (b) EDCI, DMAP, TEA, CH_2Cl_2.

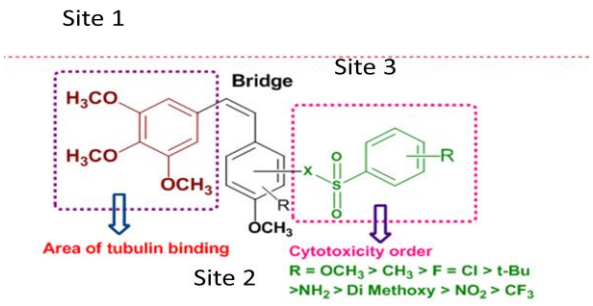
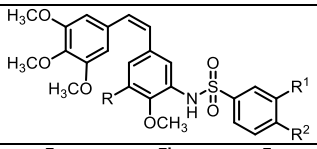
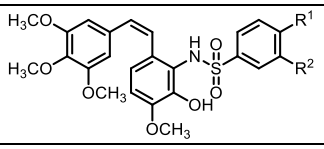


Figure 4. Structure–activity relationship (SAR) of the (Z)-3,4,5-trimethoxystyryl benzenesulfonamide /sulfonates derivatives.

Cell cycle analysis

Many anticancer compounds exert their growth inhibitory effect either by arresting the cell cycle at a particular checkpoint of cell cycle or by induction of apoptosis or a combined effect of both the cell cycle block and apoptosis.[35,36] The in vitro screening results revealed that compounds **7a** and **9a** showed significant antiproliferative activity against cervical (HeLa) and human breast (MCF-7) cancer cell lines. In this context, HeLa and MCF-7cells were treated with these compounds at 25 and 50 Nm for 48 h. The results clearly indicated that these compounds arrested the cell cycle at G2/M phase when compared to untreated control cells [Figures 5a and (Supplemental Information 5b)]. Compounds **7a** and **9a** showed 26.30 and 26.22% of cell accumulation in G_2/M phase at 25 nM, whereas they showed 28.43 and 31.85% of cell accumulation in G_2/M phase at 50 nM concentration, respectively, in HeLa cells. In case of MCF7 cells, these compounds showed 18.29 and 18.80% of cell accumulation in G_2/M phase at 25 nM concentration, whereas they showed 32.83 and 34.41% of cell accumulation in G_2/M phase at 50 nM concentration respectively [Tables 5a and (5b in supplemental information)].





	6a R=H R^1=OCH_3 R^2=H	7a R= OCH_3 R^1=OCH_3 R^2=H	7b R= OCH_3 R^1-OCH_3 R^2=OCH_3	7c R= OCH_3 R^1= Cl R^2=H	7d R= OCH_3 R^1= H R^2= Cl	9a R^1-OCH_3 R^2=H	9b R^1-OCH_3 R^2=OCH_3	9c R^1= Cl R^2=H	9g R^1= F R^2=H	9h R^1= t-Bu R^2=H	9k R^1= CH_3 R^2=H
Leukemia											
CCRF-CEM	0.17	0.03	0.34	0.38	0.05	0.03	0.04	0.15	0.05	0.46	0.04
HL-60(TB)	0.19	0.02	0.37	0.24	0.03	0.02	0.33	0.03	0.03	0.04	0.04
K-562	0.05	0.02	0.42	0.30	0.04	0.03	0.08	0.03	0.03	0.07	0.04
MOLT-4	0.38	0.05	0.70	0.67	0.04	0.04	0.48	0.03	0.05	0.20	0.04
RPMI-8226	0.31	0.04	0.56	0.38	0.06	0.04	0.45	0.20	0.05	0.50	0.05
SR	0.07	0.03	0.70	0.40	0.06	0.03	0.09	0.03	0.03	0.04	0.03
NSClung											
A549/ATCC	0.15	0.05	1.31	0.71	0.26	0.04	0.36	0.27	0.46	0.62	0.05
HOP-62	0.04	0.04	17.23	0.41	3.1	0.04	0.07	0.67	4.80	10.0	28.0
HOP92	0.10	17.5	0.20	0.72	0.07	16.0	NT	23.6	0.04	0.18	0.05
NCI-H226	12.8	NT	1.87	13.5	0.31	41.3	0.14	NT	0.33	0.54	0.04
NCI-H23	0.48	0.06	3.31	0.71	0.38	0.05	0.27	0.28	038	0.49	0.05
NCIH322M	0.43	0.05	4.71	0.75	0.37	0.06	0.74	0.48	0.84	0.69	0.10
NCI-H460	0.18	0.03	0.39	0.36	0.03	0.03	0.25	0.31	0.04	0.37	0.03
NCI-H522	0.02	0.02	0.36	0.20	0.03	0.02	0.06	0.08	0.22	0.21	0.04
Colon											
COLO-205	0.03	0.02	1.28	0.25	0.26	0.41	0.47	17.4	3.02	3.32	1.46
HCC-2998	0.44	0.04	1.83	1.98	0.31	0.03	0.33	0.42	0.37	1.50	0.09
HCT-116	0.07	0.03	0.46	0.46	0.04	0.03	0.13	0.11	0.04	0.36	0.04
HCT-15	0.06	0.03	0.67	0.39	0.14	0.04	0.33	0.05	0.14	0.23	0.05
HT29	0.08	0.03	0.48	0.34	0.04	14.0	0.41	27.6	2.53	3.51	1.28
KM12	0.07	0.04	0.63	0.57	0.04	0.03	0.07	0.12	0.07	0.58	0.04
SW-620	0.08	0.04	0.47	0.34	0.04	0.04	0.11	0.06	0.04	0.32	0.04
CNS											
SF-268	0.40	0.06	20.8	1.10	0.20	0.08	2.70	0.38	0.63	1.71	0.73
SF-295	0.04	0.03	0.47	0.31	0.04	0.03	0.27	0.25	0.34	1.37	0.07
SF-539	0.12	0.02	0.51	0.30	0.03	0.03	0.08	0.04	0.15	0.15	0.02
SNB-19	0.03	0.06	1.11	0.74	0.21	0.06	0.52	0.80	0.41	0.56	0.06
SNB-75	0.07	0.03	0.40	0.22	0.03	0.02	0.30	0.03	0.04	0.23	0.02
U251	0.10	0.03	0.68	0.46	0.05	0.04	0.34	0.28	0.47	0.59	0.05
Melanoma											
LOX IMVI	0.27	0.05	0.47	0.56	0.06	40.0	0.25	0.15	0.36	0.66	0.06
MALME-3M	0.05	NT	NT	NT	20.0	15.1	NT	NT	NT	NT	NT
M14	0.10	0.03	0.49	0.39	0.03	0.03	0.17	0.09	0.03	0.19	31.0
MDA-MB-435	0.03	0.02	0.26	0.18	0.03	0.02	0.03	0.02	0.02	0.04	0.03
SK-MEL-2	0.08	0.04	5.29	0.61	1.38	0.04	6.01	0.06	0.6	1.22	0.02
SK-MEL-28	0.14	0.08	3.27	1.14	1.61	NT	1.85	0.08	3.07	4.91	24.0
SK-MEL-5	0.05	0.03	4.88	0.29	0.22	0.03	0.06	0.05	0.27	0.34	4.0
UACC-257	2.98	41.0	NT	12.5	20.3	NT	NT	14.2	NT	13.2	0.03
UACC-62	0.04	0.04	0.49	0.43	0.06	0.03	0.05	0.06	0.05	0.11	0.05
Ovarian											
IGROV1	0.16	0.06	4.58	0.91	0.09	0.05	0.49	0.37	0.71	0.98	0.11
OVCAR-3	0.05	0.03	0.41	0.36	0.03	0.03	0.21	0.06	0.04	0.22	0.04
OVCAR-4	0.58	0.08	3.12	0.15	0.24	0.07	0.93	0.10	1.48	0.18	0.62
OVCAR-5	0.32	0.05	6.57	0.72	0.64	10.20	0.65	28.6	0.46	0.62	0.16
OVCAR-8	0.27	0.04	4.08	0.60	0.42	0.04	0.38	0.29	0.34	0.44	0.06
NCI/ADR-RES	0.07	0.03	0.48	0.36	0.09	0.15	0.94	0.26	0.27	0.30	0.21
SK-OV-3	0.09	0.04	11.4	0.44	1.15	0.03	2.75	0.22	0.86	1.42	7.80
Renal											
786-0	0.36	0.06	0.44	0.66	0.06	0.37	0.46	0.57	0.31	0.49	0.11
A498	0.03	0.02	0.15	0.17	0.02	0.02	0.02	0.02	0.02	0.02	0.02
ACHN	0.06	0.06	0.92	0.58	0.10	0.06	0.54	0.83	0.48	0.45	0.11
CAKI-1	0.05	0.05	0.81	0.37	0.05	0.05	1.28	0.05	0.18	0.07	0.14
RXF 393	0.08	0.04	0.68	0.27	0.33	0.03	0.08	0.03	0.05	0.04	0.02
SN12C	0.68	0.07	1.18	0.75	0.22	0.08	0.40	0.70	0.38	0.61	0.08
TK-10	0.08	0.06	10.3	0.77	2.01	0.07	0.76	0.99	1.44	1.30	1.23
UO-31	0.13	0.06	1.59	0.69	0.09	0.06	0.99	0.07	1.52	0.98	1.65
Prostate											
PC-3	0.12	0.04	0.37	0.39	0.04	0.04	0.28	0.15	0.05	0.36	0.05
DU-145	0.34	0.04	0.84	0.50	0.07	0.04	0.38	0.20	0.04	0.39	0.04
Breast											
MCF7	0.04	0.03	0.48	0.37	0.05	0.04	0.04	0.04	0.06	0.13	0.04
MDA-MB-231/ATCC	0.39	0.05	2.43	1.16	0.25	0.05	0.33	0.20	0.16	35	0.06
HS 578T	0.22	0.04	3.42	0.35	0.08	0.05	0.21	0.29	0.35	0.52	0.05
BT-549	0.19	0.04	0.66	0.96	0.03	0.05	0.23	0.35	0.08	0.46	0.03
T-47D	NT	52.1	NT	0.38	39.5	NT	NT	NT	NT	NT	42.5
MDA-MB-435	0.16	0.04	0.26	0.27	0.29	0.04	0.04	0.03	0.16	0.30	0.02

Table 1. GI_{50} concentrations (μM) for in vitro cytotoxic effect induced by compounds (**6a–c, 7a-d, 7f, 7g-i, 9a-c 9f-i** and **9k**) against the NCL panel of 60 human cancer cells. Data are reported as the GI_{50} value (concentration required to cause 50% inhibition of cell growth after an incubation time of 48 h). [6a] NSC774998/1. [**7a**] NSC775010/1. [7b] NSC 780186/1. [7c] NSC 775011/1 [7d] NSC780185/1. [9a] NSC775014/1 [9b] NSC780182/1 [9c] NSC 775015/1. [9g] NSC780183/1 [9h] NSC780176/1 [9j] NSC780184/1.

code	A549[b]	MCF-7[c]	HeLa[d]	code	A549[b]	MCF-7[c]	HeLa[d]
6a	0.86±0.05	0.07±0.003	0.06±0.002	**9a**	0.09±0.0005	0.07±0.001	0.04±0.001
6b	1.17±0.04	1.30±0.09	1.07±0.06	**9b**	0.69±0.08	0.07±0.05	0.06±0.05
6c	1.85±0.10	2.61±0.10	1.49±0.06	**9c**	0.64±0.06	0.07±0.05	0.07±0.05
6d	1.13±0.04	0.84±0.007	0.71±0.005	**9d**	1.08±0.11	1.14±0.05	0.80±0.05
6e	2.12±0.07	2.14±0.18	1.93±0.05	**9e**	2.2±0.18	3.12±0.05	2.02±0.05
6f	5.06±0.10	3.71±0.05	2.31±0.18	**9f**	1.21±0.08	0.09±0.05	0.08±0.05
6g	4.26±0.17	2.13±0.05	1.62±0.11	**9g**	1.06±0.07	0.95±0.05	0.76±0.05
6h	1.40±0.08	1.25±0.13	1.18±0.08	**9h**	2.89±0.14	1.54±0.05	1.17±0.05
6i	1.47±0.07	2.4±0.15	1.11±0.04	**9i**	1.32±0.05	0.86±0.05	0.76±0.05
6j	2.81±0.05	1.05±0.06	0.93±0.01	**9j**	1.86±0.04	0.72±0.05	0.624±0.05
7a	0.08±0.003	0.05±0.002	0.04±0.001	**9k**	1.02±0.008	0.08±0.007	0.072±0.003
7b	2.08±0.12	0.66±0.006	0.16±0.01	**10a**	3.12±0.14	1.8±0.05	1.21±0.05
7c	1.61±0.08	0.57±0.008	0.19±0.05	**10b**	1.67±0.05	0.53±0.05	0.35±0.05
7d	0.70±0.007	0.08±0.05	0.09±0.05	**10c**	6.30±0.24	12.6±0.32	9.95±0.18
7e	1.35±0.04	0.90±0.006	1.10±0.07	**10d**	2.80±0.12	0.88±0.05	1.12±0.04
7f	2.00±0.02	2.08±0.10	1.30±0.05	**10e**	11.74±0.31	4.25±0.22	5.14±0.10
7g	1.20±0.06	2.89±0.15	0.95±0.03	**10f**	2.31±0.15	0.92±0.009	0.56±0.008
7h	1.82±0.07	1.53±0.06	1.44±0.07	**10g**	2.30±0.14	0.85±0.03	0.41±0.01
7i	2.13±0.13	1.83±0.05	1.78±0.05	**10h**	4.80±0.20	0.88±0.10	1.12±0.05
7j	1.81±0.11	1.28±0.04	1.21±0.09	**10i**	2.88±0.19	1.29±0.06	1.64±0.11
8a	2.50±0.15	0.09±0.004	0.09±0.005	**10j**	2.87±0.28	0.48±0.05	2.59±0.22
8b	1.22±0.09	1.23±0.08	1.09±0.06	**10k**	2.20±0.05	0.61±0.04	0.58±0.008
8c	0.98±0.015	0.85±0.009	0.70±0.08	**10l**	3.80±0.25	3.25±0.18	1.23±0.015
8d	1.90±0.07	1.79±0.10	1.54±0.12	**10m**	7.91±0.28	1.73±0.08	0.63±0.055
8e	1.92±0.05	1.28±0.08	1.16±0.04	**11a**	2.93±0.12	1.36±0.04	2.16±0.045
8f	3.63±0.25	2.56±0.05	4.34±0.14	**11b**	1.04±0.009	0.74±0.04	0.49±0.009
8g	1.28±0.15	0.78±0.008	0.74±0.008	**11c**	1.38±0.05	0.84±0.07	0.80±0.08
8h	1.99±0.09	1.29±0.07	1.15±0.05	**11d**	1.57±0.08	0.39±0.004	0.38±0.002
8i	3.34±0.12	1.45±0.05	1.13±0.08	**11e**	1.99±0.02	1.29±0.09	1.15±0.08
(2a)	0.03±0.008	0.04±0.003	0.04±0.003	**11f**	3.34±0.15	1.45±0.04	1.13±0.052
(2c)	1.23±0.05	1.96±0.08	2.42±0.12	**24**	3.97±0.22	2.46±0.13	2.05±0.09
17a	2.14±0.05	3.75±0.05	3.04±0.05	**E7010**	1.22±0.03	1.97±0.10	1.98±0.05

Table 2. IC_{50} concentrations[a] (μM) for in vitro cell growth inhibition by compounds (**6a-j, 7a-i, 8a-i, 9a-k, 10a-m** and **11a-f**) treated against selected human cancer cell lines for 48 h. [a] Concentration required to inhibit 50% cell growth following 48 h treatment with the tested drug. [b] A549: non-small cell lung cancer; [c] MCF-7: breast cancer cell line; [d] HeLa: cervix cancer.

Effect of 7a and **9a on tubulin polymerization.**

The G_2/M cell cycle arrest is mostly associated with tubulin polymerization inhibition [38] and since the compounds **7a** and **9a** arrested the cell cycle at G2/M phase as compared to the untreated control cells, it was important to understand the microtubule inhibitory function of compounds **7a** and **9a**. To evaluate these compounds on tubulin polymerization, the fluorescent-based tubulin polymerization assay was conducted.

Wherein the inhibition was demonstrated by a decreased fluorescence at emission wavelength of 420 nm against excitation wavelength of 360 nm (Figures 6). Tubulin was co-incubated with or without compounds (**7a, 9a** and **CA_4**) and fluorescence readings were recorded at emission wavelength 420 nm against excitation at 360 nm using Infinite 200M multimode reader (Tecan). The IC_{50} of tubulin by both the compounds was determined at five different concentrations (0.1, 0.5, 1, 2 and 4 μM). It was observed that the tubulin IC_{50} with compound **9a** and **CA-4** was **0.6** μM and **0.7** μM, respectively, which was comparable (Table 4).

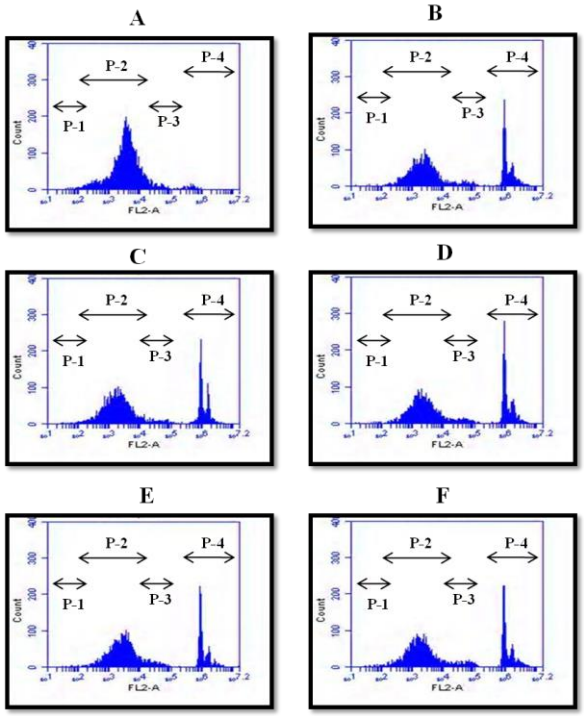


Figure 5a. Cell cycle analysis of compounds **7a** and **9a** treated on HeLa cells for 48 h. (A-F) Response of mitotic spindle checkpoints on HeLa cells to compounds **7a** and **9a**. Flow cytometric analysis showed that the majority of the cells were arrested in G_2/M phase of the cell cycle in HeLa cells; (A): Control or untreated HeLa cells, (B): treatment with 25 nM of compound CA-4; (C): treatment with 25 nM of compound **7a**; (D): treatment with 50 nM of compound **7a**; (E): treatment with 25 nM of compound **9a**; (F): treatment with 50 nM of compound **9a**. According to figure 5a; P-1 represents Sub G1 phase, P-2 represents G0/G1 phase, P-3 represents S phase and P-4 represents G2/M phase.

Sample	Sub G_1 %	G_0/G_1 %	S %	G_2/M %
A: Control (HeLa)	1.30	94.43	0.83	3.29
B: CA-4 (50 nM)	0.72	58.74	0.32	27.46
C: **7a** (25 nM)	1.18	64.43	0.46	26.30
D: **7a** (50 nM)	1.16	59.96	0.52	31.85
E: **9a** (25 nM)	1.01	66.22	0.30	26.22
F: **9a** (50 nM)	1.50	62.42	0.31	28.43

Table 3a. Distribution of HeLa cells in various phases of cell cycle.

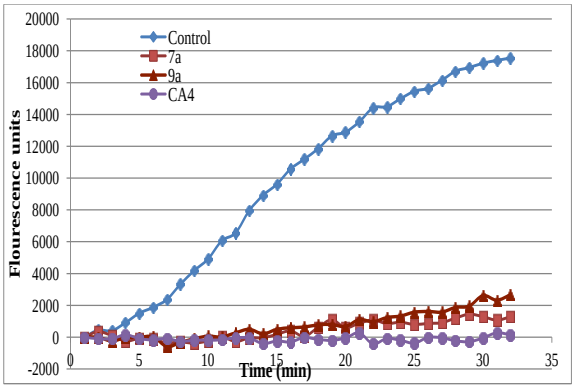


Figure 6. Effect of conjugates **7a** and **9a** on tubulin polymerization, the tubulin polymerization was monitored by the increase in fluorescence at 360 nm (excitation) and 420 nm (emission) for 1 h at 37 ˚C. All the compounds were incubated at a final concentration of 3 µM. CA-4 was used as a positive control.

Compound	Tubulin (IC_{50}, µM)
7a	1.6 ±0.08
9a	0.6 ±0.02
CA-4	0.7 ±0.03

Table 4. [a] Concentration of drug to inhibit 50% of tubulin assembly. Values indicated are the mean ± SD of two different experiments performed in triplicates.

Competitive colchicine binding assay.

Compounds **7a** and **9a** revealed parallel inhibitory effects on tubulin polymerization which was comparable to CA-4 and this prompted us to explore whether these compounds bind to the colchicine site of tubulin using fluorescence based assay. Tubulin (3 µM) was incubated with the various concentrations of compounds **7a** and **9a** (0–20 µM) in the presence of colchicine (3 µM) with CA-4 as positive control at 37 °C for 60 min and the fluorescence of tubulin–colchicine complex was monitored at 435 nm when excited at 350 nm. We noticed an increase in fluorescence of tubulin–colchicine complex in the presence of tested CA-4 analogues (**7a** and **9a**) and **CA-4**. This fact corroborates with the earlier observation that **CA-4** generates increased fluorescence upon binding at the colchicine site (Figures 7).[37] Consequently, the experiment was carried out both in the presence and absence of colchicine to obtain fluorescence values of the desired tubulin–colchicine complex, the fluorescence values of tubulin–test compounds complex was deducted from the tubulin–test compounds–colchicine complex. It was found that at low concentrations the tested compounds **7a** and **9a** and **CA-4** showed significant affinity towards colchicine binding site, whereas at higher concentration **7a** and **9a** exhibited a steady increase, while CA-4 showed lower binding affinity. Compounds **7a** and **9a** exhibited more affinity towards colchicine site, when compared to the positive control CA-4. Vinblastine was used as a negative control, which is known to bind at a different site and did not show any effect on tubulin–colchicine complex. Therefore, this study suggests that compounds **7a** and **9a** binds at the colchicine site on tubulin.

Immunohistochemistry studies on tubulin.

In addition, we investigated the alterations in the organization of the cellular microtubule network in HeLa and MCF-7cells induced by conjugates **7a** and **9a** by using fluorescence microscopy, as most antimitotic agents affect microtubules.[39] In this context, the HeLa and MCF-7cells were treated with compounds **7a** and **9a** at a concentration of 25 nM for 48 h. The results demonstrated a well-organized microtubular network in control cells. However, the cells treated with these compounds showed disrupted microtubule organization as depicted in [Figures 8a and (8b in Supplemental Information)], thus confirming the inhibition of tubulin polymerization.

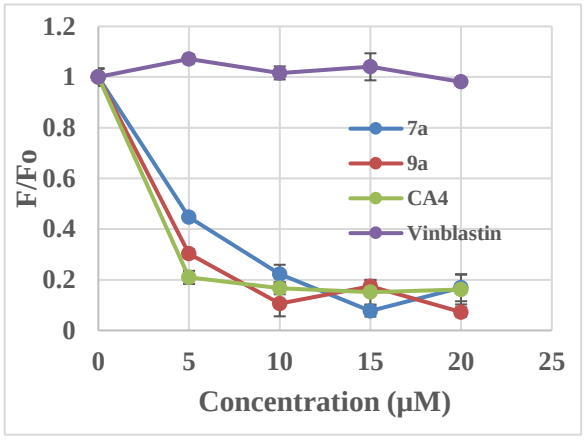


Figure 7. Fluorescence-based colchicine competitive binding assay of conjugates **7a** and **9a** were carried out at various concentrations containing 3 µM of tubulin and colchicine for 60 min at 37 °C. CA-4 was used as a positive control and vinblastine was used as negative control which binds at the vinca domain site. Fluorescence values were normalized to DMSO (control).

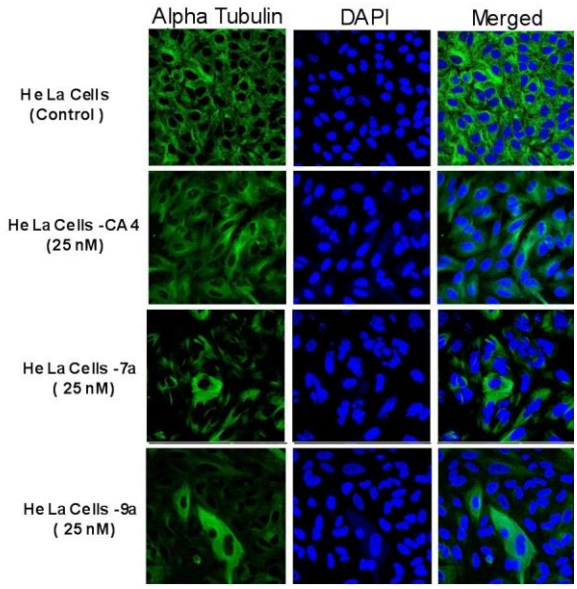


Figure 8a: Immunohistochemistry analysis of the effects of conjugates on the organization of cellular microtubule network. HeLa cells were treated with conjugates **7a** and **9a** (25 nM) for 48 h followed by staining with an anti-α-tubulin antibody. After reaction with FITC-conjugated secondary antibody, the cellular microtubules were observed by fluorescence microscopy. The microtubule organization was clearly observed as tubulin network-like structures in control cells and was found to be disrupted in cells treated with these conjugates.

Hoechst staining for apoptosis.

Apoptosis is one of the major pathways of programmed cell death. Chromatin condensation, nuclear shrinking, and fragmented nuclei are some of the salient characteristics of apoptotic cells. Disruption of microtubule formation leads to cell-cycle arrest in the G2/M phase, followed by apoptotic cell death.[40] It was considered interesting to investigate the apoptotic inducing effect of conjugates **7a** and **9a** by Hoechst staining (H-33258) in HeLa and MCF-7cells. Therefore, HeLa and MCF-7cells were treated with these compounds at concentrations of 25 and 50 nM for 48 h. After treatment with these compounds, marked morphological changes, such as nuclear fragmentation, condensation of chromatin, and formation of apoptotic bodies were observed as seen in Figures 9a and (9b in Supplemental Information).

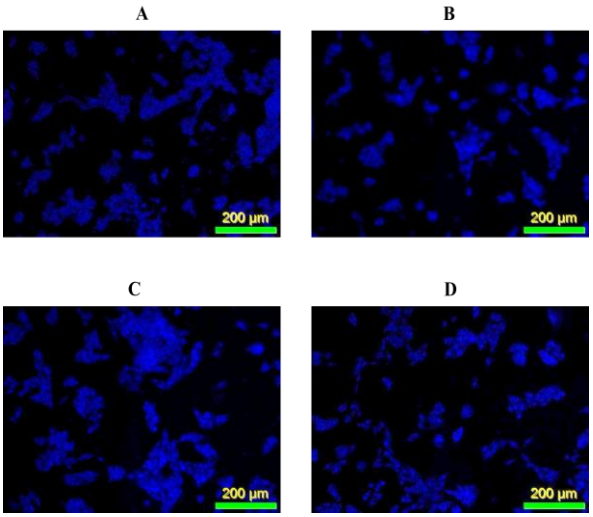


Figure 9a: Hoechst staining of HeLa cells. A: Untreated control cells (HeLa), B: **CA-4** (25 nM), C: **7a** (25 nM), D: **9a** (25 nM).

Measurement of mitochondrial membrane potential (ΔΨm).

The maintenance of mitochondrial membrane potential ((ΔΨm) is significant for mitochondrial integrity and bioenergetic function.[41] Mitochondrial changes, including loss of mitochondrial membrane potential (ΔΨm), are key events that take place during drug-induced apoptosis. Mitochondrial injury by **7a** and **9a** was evaluated by detecting a drop in mitochondrial membrane potential (ΔΨm). In this study, we have investigated the involvement of mitochondria in the induction of apoptosis by these compounds. HeLa and MCF-7cells were treated with **7a** and **9a** at 25 and 50 nM concentrations for 48 h. After 48 h of drug treatment, it was observed that reduced mitochondrial membrane potential (ΔΨm) in HeLa and MCF-7cells was assessed by JC-1 (5,5,6,6-tetrachloro-1,1,3,3-tetraethylbenz imidazolocarbo cyanine iodide) staining [Figures 10a and (10b in Supplemental Information)].

Annexin V–FITC for apoptosis.

The apoptotic effect of these compounds as studied by Hoechst staining, reduced mitochondrial membrane potential ((ΔΨm) and increased cytochrome c level suggested that these compounds induced apoptosis. Hence, the apoptotic effect of compounds **7a** and **9a** were further evaluated by using Annexin V–FITC/propidium iodide (AV/PI) dual staining assay[43] to examine the occurrence of phosphatidylserine externalization and also to understand whether it is due to physiological apoptosis or non-specific necrosis. In this study, HeLa and MCF-7cells were

treated with compounds **7a** and **9a** at concentrations of 25 and 50 nM for 48 h. After 48 h treatment, it was observed that these conjugates significantly induced apoptosis in HeLa and MCF-7 cells as shown in Figures 11a and 11b, respectively. Results indicate that this conjugate induced 64.14 and 69.07% apoptosis at 0.5 and 1 µM, respectively, and nocodazole caused 62.90% of cells to become apoptotic at 1 µM, in the untreated control, only 9.1% of cells were undergoing apoptosis [Figures 11a and (11b in Supplemental Information)].

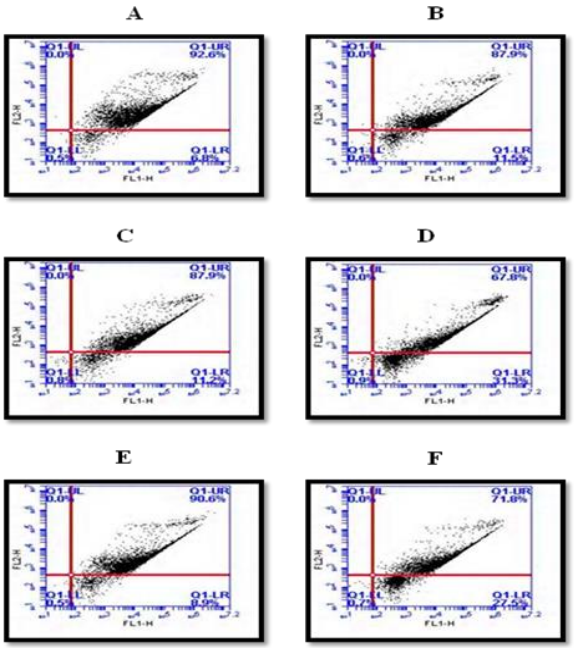


Figure 10a: Compounds **7a** and **9a** triggers mitochondrial injury. Drops in membrane potential (ΔΨm) was assessed by JC-1 staining of HeLa cells treated with test compound and samples were then subjected to flow cytometry analysis on a FACScan (Becton Dickinson) in the FL1, FL2 channel to detect mitochondrial potential. (A): HeLa untreated control cells; (B): treated with **CA-4** at 50 nM; (C): treated with compound **7a** at 25 nM; (D): treated with compound **7a** at 50 nM; (E): treated with compound **9a** at 25 nM; (F): treated with compound **9a** at 50 nM.

Cytochrome C release.

flow cytometric analysis of mitochondrial membrane potential ((ΔΨm) measurement, it was observed that reduced mitochondrial membrane potential (ΔΨm) of MCF-7 as well as HeLa cells after treatment with compound **7a** and **9a**. Thus, HeLa and MCF-7cells were treated with these compounds at 25 nM concentration for 48 h to examine the effect on cytochrome C level, and it was observed that there was an increase in cytochrome C protein levels [Figures 1**2a** and (12b in Supplemental Information)] suggesting that the cytosolic cytochrome C release from mitochondria might be responsible for apoptosis inducible capacity of these compounds.

Effect of compounds on p-Akt and p-PTEN.

The phosphatidylinositol 3-kinase or (PI3K /AKT) pathway is a pivotal signaling pathway, which controls cell growth, survival, proliferation and tumorigenesis. [44,45] The PI3K/Akt pathway is regulated by several critical upstream factors, e.g., tumor suppressor, PTEN.[46] The tumor suppressor gene PTEN is one of the most common targets of mutation in human cancers, with a mutation frequency approaching that of p53. In this study, HeLa and MCF-7cells were treated with compounds **7a** and **9a** at a concentration of 25 nM for 48 h and Western blotting was performed. The results revealed that the expression levels of p-Akt and p-PTEN were effectively suppressed in both HeLa and MCF-7cells [Figures 1**2a** and (12b in Supplemental Information)].

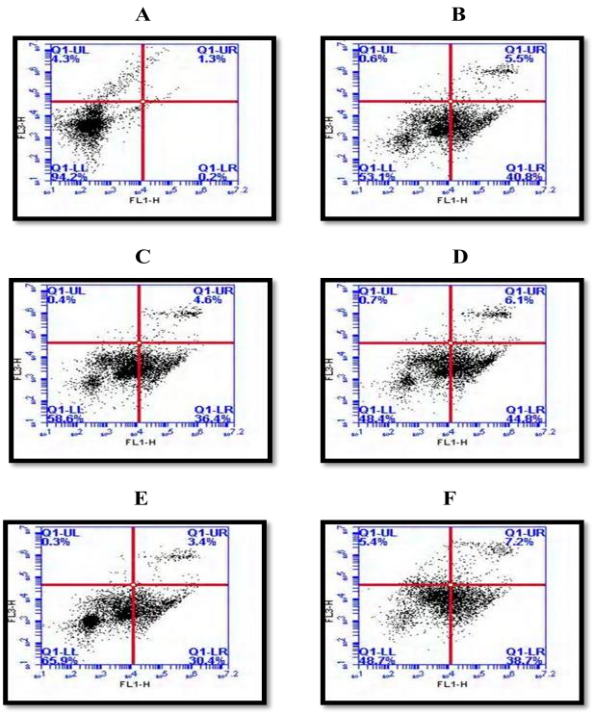


Figure 11a: Annexin V-FITC staining assay in HeLa cells. (A): HeLa untreated control cells; (B): treated with **CA-4** at 50 nM; (C): treated with compound **7a** at 25 nM; (D): treated with compound **7a** at 50 nM; (E): treated with compound **9a** at 25 nM; (F): treated with compound **9a** at 50 nM.

Sample	UL %	UR %	LL%	LR %
A: Control (HeLa)	4.29	1.35	94.17	0.20
B: Ca-4 (50 nM)	0.64	5.49	53.09	40.78
C: **7a** (25 nM)	0.37	4.63	5.61	36.39
D: **7a** (50 nM)	0.70	6.09	48.41	44.80
E: **9a** (25 nM)	0.33	3.42	65.89	30.36
F: **9a** (50 nM)	5.37	7.20	48.73	38.71

Table 5a: Distribution of apoptotic cells in Annexin-V FITC experiment of HeLa. In table 5a, Upper left (UL) represents necrotic cells, Upper right (UR) represents late apoptotic cells, Lower left (LL) represents live cells (viable cells) and Lower right (LR) represents early apoptotic cells.

***In vivo* studies.**

MTT assay with normal and tumor cell lines indicate that these two compounds, namely **9a** and **7a**, have the potential to terminate cell proliferation and induce apoptosis in tumor cells. However, the effect of synthetic molecules under *in vivo* situation provides unfeigned data on the actual potential of these molecules as anti-proliferative agents. Therefore, it would be

interesting to observe variations in tumor volume among tumor-induced mice after treatment with **7a** and **9a** molecules. The graph showing variation in tumor volume (Figure 13a) indicated that among the group of mice treated with **7a** and **9a** molecules, the tumor volume did not grow to the maximum extent in **7a** treated nude mice when compared to **9a** treated mice. In **7a** treated nude mice, there was sluggish growth of tumor and better reduction in tumor volume when compared to **9a** treated mice. The tumor volume has increased only up to ≈ 500 mm^3 (in 28 days) in **7a** treated nude mice. Whereas the tumor volume has increased approximately up to 600 mm^3 in **9a** treated nude mice (in 20-24 days). On the other hand, tumor volume has increased nearly three times (approximately > 1500 mm^3) in the case of control nude mice, to which neither **7a** nor **9a** was injected. In about 2 months time period, the variation in tumor volume before and after the treatment of **7a** and **9a** is shown in Figure 13b.

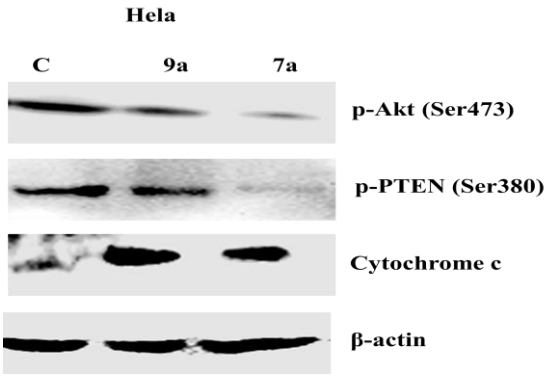


Figure 12a: Western blot analysis with antibodies specific for p-Akt (Ser473), p-PTEN (Ser380), cytochrome c and β-actin in HeLa cells.

Thus, the *in vivo* data corroborates with the earlier experimental results and indicates that **7a** has better tumor controlling capability as compared to **9a**. Further, in another set of experiments, the survival of mice treated with **7a** and **9a** molecules was checked and compared with the control group. The details of survival data obtained from three different sets of mice indicate that among the mice treated with small synthetic molecules, **7a** and **9a**, the mice treated with **7a** survived for longer period (approximately 8-9 weeks months) indicating that **7a** was efficient in controlling tumor cell proliferation without developing harmful effects in tumor-induced nude mice. Whereas among the control and **9a** treated nude mice, most of them died little earlier (in about 5-6 weeks and 7-8 weeks). Further, among **7a** and **9a** treated nude mice, the mice treated with **9a** have become weak and less active when compared to the mice that are treated with **7a**. This indicates that **7a** followed by **9a** is efficient in reducing the tumor volume in the nude mice.

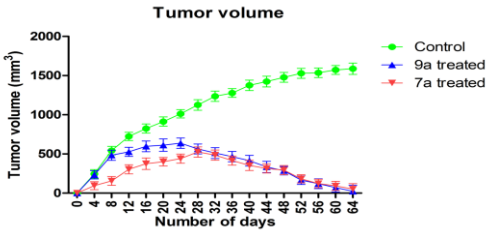


Figure 13a. Tumor growth inhibition curves for **9a** and **7a** in nude mice during 2 months period. About 2 mg/Kg of each compound was injected to the nude mice in the intra peritoneal region. Before starting the experiment each mice was weighing about 22-25 gm. But after the treatment, the nude mice weight has reduced about 2-3 gm.

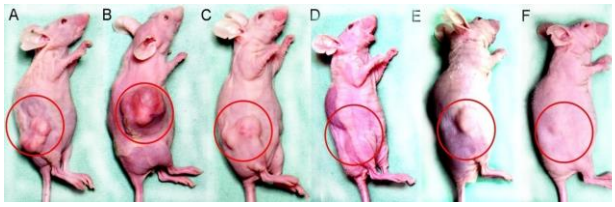


Figure 13b. Figure showing the volume of tumor, before and after the treatment with **7a** and **9a**. Every time, three sets of nude mice (each set consisting of 4 mice in the age group of 6–8 weeks and weighing about 22-25 gm) were considered. Figure A, C and E represent nude mice after tumor induction. Figure D and F represent the mice after the treatment with **7a** and **9a** for 60 days respectively. Similarly, the figure B, represent the mice to which neither **7a** nor **9a** was given (vehicle control) during the same period.

CONCLUSIONS

In summary, we have presented data that supports the potential for two molecules **7a** and **9a** with methoxy group at *para* position of C-ring of the trimethoxystyrylbenzene sulfonamide /sulfonates scaffold as novel anticancer agents. All the evidences gathered suggest that these trimethoxystyrylbenzene sulfonamide/ sulfonate analogues exert promising antiproliferative by effectively inhibiting the tubulin polymerization and disrupt the microtubule dynamics in cancer cells. Compounds **7a** and **9a** also exhibited promising efficacy in HeLa tumor xenograft model and have shown an excellent therapeutic window and we believe that these molecules have significant potential for clinical development as new anticancer agents.

Experimental Section

Chemistry.

Experimental All chemicals and reagents were obtained from Aldrich (Sigma-Aldrich), St. Louis, MO, USA), Lancaster (Alfa Aeser, Johnson Matthey Company, Ward Hill, MA, USA), or Spectrochem Pvt. Ltd. (Mumbai, India) and were used without further purification. Reactions were performer by TLC performed on silicagel glass plate containing 60 GF-254, and visualization was achieved by UV light or iodine indicator. ^1H and ^{13}C NMR spectra were determined in DMSO-d_6 by using Varian and Avance instruments. Chemical shifts are expressed in parts per million (δ in ppm) downfield from internal TMS and coupling constants are expressed in Hz. ^1H NMR spectroscopic data are reported in the following order: multiplicity (s, singlet; brs, broad singlet; d, doublet; dd, doublet of doublets; t, triplet; m, multiplet), coupling constants in Hz, number of protons. ESI mass spectra were recorded on a Micro mass Quattro LC using ESI+ software with capillary voltage 3.98 kV and an ESI mode positive ion trap detector. High-resolution mass spectra (HRMS) were recorded on QSTAR XL Hybrid MS/MS mass spectrometer. Melting points were determined with an Electro thermal melting point apparatus, and are uncorrected The purity of tested compounds was P95% as determined by HPLC performed on a Shimadzu LCMS-2020 apparatus equipped with a SPD-M20A diode array detector and a Shimadzu SIL-20AC auto injector using C18 column (Phenomenex luna 5 µM C18, 4.6 mm 250 mm column). Elution conditions: mobile phase A (75%)-acetonitrile; mobile phase B(25%)-water containing 0.1% formic acid + 10

mmol NH_4OAc. The flow rate was 1.0 mL/min and the injection volume was 5 µL at 25 °C and detection at 254 nm.

(Z)-2-methoxy-5-(3,4,5-trimethoxystyryl)phenol (**2a**).

Solution of 3-((tert-butyldimethylsilyl)oxy)-4-methoxy benzaldehyde (**15**; 2.0 g, 0.0075 mol) and triphenyl(3,4,5-trimethoxybenzyl)phosphonium bromide (**12**, 4.71 g, 0.009 mol) in dry CH2Cl2 (100 ml) was stirred under a nitrogen atmosphere. Sodium hydride (0.517 g, 0.0225 mol) was added to the mixture at 0°C. Then, the temperature of the mixture was slowly increased to RT, and the mixture was stirred for 18 h. The progress of the reaction was monitored by TLC (EtOAc/hexane= 3:7), and water was added after completion of reaction (until foaming stopped). The organic layer was separated, and the aqueous layer was extracted with CHCl3. The organic layer was washed with brine, dried with anhydrous Na_2SO4, and concentrated under reduced pressure to afford the crude compound, which was purified by column chromatography (15% EtOAc/hexanes). Yield: 1.7 g. 54%; ^{1}H NMR ($CDCl_3$): δ 3.69 (s, 6H), 3.84(s, 3H), 3.86 (s, 3H), 6.39-6.43 (d, *J* = 12.08 Hz, 1H), 6.49-6.53 (d, *J* = 12.08, 1H), 6.52 (s, 2H), 6.71-6.74 (d, *J* = 8.30 Hz, 1H), 6.78-6.81 (d, J=8.30Hz, 1H) 6.92 (d J=1.7 Hz, 1H) ppm.

(Z)-2-methoxy-5-(3,4,5-trimethoxystyryl)aniline (2c).

Compound **2c** was prepared according to the method described for compound **2a** a by employing 4-methoxy 3-nitrobenzaldehyde (13; 2.0 g, 0.013 mmol), triphenyl(3,4,5-trimethoxybenzyl) phosphonium bromide (**12**; 8.15 g, 0.0156 mol), and sodium hydride, which was employing (1 mmol) in Methanol was added Zn (3 mmol) $HCOONH_4$ (3 mmol) to obtain the pure product **22** as a white colour solid (1.5g, 53% yield); ^{1}H NMR ($CDCl_3$): δ 3.65 (s, 3H), 3.81(s, 6H), 3.86 (s, 3H), 5.50 (s, 1H), 6.29-6.33 (d, *J* = 11.33 Hz, 1H), 6.30-6.34 (d, *J* = 11.33, 1H), 6.36-6.38 (d, *J* = 6.04 Hz, 2H), 6.70-6.73 (d, *J* = 8.30Hz, 1H) 6.79-6.82 (d, *J* = 8.30Hz, 1H), 6.91- 6.92 (d *J* = 2.2 Hz, 1H) ppm.

(Z)-2-((tert-butyldimethylsilyl)oxy)-3-methoxy-6-(3,4,5-trimethoxystyryl)aniline (**22**).

Compound **22** was prepared according to the method described for compound **2c**, employing (Z)- (Z)-tert-butyl(6-methoxy-2-nitro-3-(3,4,5-trimethoxystyryl)phenoxy)dimethylsilane (1 mmol) in Methanol was added Zn (3 mmol) $HCOONH_4$ (3 mmol) to obtain the pure product **22** as a white colour solid. (1.8g, 52% yield); ^{1}H NMR (CDCl3): δ 0.17 (s, 6H), 1.00 (s, 9H), 3.63 (s, 6H), 3.75(s, 6H), 3.81 (s, 3H), 6.26-6.29 (d, *J* = 8.49 1H), 6.39-6.45 (d, *J* = 11.89 Hz, 1H), 6.41-6.47 (d, *J* = 11.89, 1H), 6.51 (s, 2H), 6.70-6.73 (d *J* = 8.49 Hz, 1H) ppm.

(Z)-4-methoxy-N-(2-methoxy-5-(3,4,5-trimethoxystyryl)phenyl)benzenesulfonamide (6a).

To a solution of (Z)-2-methoxy-5-(3,4,5-trimethoxystyryl)aniline (**2c**) (100 mg, 0.317 mmol) in a 1:4 mixture of pyridine and anhydrous CH_2Cl_2 (10 ml), 4-methoxybenzene-1-sulfonyl chloride (**23a**, 79 mg, 0.380 mmol) was slowly added at 0°C. After 5 min stirring remove ice both and stirred at room temperature 3 h, then the reaction mixture was evaporated to dryness in vacuum and the residue was taken up with CH_2Cl_2 (10 ml). The organic solution was washed with water, 10% aqueous HCl, water and brine, dried over MgSO4, and concentrated in vacuum to give 143 mg (92%) of analytically pure compound obtained from a 3:1 mixture of hexan and ethyl acetate. mp 182.0−185.0 °C; ^{1}H NMR ($CDCl_3$): δ 3.64 (s, 6H), 3.66 (s, 3H), 3.81 (s, 3H), 3.83 (s, 3H) 6.43 (s, 2H), 6.45 (s, 2H), 6.59-6.62 (d, *J* = 8.49 Hz, 1H), 6.81-6.84 (d, *J* = 9.1 Hz, 2H), 6.92-6.96 (m, 2H), 7.42 (d J=1.8, 1H), 7.60-7.63 (d, J=8.87Hz, 2H) ppm; **^{13}C NMR** ($CDCl_3$, 75 MHz) (ppm): 55.46, 55.72, 55.77, 60.82, 105.88, 110.11, 113.81, 120.86, 125.61, 126.01, 129.05, 129.28, 129.52, 130.28, 130.80, 132.51, 137.10, 148.23, 152.87, 162.92; MS(ESI): 485; HRMS (ESI) calculated for $C_{25}H_{27}O_7$ N Na S[M+Na]+ 508.14004; found: 508.13847. HPLC: t_R 6.70 min, purity 98.0%.

(Z)-3,4-dimethoxy-N-(2-methoxy-5-(3,4,5-trimethoxystyryl)phenyl)benzenesulfonamide(6b). Compound **6b** was prepared according to the method described for compound **6a**, employing (Z)-2-methoxy-5-(3,4,5-trimethoxystyryl)aniline (**2c**, 100 mg, 0.317 mmol), and 3,4-dimethoxybenzene-1-sulfonyl chloride (**23b**, 89.9 mg, 0.38 mmol) to obtain the pure product **6b** as a white colour solid. (149mg, 91% yield); mp 193.0−186.0 °C; ^{1}H NMR (CDCl3): δ 3.61 (s, 6H), 3.70 (s, 6H), 3.84 (s, 3H), 3.87 (s, 3H) 6.43 (s, 2H), 6.43 (s, 2H), 6.41-6.44 (d, *J* = 12.10 Hz, 1H), 6.45-6.48 (d, *J* = 12.10 Hz, 1H), 6.73-6.75 (d, *J* = 8.43 Hz, 2H), 6.90-6.93 (d, J=9.04, 2H), 7.06 (s, 1H), 7.10-7.13 (d, J=8.43, 2H), 7.72-7.75 (d, J=8.9Hz, 2H) ppm; **^{13}C NMR** ($CDCl_3$, 75 MHz) (ppm): 55.7, 56.2, 60.7, 105.6, 110.5, 120.0, 120.8, 125.6, 125.7, 127.6, 128.9, 129.8, 130.7, 131.7, 132.8, 134.5, 137.3, 140.6, 142.6, 146.8, 152.8; MS(ESI): 516 [M+H]+ ; HRMS (ESI) calculated for $C_{26}H_{30}O_8$ N S[M+H]+ 516.16866; found: 516.17081. HPLC: t_R 6.89 min, purity 98.0%.

(Z)-4-chloro-N-(2-methoxy-5-(3,4,5-trimethoxystyryl)phenyl)benzenesulfonamide (6c).

Compound **6c** was prepared according to the method described for compound **6a**, employing (Z)-2-methoxy-5-(3,4,5-trimethoxystyryl)aniline (**2c**, 100 mg, 0.317 mmol), and 4-chlorobenzene-1-sulfonyl chloride (**23c**, 80.3 mg, 0.38 mmol) to obtain the pure product **6c** as a white colour solid. (145mg, 93% yield); mp 162.0−165.0 °C; ^{1}H NMR ($CDCl_3$): δ 3.64 (s, 3H), 3.68 (s, 6H), 3.84 (s, 3H), 3.83 (s, 3H) 6.44 (s, 2H), 6.46 (s, 2H), 6.61 (d, J=8.3Hz 1H), 6.93 (s, 1H), 6.98(d, J = 8.3 Hz, 1H), 7.02-7.03 (m, 9.06Hz 2H), 7.40 (d J=2.26Hz, NH), 7.65-7.70 (d, J=12.086Hz, 2H)ppm; FABMAS:(M+H)=489 **^{13}C NMR** ($CDCl_3$, 75 MHz) (ppm): 55.6, 55.9, 60.8, 106.0, 110.2, 115.7, 116.0, 121.6, 125.4, 126.2, 128.8, 129.7, 129.9, 130.3, 132.5, 135.3, 137.3, 148.5, 152.0 . MS(ESI): 490 ; HRMS (ESI) calculated for $C_{24}H_{25}O_6$ N Cl S[M+H]+490.10856; found: 490.11091. HPLC: t_R 8.01 min, purity 99.0%.

(Z)-3-chloro-N-(2-methoxy-5-(3,4,5-trimethoxystyryl)phenyl)benzenesulfonamide (6d).

Compound **6d** was prepared according to the method described for compound **6a**, employing (Z)-2-methoxy-5-(3,4,5-trimethoxystyryl)aniline (**2c**, 100 mg, 0.317 mmol), and 3-chlorobenzene-1-sulfonyl chloride (**23d**, 80.3 mg, 0.38 mmol) to obtain the pure product **6d** as a white color solid. (142mg, 91% yield); mp 165.0−168.0 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 3.64 (s, 3H), 3.66 (s, 6H), 3.84 (s, 3 H), 6.43 (s, 2H), 6.45-6.46 (d, *J*=12.207 Hz, 1H), 6.46-6.47 (d, *J*=12.207 Hz, 1H), 6.61-6.63 (d, 1H), 6.99-7.01 (d, 1H), 7.26-7.32 (m, 1H), 7.40 (s, 1H), 7.45-7.47 (d, *J*= 8.08 Hz 1H), 7.52-7.53 (d, *J*= 7.9 Hz 1H), 7.72 (t, 1H), ppm; **^{13}C NMR** ($CDCl_3$, 75 MHz) (ppm): 55.6,55.8, 60.8, 105.8, 110.1, 122.0, 125.1, 125.3, 126.4, 127.1, 128.7, 129.7, 129.9, 130.3, 132.4, 132.8, 134.8, 137.2, 140.9, 148.6, 152.9; MS(ESI): 490; HRMS (ESI) calculated for $C_{24}H_{25}O_6NCl$ S[M+H]+490.10856; found: 490.10786. HPLC: t_R 6.89 min, purity 96.0%.

(Z)-3,4-dichloro-N-(2-methoxy-5-(3,4,5-trimethoxystyryl)phenyl)benzenesulfonamide (6e).

Compound **6e** was prepared according to the method described for compound **6a**, employing (Z)-2-methoxy-5-(3,4,5-trimethoxystyryl)aniline (**2c**, 100 mg, 0.317 mmol), and 3,4-dichlorobenzene-1-sulfonyl chloride (**23e**, 93.3 mg, 0.38 mmol) to obtain the pure product **6e** as a white colour solid. (152mg, 91% yield); mp 173.0−176.0 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ (ppm): 3.48 (s, 3H), 3.72 (s, 6H), 3.82 (s, 3H), 6.43 (s, 2H), 6.45-6.49 (d, *J*=12.086 Hz 1H), 6.53-6.57 (d, *J*=12.086 Hz 1H), 6.78-6.81 (d, *J*= 8.49Hz 1H), 7.0 (s, 1H), 7.34-7.37 (d, *J*=8.68 Hz 1H), 7.55-7.59 (m, 3H), 7.96 (s, 1H) ppm; **^{13}C NMR** ($CDCl_3$, 75 MHz) (ppm): 55.6, 55.8, 60.8, 105.7, 110.2, 122.1, 124.7, 126.3. 126.7, 128.6, 129.0. 129.8, 130.3, 130.6, 132.4, 133.2, 137.1, 137.5, 138.9, 148.6, 152.9; MS(ESI):

523[M+Na]+; HRMS (ESI) calculated for C_{24} H_{23} O_6 N Cl_2 Na S[M+Na]+546.05153; found: 546.05069. HPLC: t_R 10.31 min, purity 99.0%.

(Z)-4-fluoro-N-(2-methoxy-5-(3,4,5-trimethoxystyryl)phenyl)benzenesulfonamide (6f).

Compound **6f** was prepared according to the method described for compound **6a**, employing (Z)-2-methoxy-5-(3,4,5-trimethoxystyryl)aniline (**2c**, 100 mg, 0.317 mmol), and 4-fluorobenzene-1-sulfonyl chloride (**23f**, 73.9 mg, 0.38 mmol) to obtain the pure product **6f** as a white colour solid. (137mg, 91% yield); mp 188−191.0 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ (ppm): 3.64 (s, 3H), 3.68 (s, 6H), 3.84 (s, 3H), 6.44 (s, 2H), 6.42-6.46 (d, *J*=12.086 Hz 1H), 6.46-6.50 (d, *J*=12.086 1H), 6.60-6.63 (s, 1H), 6.93 (s, 1H), 6.9-7.00 (d, *J*=8.30 Hz 1H), 7.02-7.08 (t, 2H), 7.40-7.41 (d, 1H), 7.65-7.70 (d, 2H) ppm; **^{13}C NMR** ($CDCl_3$, 75 MHz) (ppm): 55.7, 55.9, 60.8, 106.0, 110.2, 115.7, 116.0, 121.6, 125.4, 126.2, 128.8, 129.7, 129.8, 130.3, 132.5, 135.3, 137.3, 148.5, 153.0; MS(ESI): 475 ; HRMS (ESI) calculated for C_{24} H_{24} O_7 N F S[M+H]+475.12213; found: 475.12404. HPLC: t_R 6.00 min, purity 98.0%.

(Z)-4-(tert-butyl)-N-(2-methoxy-5-(3,4,5-trimethoxystyryl)phenyl)benzenesulfonamide (6g).

Compound **6g** was prepared according to the method described for compound **6a**, employing (Z)-2-methoxy-5-(3,4,5-trimethoxystyryl)aniline (**2c**, 100 mg, 0.317 mmol), and 4-(tert-butyl)benzene-1-sulfonyl chloride (**23g**, 88.1 mg, 0.38 mmol) to obtain the pure product **6g** as a white colour solid. (150mg, 92% yield); mp 182.0−185.0 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 1.29 (s, 9H) 3.60 (s, 3H), 3.66 (s, 6H), 3.83 (s, 3H), 6.46 (s, 2H), 6.47 (s, 2H), 6.59-6.60 (d, 1H), 6.94 (s,1H), 6.96-6.98 (d, *J*=8.50 Hz 1H), 7.38-7.39 (d, *J*=8.69 2H), 7.46-7.47 (d, *J*=8.50 Hz 1 H),7.59-7.60 (d, *J*=8.50 Hz, 2H), ppm; **^{13}C NMR** ($CDCl_3$, 75 MHz) (ppm): 30.9, 35.0, 55.6, 55.8, 60.8, 105.7, 110.0, 121.3, 125.6, 125.8, 126.0, 126.9, 129.0, 129.4, 130.2, 132.5, 136.3, 137.0, 148.4, 152.9, 156.5; MS(ESI): 512 ; HRMS (ESI) calculated for $C_{28}H_{34}O_6N$ S[M+H]+;512.21013 found: 512.21023. HPLC: t_R 11.38 min, purity 98.0%.

(Z)-N-(2-methoxy-5-(3,4,5-trimethoxystyryl)phenyl)-4-nitrobenzenesulfonamide (6h).

Compound **6h** was prepared according to the method described for compound **6a**, employing (Z)-2-methoxy-5-(3,4,5-trimethoxystyryl)aniline (**2c**, 150 mg, 0.476 mmol), and 4-nitrobenzene-1-sulfonyl chloride (**23h**, 126.3 mg, 0.57 mmol) to obtain the pure product **6h** as a yellowcolour solid. (220 mg, 92% yield); mp 191.0−194.0 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ (ppm): 3.65 (s, 3 H), 3.70 (s, 6 H), 3.84 (s, 3 H), 6.42-6.45 (d, *J*=12.05 Hz, 1H), 6.44 (s, 1H), 6.24 (s, 2H), 6.48-6.51 (d, *J*=12.05 Hz, 1H), 6.63-6.65 (s, *J*=8.5, 2H), 6.98 (s, 1H), 7.00-7.02 (d, *J*=8.54 1H), 7.38 (s, 1H), 7.80-7.82 (d, *J* = 8.80 Hz, 2H), 8.21-8.23 (d, *J*= 9.00 Hz 2H) ppm; **^{13}C NMR** ($CDCl_3$, 75 MHz) (ppm): 55.6, 55.9, 60.8, 105.8, 112.4, 123.9, 124.0, 127.8, 129.1, 129.5, 130.4, 130.5, 132.1. 137.3, 137.7, 142.2, 150.3, 150.7, 153.0; MS(ESI): 501[M+Na]+ ; HRMS (ESI) calculated for C_{24} $H_{25}O_8N_2S$[M+H]+501.13261; found: 501.13269. HPLC: t_R 3.17 min, purity 100.0%.

(Z)-4-amino-N-(2-methoxy-5-(3,4,5-trimethoxystyryl)phenyl)benzenesulfonamide (6i).

Compound **6i** was prepared according to the method described for compound **2c**, employing (Z)-N-(2-methoxy-5-(3,4,5-trimethoxystyryl) phenyl)-4-nitrobenzenesulfonamide (**6i**, 80 mg, 0.16 mmol), in Methanol was added Zn (20.6 mg, 0.32 mmol) $HCOONH_4$ (20.6 mg, 0.32 mmol) to obtain the pure product **6i** as a white colour solid. (70mg, 93% yield); mp 199.0−202.0 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 3.63 (s, 6 H), 3.69 (s, 3 H), 3.83 (s, 3 H), 4.09 (s, 2 H), 6.41 (s, 2 H), 6.44 (s, 1H), 6.46 (s, 1H), 6.48-6.50 (d, *J=8.85* Hz, 1H), 6.61-6.63 (d, *J*=8.54, 2H), 6.91-6.94 (m, 2H), 7.39 (s, 2H), 7.44-7.46 (d, *J*= 8.69 Hz 2H) ppm; **^{13}C NMR** ($CDCl_3$, 75 MHz) (ppm): 55.69, 55.89, 60.8, 106.01, 110.2, 115.7, 116.0, 121.6, 125.4, 126.2, 128.8, 129.7, 129.9, 130.3, 132.5, 135.3, 137.3, 148.5, 153.0; MS(ESI): 470 [M+Na]+; HRMS (ESI) calculated for C_{24} $H_{26}O_6N_2NaS$[M+Na]+ 493.14038; found: 493.1392. HPLC: t_R 8.19 min, purity 95.0%.

(Z)-N-(2-methoxy-5-(3,4,5-trimethoxystyryl)phenyl)-3-(trifluoromethyl)benzenesulfonamide (6j).

Compound **6j** was prepared according to the method described for compound **6a**, employing (Z)-2-methoxy-5-(3,4,5-trimethoxystyryl)aniline (**2c**, 100 mg, 0.317 mmol), and 3-(trifluoromethyl) benzene-1-sulfonyl chloride (**23j**, 92.5 mg, 0.38 mmol) to obtain the pure product **6j** as a white colour solid. (147mg, 88% yield); mp 193.0−196.0 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 3.58 (s, 3H), 3.66 (s, 6H), 3.84 (s, 3 H), 6.43 (s, 2H), 6.43-6.46 (d, *J*=12.05 Hz, 1H), 6.47-6.50 (d, *J*=12.05 Hz, 1H), 6.58-6.60 (d, *J*=8.69 Hz 1H), 6.94 (s, 1H), 7.0-7.03 (d, *J*=9.9 Hz 1H), 7.43 (s, 1H), 7.49-7.52 (t, 1H), 7.74-7.76 (d, *J*= 7.6 Hz 1H), 7.80-7.82 (d, *J*= 7.7 Hz 1H), 8.0 (s, 1H) ppm; **^{13}C NMR** ($CDCl_3$, 75 MHz) (ppm): 55.5, 55.8, 60.8, 105.8, 110.1, 122.8, 124.1, 124.2, 124.7, 126.8, 128.6, 129.2, 129.3, 129.4, 129.8, 130.4, 130.5,132.4, 137.2, 140.3, 148.8, 152.9; MS(ESI): 524 ; HRMS (ESI) calculated for C_{25} H_{25} O_6 N F_3 S[M+H]+524.13492;found: 524.13366. HPLC: t_R 3.28 min, purity 98.0%.

(Z)-N-(2,3-dimethoxy-5-(3,4,5-trimethoxystyryl)phenyl)-4-methoxybenzenesulfonamide(7a).

Compound **7a** was prepared according to the method described for compound **6a**, employing (Z)-2,3-dimethoxy-5-(3,4,5-trimethoxystyryl) aniline (**21**, 100 mg, 0.289 mmol), and 4-methoxybenzene-1-sulfonyl chloride (**23a**, 71.3 mg, 0.34 mmol) to obtain the pure product **7a** as a white colour solid. (138mg, 92% yield); mp 187.0−190.0 °C; H^1 NMR ($CDCl_3$, 300 MHz) δ (ppm):3.57 (s, 3H), 3.58 (s, 3H), 3.63 (s, 6H), 3.81 (s, 3H), 6.42 (s, 2H), 6.45-6.49 (d, *J* = 12.275 Hz, 1H), 6.50-6.52 (d, *J* =12.275 Hz, 1 H) 6.53 (s, 1H), 6.83-6.86(d, *J* =8.87 Hz 1H) 7.12(s, 2 H), 7.65-7.68 (d, *J* =9.06 Hz, 2 H). FABMAS:(M+H)=515**^{13}C NMR** ($CDCl_3$, 75 MHz) (ppm): 55.49, 55.53, 55.79, 60.7, 60.8, 105.9, 108.6, 112.4, 114.0, 129.2, 129.3, 130.3, 130.6, 130.7, 132.3, 133.3. 137.1, 137.2, 151.5, 152.8, 163.0.; MS(ESI): 516 ; HRMS (ESI) calculated for C_{26} H_{29} O_8 N S[M+H]+516.16710; found: 516.16724. HPLC: t_R 6.66 min, purity 99.0%.

(Z)-N-(2,3-dimethoxy-5-(3,4,5-trimethoxystyryl)phenyl)-3,4-dimethoxybenzenesulfonamide (7b).

Compound **7b** was prepared according to the method described for compound **6a**, employing (Z)-2,3-dimethoxy-5-(3,4,5-trimethoxystyryl) aniline (**21**, 100 mg, 0.289 mmol), and 3,4-dimethoxybenzene-1-sulfonyl chloride (**23b**, 80.2 mg, 0.34 mmol) to obtain the pure product **7b** as a white colour solid. (143mg, 90% yield); mp 205.0−208.0 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ (ppm): 3.56 (s, 3H), 3.58 (s, 3H), 3.63 (s, 6H), 3.81 (s, 3H), 3.82 (s, 3H), 3.89, (s, 3H), 6.42 (s, 2H), 6.45-6.48 (d, *J* = 12.05 Hz, 1H),), 6.49-6.52 (d, *J* = 12.05 Hz, 1H), 6.54 (s, 1H) 6.80-6.81 (d, *J* = 8.54 1H), 7.10 (s, 1H), 7.15 (s, 1H), 7.24(s, 1H), 7.37-7.34 (dd, *J* = 8.54, J = 8.54 1H), 6.73 (d, 1H), 6.82(d,1H), ppm; **^{13}C NMR** ($CDCl_3$, 75 MHz) (ppm): 55.5, 55.8, 56.06, 60.7, 60.8, 106.0, 108.6, 109.6, 110.3, 112.6, 121.1, 129.2, 130.3, 130.6, 130.7, 132.3, 133.3, 137.3, 137.4, 148.8, 151.5, 152.7, 152.9; MS(ESI): 546; HRMS (ESI) calculated for $C_{27}H_{32}O_9NS$ [M+H]+546.17923; found: 546.18117. HPLC: t_R 6.02 min, purity 98.0%.

(Z)-4-chloro-N-(2,3-dimethoxy-5-(3,4,5-trimethoxystyryl)phenyl)benzenesulfonamide (7c).

Compound **7c** was prepared according to the method described for compound **6a**, employing (Z)-2,3-dimethoxy-5-(3,4,5-trimethoxystyryl) aniline (**21**, 100 mg, 0.289 mmol), and 4-chlorobenzene-1-sulfonyl

chloride (**23c**, 71.3 mg, 0.34 mmol) to obtain the pure product **7c** as a white colour solid. (140mg, 93% yield); mp 182.0−185.0 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ (ppm): 3.57 (s, 6H), 3.59 (s, 3H), 3.67 (s, 6H), 3.82 (s, 3H), 6.43 (s, 2H) 6.44-6.46 (d, *J* = 12.05 Hz, 1H), 6.51-6.54 (d, *J* = 12.05 Hz, 1H), 6.55 (s, 1H), 7.08 (s, 1H), 7.13 (s, 1H), 7.37-7.38 (s, *J* = 8.54 Hz, 2H), 7.65-7.67 (s, *J* = 8.54 Hz, 2H)ppm; **^{13}C NMR** ($CDCl_3$, 75 MHz) (ppm): 55.5, 55.8, 60.8, 106.0, 109.2, 112.7, 128.5, 129.2, 129.9, 130.5, 132.3, 133.3, 137.3, 137.4, 137.6, 139.4, 151.5, 153.0. MS(ESI): 519[M+Na]+; HRMS (ESI) calculated for $C_{25}H_{26}O_7NClNaS$ [M+Na]+542.10107; found: 542.09981. HPLC: t_R 3.20 min, purity 100.0%.

(Z)-3-chloro-N-(2,3-dimethoxy-5-(3,4,5-trimethoxystyryl)phenyl)benzenesulfonamide (7d).

Compound **7d** was prepared according to the method described for compound **6a**, employing (Z)-2,3-dimethoxy-5-(3,4,5-trimethoxystyryl) aniline (**21**, 100 mg, 0.289 mmol), and 3-chlorobenzene-1-sulfonyl chloride (**23d**, 71.3 mg, 0.34 mmol) to obtain the pure product **7d** as a white colour solid. (137mg, 91% yield); mp 193.0−196.0 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ (ppm): 3.57 (s, 3H), 3.60 (s, 3H), 3.66 (s, 6H), 3.82 (s, 3H), 6.43(s, 2H) , 6.45-6.48 (d, *J* = 12.05 Hz, 1H), 6.51-6.54 (d, *J* = 12.05 Hz, 1H), 6.56 (s, 1H), 7.08 (s, 1H), 7.32-7.35 (t, 1H), 7.46-7.48 (s, *J* = 7.9 Hz, 1H) 7.58-7.60 (s, *J* = 7.9 Hz, 1H), 7.78 (t, 1H), **^{13}C NMR** ($CDCl_3$, 75 MHz) (ppm): 55.5, 55.8, 60.8, 105.9, 109.2, 112.8, 125.2, 127.1, 129.1, 129.8, 130.2, 130.5, 132.3, 133.0, 133.3, 135.1, 137.3, 137.5, 140.8, 151.5, 152.9; MS(ESI): 520 [M+H]+; HRMS (ESI) calculated for C25 H26 O7 N Cl S[M+H]+ 520.11762; found: 520.11782. HPLC: t_R 7.95 min, purity 97.0%.

(Z)-N-(2,3-dimethoxy-5-(3,4,5-trimethoxystyryl)phenyl)-4-fluorobenzenesulfonamide (7e).

Compound **7e** was prepared according to the method described for compound **6a**, employing (Z)-2,3-dimethoxy-5- (3,4,5-trimethoxystyryl) aniline (**21**, 100 mg, 0.289 mmol), and 4-fluorobenzene-1-sulfonyl chloride (**23a**, 65.2 mg, 0.34 mmol) to obtain the pure product **7e** as a white colour solid. (133mg, 91% yield); mp 173.0−177.0 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 3.58 (s, 3H), 3.59 (s, 3H), 3.67 (s, 6H), 3.82 (s, 3H), 6.43 (s, 1H), 6.44-6.47 (d, *J* = 12.08 Hz, 1H), 6.51-6.55 (d, *J* = 12.08 Hz, 1H), 6.56 (s, 1H), 7.05-7.10 (m, 4H), 7.71-7.76 (m, 2H) ppm; **^{13}C NMR** ($CDCl_3$, 75 MHz) (ppm): 55.5, 55.8, 60.8, 106.0, 109.1, 112.7, 116.0, 116.3, 129.2, 129.8, 129.9, 130.1, 130.4, 132.3, 133.3, 135.2, 137.4, 151.5, 152.9; MS(ESI): 504 [M+H]+; HRMS (ESI) calculated for C25 H26 O7 F N S[M+H]+ 504.14708; found: 504.14720. HPLC: t_R 6.84 min, purity 99.0%.

(Z)-4-(tert-butyl)-N-(2,3-dimethoxy-5-(3,4,5-trimethoxystyryl)phenyl)benzenesulfonamide (7f).

Compound **7f** was prepared according to the method described for compound **6a**, employing (Z)-2,3-dimethoxy-5-(3,4,5-trimethoxystyryl) aniline (**21**, 100 mg, 0.289 mmol), and 4-(tert-butyl)benzene-1-sulfonyl chloride (**23g**, 78.8 mg, 0.34 mmol) to obtain the pure product **7f** as a brown colour solid. (143mg, 91% yield); mp 194.0−196.0 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 1.28 (s, 9H) 3.50 (s, 3H), 3.56 (s, 3H), 3.65 (s, 6H), 3.81 (s, 3H), 6.45 (s,1H), 6.47-6.49 (d, *J*=11.476 1H), 6.51-6.53 (d, *J*=12.476 1H), 6.54 (s, 1H), 7.08 (s,1H), 7.17(s, 1H), 7.41-7.42 (d, *J*=8.80 2H),7.65-7.67 (d, *J*=8.80 Hz, 2H), ppm;**^{13}C NMR** ($CDCl_3$, 75 MHz) (ppm): 35.0, 30.9, 55.5, 55.8, 60.6, 105.7, 108.7, 112.8, 125.9, 126.9, 129.3, 130.2, 132.2, 132.4, 136.1, 137.1, 137.3, 151.4, 152.9, 156.8; MS(ESI): 542 [M+H]+; HRMS (ESI) calculated for C29 H35 O7 N S[M+H]+ 542.21953; found: 542.21970. HPLC: t_R 3.17 min, purity 100.0%.

(Z)-N-(2,3-dimethoxy-5-(3,4,5-trimethoxystyryl)phenyl)-4-nitrobenzenesulfonamide (7g).

Compound **7g** was prepared according to the method described for compound **6a**, employing (Z)-2,3-dimethoxy-5-(3,4,5-trimethoxystyryl)aniline (**21**, 100 mg, 0.289 mmol), and 4-nitrobenzene-1-sulfonyl chloride (**23h**, 75.1 mg, 0.34 mmol) to obtain the pure product **7g** as a white colour solid. (138mg, 90% yield); mp 198.0−201.0 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ (ppm): 3.61 (s, 3H), 3.63 (s, 3H), 3.70 (s, 6H), 3.82 (s, 3H), 6.43(s, 1H), 6.43-6.45 (d, *J* = 12.05 Hz, 1H), 6.53-6.55 (d, *J* = 12.05 Hz, 1H), 6.58 (s, 1H), 7.04 (s, 1H), 7.22 (s, 1H), 7.86-7.87 (s, *J* = 9.00 Hz 2H), 8.23-8.26 (s, *J* = 8.54 Hz, 2H) ppm; **^{13}C NMR** ($CDCl_3$, 75 MHz) (ppm): 55.6, 55.9, 60.8, 60.9, 105.9, 109.6, 112.5, 124.2, 128.3, 129.0, 129.3, 130.7, 132.3, 133.3, 137.3, 137.5, 144.7, 150.1, 151.6, 153.0. . MS(ESI): 548 [M+H]+; HRMS (ESI) calculated for C25 H26 O9 N2 S[M+H]+ 548.16929; found: 548.16930. HPLC: t_R 6.61 min, purity 99.0%.

(Z)-4-amino-N-(2,3-dimethoxy-5-(3,4,5-trimethoxystyryl)phenyl)benzenesulfonamide (7h).

Compound **7h** was prepared according to the method described for compound **2c**, employing (Z)-N-(2,3-dimethoxy-5-(3,4,5-trimethoxystyryl) phenyl)-4-nitrobenzenesulfonamide (**7h**, 80 mg, 0.094 mmol), in Methanol was added Zn (13 mg, 0.18 mmol) $HCOONH_4$ (13 mg, 0.32 mmol) to obtain the pure product **7h** as a white colour solid. (70mg, 92% yield); mp 210.0−213.0 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 3.57 (s, 3H), 3.59 (s, 3H), 3.67 (s, 6H), 3.83 (s, 3H), 6.43(s, 1H), 6.45-6.47 (d, *J* = 12.05 Hz, 1H), 6.52-6.54 (d, *J* = 12.05 Hz, 1H), 6.56 (s, 1H), 7.08 (s, 1H), 7.15 (s, 1H), 7.37-7.38 (s, *J* = 8.54 Hz 2H), 7.66-7.67 (s, *J* = 8.54 Hz, 2H) ppm; **^{13}C NMR** ($CDCl_3$, 75 MHz) (ppm): 55.5, 55.7, 60.7, 60.8, 105.9, 108.2, 112.1, 113.7, 126.8, 126.9, 129.2, 129.4, 130.1, 131.0, 132.3, 133.4, 137.0, 150.9, 151.5, 152.8; MS(ESI): 500[M+Na]+; HRMS (ESI) calculated for C25 H28 O7 N2 Na S[M+Na]+523.1594; found: 523.14958. HPLC: t_R 5.09 min, purity 99.0%.

(Z)-N-(2,3-dimethoxy-5-(3,4,5-trimethoxystyryl)phenyl)-3-(trifluoromethyl)benzenesulfonamide (7i).

Compound **7i** was prepared according to the method described for compound **6a**, employing (Z)-2,3-dimethoxy-5-(3,4,5-trimethoxystyryl) aniline (**21**, 100 mg, 0.289 mmol), and 3-(trifluoromethyl)benzene-1-sulfonyl chloride (**23j**, 84.8 mg, 0.34 mmol) to obtain the pure product **7i** as a white colour solid. (146mg, 91% yield); mp 203.0−206.0 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 3.56 (s, 6H), 3.66 (s, 6H), 3.82 (s, 3 H), 6.43 (s, 2H), 6.45-6.47 (d, *J*=12.05 Hz, 1H), 6.52-6.54 (d, *J*=12.05 Hz, 1H), 6.57 (s, 1H), 7.10 (s, 1H), 7.19 (s, 1H), 7.53-7.56 (t, 1H), 7.76-7.78 (d, *J*= 7.9 Hz 1H), 7.87-7.89 (d, *J*= 7.9 Hz 1H), 8.06 (s, 1H), ppm; **^{13}C NMR** ($CDCl_3$, 75 MHz) (ppm): 55.5, 55.7, 56.0, 60.7, 105.9, 108.5, 109.5, 110.3, 112.6, 121.1. 129.2, 130.3, 130.5, 130.6, 132.9, 133.2, 137.2, 137.3, 148.8, 151.8, 152.7, 152.8; MS(ESI): 571 [M+H]+; HRMS (ESI) calculated for C26 H30 O7 N2 F3 S[M+H]+ 571.17203; found: 571.17135. HPLC: t_R 5.09 min, purity 99.0%.

(Z)-2-methoxy-5-(3,4,5-trimethoxystyryl)phenyl 4-methoxybenzenesulfonate (8a).

To a solution of (Z)-2-methoxy-5-(3,4,5-trimethoxystyryl)phenol (**2a**) (100 mg, 0.316 mmol) in a tryethylamine (TEA) (0.632 mmol) and anhydrous CH_2Cl_2 (10 ml), 4-methoxybenzene-1-sulfonyl chloride (**23a**, 79 mg, 0.380 mmol) was slowly added at 0°C. After 5 min stirring remove ice both and stirred at room temperature 3 h, then the reaction mixture was evaporated to dryness in vacuum and the residue was taken up with CH_2Cl_2 (10 ml). The organic solution was washed with water and brine, dried over MgSO4, and concentrated in vacuum to give 139 mg (89%) of analytically pure compound (**8a**) obtained from a 3:1 mixture of hexan and ethyl acetate. mp 193.0−196.0 °C; ^{1}H NMR ($CDCl_3$) δ (ppm): 3.62 (s, 3H), 3.70 (s, 3H), 3.84 (s, 6H), 3.87 (s, 3H) 6.42 (s, 2H), 6.41-6.44 (d, *J* = 12.2 Hz, 1H), 6.46-6.49 (d, *J* = 12.2 Hz, 1H), 6.73-6.76 (d, *J* = 8.9 Hz, 2H), 6.90-6.93 (d, *J* = 8.4 Hz, 2H), 7.05 (d, NH), 7.12 (d, *J* = 1.71 Hz, 1H), 7.72-7.75 (d, *J*=8.8Hz, 2H) ppm; **^{13}C NMR** ($CDCl_3$, 75 MHz) (ppm): 55.6,

55.7, 55.8, 60.8, 105.9, 112.2, 113.8, 124.2, 127.8, 128.1, 128.4, 130.0, 130.1, 130.5, 132.2, 137.2, 138.1, 150.8, 152.9, 163.3; MS(ESI): 486[M+H]+; HRMS (ESI) calculated for $C_{25}H_{26}O_8NaS$ [M+Na]+ 509.12406; found: 509.12278. HPLC: t_R 8.15 min, purity 98.0%.

(Z)-2-methoxy-5-(3,4,5-trimethoxystyryl)phenyl 3,4-dimethoxybenzenesulfonate (8b).

Compound **8b** was prepared according to the method described for compound **8a**, employing (Z)-2-methoxy-5-(3,4,5-trimethoxystyryl)phenol (**2a**, 100 mg, 0.316 mmol), and 3,4-dimethoxy benzene-1-sulfonyl chloride (**23b**, 89.9 mg, 0.38 mmol) to obtain the pure product **8b** as a white colour solid. (144mg, 88% yield); mp 173.0−176.0 °C; ^{1}H NMR ($CDCl_3$) δ (ppm): 3.64 (s, 3H), 3.70 (s, 6H), 3.84 (s, 3H), 3.88 (s, 3H), 3.94 (s, 3H), 6.40-6.43 (d, *J* = 12.10 Hz, 1H), 6.43 (s, 2H), 6.45-6.48 (d, *J* = 12.10 Hz, 1H), 6.75-6.77 (d, *J*=8.43 Hz 1H), 6.85-6.87 (d, *J* = 8.55 Hz, 1H), 7.05 (d, *J* = 2.07 Hz, 1H), 7.11-7.14 (d *J*=8.43, 1H), 7.33 (d, *J*=2.20Hz, 1H), 7.35-7.39 (d *J*=8.43, 1H)ppm; **^{13}C NMR** ($CDCl_3$, 75 MHz) (ppm): 55.8, 55.86, 56.17, 60.8, 105.7, 110.0, 110.4, 112.2, 122.6, 124.1, 127.7, 128.0, 128.5, 130.0, 130.1, 132.1, 137.1, 138.1, 148.8, 150.9, 152.9, 153.5; MS(ESI): 516[M+H]+; HRMS (ESI) calculated for $C_{26}H_{28}O_7NaS$ [M+Na]+539.13462; found: 539.13289. HPLC: t_R 7.16 min, purity 98.0%.

(Z)-2-methoxy-5-(3,4,5-trimethoxystyryl)phenyl 4-chlorobenzene sulfonate (8c).

Compound **8c** was prepared according to the method described for compound **8a**, employing (Z)-2-methoxy-5-(3,4,5-trimethoxystyryl)phenol (**2a**, 100 mg, 0.316 mmol), and 4-chlorobenzene-1-sulfonyl chloride (**23c**, 80.3 mg, 0.38 mmol) to obtain the pure product **8c** as a white colour solid. (140mg, 90% yield); mp 188.0−191.0 °C; ^{1}H NMR ($CDCl_3$, DMSO) δ (ppm): 3.64 (s, 3H), 3.68 (s, 6H), 3.84 (s, 3H), 3.83 (s, 3H) 6.44 (s, 2H), 6.46 (s, 2H), 6.61 (d, *J*=8.3Hz 1H), 6.93 (s, 1H), 6.98(d, *J* = 8.3 Hz, 1H), 7.02-7.03 (m, 9.06Hz 2H), 7.40 (d *J*=2.26Hz, NH), 7.65-7.70 (d, *J*=12.086Hz, 2H)ppm; **^{13}C NMR** ($CDCl_3$, 75 MHz) (ppm): 55.6, 55.9, 60.9, 105.8, 112.2, 124.3, 129.0, 128.0, 128.8, 129.7, 130.3, 132.2, 134.9, 137.3, 137.9, 140.5, 150.6, 153.0. MS(ESI): 491[M+H]+; HRMS (ESI) calculated for C24 H24 O7 Cl S[M+H]+491.09258; found: 491.09246. HPLC: t_R 10.77 min, purity 99.0%.

(Z)-2-methoxy-5-(3,4,5-trimethoxystyryl)phenyl 3-chlorobenzenesulfonate (8d).

Compound **8d** was prepared according to the method described for compound **8a**, employing (Z)-2-methoxy-5-(3,4,5-trimethoxystyryl)phenol (**2a**, 100 mg, 0.316 mmol), and 3-chlorobenzene-1-sulfonyl chloride (**23d**, 80.3 mg, 0.38 mmol) to obtain the pure product **8d** as a white color solid. (143mg, 93% yield). mp 183.0−186.0 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 3.57 (s, 3H), 3.70 (s, 6H), 3.84 (s, 3 H), 6.44 (s, 2H), 6.42-6.44 (d, *J*=12.05 Hz, 1H), 6.48-6.51 (d, *J*=12.05 Hz, 1H), 6.73-6.75 (d, *J*=8.54 1H), 7.13-7.11 (s, 1H), 7.13-7.14 (d, *J*=8.39 1H), 7.41-7.44 (t, 1H), 7.58-7.60 (d, *J*= 9.00 Hz 1H), 7.68-7.70(d, *J*= 7.78 Hz 1H), 7.87 (s, 1H), ppm; **^{13}C NMR** ($CDCl_3$, 75 MHz) (ppm): 55.87, 60.8, 105.7, 112.0, 122.6, 122.8, 124.5, 125.6, 127.8, 127.9, 129.0, 129.5, 130.3, 137.2, 137.6, 138.9, 143.9, 153.0 MS(ESI): 491[M+H]+; HRMS (ESI) calculated for $C_{24}H_{24}O_7ClS$ [M+H]+491.09258; found: 491.09251. HPLC: t_R 10.91 min, purity 99.0%.

(Z)-2-methoxy-5-(3,4,5-trimethoxystyryl)phenyl 3,4-dichlorobenzene sulfonate (8e).

Compound 8e was prepared according to the method described for compound 8a, employing (Z)-2-methoxy-5-(3,4,5-trimethoxystyryl)phenol (**2a**, 100 mg, 0.316 mmol), and 3,4-dichloro benzene-1-sulfonyl chloride (23e, 93.3 mg, 0.38 mmol) to obtain the pure product 8e as a white colour solid. (148mg, 89% yield). mp 193.0−196.0 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 3.60 (s, 3H), 3.71 (s, 6H), 3.85 (s, 3 H), 6.43 (s, 2H), 6.42-6.45 (d, *J*=11.98 Hz, 1H), 6.49-6.52 (d, *J*=11.92 Hz, 1H), 6.74-6.76 (d, *J*=8.55 1H), 7.10-7.11 (s, 1H), 7.14-7.16 (dd, *J*=8.55 1H), 7.54-7.56 (d, *J*=8.43 1H), 7.60-7.63 (dd, *J*= 8.43 Hz 1H), 7.98 (s, 1H), ppm; ^{13}C NMR ($CDCl_3$, 75 MHz) (ppm): 55.5, 55.8, 60.8, 105.8, 112.2, 124.4, 127.3, 127.8, 129.0, 130.2, 130.4, 130.6, 132.1, 133.4, 136.0, 137.3, 137.6, 138.8, 150.3, 153.0. MS(ESI): 525[M+H]+; HRMS (ESI) calculated for $C_{24}H_{23}O_7Cl_2S$ [M+H]+525.05361; found: 525.05607. HPLC: t_R 11.24 min, purity 96.0%.

(Z)-2-methoxy-5-(3,4,5-trimethoxystyryl)phenyl 4-fluorobenzenesulfonate (8f).

Compound **8f** was prepared according to the method described for compound **8a**, employing (Z)-2-methoxy-5-(3,4,5-trimethoxystyryl)phenol (**2a**, 100 mg, 0.316 mmol), and 4-fluorobenzene-1-sulfonyl chloride (**23f**, 73.9 mg, 0.38 mmol) to obtain the pure product **8f** as a white colour solid. (135mg, 90% yield); mp 194.0−196.0 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ (ppm): 3.60 (s, 3H), 3.71 (s, 6H), 3.85 (s, 3H), 6.43 (s, 2H), 6.42-6.44 (d, *J*=12.054 Hz 1H), 6.46-6.50 (d, *J*=12.086 1H), 6.74-6.76 (s, *J*=8.54 Hz 1H), 7.04 (s, 1H), 7.12-7.17 (m, 3H), 7.81-7.84(m, 2H) ppm; **^{13}C NMR** ($CDCl_3$, 75 MHz) (ppm): 55.6, 55.8, 60.8, 105.7, 112.3, 123.9, 124.0, 127.8, 129.1, 129.5, 130.4, 130.5, 132.1, 137.2, 137.6, 142.1, 150.4, 150.6, 153.0. MS(ESI): 492[M+H]+; HRMS (ESI) calculated for $C_{24}H_{27}O_7NFS$ [M+H]+492.1486; found: 492.14917. HPLC: t_R 8.18 min, purity 99.0%.

(Z)-2-methoxy-5-(3,4,5-trimethoxystyryl)phenyl 4-(tert-butyl)benzenesulfonate (8g).

Compound **8g** was prepared according to the method described for compound **8a**, employing (Z)-2-methoxy-5-(3,4,5-trimethoxystyryl)phenol (**2a**, 100 mg, 0.316 mmol), and 4-(tert-butyl)benzene-1-sulfonyl chloride (**23g**, 88.1 mg, 0.38 mmol) to obtain the pure product **8g** as a white colour solid. (153mg, 94% yield); mp 192.0−194.0 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 1.33 (s, 9H) 3.53 (s, 3H), 3.70 (s, 6H), 3.84 (s, 3H), 6.44 (s, 2H), 6.41-6.44 (d, *J*=12.08 Hz 2H), 6.47-6.50 (d, *J*=12.08 Hz 1H), 6.71-6.73 (d, *J*=8.30 Hz 1H), 7.09-7.14 (m, 2H), 7.46-7.49 (d, *J*=8.68 1 H),7.72-7.75 (d, *J*=8.68 Hz, 2H), ppm; **^{13}C NMR** ($CDCl_3$, 75 MHz) (ppm): 30.97, 35.07, 55.66, 55.81, 60.87,105.82, 110.09, 121.39, 125.68, 125.83, 125.91, 126.96, 129.06, 129.53, 130.28, 132.57, 136.36, 137.097, 48.41, 152.94 156.56; MS(ESI): 530[M+H]+; HRMS (ESI) calculated for C28 H36 O7 N S[M+H]+530.22070; found: 530.22153. HPLC: t_R 3.21 min, purity 100.0%.

(Z)-2-methoxy-5-(3,4,5-trimethoxystyryl)phenyl 4-nitrobenzenesulfonate (8h).

Compound **8h** was prepared according to the method described for compound **8a**, employing (Z)-2-methoxy-5-(3,4,5-trimethoxystyryl)phenol (**2a**, 150 mg, 0.476 mmol), and 4-nitrobenzene-1-sulfonyl chloride (**23h**, 126.3 mg, 0.57 mmol) to obtain the pure product **8h** as a yellow colour solid. (210 mg, 88% yield); mp 198.0−201.0 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ (ppm): 3.61 (s, 3H), 3.71 (s, 6H), 3.85 (s, 3H), 6.41 (s, 2 H), 6.42-6.45 (d, *J*=12.05 Hz, 1H), 6.49-6.52 (s, *J*=12.05, 1H), 6.78-6.70 (d, *J*=8.54 1H), 7.01 (d, *J*=2.13 1H), 7.15-7.17 (d, *J*=8.54 1H), 7.99-8.01 (d, *J* = 9.00 Hz, 2H), 8.31-8.33 (d, *J*= 9.00 Hz 2H) ppm; **^{13}C NMR** ($CDCl_3$, 75 MHz) (ppm): 55.70, 55.91, 60.88, 105.84, 123.92, 124.04, 127.87, 129.15, 129.59, 130.00, 130.47, 130.56, 132.12, 137.33, 137.74, 142.23, 150.44, 150.70, 153.09; MS(ESI): 502[M+H]+; HRMS (ESI) calculated for C24 H24 O9 N S[M+H]+502.11663; found: 502.11672; [M+Na]+; calculated 524.09857;found: 524.09808. HPLC: t_R 3.41 min, purity 97.0%.

(Z)-2-methoxy-5-(3,4,5-trimethoxystyryl)phenyl 3-(trifluoromethyl) benzenesulfonate (8i).

Compound **8i** was prepared according to the method described for compound **8a**, employing (Z)-2-methoxy-5-(3,4,5-trimethoxystyryl)phenol (**2a**, 100 mg, 0.316 mmol), and 3-(trifluoromethyl) benzene-1-sulfonyl chloride (**23i**, 92.5 mg, 0.38 mmol) to obtain the pure product **8i** as a white colour solid. (152mg, 91% yield). mp 200.0−203.0 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 3.51 (s, 3H), 3.71 (s, 6H), 3.85 (s, 3 H), 6.44 (s, 2H), 6.42-6.45 (d, *J*=12.05 Hz, 1H), 6.49-6.52 (d, *J*=12.05 Hz, 1H), 6.71-6.72 (d, *J*=9.15 1H), 7.13-7.15 (m, 2H), 7.63-7.66 (t, 1H), 7.88-7.89 (d, *J*= 7.93 Hz 1H), 8.00-8.01 (d, *J*= 7.93 Hz 1H), 8.17 (s, 1H), ppm; **^{13}C NMR** ($CDCl_3$, 75 MHz) (ppm): 55.4, 55.8, 60.8, 105.8, 112.1, 124.6, 125.5, 125.6, 127.9, 129.0, 129.5, 130.3, 131.3, 131.5, 131.6, 132.1, 137.3, 137.6, 137.7, 150.2, 153.0. MS(ESI): 542[M+H]+; HRMS (ESI) calculated for C_{25} H_{27} O_7 N F_3 S[M+H]+542.14548; found: 542.14633. HPLC: t_R 3.27 min, purity 94.0%.

General procedure for the synthesis of (Z)-N-(2-hydroxy-3-methoxy-6-(3,4,5-trimethoxystyryl)phenyl) benzenesulfonamides (9a-k).

(a) Compounds (**24a-k**) were prepared according to the method described for compound **6a**, employing (Z)-2-((tert-butyldimethylsilyl)oxy)-3-methoxy-6-(3,4,5-trimethoxystyryl) aniline (**22**, 1 mmol), and substituted benzene-1-sulfonyl chlorides (**23-a-k,** 1.2 mmol) to obtain the pure products (**24a-k**) which were used without purification in the next step. (b) To a solution of compounds (**24a-k**, 1 mmol) in dry tetrahydrofuran, TBAF (1.0M in THF, 2.5mmol) was added at 0 °C and stirred at room temperature for 1 h. After completion of reaction, the reaction mixture was diluted with ethyl acetate, washed with water and brine solution, dried over anhydrous Na_2SO_4. The solution was filtered and the solvent was removed under reduced pressure followed by the purification of reside by column chromatography using ethyl acetate and hexane as eluents to afford respective desired products (**9a-k**).

(Z)-N-(2-hydroxy-3-methoxy-6-(3,4,5-trimethoxystyryl) phenyl)-4-methoxybenzenesulfonamide (9a).

The compound **9a** was prepared according to the general procedure by employing (Z)-2-((tert-butyldimethylsilyl)oxy)-3-methoxy-6-(3,4,5-trimethoxystyryl)aniline (**22,** 100 mg, 0.2275 mmol) and 4-methoxybenzene-1-sulfinyl chloride (**23a**, 55.2 mg, 0.27 mmol) to afford **24a,** which on deportation with TBAF (1.0M in THF, 2.5mmol) to obtain the pure product **9a** as a white colour solid. (103mg, 91% yield). mp 203.0−207.0 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 3.61(s, 6H), 3.81 (s, 3H), 3.82 (s, 3H), 3.86 (s, 3H), 5.87 (d, *J* = 12.086 Hz, 1H), 6.04 (s, 1H) 6.27 (s,2H), 6.31 (d, *J* = 12.086 Hz, 1H) 6.72 (m, 3H), 7.62 (d, *J* = 8.498, 2H) ppm; **^{13}C NMR** ($CDCl_3$, 75 MHz) (ppm): 55.5, 55.7, 56.2, 60.8, 105.7, 110.6, 113.8, 120.5, 120.6, 125.4, 128.4, 129.8, 129.9, 131.2, 131.4, 137.6, 142.9, 147.6, 152.9, 163.3; MS(ESI): 502[M+H]+; HRMS (ESI) calculated for C_{25} H_{28} O_8 N S[M+H]+502.15301; found: 502.15404. HPLC: t_R 4.96 min, purity 98.0%.

(Z)-N-(2-hydroxy-3-methoxy-6-(3,4,5-trimethoxystyryl) phenyl)-3,4-dimethoxybenzenesulfonamide (9b).

The compound **9b** was prepared according to the general procedure by employing (Z)-2-((tert-butyldimethylsilyl)oxy)-3-methoxy-6-(3,4,5-trimethoxystyryl)aniline (**22,** 100 mg, 0.227 mmol) and 4-methoxybenzene-1-sulfinyl chloride (**23b**, 64.2 mg, 0.27 mmol) to afford **24b,** which on deportation with TBAF (1.0M in THF, 2.5mmol) to obtain the pure product **9b** as a white colour solid. (108mg, 91% yield). mp 210.0−213.0 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 3.61 (s, 6H), 3.76 (s, 3H), 3.81 (s, 3H), 3.86 (s, 3H), 3.91 (s, 3H), 5.86 (d, 12.086 Hz 1H), 6.26 (d, *J* = 12.086 Hz 1H), 6.27 (s, 2H), 6.63(s, OH), 6.70 (d, 1H), 6.73 (d, 1H), 6.82(d,1H), 7.12 (d,1H), 7.63 (d, 1H). **^{13}C NMR** ($CDCl_3$, 75 MHz) (ppm): 55.5, 55.7, 56.1, 60.7, 60.8, 105.9, 108.5, 109.5, 110.2, 112.6, 121.1, 129.2, 130.3, 130.5, 130.6, 132.3, 133.3, 137.1, 137.3, 148.8, 151.5, 152.7, 152.8; MS(ESI): 532[M+H]+; HRMS (ESI) calculated for $C_{26}H_2O_9$ NS [M+H]+ 532.16123; found: 532.16137. HPLC: t_R 4.65 min, purity 95.0%.

(Z)-4-chloro-N-(2-hydroxy-3-methoxy-6-(3,4,5-trimethoxystyryl)phenyl)benzenesulfonamide (9c).

The compound **9c** was prepared according to the general procedure by employing (Z)-2-((tert-butyldimethylsilyl)oxy)-3-methoxy-6-(3,4,5 trimethoxystyryl)aniline (**22,** 100 mg, 0.227 mmol) and 4-methoxybenzene-1-sulfinyl chloride (**23c**, 57.4 mg, 0.27 mmol) to afford **24c,** which on deportation with TBAF (1.0M in THF, 2.5mmol) to obtain the pure product **9c** as a white colour solid. (105mg, 92% yield). mp 183.0−186.0 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 3.63 (s, 6H), 3.82(s, 3H), 3.85 (s, 3H), 6.02-6.06(d, *J*= 12.08 1H), 6.19 (s, *OH)*, 6.27-6.30 (d, *J*= 12.086 1H), 6.31 (s, 2H), 6.72 (s, 2H), 7.35-7.38 (d, *J*= 8.30 2H), 7.65-7.68 (s, *J*= 9.06 2H), ppm; **^{13}C NMR** ($CDCl_3$, 75 MHz) (ppm): 55.5, 55.8, 60.8, 106.0, 109.2, 112.7, 128.5, 129.2, 129.9, 130.5, 132.3, 133.3, 137.3, 137.4, 137.6, 139.4, 151.5, 153.0; MS(ESI): 506[M+H]+; HRMS (ESI) calculated for C24 H25 O7 N Cl S[M+H]+506.10348; found: 506.10510. HPLC: t_R 3.02 min, purity 99.0%.

(Z)-3-chloro-N-(2-hydroxy-3-methoxy-6-(3,4,5-trimethoxystyryl)phenyl) benzenesulfonamide (9d).

The compound **9d** was prepared according to the general procedure by employing (Z)-2-((tert-butyldimethylsilyl)oxy)-3-methoxy-6-(3,4,5-trimethoxystyryl)aniline (**22,** 100 mg, 0.227 mmol) and 4-methoxybenzene-1-sulfinyl chloride (**23d**, 57.4 mg, 0.27 mmol) to afford **24d,** which on deportation with TBAF (1.0M in THF, 2.5mmol) to obtain the pure product **9d** as a white colour solid. (102mg, 90% yield). mp 193.0−196.0 °C; ^{1}H NMR ($CDCl_3$) δ (ppm): 3.64 (s, 6H), 3.82 (s, 3H), 3.85(s, 3H), 6.07-6.10 (d, *J*= 12.086 1H), 6.13 (s, 1H), 6.29-6.32 (d, *J*= 12.086 1H), 6.33 (s, 2H) 6.73 (s, 2H), 7.33-7.36 (t, 1H), 7.50-7.52 (d, *J*= 7.62 1H), 7.61-7.63 (d, *J*= 7.62 1H), 7.71 (s, 1H) ppm; **^{13}C NMR** ($CDCl_3$, 75 MHz) (ppm): 55.8, 56.1, 60.8, 105.8, 110.0, 110.5, 112.2, 122.6, 124.2, 127.7, 128.1, 128.5, 130.0, 130.1, 132.1, 137.2, 138.1, 148.8, 150.9, 152.9, 153.5. . MS(ESI): 506[M+H]+; HRMS (ESI) calculated for $C_{24}H_{25}O_7$NCl S[M+H]+506.10348; found: 506.10533. HPLC: t_R 5.60 min, purity 98.0%.

(Z)-3,4-dichloro-N-(2-hydroxy-3-methoxy-6-(3,4,5-trimethoxystyryl)phenyl)benzene sulfonamide (**9e**).

The compound **9e** was prepared according to the general procedure by employing (Z)-2-((tert-butyldimethylsilyl)oxy)-3-methoxy-6-(3,4,5-trimethoxystyryl)aniline (**22**, 100 mg, 0.227 mmol) and 4-methoxybenzene-1-sulfinyl chloride (**23e**, 66.6 mg, 0.27 mmol) to afford **24e**, which on deportation with TBAF (1.0M in THF, 2.5mmol) to obtain the pure product **9e** as a white colour solid. (107mg, 88% yield). mp 193.0−186.0 °C; ^{1}H NMR (CDCl3) δ (ppm): 3.60 (s, 3H), 3.71 (s, 6H), 3.85(s, 3H), 6.42-6.45 (d, J= 12.086 1H), 6.43 (s, 2H), 6.49-6.52 (d, J= 12.086 1H), 6.74-6.76 (s, J= 8.55 1H) 7.10 (s, 1H), 7.14-7.16 (d, J= 8.55 1H), 7.54-7.57 (d, J= 8.43 1H), 7.61-7.63 (d, J= 7.62 1H), 7.71 (s, 1H) ppm; **^{13}C NMR** ($CDCl_3$, 75 MHz) (ppm): 55.8, 56.2, 60.8, 105.7, 110.6, 120.0, 120.8, 125.6, 127.7, 129.0, 129.8, 130.9, 131.7, 132.9, 134.6, 137.5, 140.7, 142.6, 146.9, 152.9. MS(ESI): 540[M+H]+; HRMS (ESI) calculated for C24 H24 O7 N Cl2 S[M+H]+540.06450; found: 540.06412. HPLC: t_R 11.06 min, purity 98.0%.

(Z)-4-fluoro-N-(2-hydroxy-3-methoxy-6-(3,4,5-trimethoxystyryl)phenyl) benzenesulfonamide (9f).

The compound **9f** was prepared according to the general procedure by employing (Z)-2-((tert-butyldimethylsilyl)oxy)-3-methoxy-6-(3,4,5-trimethoxystyryl)aniline (**22,** 100 mg, 0.227 mmol) and 4-methoxybenzene-1-sulfinyl chloride (**23a**, 66.6 mg, 0.27 mmol) to afford **24a,** which on deportation with TBAF (1.0M in THF, 2.5mmol) to obtain the pure product **9a** as a white colour solid. (102mg, 89% yield). mp 194.0−197.0 °C; ^{1}H NMR ($CDCl_3$) δ (ppm): 3.63 (s, 6H), 3.82 (s, 3H), 3.86 (s, 3H), 5.98-6.01 (d, *J*=12.05 Hz 1H), 6.30-6.32 (d, *J*=12.05 3H), 6.31 (s, 2H), 6.70-6.74 (m, 2H), 7.07-7.10 (t, 2H), 7.72-7.75 (m, 2H),

ppm; **^{13}C NMR** ($CDCl_3$, 75 MHz) (ppm): 55.7, 56.2, 60.8, 105.5, 110.5, 119.9, 120.8, 125.6, 127.7, 128.9, 129.8, 130.8, 132.9, 134.6, 137.4, 140.6, 142.6, 146.9, 152.9. MS(ESI): 490[M+H]+; HRMS (ESI) calculated for C24 H25 O7 N F S[M+H]+490.13303; found: 490.13201. HPLC: t_R 5.11 min, purity 97.0%.

(Z)-4-tert-butyl-N-(2-hydroxy-3-methoxy-6-(3,4,5-trimethoxystyryl)phenyl) benzenesulfonamide(9g).

The compound **9g** was prepared according to the general procedure by employing (Z)-2-((tert-butyldimethylsilyl)oxy)-3-methoxy-6-(3,4,5-trimethoxystyryl)aniline (**22,** 100 mg, 0.227 mmol) and 4-(tert-butyl)benzene-1-sulfonyl chloride (**23g**, 55.2 mg, 0.28 mmol) to afford **24g,** which on deportation with TBAF (1.0M in THF, 2.5mmol) to obtain the pure product **9g** as a white colour solid. (118mg, 88% yield). mp 203.0–205.0 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 1.30 (s, 9H) 3.62 (s, 6H), 3.81 (s, 3H), 3.87 (s, 3H), 5.76 (d, *J*=11.897 1H), 6.22 (d, *J*=11.897 1H), 6.26(s, 2H), 6.68(d,1H), 6.72(d, 1H), 7.40 (d, *J*=8.498 2H),7.63 (d, *J*=8.498 Hz, 2H), ppm; **^{13}C NMR** ($CDCl_3$, 75 MHz) (ppm): 30.9, 35.1, 55.7, 56.2, 60.8, 105.7, 110.6, 120.4, 120.5, 125.3, 125.6, 127.5, 128.5, 131.1, 131.4, 135.3, 137.5, 143.0, 147.5, 152.8, 157.2; FABMAS:(M+H)=527. MS (ESI): 528[M+H]$^+$; HRMS (ESI) calculated for $C_{28}H_{33}NO_7S$[M+H]+528.20388; found: 528.20379. HPLC: t_R 7.28 min, purity 95.0%.

(Z)-N-(2-hydroxy-3-methoxy-6-(3,4,5-trimethoxystyryl)phenyl)-4-nitrobenzenesulfonamide (9h).

The compound **9h** was prepared according to the general procedure by employing (Z)-2-((tert-butyldimethylsilyl)oxy)-3-methoxy-6-(3,4,5-trimethoxystyryl)aniline (**22,** 100 mg, 0.227 mmol) and 4-(trifluoromethyl)benzene-1-sulfonyl chloride (**23h**, 59.2 mg, 0.29 mmol) to afford **24h,** which on deportation with TBAF (1.0M in THF, 2.5mmol) to obtain the pure product **9h** as a white colour solid. (118mg, 89% yield). mp 213.0–215.0 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 3.64 (s, 3 H), 3.67 (s, 6 H), 3.84 (s, 3 H),6.44 (s, 2H), 6.42-6.44 (d, *J*=12.08 Hz, 1H), 6.46-6.50 (d, *J*=12.08 Hz, 1H), 6.60-6.63 (d, *J*=8.30 1H), 6.93 (s, 1H), 6.96-7.00 (dd, *J*=8.30, 1H), 7.02-7.08 (d, *J*=9.06 2H), 7.40 (s, 1H), 7.65-7.70 (dd, *J*= 9.06 Hz 2H) ppm; mp 208.0–211.0 °C; ^{13}C NMR (CDCl3, 75 MHz) (ppm): 55.8, 56.1, 60.8, 105.8, 110.0, 110.5, 112.2, 122.2, 122.6, 124.2, 128.1, 128.5, 130.1, 132.1, 137.2, 138.1, 148.8, 150.9, 152.9, 153.5; MS(ESI): 517[M+H]+; HRMS (ESI) calculated for $C_{24}H_{24}O_9N_2S$[M+H]+517.12800; found: 517.12809. HPLC: t_R 4.26 min, purity 99.0%.

(Z)-4-amino-N-(2-hydroxy-3-methoxy-6-(3,4,5-trimethoxystyryl)phenyl) benzenesulfonamide (9i).

The compound **9a** was prepared according to the general procedure by employing (Z)-2-((tert-butyldimethylsilyl)oxy)-3-methoxy-6-(3,4,5-trimethoxystyryl)aniline (**22,** 100 mg, 0.227 mmol) and 4-methoxybenzene-1-sulfinyl chloride (**23a**, 55.2 mg, 0.27 mmol) to afford **26a,** which on deportation with TBAF (1.0M in THF, 2.5mmol) to obtain the pure product **9i** as a white colour solid. (118mg, 89% yield). mp 222.0–225.0 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 3.60 (s, 6 H), 3.80 (s, 3 H), 3.85 (s, 3 H), 5.79-5.83 (d, *J*=12.08 Hz, 1H), 5.98 (s, 1H), 6.24 (s, 2H), 6.28-6.32 (d, *J*=12.08 Hz, 1H), 6.53-6.56 (d, *J*=8.68, 2H), 6.63-6.66 (d, *J*=8.876 2H), 6.70-6.73 (d, *J* = 8.68 Hz, 2H), 7.42-7.45 (d, *J*= 8.68 Hz 2H) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz) (ppm): 152.8, 151.1, 147.8, 142.9, 137.6, 131.4, 131.3, 129.8, 128.2, 125.8, 125.4, 120.8, 120.3, 113.6, 110.6, 105.6, 60.8, 56.2, 55.7. MS(ESI): 487[M+H]+; HRMS (ESI) calculated for C24 H27 O7 N2 S[M+H]+487.15335; found: 487.15414. HPLC: t_R 5.01 min, purity 92.0%.

(Z)-N-(2-hydroxy-3-methoxy-6-(3,4,5-trimethoxystyryl)phenyl)-4-methylbenzenesulfonamide (**9k**).

^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 2.89 (s, 3H), 3.80 (s, 3H), 3.88 (s, 3H), 3.88 (s, 6H), 6.43 (s, 1H), 6.45 (s, 1H), 6.78-6.81 (d, *J*=11.99 Hz, 1H), 6.83-6.86 (d, *J*=11.99 Hz, 1H), 5.57 (s, 1H), 5.88 (s, 1H), 6.89(s, 1H), 6.95-6.97 (d, *J*=7.99 Hz, 2H), 7.12 (s, 1H), 7.25 (s, 1H) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz) (ppm): 30.8, 56.4, 56.6, 61.1, 106.1, 113.3, 126.1, 127.8, 128.1, 129.1, 130.0, 136.2, 136.6, 138.2, 138.4, 139.2, 140.7, 153.6, 155.0; MS(ESI): 486[M+H]+; HRMS (ESI) calculated for $C_{25}H_{28}O_7NS$[M+H]+486.15810; found: 486.15722. HPLC: t_R 4.94 min, purity 97.0%.

(E)-N-((4-fluorophenyl)sulfonyl)-3-(4-methoxyphenyl)-2-(3,4,5-trimethoxyphenyl)acrylamide (10a).

To a vigorously stirred mixture of 4-fluorobenzenesulfonamide (50 mg, 0.285 mmol) and potassium iodide (KI) (50 mol%) in acetonitrile (ACN), (E)-3-(4-methoxyphenyl)-2-(3,4,5-trimethoxyphenyl)acryloyl chloride (155 mg, 0.428 mmol) was added under reflux condition. The progress of the reaction was monitored by TLC. After completion of the reaction, quenched with HYPO solution and extracted in to ethyl acetate (20 ml). The solvent was washed with water and dried over MgSO4. After evaporation of the solvent, the crude product was purified by column chromatography on silica gel (60–120 mesh, EtOAc–petroleum ether) or by recrystallization (toluene or ethyl acetate–n-hexane) to afford the corresponding N-acyl sulfonamide 130mg (91%).

^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 3.53 (s, 3H), 3.79 (s, 6H), 3.86 (s, 3H), 6.22 (s, 2H), 7.03-7.06 (d, *J*=8.49 Hz 2H), 7.16-7.19 (d, *J*=8.49 Hz 2H), 7.51-7.54 (d, *J*=8.49 Hz 2H), 7.69 (s, 1H), 7.94 (s, 1H),), 8.01-8.04 (d, *J*=8.49 Hz 2H), ppm; mp 193.0–186.0 °C; ^{13}C NMR ($CDCl_3$, 75 MHz) (ppm): 55.4, 55.6, 60.7, 108.1, 108.3, 115.7, 115.9, 116.2, 15.9, 129.0, 130.0, 131.3, 131.5, 131.6, 134.4, 134.5, 141.3, 152.6, 160.4. MS(ESI): 501.5; HRMS (ESI) calculated for $C_{25}H_{24}O_7$ N F S[M+H]+ 502.13303; found: 502.13378. HPLC: t_R 4.15 min, purity 95.0%.

(E)-N-((4-chlorophenyl)sulfonyl)-3-(4-methoxyphenyl)-2-(3,4,5-trimethoxyphenyl)acrylamide (10b).

Compound **10b** was prepared according to the method described for compound **10a**, employing 4-chlorobenzenesulfonamide (50 mg, 0.261 mmol) and potassium iodide (KI) (50 mol%) (ACN) and (E)-3-(4-methoxyphenyl)-2-(3,4,5-trimethoxyphenyl)acryloyl chloride (142 mg, 0.392 mmol) in acetonitrile, obtain the pure product **10b** as a white color solid 125mg (92%). mp 218.0–221.0 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 3.50 (s, 3H), 3.78 (s, 6H), 3.88 (s, 3H), 6.43 (s, 2H), 6.52-6.54 (d, *J*=8.39 Hz 1H), 6.71-6.74 (m, 1H), 6.90-6.94 (dd, *J*=8.39 Hz 1H), 7.21-7.24 (t, 2H), 7.61 (s, 1H), 8.11-8.14 (dd, *J*=5.03 Hz 2H), 7.74 (s, 1H), 9.88 (s, NH 1H) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz) (ppm): 55.4, 55.5, 60.7, 108.2, 115.7, 125.7, 128.9, 129.1, 129.8, 130.1, 131.3, 136.7, 139.5, 104.6, 141.4, 152.5, 160.4, 164.2; MS(ESI): 518 ; HRMS (ESI) calculated for $C_{25}H_{24}O_7$ N Cl S[M+H]+ 518.1000; found: 518.10260; HPLC: t_R 5.11 min, purity 88.0%.

(E)-N-((3,4-dichlorophenyl)sulfonyl)-3-(4-methoxyphenyl)-2-(3,4,5-trimethoxyphenyl)acrylamide (10c).

Compound **10c** was prepared according to the method described for compound **10a**, employing 3,4-dichlorobenzenesulfonamide (50 mg, 0.231 mmol) and potassium iodide (KI) (50 mol%) (ACN) and (E)-3-(4-methoxyphenyl)-2-(3,4,5-trimethoxyphenyl)acryloyl chloride (121 mg, 0.334 mmol) in acetonitrile, obtain the pure product **10c** as a white color solid 115mg (90%). mp 223.0–226.0 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 3.60 (s, 6H), 3.80 (s, 3H), 3.85 (s, 3H), 5.79-5.83 (d, *J*=9.39 Hz 1H), 6.24 (s, 2H), 6.28-6.31 (d, *J*=9.39 Hz 2H), 6.53-6.56 (d, *J*=8.68 Hz 1H), 6.66-6.72 (m, 2H), 7.42-7.45 (d, *J*=8.68 Hz 2H), ppm; **^{13}C NMR** ($CDCl_3$, 75 MHz) (ppm): 54.08, 54.90, 59.52, 105.63, 112.65, 125.32, 126.38, 129.01, 129.32, 129.46, 130.02, 131.29, 132.76, 134.44, 136.73, 138.44, 138.73, 152.59, 159.45, 165.33; MS(ESI): 552.4 ; HRMS (ESI)

calculated for $C_{25}H_{23}O_7NCl_2S$[M+H]+ 552.06450; found: 552.06432; HPLC: t_R 3.33 min, purity 94.0%.

(E)-4-(N-(3-(3,4-dichlorophenyl)-2-(3,4,5-trimethoxyphenyl)acryloyl)sulfamoyl)phenyl acetate (10d)

Compound **10d** was prepared according to the method described for compound **10a,** employing 4-sulfamoylphenyl acetate (50 mg, 0.232 mmol) and potassium iodide (KI) (50 mol%) (ACN) and (E)-3-(3,4-dichlorophenyl)-2-(3,4,5-trimethoxyphenyl)acrylaldehyde (128 mg, 0.348 mmol) in acetonitrile, obtain the pure product **10d** as a white color solid 123mg (93%). mp 226.0–229.0 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 2.26 (s, 3H), 3.81 (s, 6H), 3.97 (s, 3H), 6.45 (s, 2H), 6.90-6.93 (d, *J*=8.49 Hz 2H), 6.99-7.02 (d, *J*=8.49 Hz 2H), 7.49-7.54 (m, 2H), 7.75 (s, 1H), 8.19 (s, NH 1H), 8.27-8.30 (d, *J*= 8.68 Hz 1H), ppm; **^{13}C NMR** ($CDCl_3$, 75 MHz) (ppm): 21.0, 56.2, 61.0, 105.9, 121.8, 127.7, 128.5, 130.6, 131.0, 131.4, 132.5, 134.3, 138.9, 140.7, 141.0, 138.9, 151.8, 154.8, 163.7, 168.9; MS(ESI): 580.4 ; HRMS (ESI) calculated for $C_{26}H_{23}O_8NCl_2S$[M+H]+ 580.05969; found: 580.05965[M+Na$^+$]calculated 602.04136;found: 602.04160; HPLC: t_R 3.31 min, purity 72.0%.

(E)-3-(3,4-dimethoxyphenyl)-N-(phenylsulfonyl)-2-(3,4,5-trimethoxyphenyl)acrylamide (10e).

Compound **10e** was prepared according to the method described for compound **10a**, employing benzenesulfonamide (50 mg, 0.318 mmol) and potassium iodide (KI) (50 mol%) (ACN) and (E)- (E)-3-(3,4-dimethoxyphenyl)-2-(3,4,5-trimethoxyphenyl)acryloyl chloride (171 mg, 0.477 mmol) in acetonitrile, obtain the pure product **10e** as a white color solid 147mg (90%). mp 233.0–236.0 °C; ^{1}H NMR ($CDCl_3$+DMSO 300 MHz) δ (ppm): 3.55 (s, 6H), 3.77 (s, 6H), 3.89 (s, 3H), 3.90 (s, 3H), 6.34 (s, 2H), 6.72 -6.78(m, 2H), 6.96(s, 1H), 7.51-7.58 (m, 3H), 7.65-7.67 (d, 1H), 8.0 (d, 2H), ppm; ^{13}C NMR ($CDCl_3$+DMSO 75 MHz) (ppm): 53.43, 55.38, 59.87, 101.9, 102.0, 104.3, 104.6, 121.95. 122.0, 124.7, 127.6, 127.8, 127.9, 128.1, 129.6, 137.2, 137.4, 152.5, 152.7; MS(ESI): 513.6 ; HRMS (ESI) calculated for $C_{26}H_{28}O_8NS$ [M+H]+ 514.15301; found: 514.15408; HPLC: t_R 3.86 min, purity 82.0%.

(E)-3-(3,4-dimethoxyphenyl)-N-((4-fluorophenyl)sulfonyl)-2-(3,4,5-trimethoxyphenyl)acrylamide (10f).

Compound **10f** was prepared according to the method described for compound **10a**, employing 4-fluorobenzenesulfonamide (50 mg, 0.285 mmol) and potassium iodide (KI) (50 mol%) (ACN) and (E)- (E)-3-(3,4-dimethoxyphenyl)-2-(3,4,5-trimethoxyphenyl) acryloyl chloride (161 mg, 0.427 mmol) in acetonitrile, obtain the pure product **10f** as a white color solid 133mg (87%). mp 225.0–228.0 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 3.45 (s, 3H), 3.82 (s, 6H), 3.84 (s, 3H), 3.92 (s, 3H), 6.36 (s, 1H), 6.46 (s, 2H), 6.70-6.73 (d, *J*=8.30 Hz 1H), 6.78-6.80 (d, *J*=8.30Hz 1H), 7.21-7.23 (d, *J*=8.49 Hz 2H), 7.74 (s, 1H), 7.99 (s, NH 1H), 8.11-8.16 (d, *J*= 8.68 Hz 1H), ppm; **^{13}C NMR** ($CDCl_3$, 75 MHz) (ppm): 55.14, 55.79, 56.36, 60.83, 106.44, 110.58, 111.95, 116.05, 116.24, 126.30, 126.51, 128.32, 129.55, 131.65, 134.38, 138.59, 141.52, 148.31, 150.83, 154.84, 164.01; MS(ESI): 531 ; HRMS (ESI) calculated for $C_{26}H_{26}O_8NFS$[M+H]+ 532.14359; found: 532.14481; HPLC: t_R 3.16 min, purity 96.0%.

(E)-N-((4-chlorophenyl)sulfonyl)-3-(3,4-dimethoxyphenyl)-2-(3,4,5-trimethoxyphenyl) acrylamide (10g).

Compound **10g** was prepared according to the method described for compound **10a**, employing 4-chlorobenzenesulfonamide (50 mg, 0.261 mmol) and potassium iodide (KI) (50 mol%) (ACN) and (E)- (E)-3-(3,4-dimethoxyphenyl)-2-(3,4,5-trimethoxyphenyl)acryloyl chloride (148 mg, 0.395 mmol) in acetonitrile, obtain the pure product **10g** as a white color solid 128mg (89%). mp 217-220.0 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 3.45 (s, 3H), 3.78 (s, 6H), 3.85 (s, 6H), 6.42-6.46 (m, 3H), 6.76-6.78 (s, *J*=8.43 Hz 2H), 6.51-7.55 (d, *J*=5.30 Hz 2H), 7.61 (s, 1H), 8.02-8.05 (t, 2H) ppm; **^{13}C NMR** ($CDCl_3$ +DMSO, 75 MHz) (ppm): 43.99, 55.10, 55.17, 60.0, 105.2, 111.7, 115.4, 123.3, 127.0, 127.4, 127.9, 128.6, 129.3, 131.5, 136.4, 137.4, 144.9, 150.1, 152.2, 158.0; MS(ESI): 548 ; HRMS (ESI) calculated for $C_{26}H_{27}O_8NClS$ [M+H]+ 548.11404; found: 548.11559.

(E)-3-(3,4-dimethoxyphenyl)-N-((4-nitrophenyl)sulfonyl)-2-(3,4,5-trimethoxyphenyl) acrylamide (10h).

Compound **10h** was prepared according to the method described for compound **10a**, employing 4-nitrobenzenesulfonamide (50 mg, 0.247 mmol) and potassium iodide (KI) (50 mol%) (ACN) and (E)- (E)-3-(3,4-dimethoxyphenyl)-2-(3,4,5-trimethoxyphenyl)acryloyl chloride (140 mg, 0.371 mmol) in acetonitrile, obtain the pure product **10h** as a white color solid 126mg (91%). mp 223.0–226.0 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 3.61 (s, 6H), 3.80 (s, 3H), 3.82 (s, 3H), 3.93 (s, 3H), 6.41 (s, 2H), 6.60-6.63 (d, *J*=8.49 1H), 6.72(s, 1H), 7.10 (s, 1H), 7.43 (s, 1H), 7.31-56 (d, *J*=9.06 Hz 1H), 7.61-7.64 (d, *J*= 9.06 Hz 2H), ppm; **^{13}C NMR** ($CDCl_3$ +DMSO, 75 MHz) (ppm): 55.08, 55.51, 60.21, 107.56, 111.41, 112.76, 122.18, 123.31, 126.25, 128.80, 129.35, 131.24, 138.64, 139.84, 144.49, 148.73, 149.02, 149.79, 151.99, 165.93; MS(ESI): 558.6 ; HRMS (ESI) calculated for $C_{26}H_{27}O_{10}N_2S$[M+H]+ 559.13809; found: 559.14020.

(E)-N-((4-aminophenyl)sulfonyl)-3-(3,4-dimethoxyphenyl)-2-(3,4,5-trimethoxyphenyl)acrylamide (10i).

Compound **10i** was prepared according to the method described for compound **10a**, employing 4-aminobenzenesulfonamide (50 mg, 0.290 mmol) and potassium iodide (KI) (50 mol%) (ACN) and (E)- (E)-3-(3,4-dimethoxyphenyl)-2-(3,4,5-trimethoxyphenyl)acryloyl chloride (164 mg, 0.436 mmol) in acetonitrile, obtain the pure product **10i** as a white color solid 132mg (86%). mp 230.0–233.0 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 3.54 (s, 6H), 3.77 (s, 3H), 3.79 (s, 3H), 3.90 (s, 3H), 5.12 (s, NH_2 2H), 6.29 (s, 2H), 6.66 -6.71(m, 4H), 6.78-6.81(d, *J*=8.12 Hz 1H), 6.96-6.99 (d, *J*=8.12 Hz 1H), 7.51-53 (d, *J*=11.89 Hz 1H), 7.74-7.77 (d, *J*= 8.68 Hz 2H), ppm; **^{13}C NMR** ($CDCl_3$, 75 MHz) (ppm): 54.56, 54.80, 59.56, 59.67, 105.09, 108.09, 112.9, 122.7, 126.2, 128.4, 129.1, 129.6, 131.3, 131.8, 133.53, 136.0, 137.5, 146.8, 150.8, 151.7, 153.5; MS(ESI): 528.6 ; HRMS (ESI) calculated for $C_{26}H_{29}O_8N_2S$[M+H]+ 529.16391; found: 529.16386 [M+Na$^+$] calculated was 551.14586;found:567.14518.

(E)-3-(3-fluoro-4-methoxyphenyl)-N-((4-fluorophenyl) sulfonyl)-2-(3,4,5-trimethoxyphenyl)acrylamide (10j).

Compound **10j** was prepared according to the method described for compound **10a**, employing 4-fluorobenzenesulfonamide (50 mg, 0.285 mmol) and potassium iodide (KI) (50 mol%) (ACN) and (E)- (E)-3-(3-fluoro-4-methoxyphenyl)-2-(3,4,5-trimethoxy phenyl)acryloyl chloride (162 mg, 0.427 mmol) in acetonitrile, obtain the pure product **10j** as a white color solid 136mg (92%). mp 233.0–236.0 °C; ^{1}H NMR (CDCl3, 300 MHz) δ (ppm): 3.77 (s, 3H), 3.90 (s, 6H), 3.94 (s, 3H), 6.39 (s, 2H), 6.94 (d, J=8.55 Hz 1H), 7.17-7.19 (d, J=8.68 Hz 1H), 7.54-7.59 (m, 3H), 7.64-7.65 (d, J=7.70 Hz 1H), 8.08-8.09 (d, J= 5.74 Hz 2H), 10.53 (s, 1H) ppm;**^{13}C NMR** ($CDCl_3$, 75 MHz) (ppm): 54.96, 55.09, 59.69, 105.85, 111.7, 114.76, 115.0, 116.03, 116.28, 125.96, 126.90, 128.63, 130.10, 130.22, 131.22, 134.49, 137.00, 147.45, 152.68, 165.19; MS(ESI): 519.5 ; HRMS (ESI) calculated for $C_{25}H_{23}O_7NF_2S$[M+H]+ 520.1236; found: 520.12462.

(E)-N-((4-chlorophenyl)sulfonyl)-3-(3-fluoro-4-methoxy phenyl)-2-(3,4,5-trimethoxyphenyl)acrylamide (10k).

Compound **10k** was prepared according to the method described for compound **10a**, employing 4-chlorobenzenesulfonamide (50 mg, 0.261 mmol) and potassium iodide (KI) (50 mol%) (ACN) and (E)- (E)-3-(3-fluoro-4-methoxyphenyl)-2-(3,4,5-trimethoxyphenyl)acryloyl chloride (150

mg, 0.395 mmol) in acetonitrile, obtain the pure product **10k** as a white color solid 123mg (88%). Mp231.0−234.0 °C; 1H NMR (CDCl3, 300 MHz) δ (ppm): 3.43 (s, 3H), 3.72 (s, 6H), 3.82 (s, 3H), 6.44 (s, 2H), 6.48 (s, 1H), 6.75-6.77 (d, J=2.13 Hz 1H), 7.32-7.34 (d, J=8.54 Hz, 1H), 7.58-7.61 (d, J=9.15 Hz 1H), 7.66-7.69 (d, J= 9.15 Hz 2H) ppm;^{13}C NMR (CDCl$_3$,DMSO, 75 MHz) (ppm): 55.1, 55.9, 60.4, 106.4, 114.0, 115.5, 115.6, 115.8, 124.5, 129.1, 130.0, 130.9, 131.1, 131.8, 134.6, 137.9, 138.8, 146.7, 153.8, 165.0; MS(ESI): 536 ; HRMS (ESI) calculated for $C_{25}H_{23}O_7ClNF$ S[M+H]+ 536.09406; found: 536.09358.

(E)-N-((4-chlorophenyl)sulfonyl)-3-(4-methoxy-3-nitrophenyl)-2-(3,4,5-trimethoxyphenyl)acrylamide (10l).

Compound **10l** was prepared according to the method described for compound **10a**, employing 4-chlorobenzenesulfonamide (50 mg, 0.261 mmol) and potassium iodide (KI) (50 mol%) (ACN) and (E)-3-(4-methoxy-3-nitrophenyl)-2-(3,4,5-trimethoxyphenyl) acryloyl chloride (160 mg, 0.395 mmol) in acetonitrile, obtain the pure product **10l** as a white color solid 131mg (89%). mp 225.0−238.0 °C; ^{1}H NMR (CDCl3, 300 MHz) δ (ppm): 3.81 (s, 3H), 3.91 (s, 6H), 3.95 (s, 3H), 6.39 (s, 2H), 6.88-6.90 (d, J=8.54 Hz 1H), 7.13-7.15 (d, J=8.54 Hz 2H), 7.46 (s, NH 1H), 7.53-7.54 (d, J=6.71 Hz 1H), 7.69 (s,1H), 8.03-8.04 (d, J= 7.19 Hz 3H), ppm; ^{13}C NMR (CDCl3, 75 MHz) (ppm): 56.4, 56.6, 61.1, 106.06, 113.3, 126.0, 127.9, 129.2, 130.17, 131.5, 136.2, 136.5, 136.6, 138.4, 139.2, 139.3, 153.7, 153.8, 155.1, 163.4; MS(ESI): 563 ; HRMS (ESI) calculated for $C_{25}H_{23}O_7ClN_2$ S[M+Na$^+$]+ 585.07050; found: 585.07057.

(E)-3-(3-amino-4-methoxyphenyl)-N-(phenylsulfonyl)-2-(3,4,5-trimethoxyphenyl)acrylamide (10m).

Compound **10m** was prepared according to the method described for compound **2c**, employing (E)-N-((4-chlorophenyl)sulfonyl)-3-(4-methoxy-3-nitrophenyl)-2-(3,4,5-trimethoxyphenyl) acrylamide (**10l**) (6h, 80 mg, 0.15 mmol), in Methanol was added Zn (19.3 mg, 0.30 mmol) $HCOONH_4$ (20.1 mg, 0.31 mmol) to obtain the pure product **10m** as a white colour solid. (72mg, 90% yield); mp 223.0−226.0 °C; ^{1}H NMR (CDCl3, 300 MHz) δ (ppm): 3.77 (s, 3H), 3.81 (s, 6H), 3.94 (s, 3H), 6.46 (s, 2H), 6.70-6.72 (d, J=8.80 Hz 1H), 6.95-6.97 (d, J=8.80 Hz 2H), 7.48-7.50 (d, J=7.21 Hz 1H), 7.55 (s, 1H), 7.69 (s, 1H), 8.24-8.27(d, J= 8.55 Hz 2H), ppm;^{13}C NMR (CDCl3, 75 MHz) (ppm): 54.7, 55.5, 60.1, 102.4, 105.7, 106.3, 115.9, 121.5, 126.0, 128.3, 129.2, 129.5, 135.3, 137.2, 139.1, 140.0, 147.9, 152.4, 153.1, 165.5; MS(ESI): 533.0 ; HRMS (ESI) calculated for $C_{25}H_{26}O_7N_2ClS$[M+H]+ 533.11438; found: 533.11617.

(E)-N-((4-fluorophenyl)sulfonyl)-2-(4-methoxyphenyl)-3-(3,4,5-trimethoxyphenyl)acrylamide (11a).

Compound **11a** was prepared according to the method described for compound **10a**, employing 4-fluorobenzenesulfonamide (50 mg, 0.285 mmol) and potassium iodide (KI) (50 mol%) (ACN) and (E)-2-(4-methoxyphenyl)-3-(3,4,5-trimethoxyphenyl)acryloyl chloride (142 mg, 0.421 mmol) in acetonitrile, obtain the pure product **11a** as a white color solid 130mg (91%). mp 215.0−218.0 °C; ^{1}H NMR (CDCl$_3$, 300 MHz) δ (ppm): 3.75 (s, 3H), 3.80 (s, 6H), 3.96 (s, 3H), 6.41 (s, 2H), 6.68-6.70 (d, *J*=9.00 Hz 2H), 6.92-6.94 (d, *J*=9.00 Hz 2H), 7.21-7.25 (t, 2H), 7.74 (s, 1H), 7.94 (s, 1H) 8.07 (s, 1H), 8.11-8.13 (d, *J*=8.85 Hz 2H), ppm; **^{13}C NMR** (CDCl$_3$, 75 MHz) (ppm): 55.47, 55.58, 60.78, 108.26, 115.77, 125.78, 128.95, 129.16, 129.82, 129.9, 130.1, 131.3, 136.8, 139.5, 140.6, 141.4, 152.5, 160.4, 164.2; MS(ESI): 501.5 ; HRMS (ESI) calculated for $C_{25}H_{24}O_7NFS$[M+H]+ 502.13303; found: 502.1472; HPLC: t_R 3.15 min, purity 100.0%.

(E)-N-((4-chlorophenyl)sulfonyl)-2-(4-methoxyphenyl)-3-(3,4,5-trimethoxyphenyl)acrylamide (11b).

Compound **11b** was prepared according to the method described for compound **10a**, employing 4-chlorobenzenesulfonamide (50 mg, 0.261 mmol) and potassium iodide (KI) (50 mol%) (ACN) and (E)-2-(4-methoxyphenyl)-3-(3,4,5-trimethoxyphenyl)acryloyl chloride (142 mg, 0.392 mmol) in acetonitrile, obtain the pure product **11b** as a white color solid 127mg (94%).^{1}H NMR (CDCl$_3$, 300 MHz) δ (ppm): 3.64 (s, 3H), 3.67 (s, 6H), 3.84 (s, 3H), 6.44 (s, 2H), 6.45-6.46 (d, *J*=6.69 Hz 2H), 6.61-6.62 (d, *J*=8.39 Hz 1H), 6.95 (s, 1H), 6.97-6.99 (m, 1H), 7.04-7.06 (d, 2H) 7.40 (s, NH 1H), 7.66-7.68 (d, *J*=8.85 Hz 2H), ppm; **^{13}C NMR** (CDCl$_3$, 75 MHz) (ppm): 56.0, 56.4, 61.0, 105.9, 110.8, 113.8, 120.5, 121.0, 125.6, 126.1, 128.4, 130.0, 131.7, 137.8, 143.2, 148.0, 151.3, 153.1; MS(ESI): 518 ; HRMS (ESI) calculated for $C_{25}H_{24}O_7NCl$ S[M+NH$_4$]+ 536.13785; found: 536.13442; HPLC: t_R 8.58 min, purity 93.0%.

(E)-2-(3,4-dimethoxyphenyl)-N-((4-fluorophenyl)sulfonyl)-3-(3,4,5-trimethoxyphenyl)acrylamide (11c).

Compound **11c** was prepared according to the method described for compound **10a**, employing 4-fluorobenzenesulfonamide (50 mg, 0.285 mmol) and potassium iodide (KI) (50 mol%) (ACN) and (E)-2-(3,4-dimethoxyphenyl)-3-(3,4,5-trimethoxyphenyl)acryloyl chloride (161 mg, 0.427 mmol) in acetonitrile, obtain the pure product **11c** as a white color solid 140mg (92%). mp 221.0−224.0 °C; ^{1}H NMR (CDCl$_3$, 300 MHz) δ (ppm): 3.45 (s, 3H), 3.82 (s, 6H), 3.84 (s, 3H), 3.92 (s, 3H), 6.36 (s, 1H), 6.46 (s, 2H), 6.70-6.73 (d, *J*=8.43 Hz 1H), 6.78-6.80 (d, *J*=8.31Hz 1H), 7.21-7.27 (dd, *J*=8.43 Hz 2H), 7.74 (s, 1H), 7.98 (s, NH 1H), 8.12-8.15 (d, *J*= 8.68 Hz 2H), ppm; ^{13}C NMR (CDCl$_3$, 75 MHz) (ppm): 55.17, 55.80, 56.39, 60.84, 106.52, 110.62, 112.03, 116.06, 116.24, 126.35, 126.50, 128.39, 129.57, 131.59, 131.66, 138.69, 141.51, 148.36, 150.88, 154.88, 164.00; MS(ESI): 531.5 ; HRMS (ESI) calculated for $C_{26}H_{26}O_8NF$ S[M+H]+ 532.14359; found: 532.14324; HPLC: t_R 3.34 min, purity 90.0%.

(E)-N-((4-chlorophenyl)sulfonyl)-2-(3,4-dimethoxyphenyl)-3-(3,4,5-trimethoxyphenyl)acrylamide (11d).

Compound **11d** was prepared according to the method described for compound **10a**, employing 4-chlorobenzenesulfonamide (50 mg, 0.261 mmol) and potassium iodide (KI) (50 mol%) (ACN) and (E)- (E)-2-(3,4-dimethoxyphenyl)-3-(3,4,5-trimethoxyphenyl)acryloyl chloride (148 mg, 0.395 mmol) in acetonitrile, obtain the pure product **11d** as a white color solid 131mg (91%). mp 193.0−186.0 °C; mp 233.0−236.0 °C; ^{1}H NMR (CDCl3, 300 MHz) δ (ppm): 3.45 (s, 3H), 3.78 (s, 6H), 3.85 (s, 6H), 6.42-6.46 (m 3H), 6.76-6.84 (m, 2H), 7.51-7.55 (t, 1H), 7.61 (s, 1H), 8.02-8.05 (t, 2H), 10.65 (s, NH) ppm; ^{13}C NMR (CDCl$_3$, 75 MHz) (ppm): 54.30, 55.01, 55.44, 59.86, 106.30, 109.90, 111.29, 125.26, 125.97, 128.22, 128.81, 129.11, 129.55, 129.76, 137.20, 38.96, 139.25, 147.37, 149.62, 153.15, 165.32; MS(ESI): 548 ; HRMS (ESI) calculated for $C_{26}H_{26}O_8NClS$[M+H]+ 548.11404; found: 548.11372[M+Na$^+$] calculated was 570.09599; found: 570.09506. HPLC: t_R 3.28 min, purity 83.0%.

(E)-N-((4-fluorophenyl)sulfonyl)-2-(4-methoxyphenyl)-3-(3,4,5-trimethoxyphenyl)acrylamide (11e).

Compound **11e** was prepared according to the method described for compound **10a**, employing 4-fluorobenzenesulfonamide (50 mg, 0.285 mmol) and potassium iodide (KI) (50 mol%) (ACN) and (E)- (E)-2-(4-methoxyphenyl)-3-(3,4,5-trimethoxyphenyl)acryloyl chloride (162 mg, 0.427 mmol) in acetonitrile, obtain the pure product **11e** as a white color solid 133mg (90%). mp 228.0−231.0 °C; ^{1}H NMR (CDCl$_3$, 300 MHz) δ (ppm): 3.50 (s, 3H), 3.82 (s, 6H), 3.93 (s, 3H), 6.43 (s, 2H), 6.47-6.49 (d, *J*=8.12 Hz 1H), 6.68-6.72 (m, 1H), 6.89-6.95 (t, 1H), 7.21-7.24 (d, *J*=8.49 Hz 2H), 7.71 (s,1H), 8.00 (s, NH 1H), 8.11-8.16 (dd, *J*= 8.68 Hz 3H), ppm; **^{13}C NMR** (CDCl$_3$, 75 MHz) (ppm): 54.3, 54.7, 59.2, 106.7, 110.7, 110.7, 112.2, 121.4, 125.9, 126.8, 127.5, 128.3, 131.3, 132.1, 137.5, 137.7, 138.3, 147.8, 148.1, 151.2, 165.2; MS(ESI): 519.5 ; HRMS (ESI) calculated for $C_{25}H_{23}O_7NF_2$ S[M+H]+ 520.12361; found: 520.12287; HPLC: t_R 3.30 min, purity 93.0%.

(E)-N-(4-chlorophenylsulfonyl)-2-(4-methoxyphenyl)-3-(3,4,5-trimethoxyphenyl)acrylamide (11f).

Compound **11f** was prepared according to the method described for compound **10a**, employing 4-chlorobenzenesulfonamide (50 mg, 0.261 mmol) and potassium iodide (KI) (50 mol%) (ACN) and (E)- (E)-2-(4-methoxyphenyl)-3-(3,4,5-trimethoxyphenyl)acryloyl chloride (150 mg, 0.395 mmol) in acetonitrile, obtain the pure product **11f** as a white color solid 127mg (91%). mp 233.0−237.0 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 3.62 (s, 6H), 3.68 (s, 6H), 3.83 (s, 3H), 6.41 (s, 2H), 6.43-6.46 (d, *J*=9.12 Hz 1H), 6.48-6.52 (d, *J*=8.28 2H), 6.61-6.63 (d, *J*=8.65 1H), 6.92-6.95 (m, 2H), 7.39 (s,1H), 7.44-7.46 (d, *J*= 8.28 Hz 2H), ppm; ^{13}C NMR ($CDCl_3$,DMSO, 75 MHz) (ppm): 54.8, 55.8, 60.5, 106.0, 113.5, 125.8, 127.2, 128.6, 129.2, 130.9, 132.1, 133.7, 134.5, 137.9, 140.1, 140.5, 154.0, 160.6, 164.6; MS(ESI): 536; HRMS (ESI) calculated for $C_{25}H_{23}O_7NClFS$[M+H]+ 536.09406; found: 536.09342; HPLC: t_R 3.23 min, purity 94.0%.

MTT assay.

The anticancer activity of the compounds was determined using MTT (3-(4, 5-dimethylthiazol-2 yl)-2,5-diphenyl tetrazolium bromide) reduction assay.[47] 1×10^6 cells/well were seeded in 100 µl DMEM, supplemented with 10% FBS in each well of 96-well micro culture plates and incubated for 24 h at 37 °C in a CO2 incubator. Compounds, diluted to the desired concentrations in culture medium, were added to the wells with respective vehicle control. After 48 h of incubation, MTT (10 µl, 5 mg/mL) was added to each well and the plates were further incubated for 4 h. The supernatant from each well was carefully removed, formazon crystals were dissolved in DMSO (100 µl) and absorbance at 540 nm wavelength was recorded.

Cell cycle analysis

Cell cycle analysis Flow cytometric analysis (FACS) was performed to evaluate the distribution of the cells through the cell-cycle phases. HeLa and MCF-7cells were incubated for 48 h with compounds **7a** and **9a** at concentrations 25 and 50 nM. Untreated and treated cells were harvested, washed with phosphate-buffered saline (PBS), fixed in ice-cold 70% ethanol, and stained with propidium iodide (Sigma–Aldrich). Cell-cycle analysis was performed by flow cytometry (Becton Dickinson FACS Caliber instrument) as described earlier.[48]

Tubulin polymerization assay

A fluorescence based in vitro tubulin polymerization assay was performed according to the manufacturer's protocol (BK011, Cytoskeleton, Inc.). Briefly, the reaction mixture in a total volume of 10 lL contained PEM buffer, GTP (l µM) in the presence or absence of test compounds (final concentration of 3 µM). Tubulin polymerization was followed by a time dependent increase in fluorescence due to the incorporation of a fluorescence reporter into microtubules as polymerization proceeds. Fluorescence emission at 420 nM (excitation wavelength is 360 nM) was measured by using a Varioscan multimode plate reader (Thermo scientific Inc.). CA-4 was used as positive control in each assay. The IC50 value was defined as the drug concentration required inhibiting 50% of tubulin assembly compared to control. The reaction mixture for these experiments include: tubulin (3 mg/ml) in PEM buffer, GTP (1 l µM), in the presence or absence of test compounds at 0.1, 0.5, 1, 2 and 4 µM concentrations. Polymerization was monitored by increase in the Fluorescence as mentioned above at 37 °C.[49]

Colchicine competition assay

The test compounds (**7a** and **9a**) of various concentrations 0.1 µM, 0.5 µM, 1 µM, 5 µM and 10 µM were incubated with 3 µM tubulin in the presence and absence of 3 µM colchicine in 30 µM Tris buffer for 60 min at 37 °C. CA-4 was used as a positive control whereas taxol was used as negative control which binds at the taxane site. After incubation the fluorescence of tubulin–colchicine complex was determined by using Tecan multimode reader with excitation wavelength of 350 nm and emission wavelength of 435 nm. 30 mM Tris buffer was used as blank which was subtracted from all the samples and the fluorescence values are normalized to DMSO (control).[50]

Immunohistochemistry

HeLa and MCF-7cells were seeded on glass cover slips, incubated for 48 h in the presence or absence of test compounds **7a**, **9a** and CA-4 at 25 nM concentrations. Following the termination of incubation, cells were fixed with 3% paraformaldehyde, 0.02% glutaraldehyde in PBS and permeabilized by dipping the cells in 100% methanol (20 °C). Later, cover slips were blocked with 1% BSA in phosphate buffered saline for 1 h followed by incubation with a primary anti tubulin (mouse monoclonal) antibody and FITC conjugated secondary mouse anti IgG antibody. Photographs were taken using the confocal microscope, equipped with FITC settings and the pictures were analyzed for the integrity of microtubule network.[51]

Hoechst staining for morphological analysis of apoptosis

Cells (Hela and MCF-7) were seeded at a density of 10,000 cells over 18-mm cover slips and incubated for 24 h. Then, the medium was replaced, and cells were treated with **7a** and **9a** at 25 nM concentration for 48 h. Cells treated with vehicle (0.001% DMSO) were included as controls for all experiments. After 48 h treatment, Hoechst 33258 (SigmaeAldrich) staining was added to the medium at a concentration of 0.5 mg/ml. After incubation for 30 min at 37 °C, cells from each dish were captured from randomly selected fields under fluorescent microscope (Olympus microscope) to qualitatively determine the proportion of viable and apoptotic cells based on their relative fluorescence and nuclear fragmentation.[52]

Mitochondrial membrane potential

HeLa and MCF-7(1×10^6 cells/well) cells were cultured in six-well plates after treatment with compounds **7a** and **9a** at 25 and 50 nM concentrations for 48 h. After 48 h of treatment, cells were collected by trypsinization and washed with PBS followed by resuspending in JC-1 (5 µg/ml) and incubated at 37 °C for 15 min. Cells were rinsed three times with medium and suspended in pre warmed medium. The cells were then subjected to flow cytometric analysis on a flow cytometer (Becton Dickinson) in the FL1, FL2 channel to detect mitochondrial potential.[53]

Annexin staining assay for apoptosis

HeLa and MCF-7(1×10^6) cells were seeded in six-well plates and allowed to grow overnight. The medium was then replaced with complete medium containing compounds **7a** and **9a** at 25 and 50 nM concentrations. After 48 h of drug treatment, cells from the supernatant and adherent monolayer cells were harvested by trypsinization, washed with PBS at 5000 rpm. Then the cells were stained with Annexin VFITC and propidium iodide using the Annexin-V-FITC apoptosis detection kit (Sigma aldrich). Flow cytometry was performed for this study as described earlier.[54]

Protein extraction and Western blot analysis of caspase 3

After treatment with test compounds **7a** and **9a** at 25 nM concentrations for 48 h. Protein was isolated with RIPA (radioimmunoprecipitation assay) buffer. Protein (50 µg per lane) was applied in 10 % SDS-PAGE (Sodium dodecyl sulfate Polyacrylamide gel electrophoresis). After electrophoresis, the protein was transferred to a polyvinylidine difluoride (PVDF) membrane (Thermo Scientific Inc.) and blocked with BSA

(bovine serum albumin). The membrane was washed with TBST for 5 min, then primary antibody was added. After 24 h, the membrane was incubated with the corresponding horseradish peroxidase labeled secondary antibody and incubated for another 1 h. Membranes were washed with TBST three times for 15 min and the protein blots were visualized with chemiluminescence reagent (Thermo Scientific Inc.). Images were captured by using the chemiluminescence (vilber lourmat).[55]

Materials and Methods: Preclinical studies

Nude mice were used from the animal house facility located at CCMB (Hyderabad, India). All animal experimental studies were carried out in strict accordance with the recommendations in the guide for the care and use of laboratory animals of Centre for Cellular and Molecular Biology (CCMB). All the animal experimental protocols were approved by the Institutional Animal Ethical Committee (IAEC) of Centre for Cellular and Molecular Biology (CCMB with Permit number: CPCSEA 20/1999, Ministry of Environment and Forest, Government of India). The protocol was approved by the Institutional Animal Ethical Committee (IAEC) of CCMB (Protocol number: IAEC16/2012). All efforts were made to minimize suffering and the nude mice, 6–8 weeks old, were subcutaneously injected with $2x10^5$ HeLa cells, in the intraperitoneal region. After the tumor attained a minimum size of 500–1000 mm^3 (<9 days following cancer cell implantation), mice were grouped and treated as follows. Group (i) was treated with vehicle control (4 mice), group (ii) with 2 mg/kg of **7a** per day (4 mice), group (iii) with 2 mg/kg of **9a** per day (4 mice). These experiments were repeated thrice. Photographs of the nude mice in each category were taken after the tumor has attained maximum size as well as after 8 weeks of molecules treatment. To validate the effect of molecules on mice survival, in the same manner, three groups of mice were taken and 2 mg/kg of each molecule per day was injected intraperitoneal region on the alternate days for about 2 months and their activity was observed. In conclusion, the nude mice weight was around 22- 25 gm before starting the experiment. But after treatment the weight has slightly reduced to around 18-20 gm.

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Keywords: Combretastatin sulfonamides/sulfonates, molecular docking, cytotoxicity, HeLa and MCF7 cell lines, tubulin polymerization, colchicine binding assay, immunohistochemistry, hoechst staining, mitochondrial membrane potential, annexin V–FIT , western blot analysis and *in-vivo* antitumor activity.

References:

[1] (a). M. A. Jordan, L. Wilson, *Nat. Rev. Cancer* **2004**, *4*, 253–265. (b) V. M. Sánchez-Pedregal, C. Griesinger, *Top. Curr. Chem.* **2009**, *286*, 151−208. (c) J. H. Nettles, K. H. Downing, *Top. Curr. Chem.* **2009**, *286*, 209−257.

[2] Y. Fu, S. Li, Y. Zu, G. Yang, S. Jiang, M. Wink, *Curr. Med. Chem.* **2009**, *16*, 3966−3985.

[3] (a) J. H. Cutts, C. T. Beer, R. L. Noble, *Cancer Res.* **1960**, *20,* 1023−1031. (b) P. Keglevich, L. Hazai, G. Kalaus, C. Szántay, *Molecules* **2012**, *17*, 5893−5914.

[4] J. Chen, T. Liu, X. Dong, Y. Hu, *Mini-Rev. Med. Chem.* **2009**, *9*, 1174−1190.

[5] N. H. Nam, *Curr. Med. Chem.* **2003**, *10*, 1697−1722.

[6] Y. Lu, J. Chen, M. Xiao, D. D. Miller, *Pharm. Res.* **2012**, *29* (11), 2943−2971.

[7] C. Giulio, N. Dario, *J. Med. Chem.* **2015**, *58*, 8751−8761.

[8] (a) G. J. S. Rustin, S. M. Galbraith, L. Gumbrell, P. M. Price, *J. Clin Oncol.* **2003**, *21* (15), 2815−2822. (b) P. Nathan, M. Zweifel, A. R. Padhani, D. M. Koh, M. O. Leach, G. J. S. Rustin, I. Judson*, Clin. Cancer Res.* **2012**, *18* (12), 3428−3439.

[9] J. Liou, Y. Chang, F. Kuo, Y. Yang, H. Hsieh, *J. Med. Chem.* **2004**, *47*, 4247-4257.

[10] M. Banerjee, A. Poddar, G. Mitra, A. Surolia, T. Owa, and B. Bhattacharyya, *J. Med. Chem.* **2005**, *48*, 547-555.

[11] D. Guianvarc'h, M. Duca, C. Boukarim, L. Kraus-Berthier, P. Arimondo, and D. Dauzonne*, J. Med. Chem.* **2004**, *47*, 2365-2374.

[12] H. Yoshino, N. Ueda, J. Nijima, H. Sugumi, K. Yoshimatsu, M. Asada, T. Watanabe, *J. Med. Chem.* **1992**, *35*, 2496−2497.

[13] (a) T. Owa, H. Yoshino, T. Okauchi, K. Yoshimatsu, Y. Ozawa, N. Sugi, K. Kitoh, *J. Med. Chem.* **1999**, *42*, 3789−3799.

[14] Y. Ozawa, N. H. Sugi, T. Nagasu, T. Owa, T. Watanabe, N. Koyanagi, Y. oshimatsu, *Eur. J. Cancer* **2001**, *37*, 2275− 2282.

[15] K. Fukuoka, J. Usuda, Y. Iwamoto, N. Saijo, K. Nishio, *Invest New Drugs* **2001**, *19*, 219−227.

[16] M. Lai, H. Lee, H. Chuang, L. Li-Hsun Chang, and J. Liou, *J. Med. Chem.* **2015**, *58*, 6549−6558.

[17] (a) A. Kamal, G.B. Kumar, S. Polepalli, A.B. Shaik, M. Rasala, J.S. Kapure, N. Jain, *Chem. Med. Chem.* **2014**, *9*, 2565-79. (b) A. Kamal, A.B. Shaik, S. Polepalli, G.B. Kumar, M. Rasala, J.S. Kapure, N. Jain, *Bioorg. Med. Chem.* **2015**, *23*, 1082–1095.

[18] (a) R. T. Kroemer, 2007, 8, 312-328. (b) K. R. Valasani, J. Vangavaragu, and S. Yan, J. Chem. Inf. Model. 2014, 54 (3), 902–912.

[19] P. L. Mallipeddi, M. Joshi, J. M. Briggs**,** *Chem. Biol. Drug. Des.* **2012**, *80* (6), 828-842.

[20] A. Kamal, M. Rasala, Ch. R. Reddy, G.B. Kumar, K.N.V. Sastry, A.B. Shaik, V.S. Reddy, (3076DEL2014), PCT/IN2015/050148.

[21] G. M. Morris, R. Huey, W. Lindstrom, M. F. Sanner, and A. J. Olson, *J. Computational Chemistry* 2009, 16: 2785-91. (b) Q. Gao, L. Yang, Y. Zhu, *Curr. Comput. Aided Drug Des.* **2010**, *6* (1), 37-49.

[22] P. L. Mallipeddi, G. Kumar, S. W. White, T. R. Webb, *Curr Top Med Chem.* **2014**, *14* (16),1875-1889.

[23] J. M. Andreu, B. Perez-Ramirez, M. J. Gorbunoff, D. Ayala, S.N. Timasheff, *Biochemistry,* **1998**, *37* (23), 8356-68.

[24] B. Pérez-Ramírez, M. J. Gorbunoff, S.N. Timasheff*, Anticancer Drug Des. Biochemistry* **1998**, *37* (6):1646-1661**.**

[25] A. T. McGown, B.W. Fox, *Anti-cancer drug design* **1989**, *3* (4), 249-254.

[26] M. Jose, Andreu, *Biochemistry.* **1998**, *37*, 8356-8368.

[27] L. N. Tam, *J. Med. Chem.* **2005**, *48*, 6107-6116.

[28] T. J. Snape, K. Karakoula, F.Rowther, T.Warr, *RSC Advances,* **2012**, *2*, 7557–7560.

[29] O. Takashi, Y. Akira, Y. Kanami, Y. Kentaro, T. Yamori , and N. Takeshi, *J. Med. Chem.* **2002**, *45* (22), 4913–4922.

[30] Y.E. Tracy, Liaw, *Mol. Cancer Ther.* **2008**, *7*(10), 3150-3159.

[31] H. H. Xuequn, *Cancer Res*. **2001**, *61*, 7248-7254.

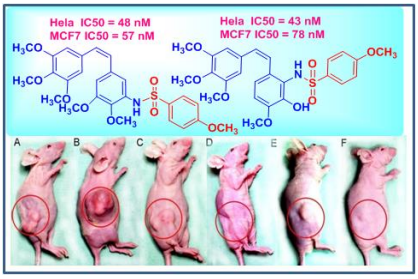
[32] A. Sebastian, T.M. Lee, R.T. Staran, M. Chang, ACS Med. Chem. Lett. **2011**, *2*, 177–181.

[33] D. Vidović, S. A. Busby, P. R. Griffin, Chem.Med.Chem. **2011**, *6*, 94–103.

[34] Mallipeddi PL, Joshi M, Briggs J M. Chem Biol Drug Des. **2012**.

[35] K. T. Chan, F. Y. Meng, W. H. Lee, K. H. Chu, M. Toh, *Cancer Lett.* **2010**, *294*, 118-124. (b). P. Wanitchakool, S. Jariyawat, K. Suksen, D. Soorukram, P. Tuchinda, P. Piyachaturawat, European Journal of Pharmacology **2012,** *696,* 35–42.

[36] J. K. Shen, H. P. Du, M. Yang, Y. G. Wang, J. Jin, Ann. Hematol. **2009,** *88*, 743-752. (b). V. Srivastava, H. Lee Bioorganic & Medicinal Chemistry **2015**, *23,* 7629–7640. (c). A. Kamal, A. Mallareddy, M. J.Ramaiah, S.N.C.V.L. Pushpavalli, P. Suresh, C. Kishor, S. Ghosh, A. Addlagatta , M. Pal-Bhadra, European Journal of Medicinal Chemistry **2012**, *56*, 166-178.
[37] C. Kanthou, O. Greco, A. Stanford, I. Cook, R. Knight, O. Benzakour, G. Tozer, *Am. J. Pathol.* **2004**, *165*, 1401-1411.
[38] R. Catherine, B. Pascale, B. R. Véronique, G. Catherine, F. Jean-Pierre, P. Vincent, *Biochemistry* **2006**, *45*, 9210.
[39] L. M. Leoni, E. Hamel, D. Genini, H. Shih, C. J. Carrera, D. A. Carson, *J. Natl. Cancer Inst*. **2000**, *92*, 217– 224.
[40] E. Pasquier, M. Kavallaris, *IUBMB Life* **2008**, *60*, 165– 170.
[41] K. Gonda, H. Tsuchiya, T. Sakabe, Y. Akechi, R. Ikeda, R. Nishio, K. Terabayashi, Y. Watanabe, G. Shiota, *Biochem. Biophys. Res. Commun.* **2008**, *370*, 629-633.
[42] X. Wang, X. Jiang*, Ann. Rev. Biochem.* **2004**, *3*, 87-106.
[43] S. M. Konstantinov, M. R. Berger, *Cancer Lett.* **1999**, *144*, 153– 160.
[44] T.F. Franke, C.P. Hornik, L. Segev, G.A. Shostak, C. Sugimoto, *Oncogene.* **2003**, *22*, 8983–8998.
[45] T.F. Franke, S.I. Yang, T.O. Chan, K. Datta, D.K. Morrison, P.N. Tsichlis, *Cell.* **1995**, *81*, 727–736.
[46] L.C. Cantley, B.G. Neel, *Proc. Natl. Acad. Sci. U.S.A.* **1999**, *96*, 4240–4245.
[47] A. Kamal, M. Rasala, V.L. Nayak, K.S. Babu, G.B. Kumar, A.B. Shaik, *Eur. J. Med. Chem.* **2016**, *108*, 476-485.
[48] M. Szumilak, M. A. Szulawska, K. Koprowska, M. Stasiak, W. Lewgowd, A. Stanczak, M. Czyz, *Eur. J. Med. Chem.* **2010**, *45*, 5744-5751.
[49] A. Kamal, B. Shaik, V.L. Nayak, B. Nagaraju, S. Malik, T.B. Shaik, B. Prasad, Bio. Org. *Med. Chem* **2014**, *22*, 5155–5167.
[50] M. I. Brett, L. Luca, A. Esther, J. O. C. Cornelius, S. T. Yaw, R. V. Ashok, R. S. David, *Nat. Commun.* **2013**, *5*, 3155-3160.
[51] A. Kamal, G.B. Kumar, M.V.P.S. Vishnuvardan, A.B. Shaik, M. Rasala, I.B. Sayeed, J.S. Kapure, *Org. Biomol. Chem*. **2015**, *13*, 3963-3981.
[52] R. Shankar, V. Chakravarti, U.S. Singh, M.I. Ansari, A. Dwivedi, K. Hajela*, Bioorg. Med. Chem*. **2009**, *17*, 3847-3856.
[53] B. Chakravarti, R. Maurya, J.A. Siddiqui, H.K. Bid, S.M. Rajendran, P.P. Yadav, R. Konwar, *Journal of Ethnopharmacology* **2012**, *142*, 72- 79.
[54] L.J. Browne, C. Gude, H. Rodriguez, R.E. Steele, A.J. Bhatnager, *J. Med. Chem.* **1991**, *34*, 725-736.
[55] S. Gowhar, M. Anjana, H. Tarique, A.A. Ali, A. Jyothy, L.K.Y. David, *Cancer Cell Int.* **2009**, *9*, 01–08.



A series of (*Z*)-3,4,5-Trimethoxy styryl Benzene sulfonamides /Sulfonates have been designed, synthesized and evaluated for their cytotoxicity against the NCI panel of sixty human cancer cell lines, majority of these compounds exhibited promising cytotoxicity with GI_{50} values ranging between **18-50 nM**. Further studies elucidate the mechanism of action of these new analogues inhibited the *in vitro* tubulin polymerization and disorganized the microtubule assembly in MCF-7 and HeLa cancer cells. The lead compounds **7a** and **9a** displayed notable *in vivo* antitumor activity in HeLa tumor xenograft model. Our studies resulted in the identification of a scaffold that can target tubulin polymerization having significant potential towards the development of new antitumor drugs.