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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Synthesis and anticancer activity of novel hydrazone linkage-based aryl sulfonate derivatives as apoptosis inducers

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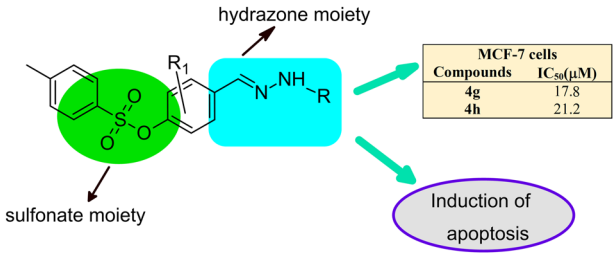
Abstract

In the present study, the various 28 hybrid molecules containing hydrazone and sulfonate moieties were synthesized and characterized by FTIR, ^{1}H-NMR, ^{13}C-NMR spectroscopy and LC-MS spectrometry, besides elemental analysis. The compounds were evaluated for their antiproliferative effects against six cancer cell lines, namely A549 (non-small cell lung cancer), MCF-7 (breast cancer), HT-29 (colorectal adenocarcinoma cancer), PC-3 (androgen-independent prostate adenocarcinoma), Hep3B (hepatocellular carcinoma cancer), and HeLa (epitheloid cervix carcinoma cancer). Among all the target compounds, compounds **4g** and **4h** exhibited more promising effects on MCF-7 cell lines ($IC_{50} = 17.8$ µM and 21.2 µM, respectively) with high selectivity. Further mechanistic studies proposed that compounds **4g** and **4h** induced apoptosis is mediated through the intrinsic apoptotic pathway with changes in mitochondrial membrane potential by finally activating caspase-9 and caspase-3. The results have been encouraging enough to merit further investigation.

Graphical Abstract



Keywords Hydrazone · Sulfonate · Anticancer activity · Apoptosis · Caspase activity

Introduction

Hydrazone derivatives are known for their broad spectrum of biological activities [1]. A variety of hydrazones have been utilized as anticancer drugs. Representative members of this class are zorubicin and bisantrene which are widely used for treatment of different cancer types (Fig. 1).

As shown in Fig. 2, 2',4'-difluoro-4-hydroxy-*N*'-(2-pyridyl methylidene)biphenyl-3-carbohydrazide has been reported as a hepatocellular carcinoma inhibitor [2]. Zhang et al. [3] studied a series of sulfonylhydrazone-substituted 8-ethoxy-3-nitro-2*H*-chromenes which were active against various cancer cell lines. Moreover, the tolmetin hydrazide–hydrazone having 2,6-dichlorophenyl moiety exhibited significant cytotoxicity and induction of apoptosis

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in the HT-29 cancer line [4]. A very recent report deals with, the apoptosis-inducing effect and VEGFR-2 inhibition of (S)-2-(6-methoxynaphthalen-2-yl)-*N*'-{(E)-[2-(trifluoromethoxy)phenyl]methylidene} propanehydrazide [5].

Sulfonates are widely used in medicine researches and have significant pharmacological applications such as antifungal [6], acaricidal [7] and antioxidant [8]. In particular, there have been many reports on the anticancer properties of compounds bearing aryl sulfonate moiety [9–11] (Fig. 2). Sulfonate-based compounds have a great affinity for lipid phases and can easily pass the membrane to attach to target sites due to their physicochemical features [7]. Also, the irreversible enzyme inhibitors usually possess reactive functional groups such as nitrogen mustards, aldehydes, alkenes and phenyl sulfonates [12]. These irreversible enzyme inhibitors may block certain enzymes that cancer cells.

On a pharmaceutical target, combining two or more effective pharmacophores of various potent bioactive agents can lead to potent new compounds. Based on the aforementioned compounds and in continuation of our work on hydrazones we were interested in studying the reaction of hydrazides with sulfonate aldehydes. Thus, we report here on the synthesis, characterization and anticancer evaluation of hydrazone derivatives with tosyl sulfonate moieties.

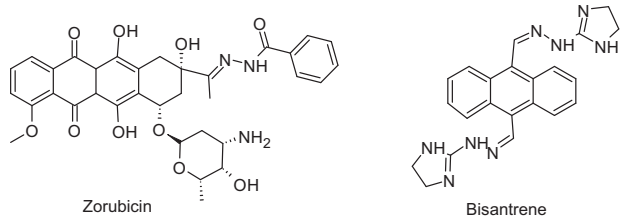


Fig. 1 Chemical structures of known hydrazone linkage-based anticancer drugs

Results and discussion

Chemistry

The synthesis route of hydrazides **(1a–h** and **1l–n)** and semicarbazide **(1k)** is shown in Scheme 1. First, acid hydrazides **(1a–h)** were synthesized by refluxing corresponding esters and hydrazine hydrate in ethanol according to the reported method [4, 13–17]. The compounds **(1i–j)** were synthesized according to the previously reported procedure starting from benzocaine [18]. Methyl [(5-propylsulfanyl-3*H*-benzoimidazol-2-yl)amino]formate (0.01 mol) (Albendazole) was refluxed hydrazine hydrate (80%, 0.2 mol) in methanol

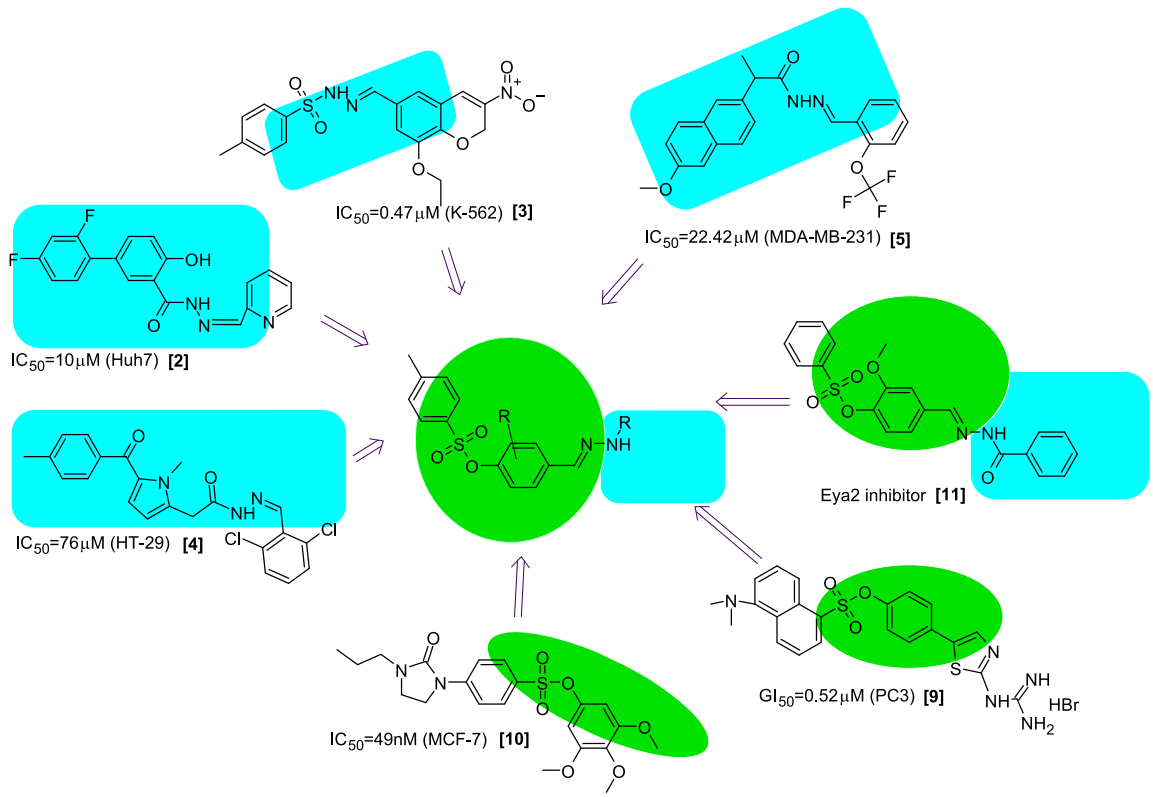
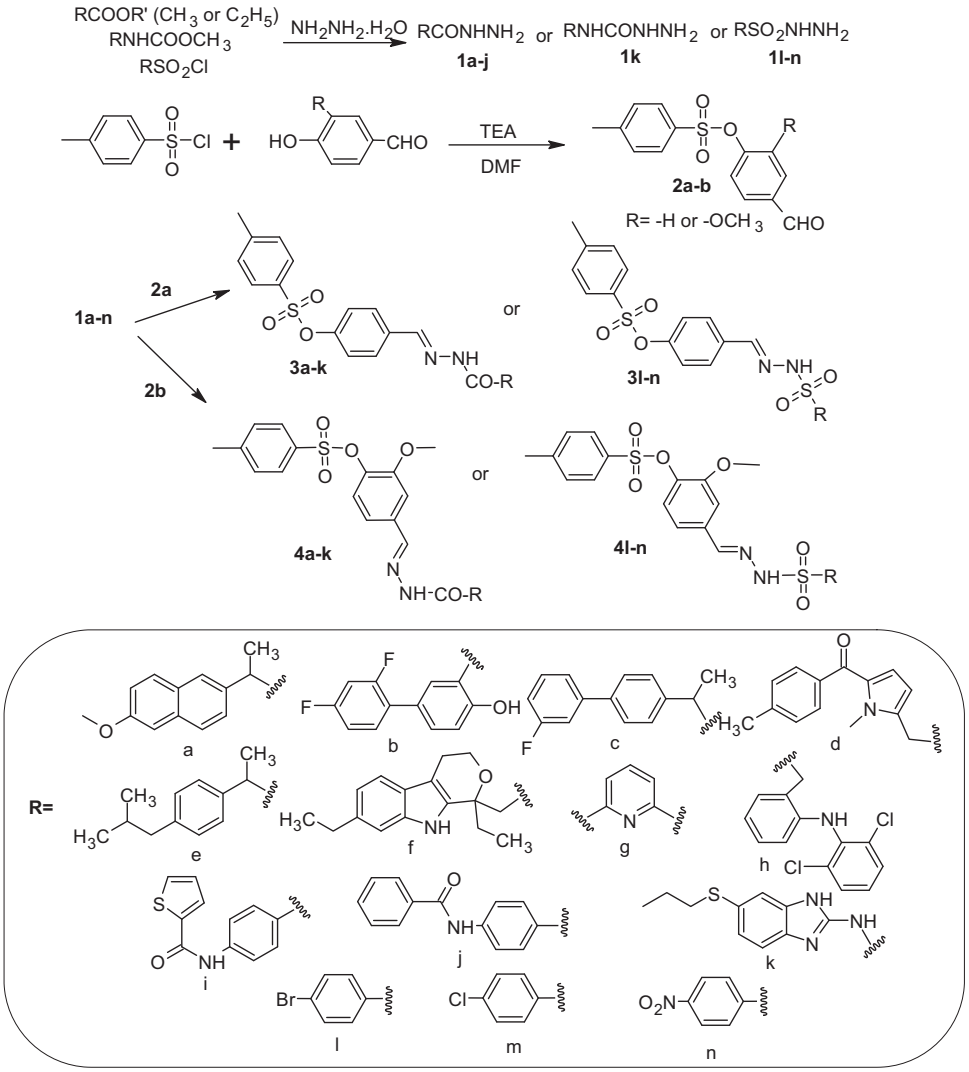


Fig. 2 Rationale for the design of the new compounds

Scheme 1 Synthetic route to target compounds



until the reaction was complete. After solvent evaporation and crystallization, compound **1k** was obtained [19]. Sulfonyl hydrazides **(1l–n)** were synthesized through the reaction between corresponding sulfonyl chlorides and hydrazine hydrate in THF [20].

Treatment of vanillin/p-hydroxybenzaldehyde with tosyl chloride and triethylamine in dimethylformamide gave the aldehyde derivatives **(2a-b)** [21]. In the final step of this study, hydrazone linkage-based aryl sulfonate derivatives were obtained by the reaction of compounds **1a–n** with related aldehydes **(2a-b)** in ethanol, as shown in Scheme 1.

The title compounds were characterized by FT-IR, ^{1}H-NMR, ^{13}C-NMR and LC-MS spectroscopy, besides elemental analysis and melting point. All of the spectral data are listed in Supplementary Material.

The C=N and C=O groups of the synthesized compounds were confirmed by IR spectra. The IR spectral peaks of compounds were recognized for C=O of CONH from 1637 to 1703 cm^{-1}; for C=N at 1583–1627 cm^{-1}.

In the ^{1}H-NMR spectra of compounds, characteristic singlet signals in the range of 2.38–2.44 ppm are attributable to the tosyl groups. In agreement with the literature data, CH=N and CONH groups exhibited two separate singlet signals in the ^{1}H-NMR and ^{13}C-NMR spectra of compounds **3a**, **3c–f**, **3h**, **4a**, **4c–f**, and **4h** due to the restricted rotation around the C–N bond [22]. In the cases of aromatic aldehydes-condensed *N*-acylhydrazones, ^{1}H-NMR spectra in DMSO-d_6 showed two peaks of the –CH_2CO and CH–CH_3 groups that be attributed to the presence of two possible syn-anti isomers of the amide bond or E-Z isomer. For all the final compounds, the protons of azomethine and amide resonated at the expected regions in the literature [13–15, 23].

The ^{13}C-NMR signals corresponding to the carbons from the azomethine and amide groups appear in the range 145.5-149.3 ppm and 160.6–184.8 ppm, respectively. MS spectra of the compounds displayed $[M+H]^+$, $[M+2H]^+$, and/or species exhibiting sodiated and potassiated adducts.

Table 1 Percentage growth inhibition (GI %) of various cell lines at 10 µM for compounds and IC_{50} values (µM) for compounds **4g** and **4h** for 24 h against MCF-7 cancer cell line

Compounds	GI%							IC_{50}(µM) (MCF-7)
	NIH3T3	HT-29	MCF-7	HEP3B	PC-3	HeLa	A549	
3a	27.18	18.32	7.83	NA	26.11	10.29	NA	
3b	36.61	21.63	27.25	26.71	42.14	34.73	NA	
3c	−3.16	2.06	3.28	NA	34.22	7.63	1.92	
3d	0.11	7.91	NA	NA	28.21	1.54	NA	
3e	9.60	NA	8.80	NA	31.04	8.58	NA	
3f	20.92	16.21	19.49	NA	32.78	15.16	NA	
3g	10.86	7.72	8.42	2.34	11.98	15.41	3.43	
3h	−6.09	NA	7.42	NA	18.79	NA	25.14	
3i	38.56	37.07	22.18	19.95	17.14	23.98	33.93	
3j	24.66	35.25	30.97	1.88	38.02	11.87	32.26	
3k	−6.04	NA	30.27	19.42	9.69	NA	4.17	
3l	−0.28	31.13	NA	NA	NA	NA	1.59	
3m	−0.67	19.29	NA	8.49	5.75	NA	8.63	
3n	−5.30	23.99	4.15	NA	6.84	5.29	8.79	
4a	5.81	22.28	17.27	1.03	1.85	11.74	5.81	
4b	7.22	38.97	32.85	20.62	19.63	15.57	14.55	
4c	−19.02	10.71	NA	17.96	NA	NA	9.57	
4d	−18.17	NA	NA	23.43	NA	NA	8.30	
4e	−19.97	NA	NA	19.43	NA	NA	11.61	
4f	−26.38	NA	25.82	NA	NA	NA	14.06	
4g	**−10.29**	NA	**50.37**	NA	NA	NA	28.58	**17.8**
4h	**−2.21**	NA	**53.98**	NA	16.06	2.70	36.59	**21.2**
4i	−25.33	NA	28.81	NA	NA	3.42	11.04	
4j	−11.93	NA	38.57	1.75	31.88	3.33	28.95	
4k	−11.27	NA	20.74	16.06	NA	NA	NA	
4l	−23.04	16.22	18.32	9.20	NA	NA	9.57	
4m	−5.06	NA	15.90	NA	NA	10.17	11.90	
4n	−10.05	3.61	15.78	NA	31.89	10.39	34.30	
Imatinib	−10.21	–	–	–	34.52	30.63	26.10	
Etoposide	−2.6	3.64	−0.4	6.03	–	–	–	

Bold entries represent the candidate molecules with inhibition ≥50% and safe the noncancerogenic cells.
NA GI% ≤ zero

Biological evaluation

The in vitro antiproliferative activity of the title compounds was evaluated against A549 (non-small cell lung adenocarcinoma), MCF-7 (breast adenocarcinoma), HT-29 (colorectal adenocarcinoma), PC-3 (androgen-independent prostate adenocarcinoma), Hep3B (hepatocellular carcinoma), and HeLa (cervical carcinoma) cells by MTT method. The anticancer screening results at 10 µM concentration are summarized in Table 1. Also, whether or not compounds caused cytotoxic effects in noncancer mouse embryonic fibroblast cell line (NIH3T3) was tested. Compounds showed no cytotoxicity effect on NIH3T3 cells.

The structures of the compounds **3a–n** and **4a–n** differ from each other due to substituent on phenyl ring (–$2OCH_3$ or –H). Compounds showed strong antiproliferative activity against cancer cells. Compound **3b** exerted cytotoxic activity with GI more than 40% against prostate (PC-3) cell line. The compounds **4g** and **4h** were found to be the best anticancer activity against the MCF-7 cell line (50.37 and 53.98%, respectively) with no effect on normal cell lines. Compound **3b** was less potent on normal cells compared to cancer cells. So, two compounds (**4g** and **4h**) were selected for further studies because of their high anticancer activity and low toxicity to normal cells. The cell growth-inhibitory potencies, expressed as IC_{50} values of these compounds, are listed in Table 1. Compounds **4g** and **4h** showed cytotoxicity with IC_{50} values of 17.8 and 21.2 µM against MCF-7 cell line, respectively.

In this study, mitochondrial disfunction was determined based on the mitochondria membrane potential (MMP)

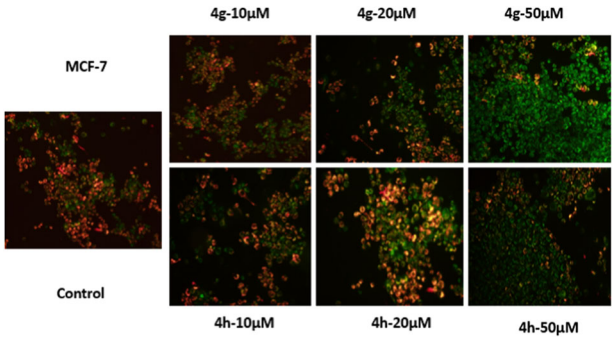


Fig. 3 Mitochondrial membrane potential (ΔΨm) of MCF-7 cancer cells after treated with compounds **4g** and **4h** was accessed via JC-1 staining assay

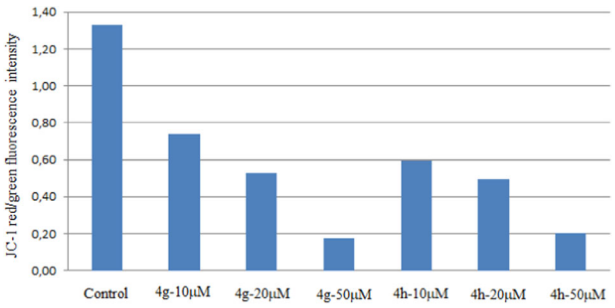


Fig. 4 Red/green fluorescence intensity for JC-1 staining of MCF-7 cells after treatment of compounds **4g** and **4h** at different concentrations (10, 20, and 50 μM) for 24 h

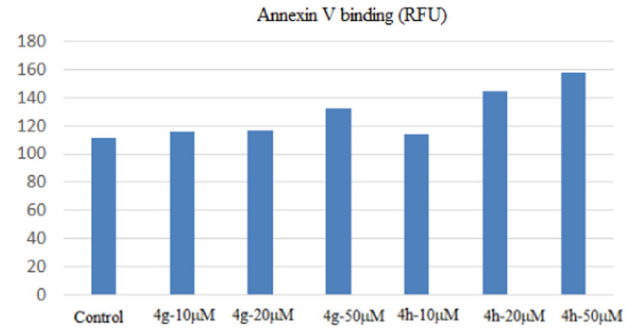


Fig. 5 Early apoptotic effects of compounds **4g** and **4h** on MCF-7 cells at different concentrations

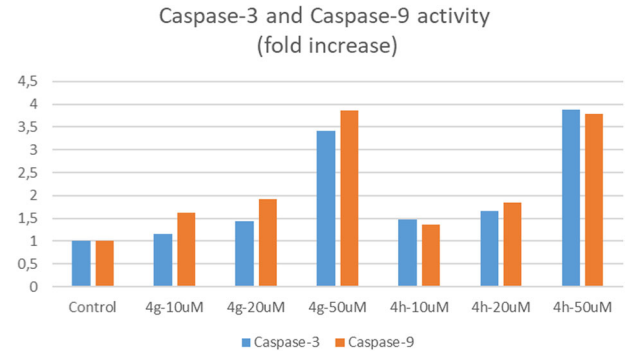


Fig. 6 Caspase-3 and caspase-9 activities induced by compounds **4g** and **4h** in MCF-7 cells

index that was measured using JC-1 (5,5′,6,6′-tetrachloro-1,1′,3,3′-tetraethylbenzimidazolylcarbocyanine iodide) dye as a fluorescent probe. A loss of mitochondrial mass was characterized by a decrease in red fluorescence and an increase in the green fluorescent intensity [24]. As shown in Fig. 3, before the treatment of compounds, the untreated MCF-7 cancer cells exhibited red fluorescence intensity because of the JC-1 dye aggregation into the mitochondria. Compounds **4g** and **4h**-treated cells displayed a reduction in red emission intensity and an increase in green emission intensity when compared to control cells.

The red/green fluorescence intensity ratio in the MCF-7 cells treated with different concentrations of compounds (10, 20, and 50 μM) was displayed in Fig. 4. A clear concentration-dependent decrease in the ratio can be observed for both compounds. Therefore, one of the first steps by which the studied compounds trigger apoptosis is likely to be through changes in mitochondrial membrane potential.

Annexin V is a fluorescent probe that binds to translocated phosphatidylserine (PS) in apoptotic cells and is used to indicate early apoptotic cells [25]. To determine whether selected compounds undergo apoptosis, an annexin V assay was also performed. As shown in Fig. 5, compounds initiated early apoptotic processes in MCF-7 cells and were dependent on dose, especially for the compound **4h**.

Apoptosis can be an extrinsic pathway mediated via activation of death receptors or by an intrinsic mitochondria-mediated pathway. In the intrinsic pathway, proapoptotic and antiapoptotic proteins stabilize the outer membrane of the mitochondria and activate caspase-9 and caspase-3. Caspase-3 is activated in both extrinsic and intrinsic apoptosis pathways, the initiator caspase-9 protein is only activated via the intrinsic pathway [26]. MMP depolarization results in the release of cytochrome into the cytosol, which activates caspase 9 via the formation of an apoptosome and the subsequent cleavage of caspase 3/7 effectors [27].

To determine whether caspases were involved in the apoptotic cell death induced by hybrid derivatives **4g** and **4h** in MCF-7 cells, we examined the effect of these compounds on caspase-3 and caspase-9 activation. It is important to underline that compounds significantly suppressed caspase-3 and caspase-9 activation (Fig. 6). These caspases were highly activated (~3.5–4-fold) with 50 μM concentrations of **4g** and **4h** in MCF-7 cells, showing that apoptotic cell death takes place in a caspase-dependent pathway.

Conclusions

In conclusion, we designed two series of hybrid molecules (**3a–n** and **4a–n**) based on the biological significance of hydrazone and sulfonate moieties. All the derivatives were characterized and evaluated for in vitro antiproliferative activity. The numerous compounds displayed a wide variety of cytotoxicity against multiple cancer cell lines. The activity results showed that compounds **4g** and **4h** were found to be most effective against MCF-7 cell assayed with IC_{50} values of 17.8 and 21.2 µM, respectively, besides their selectivity. Annexin V staining assay results showed that the selected compounds were induced apoptosis. This result is associated with depolarization of MMP and activation of caspase-3 and caspase-9. These compounds look like promising leads for further modification for the design of the new anticancer agents with high selectivity.

Materials and methods

Experimental

All chemical compounds were purchased from Merck and Sigma Aldrich. Melting points were measured with a Thermoscientific 9300 melting point apparatus and were uncorrected. Infrared (IR) Spectra were recorded using Shimadzu FTIR 8400S spectrophotometer. ^{1}H-NMR and ^{13}C-NMR experiments were carried out using BRUKER NMR spectrometer, and chemical shifts (δH) are reported relative to TMS as the internal standard. Mass spectra were recorded using Agilent LC/MSD and Xevo G2-XS QTof spectrometer. All reagents and solvents were dried and purified by the standard techniques. Chemical shift (δ) values of rotameric hydrogens whenever identified are presented within parentheses by assigning an asterisk (*) along with that of other forms [28]. Compounds **1a–n** and **2a–b** are already recorded in the literature [4, 13–21]. Compounds **1i**, **3e**, **3j** and methyl 4-[(thiophene-2-carbonyl) amino]benzoate have CAS Registry Numbers but no reference, analytical, or spectral data.

Synthesis

Methyl 4-[(thiophene-2-carbonyl)amino]benzoate

White cream solid; yield: 56%; m.p.185–187 °C; FTIR υ_{max} (cm^{-1}): 3360 (N-H), 1666 (C=O), 1593 (N-H bending); ^{1}H-NMR (300 MHz), (DMSO-d_6/TMS) δ ppm: 1.32 (t, 3H, CH_2-C**H$_3$**), 4.30 (q, 2H, C**H$_2$**-CH_3), 7.23–8.08 (m, 7H, Ar-**H**), 10.52 (s, 1H, CON**H**); Anal. calcd. for $C_{14}H_{13}NO_3S.1/2C_2H_5OH$: **C:** 60.38, **H:** 5.41, **N:** 4.69, **S:** 10.75. Found: **C:** 60.51, **H:** 5.19, **N:** 4.87, **S:** 10.51.

N-[4-(hydrazinecarbonyl)phenyl]thiophene-2-carboxamide (1i)

White cream solid; yield: 76%; m.p. 230–231 °C; FTIR υmax (cm^{-1}): 3306 (N-H), 1633 (C=O), 1600 (N-H bending); ^{1}H-NMR (300 MHz), (DMSO-d_6/TMS) δ ppm: 4.46 (s, 2H, CONHN**H$_2$**); 7.23–8.06 (m, 7H, Ar-**H**); 9.69 (s, 1H, CON**H**); 10.41 (s, 1H, CON**H**); Anal. calcd. for $C_{12}H_{11}N_3O_2S.1/5H_2O$: C: 54.41, H: 4.34, N: 15.86, S: 12.10. Found: C: 54.85, H: 4.45, N: 15.71, S: 12.34.

General procedure for the synthesis of target compounds

The mixture of aldehydes **2a-b** (1 mmol) and **1a-n** derivatives (1 mmol) was refluxed in ethanol (20 ml) in the presence of glacial acetic acid as the catalyst. After completion of the reaction (checked by TLC, t:25°C, acetone/petroleum ether 50:50 (v/v)), ethanol was evaporated, and the solid compounds **3a–n** and **4a–n** were dried and recrystallized with ethanol.

Synthetic route and chemical structures of compounds **3a-n** and **4a-n** are presented in Scheme 1.

4-((2-(2-(6-methoxynaphthalen-2-yl)propanoyl)hydrazinylidene)methyl)phenyl 4-methylbenzenesulfonate (3a)

White cream solid; yield: 81%; m.p.155–156 °C; FTIR υ_{max} (cm^{-1}): 3185 (N-H), 1660 (C=O), 1600 (C=N), 1373&1174 (S=O); ^{1}H-NMR (300 MHz), (DMSO-d_6/TMS) δ ppm: 1.46 (t, 3H, $J = 7.2$ Hz, CH-C**H3**); 2.43 (2.41*, s, 3H, Ar-C**H$_3$**); 3.85- 4.74 (m, 4H, OC**H$_3$** & C**H**-CH_3); 7.28–7.95 (m, 14H, Ar-**H**); 8.16 (7.85*, s, 1H, C**H**=N); 11.63 (11.34*, s, 1H, CON**H**); ^{13}C-NMR (75 MHz), (DMSO-d_6/TMS) δ ppm: 18.9 (CH-**C**H$_3$), 21.6 (Ar- **C**H$_3$), 44.4 (**C**H-CH_3), 55.6 (O-**C**H$_3$), 106.1, 119.0, 119.1, 122.9, 123.3, 125.9, 126.1, 126.7, 127.1, 127.2, 127.3, 128.7, 128.8, 128.9, 129.4, 129.5, 130.7, 131.6, 131.7, 131.9, 133.5, 133.7, 133.9, 137.0, 137.5, 141.5, 145.5&146.3 (**C**H=N), 150.0&150.2 (**C**-OSO_2), 157.4&157.5 (**C**-OCH_3), 170.4&175.5 (**C**=O); Anal. calcd. for $C_{28}H_{26}N_2O_5S.1/3H_2O$: **C:** 66.03, **H:** 5.85, **N:** 5.33, **S:** 6.52. Found: **C:** 66.12, **H:** 5.28, **N:** 5.51, **S:** 6.30; LCMS (ES-API) m/z: 504 $[M+H]^+$, 527 $[M+H+Na]^+$.

4-((2-(2′,4′-difluoro-4-hydroxy-[1,1′-biphenyl]-3-carbonyl) hydrazinylidene)methyl)phenyl 4-methylbenzenesulfonate (3b)

White solid; yield: 79%; m.p. 218–219 °C; FTIR υ_{max} (cm^{-1}): 3185 (N-H), 1637 (C=O), 1595 (C=N), 1373&1166 (S=O); ^{1}H-NMR (300 MHz), (DMSO-d_6/TMS) δ ppm: 2.42 (s, 3H, Ar-C**H$_3$**); 7.07–8.01 (m, 14H, Ar-**H**); 8.42 (s, 1H, C**H**=N); 11.92 (s, 2H, Ar- O**H**&CO-N**H**); 13C-NMR (75 MHz), (DMSO-*d6*/TMS) δ ppm: 21.6 (Ar-**C**H$_3$), 104.9, 112.3, 116.8, 118.0, 123.1, 125.5, 128.7, 129.2, 129.4, 130.7, 131.6, 132.1, 133.7, 146.4, 147.7 (**C**H=N), 150.5 (**C**-OSO_2), 158.9, 157.7&161.0 (**C**-F, $J = 246$ Hz), 160.2&163.5

(**C**-F, $J = 252$ Hz), 164.8 (**C**ONH); Anal. calcd. for $C_{27}H_{20}F_2N_2O_5S.1/4\ H_2O$: **C:** 61.53, **H:** 3.92, **N:** 5.32, **S:** 6.08. Found: **C:** 61.88, **H:** 4.06, **N:** 5.39, **S:** 6.17; LCMS (ES-API) m/z: 523 $[M+H]^+$, 546 $[M+H+Na]^+$.

4-((2-(2-(2-fluoro-[1,1′-biphenyl]-4-yl)propanoyl)hydrazinylidene)methyl)phenyl 4-methylbenzenesulfonate (3c) White solid; yield: 87%; m.p. 146–147 °C; FTIR υ_{max} (cm^{-1}): 3228 (N-H), 1651 (C=O), 1599 (C=N), 1345&1170 (S=O); ^{1}H-NMR (300 MHz), (DMSO-d_6/TMS) δ ppm: 1.06 (C**H**$_3$CH$_2$OH, ethanol); 1.43 (1.40*, d, 3H, $J = 6.9$ Hz, CH-C**H**$_3$); 2.42 (s, 3H, Ar-C**H**$_3$); 3.46 (CH3C**H**$_2$OH, ethanol); 4.36 (CH$_3$CH$_2$O**H**, ethanol); 4.74 (3.77*, q, 1H, $J = 6.9$ Hz, C**H**-CH$_3$); 7.07–7.76 (m, 16H, Ar-**H**); 8.19 (7.92*, s, 1H, C**H**=N); 11.65 (11.44*, s, 1H, CO-**NH**); ^{13}C-NMR (150 MHz), (DMSO-d_6/TMS) δ ppm: 18.6 (**C**H$_3$CH$_2$OH), 18.7&19.0 (CH-**C**H$_3$), 21.6 (Ar-**C**H$_3$), 43.9 (**C**H-CH$_3$), 56.5 (CH$_3$**C**H$_2$OH), 115.3, 115.4, 115.5, 115.7, 122.9,123.0, 126.8, 126.9, 127.1, 127.2, 128.2, 128.2, 128.7, 128.7, 129.0, 129.0, 129.0, 129.1, 130.7, 131.08, 131.1, 131.1, 131.1, 131.6, 131.7, 133.8, 135.3, 142.0, 143.7, 143.8, 144.2, 144.2, 145.9, 146.3&146.4 (**C**H=N), 150.1&150.3 (**C**-OSO$_2$), 158.5&160.1 (**C**-F, $J = 245$ Hz), 169.7&174.9 (**C**ONH); Anal. calcd. for $C_{29}H_{25}FN_2O_4S.1/3\ C_2H_5OH$: **C:** 66.98, **H:** 5.12, **N:** 5.27, **S:** 6.03. Found: **C:** 66.06, **H:** 4.86, **N:** 5.46, **S:** 6.18; LCMS (ES-API) m/z: 539 $[M+Na]^+$.

4-((2-(2-(1-methyl-5-(4-methylbenzoyl)-1H-pyrrol-2-yl) acetyl)hydrazinylidene)methyl)phenyl 4-methylbenzenesulfonate (3d) White solid; yield: 80%; m.p. 183–184 °C; FTIR υ_{max} (cm^{-1}): 3352 (O-H), 3230 (N-H), 1651 (C=O), 1599 (C=N), 1373&1170 (S=O); ^{1}H-NMR (300 MHz), (DMSO-d_6/TMS) δ ppm: 2.39 (s, 3H, ArC**H**$_3$); 2.42 (s, 3H, ArC**H**$_3$); 3.75–4.17 (m, 5H, N-C**H**$_3$ ve C**H**$_2$CO); 6.11 (d, 1H, $J = 3.9$ Hz, C**H**$_2$, pyrrole); 6.57 (d, 1H, $J = 3.9$ Hz, pyrrole); 7.07–7.76 (m, 12H, Ar-**H**); 8.19 (8.00*, s, 1H, -C**H**=N); 11.64 (s, 1H, - CON**H**); ^{13}C-NMR (150 MHz), (DMSO-d_6/TMS) δ ppm: 21.5 (Ar-**C**H$_3$), 21.6 (Ar-**C**H$_3$), 31.1 (N-**C**H$_3$), 33.0&33.4 (**C**H$_2$CO), 109.7, 110.0, 122.1, 122.2, 123.0, 128.7, 128.8, 129.0, 129.1, 129.4, 129.4, 130.7, 131.6, 131.7, 133.7, 133.8, 137.3, 137.4, 137.5, 137.7, 141.9, 141.9, 142.3, 145.7, 146.4&146.4 (**C**H=N), 150.2&150.3 (**C**-OSO$_2$), 165.2&170.8 (**C**ONH), 184.7&184.8 (**C**=O); Anal. calcd. for $C_{29}H_{27}N_3O_5S.1/2\ H_2O$: **C:** 64.67, **H:** 5.24, **N:** 7.80, **S:** 5.95. Found: **C:** 64.50, **H:** 5.33, **N:** 7.91, **S:** 6.22; LCMS (ES-API) m/z: 553 $[M+H+Na]^+$.

4-((2-(2-(4-isobutylphenyl)propanoyl)hydrazinylidene) methyl)phenyl 4-methylbenzenesulfonate (3e) White solid; yield: 82%; m.p. 99–101 °C; FTIR υ_{max} (cm^{-1}): 3230 (N-H), 1651 (C=O), 1599 (C=N), 1346,&1170 (S=O); ^{1}H-NMR (300 MHz), (DMSO-d_6/TMS) δ ppm: 0.81 (m, 6H, -CH(C**H**$_3$)$_2$); 1.36 (t, 3H, $J = 6.9$ Hz, -CHC**H**$_3$); 1.72–1.83 (m, 1H, -C**H**(CH$_3$)$_2$); 2.36–2.42 (m, 5H, ArC**H**$_3$&C**H**$_2$CH(CH$_3$)$_2$); 4.60 (3.64*, q, 1H, $J = 6.9$ Hz, C**H**CH$_3$); 7.04–7.76 (m, 12H, Ar-**H**); 8.16 (7.87*, s, 1H, -C**H**=N); 11.56 (11.04*, s, 1H, -CON**H**); ^{13}C-NMR (75 MHz), (DMSO-d_6/TMS) δ ppm: 18.8&18.9 (CH**C**H$_3$), 21.6 (Ar-**C**H$_3$), 22.6 (CH(**C**H$_3$)2), 30.0 (**C**H(CH$_3$)$_2$), 44.0 (**C**H$_2$CH(CH$_3$)$_2$), 44.6 (**C**HCH$_3$), 122.9, 127.4, 127.7, 128.6, 128.7, 128.9, 129.3, 129.4, 130.7, 131.6, 131.7, 133.9, 139.1, 139.5, 139.6, 140.0, 141.5, 145.5, 146.3&146.4 (**C**H=N), 150.0&150.2 (**C**-OSO$_2$), 170.5& 175.6 (C=O); Anal. calcd. for $C_{27}H_{30}N_2O_4S$: **C:** 67.76, **H:** 6.32, **N:** 5.85, **S:** 6.70. Found: **C:** 68.15, **H:** 5.96, **N:** 5.99, **S:** 6.73; LCMS (ES-API) m/z: 501 $[M+Na]^+$.

4-((2-(2-(1,8-diethyl-1,3,4,9-tetrahydropyrano[3,4-b] indol-1-yl)acetyl) hydrazinylidene)methyl)phenyl 4-methylbenzenesulfonate (3f) Dark yellow solid; yield: 77%; m.p. 107–108 °C; FTIR υ_{max} (cm^{-1}): 3223 (N-H), 1651 (C=O), 1599 (C=N), 1346&1170 (S=O); ^{1}H-NMR (300 MHz), (DMSO-d_6/TMS) δ ppm: 0.65 (0.57*, t, 3H, $J = 7.2$ Hz, -CH$_2$-C**H**$_3$); 1.06 (t, ethanol); 1.24 (t, 3H, -CH$_2$-C**H**$_3$); 2.03–2.15 (m, 2H, C**H**$_2$-CH$_3$); 2.42 (s, 3H, Ar-C**H**$_3$); 2.58–2.68 (m, 2H, -C**H**$_2$-CH$_3$); 2.78–2.98 (m, 4H, - C**H**$_2$CONH & -C**H**$_2$); 3.45 (m, ethanol); 3.69–4.00 (m, 2H, -C**H**$_2$); 4.36 (t, ethanol); 6.86–7.75 (m, 11H, Ar-**H**); 8.19 (7.94*, s, 1H, N=C**H**); 10.51 (10.49*, s, 1H, indole N-**H**); 11.37 (11.24*, s, 1H, CO-N**H**); 13C-NMR (75 MHz), (DMSO-d_6/TMS) δ ppm: 8.3 (pyran CH$_2$**C**H$_3$), 14.9 (indole CH$_2$**C**H$_3$), 21.6 (Ar**C**H$_3$), 24.2 (pyran -**C**H$_2$CH$_2$O-), 22.3 (indole **C**H$_2$CH$_3$), 31.2 (pyran **C**H$_2$CH$_3$), 6.2&76.5 (- CH$_2$O**C**H-), 107.5, 107.7, 115.8, 119.1, 12.9, 126.5, 127.0, 128.6, 128.7, 128.9, 130.7, 131.7, 134.0, 134.9, 136.7, 137.0, 146.4 (**C**H=N), 150.0& 150.2 (**C**-OSO$_2$), 166.1,&171.9 (**C**=O); Anal. calcd. for $C_{31}H_{33}N_3O_5S.3/2\ C_2H_5OH$: **C:** 65.78, **H:** 6.32, **N:** 7.12, **S:** 5.43. Found: **C:** 65.16, **H:** 5.67, **N:** 7.14, **S:** 5.54; LCMS (ES-API) m/z: 582 $[M+Na]^+$.

4-((2-(6-(2-(4-(tosyloxy)benylidene)hydrazine-1-carbonyl)picolinoyl) hydrazinylidene)methyl)phenyl 4-methylbenzenesulfonate (3g) White solid; yield: 82%; m.p. 227–228 °C; FTIR υ_{max} (cm^{-1}): 3230, 3171 (N-H), 1668, 1651, 1599 (C=O & C=N), 1344,1170 (S=O); ^{1}H-NMR (300 MHz), (DMSO-d_6/TMS) δ ppm: 2.44 (s, 6H, C**H**$_3$), 7.16–7.84 (m, 16H, Ar- **H**), 8.26–8.38 (m, 3H, pyridine-**H**), 8.74 (s, 2H, C**H**=N), 12.37 (s, 2H, CON**H**-N=); ^{13}C-NMR (150 MHz), (DMSO-d_6/TMS) δ ppm: 21.6 (2Ar-**C**H$_3$), 123.1, 126.1, 128.7, 129.3, 130.7, 131.7, 133.7, 140.5, 146.4, 148.6 (pyridin 2**C**-N), 149.0 (2**C**H=N), 150.6 (2**C**-OSO$_2$), 160.0 (2**C**=O); Anal. calcd. for $C_{35}H_{29}N_5O_8S_2.4H_2O$: **C:** 53.63, **H:** 4.76, **N:**

8.93, **S:** 8.18. Found: **C:** 53.99, **H:** 4.37, **N:** 9.21, **S:** 8.54; LCMS (ES-API) m/z: 734 $[M+Na]^+$.

4-((2-(2-(2-((2,6-dichlorophenyl)amino)phenyl)acetyl)hydrazinylidene)methyl)phenyl 4-methylbenzenesulfonate (3h) White solid; yield: 88%; m.p. 228–229; FTIR υ_{max} (cm^{-1}): 3317 (N-H), 1658 (C=O), 1614 (C=N), 1357&1178 (S=O); ^{1}H-NMR (300 MHz), (DMSO-d_6/TMS) δ ppm: 2.43 (s, 3H, C**H**$_3$), 4.12 (3.70*, s, 2H, C**H**$_2$CO), 6.27–8.04 (m, 16H, Ar-**H**& C**H**=N), 8.20 (s, 1H, N**H**), 11.89 (11.68*, s, 1H, CON**H**-N=); 13C-NMR (150 MHz), (DMSO-d_6/TMS) δ ppm: 21.6&21.7 (Ar-**C**H$_3$), 35.8&36.0 (**C**H$_2$CO), 146.4&146.5 (**C**H=N), 150.2&150.4 (**C**-OSO$_2$), 168.3 (**C**=O); Anal. calcd. for $C_{28}H_{23}Cl_2N_3O_4S_2.1/2H_2O$: **C:** 58.24, **H:** 4.19, **N:** 7.28, **S:** 5.55. Found: **C:** 58.84, **H:** 4.29, **N:** 7.42, **S:** 5.80; LCMS (Q-TOF) m/z: 568 $[M+H]^+$.

4-((2-(4-(thiophene-2-carboxamido)benzoyl)hydrazinylidene)methyl)phenyl 4-methylbenzenesulfonate (3i) White cream solid; yield: 76%; m.p. 281–283 °C; FTIR υ_{max} (cm^{-1}): 3354, 3292 (N-H), 1703, 1641 (C=O), 1599 (C=N), 1340&1172 (S=O); ^{1}H-NMR (300 MHz), (DMSO-d_6/TMS) δ ppm: 2.43 (s, 3H, Ar-C**H$_3$**), 7.25–8.09 (m, 15H, Ar-**H**), 8.43 (s, 1H, C**H**=N), 10.49 (s,1H, thiophene-CON**H**), 11.87 (s, 1H, CON**H**); ^{13}C-NMR (75 MHz), (DMSO-d_6/TMS) δ ppm: 21.6 (Ar-**C**H$_3$), 119.9, 123.0, 128.4, 128.6, 128.7, 129.0, 130.0, 130.7, 131.6, 132.9, 134.0, 140.0, 142.4, 146.3, 146.4 (**C**-OSO$_2$),150.3 (**C**H=N), 160.6 (**C**=O), 163.0 (**C**=O); Anal. calcd. for $C_{26}H_{21}N_3O_5S_2$: **C:** 60.10, **H:** 4.07, **N:** 8.09, **S:** 12.34. Found: **C:** 59.68, **H:** 4.16, **N:** 8.06, **S:** 12.91; LCMS (Q-TOF) m/z: 520 $[M+H]^+$.

4-((2-(4-benzamidobenzoyl)hydrazinylidene)methyl)phenyl 4-methylbenzenesulfonate (3j) White solid; yield: 70%; m.p. 286 °C; FTIR υ_{max} (cm^{-1}): 3338, 3230 (N-H), 1668, 1651, 1599 (C=O & C=N), 1373&1172 (S=O); ^{1}H-NMR (300 MHz), (DMSO-d_6/TMS) δ ppm: 2.43 (s, 3H, Ar-C**H$_3$**), 7.53–8.00 (m, 17H, Ar-**H**), 8.43 (s, 1H, C**H**=N), 10.53 (s, 1H, amide-CON**H**), 11.87 (s, 1H, CON**H**); ^{13}C-NMR (75 MHz), (DMSO-d_6/TMS) δ ppm: 21.6 (Ar-**C**H$_3$), 119.9, 123.0, 128.2, 128.7, 128.9, 130.7, 131.6, 132.3, 134.0, 135.0, 146.4 (**C**H=N), 150.2 (**C**-OSO$_2$), 163.0 (**C**=O), 165.3 (**C**=O); Anal. calcd. for $C_{28}H_{23}N_3O_5S.1/2H_2O$: **C:** 64.35, **H:** 4.63, **N:** 8.04, **S:** 6.14. Found: **C:** 64.79, **H:** 4.13, **N:** 8.20, **S:** 6.11; LCMS (ES-API) m/z: 537 $[M+H+Na]^+$.

4-((2-((5-(propylthio)-2,3-dihydro-1H-benzimidazol-2-yl)carbamoyl) hydrazinylidene)methyl)phenyl 4-methylbenzenesulfonate (3k) White solid; yield: 79%; m.p. 228–230 °C; FTIR υ_{max} (cm^{-1}): 3365, 3236 (N-H), 1699, 1626 (C=O & C=N), 1367&1174 (S=O); ^{1}H-NMR (300 MHz), (DMSO-d_6/TMS) δ ppm: 0.95 (t, 3H, $J = 7.2$ Hz, propyl C**H$_3$**); 1.48–1.60 (m, 2H, propyl C**H$_2$**); 2.43 (s, 3H, Ar-C**H$_3$**); 2.86 (t, 2H, $J = 7.2$ Hz, propyl C**H$_2$**); 7.02–7.97 (m, 12H, Ar- **H**&C**H**=N); 10.53 (s, 1H, N**H**CONHN=); 11.28 (s, 1H, benzimidazole N**H**); 11.94 (s, 1H, NHCONH**N**=); ^{13}C-NMR (150 MHz), (DMSO-d_6/TMS) δ ppm: 13.5 (propyl **C**H$_3$), 21.6 (Ar- **C**H$_3$), 22.5 (propyl **C**H$_2$), 37.2 (propyl **C**H$_2$), 122.7, 128.7, 129.2, 130.7, 131.7, 133.9, 141.5, 146.3 (**C**H=N), 150.0 (**C**-OSO$_2$), 159.1 (**C**=N, benzimidazole); Anal. calcd. for $C_{25}H_{25}N_5O_4S_2$: 57.34, **H:** 4.81, **N:** 13.37, **S:** 12.25. Found: **C:** 57.84, **H:** 5.03, **N:** 13.22, **S:** 12.69; LCMS (ES-API) m/z: 525 $[M+2H]^+$.

4-((2-((4-bromophenyl)sulfonyl)hydrazinylidene)methyl) phenyl 4-methylbenzenesulfonate (3l) Dark yellow solid; yield: 73%; m.p. 127–129 °C; FTIR υ_{max} (cm^{-1}): 3234 (N-H), 1599 (C=N), 1346&1177 (S=O); ^{1}H-NMR (300 MHz), (DMSO-d_6/TMS) δ ppm: 2.42 (s, 3H, C**H$_3$**), 7.47–7.85 (m, 12H, Ar-**H**), 7.90 (s, 1H, C**H**=N), 11.72 (s, 1H, CON**H**-N=); ^{13}C-NMR (150 MHz), (DMSO-d_6/TMS) δ ppm: 21.6 (Ar-**C**H$_3$), 128.0, 123.1, 123.5, 128.2, 128.7, 128.9, 129.6, 130.8, 131.6, 131.9, 132.8, 133.1, 138.5, 146.4, 146.6 (**C**H=N), 150.4 (**C**-OSO$_2$); Anal. calcd. for $C_{20}H_{17}BrN_2O_5S_2.1/2H_2O$: **C:** 46.34, **H:** 3.50, **N:** 5.40, **S:** 12.37. Found: **C:** 46.75, **H:** 3.95, **N:** 5.33, **S:** 12.77; LCMS (ES-API) m/z: 546 $[M+K]^+$.

4-((2-((4-chlorophenyl)sulfonyl)hydrazinylidene)methyl) phenyl 4-methylbenzenesulfonate (3m) Dark yellow solid; yield: 73%; m.p. 127–129 °C; FTIR υ_{max} (cm^{-1}): 3223 (N-H), 1599 (C=N), 1346&1161 (S=O); ^{1}H-NMR (300 MHz), (DMSO-d_6/TMS) δ ppm: 2.41 (s, 3H, C**H$_3$**), 7.47–7.91 (m, 12H, Ar-**H**), 8.66 (s, 1H, C**H**=N), 11.74 (s, 1H, CON**H**-N=); ^{13}C-NMR (150 MHz), (DMSO-d_6/TMS) δ ppm: 21.6 (Ar-**C**H$_3$), 123.0, 123.1, 127.9, 128.1, 128.7, 129.6, 129.9, 130.5, 130.7, 131.6, 133.1, 133.2, 138.1, 138.3, 138.5, 146.4, 146.5, 146.6 (**C**H=N), 150.4 (**C**-OSO$_2$); Anal. calcd. for $C_{20}H_{17}ClN_2O_5S_2$. $1/2C_2H_5OH$: **C:** 51.69, **H:** 4.13, **N:** 5.74, **S:** 13.14. Found: **C:** 51.02, **H:** 4.54, **N:** 5.79, **S:** 13.29; LCMS (ES-API) m/z: 464 $[M+2H]^+$.

4-((2-((4-nitrophenyl)sulfonyl)hydrazinylidene)methyl)phenyl 4-methylbenzenesulfonate (3n) White cream solid; yield: 86%; m.p. 153–154 °C; FTIR υ_{max} (cm^{-1}): 3185 (N-H), 1599 (C=N), 1348&1174 (S=O); ^{1}H-NMR (300 MHz), (DMSO-d_6/TMS) δ ppm: 2.42 (s, 3H, C**H$_3$**), 7.58–8.45 (m, 13H, Ar-H&C**H**=N), 11.98 (s, 1H, CON**H**-N=);^{13}C-NMR (75 MHz), (DMSO-d_6/TMS) δ ppm: 21.6 (Ar-**C**H$_3$), 123.0, 125.1, 123.6, 129.0, 129.2, 130.7, 131.6, 132.9, 144.6, 146.4, 147.2 (**C**H=N), 150.4 (**C**-NO$_2$), 150.5 (**C**-OSO$_2$); Anal. calcd. for $C_{20}H_{17}N_3O_7S_2.H_2O$: **C:** 48.67, **H:** 3.88, **N:** 8.51, **S:** 12.99. Found: **C:** 48.82, **H:** 3.81, **N:** 8.06, **S:** 13.08; LCMS (ES-API) m/z: 476 $[M+H]^+$, 497 $[M+Na]^+$.

2-methoxy-4-((2-(2-(6-methoxynapthalen-2-yl)propanoyl) hydrazinylidene)methyl)phenyl 4-methylbenzenesulfonate (4a) Off-white solid; yield: 90%; m.p. 164–165 °C; FTIR υ_{max} (cm^{-1}): 3176 (N-H), 1660 (C=O), 1604 (C=N), 1373&1169 (S=O); ^{1}H-NMR (300 MHz), (DMSO-d_6/TMS) δ ppm: 1.42–1.49 (m, 3H, CH-C**H$_3$**); 2.43 (s, 3H, Ar-C**H$_3$**); 3.51 (s, 3H, ArOC**H$_3$**); 3.57–4.76 (m, 4H, OC**H$_3$** & C**H**-CH$_3$); 7.25–7.79 (m, 13H, Ar-**H**); 8.15 (7.81*, s, 1H, C**H**=N); 11.65 (11.39*, s, 1H, CON**H**); ^{13}C-NMR (75 MHz), (DMSO-d_6/TMS) δ ppm: 18.9&19.2 (CH-**C**H$_3$), 21.6 (Ar-**C**H$_3$), 44.3 (**C**H-CH$_3$), 55.6 (O-**C**H$_3$), 56.0&56.1 (ArO**C**H$_3$), 106.1, 110.6, 119.0, 119.1, 120.0, 120.6, 124.2, 125.9, 126.7, 127.3, 128.7, 128.8, 128.9, 129.3, 129.5, 130.2, 130.4, 132.4, 132.4, 133.5, 133.7, 134.9, 136.3, 137.0, 137.8, 138.7, 139.0, 141.5, 145.9 (**C**-OSO$_2$), 146.0&146.1 (**C**H=N), 151.9 (**C**-OCH$_3$), 157.4&157.5 (**C**-OCH$_3$), 170.4&175.5 (**C**=O); Anal. calcd. for $C_{29}H_{28}N_2O_6S.1/2H_2O$: **C:** 64.31, **H:** 5.40, **N:** 5.17, **S:** 5.92. Found: **C:** 64.33, **H:** 5.62, **N:** 4.96, **S:** 6.10; LCMS (ES-API) m/z: 555 $[M+Na]^+$.

2-methoxy-4-((2-(2′,4′-difluoro-4-hydroxy-[1,1′-biphenyl]-3-carbonyl)hydrazinylidene)methyl)phenyl 4-methylbenzenesulfonate (4b) White solid; yield: 72%; m.p. 221–222 °C; FTIR υ_{max} (cm^{-1}): 3244 (N-H), 1643 (C=O), 1606 (C=N), 1354&1169 (S=O); ^{1}H-NMR (300 MHz), (DMSO-d_6/TMS) δ ppm: 2.43 (s, 3H, Ar-C**H$_3$**); 3.56 (s, 3H, ArOC**H$_3$**); 7.29–8.00 (m, 13H, Ar-**H**); 8.41 (s, 1H, C**H**=N); 11.94 (s, 2H, CON**H**&Ar-O**H**; ^{13}C-NMR (75 MHz), (DMSO-d_6/TMS) δ ppm: 21.6 (Ar-**C**H$_3$), 56.1 (O-**C**H$_3$), 110.8, 117.0, 118.0, 121.0, 124.4, 125.5, 128.7, 129.5, 130.3, 132.4, 134.7, 139.3, 146.2 (**C**-OSO$_2$), 148.0 (**C**H=N), 157.6&161.0 (**C**-F, $J = 253$ Hz), 158.8 (**C**-OH), 160.2&163.5 (**C**-F, $J = 243$ Hz). 164.7 (**C**=O) Anal. calcd. for $C_{28}H_{22}F_2N_2O_6S$: **C:** 60.86, **H:** 4.01, **N:** 5.07, **S:** 5.80. Found: **C:** 60.59, **H:** 3.85, **N:** 5.09, **S:** 5.61; LCMS (ES-API) m/z: 574.9 $[M+Na]^+$.

2-methoxy-4-((2-(2-(2-fluoro-[1,1′-biphenyl]-4-yl)propanoyl) hydrazinylidene)methyl)phenyl 4-methylbenzenesulfonate (4c) White solid; yield: 86%; m.p. 150–151 °C; FTIR υ_{max} (cm^{-1}): 3232 (N-H), 1651 (C=O), 1599 (C=N), 1373&1170 (S=O); ^{1}H-NMR (300 MHz), (DMSO-d_6/TMS) δ ppm: 1.45 (1.40*, d, 3H, $J = 6.9$ Hz, CH-C**H$_3$**); 2.42 (2.38*, s, 3H, Ar-C**H$_3$**); 3.57 (3.52*, s, 3H, ArOC**H$_3$**); 4.71 (3.77*, q, 1H, $J = 6.9$ Hz, C**H**-CH$_3$); 7.37–7.71 (m, 15H, Ar-**H**); 8.17 (7.86*, s, 1H, C**H**=N); 11.68 (11.48*, s, 1H, CO-**NH**); ^{13}C-NMR (75 MHz), (DMSO-d_6/TMS) δ ppm: 18.6&19.0 (CH-**C**H$_3$), 21.5&21.6 (Ar-**C**H$_3$), 43.9 (**C**H-CH$_3$), 56.0 (Ar-O**C**H$_3$), 110.5, 110.7, 115.5, 115.8, 120.2, 120.6, 124.2, 128.2, 128.7, 129.0, 129.0, 129.1, 130.2, 131.1, 132.4, 132.4, 134.9, 135.3, 138.8, 139.0, 142.0, 146.0 (ArO**C**H$_3$), 146.1 (**C**H=N), 152.0 (**C**-OSO$_2$), 157.6&160.9 (**C**-F, $J =$ 252 Hz), 169.7&174.9 (**C**ONH); Anal. calcd.for $C_{30}H_{27}FN_2O_5S$: **C:** 65.92, **H:** 4.98, **N:** 5.12, **S:** 5.87. Found: **C:** 65.23, **H:** 4.68, **N:** 5.07, **S:** 5.56; LCMS (ES-API) m/z: 571 $[M+H+Na]^+$.

2-methoxy-4-((2-(2-(1-methyl-5-(4-methylbenzoyl)-1*H*-pyrrol-2-yl)acetyl) hydrazinylidene)methyl)phenyl 4-methylbenzenesulfonate (4d) White solid; yield: 83%; m.p. 215–216 °C; FTIR υ_{max} (cm^{-1}): 3190 (N-H), 1662 (C=O), 1620 (C=N), 1365&1170 (S=O); ^{1}H-NMR (300 MHz), (DMSO-d_6/TMS) δ ppm: 2.38 (s, 3H, ArC**H$_3$**); 2.42 (s, 3H, ArC**H$_3$**); 3.55 (s, 3H, ArOC**H$_3$**); 3.86 (s, 3H, N-C**H$_3$**), 4.18 (s, 2H, C**H$_2$**CO); 6.12 (d, 1H, $J =$ 3.9 Hz, C**H$_2$**, pyrrole); 6.58 (d, 1H, $J = 3.9$ Hz, C=O, pyrrole); 7.16–7.72 (m, 11H, Ar-**H**); 8.17 (7.97*, s, 1H, -C**H**=N); 11.66 (s, 1H, -CON**H**); ^{13}C-NMR (75 MHz), (DMSO-d_6/TMS) δ ppm: 21.5 (Ar-**C**H$_3$), 21.6 (Ar-**C**H$_3$), 31.2 (N-**C**H$_3$), 33.4 (**C**H$_2$CO), 56.1 (Ar-O**C**H$_3$), 110.0, 111.2, 120.0, 122.2, 124.2, 124.3, 128.7, 129.1, 129.4, 130.3, 130.6, 132.4, 132.4, 134.8, 137.3, 137.5, 137.7, 138.9, 139.1, 141.9, 142.5 (**C**-OCH$_3$), 146.1 (**C**H=N), 152.0 (**C**-OSO$_2$), 170.9 (**C**ONH), 184.7 (**C**=O); Anal. calcd. for $C_{30}H_{29}N_3O_6S$: **C:** 64.39, **H:** 5.22, **N:** 7.51, **S:** 5.73. Found: **C:** 64.34, **H:** 5.21, **N:** 7.52, **S:** 5.55; LCMS (ES-API) m/z: 582 $[M+Na]^+$.

4-((2-(2-(4-isobutylphenyl)propanoyl)hydrazinylidene) methyl)-2-methoxyphenyl 4-methylbenzenesulfonate (4e) White solid; yield: 76%; m.p. 125–127 °C; FTIR υ_{max} (cm^{-1}): 3230 (N-H), 1668 (C=O), 1597 (C=N), 1375&1172 (S=O); ^{1}H-NMR (300 MHz), (DMSO-d_6/TMS) δ ppm: 0.80–0.86 (m, 6H, -CH(C**H$_3$**)$_2$); 1.36 (q, 3H, $J = 7.2$ Hz, -CHC**H$_3$**); 1.72–1.84 (m, 1H, -C**H**(CH$_3$)$_2$); 2.36–2.43 (m, 5H, ArC**H$_3$**&C**H$_2$**CH(CH$_3$)$_2$); 3.57 (3.52*, s, 3H, Ar-OC**H$_3$**); 4.57 (3.65*, q, 1H, $J = 6.9$ Hz, C**H**CH$_3$); 7.04–7.72 (m, 11H, Ar-**H**); 8.14 (7.82*, s, 1H, -C**H**=N); 11.58 (11.34*, s, 1H, -CON**H**); ^{13}C-NMR (75 MHz), (DMSO-d_6/TMS) δ ppm: 18.8&19.2 (CH**C**H$_3$), 21.6 (Ar-**C**H$_3$), 22.6 (CH(**C**H$_3$)$_2$), 30.0&30.0 (**C**H(CH$_3$)$_2$), 44.0 (**C**H$_2$CH(CH$_3$)$_2$), 44.6 (**C**HCH$_3$), 56.0 (Ar-O**C**H$_3$), 110.6, 120.6,. 124.2, 127.4, 127.6, 128.7, 129.3, 130.2, 132.4, 132.5, 135.0, 138.7, 139.0, 139.1, 139.6, 139.8, 140.0, 141.4, 145.8 (C-O**C**H$_3$), 146.0&146.1 (**C**H=N), 151.9 (**C**-OSO$_2$), 170.4& 175.6 (**C**=O); Anal. calcd. for $C_{28}H_{32}N_2O_5S.1/3\ H_2O$: **C:** 65.35, **H:** 6.40, **N:** 5.44, **S:** 6.03. Found: **C:** 65.31, **H:** 6.06, **N:** 5.45, **S:** 6.11; LCMS (ES-API) m/z :509 $[M+H]^+$, 531 $[M+Na]^+$.

4-((2-(2-(1,8-diethyl-1,3,4,9-tetrahydropyrano[3,4-b]indol-1-yl)acetyl) hydrazinylidene)methyl)-2-methoxyphenyl 4-methylbenzenesulfonate (4f) Off-white solid; yield: 78%; m.p. 175–176 °C; FTIR υ_{max} (cm^{-1}): 3342 (O-H), 3223 (N-H), 1645 (C=O); 1599 (C=N); 1369&1175

(S=O); ^{1}H-NMR (300 MHz), (DMSO-d_6/TMS) δ ppm: 0.66 (0.57*, t, 3H, $J = 7.2$ Hz, -CH_2-C**H$_3$**); 1.25 (t, 3H, $J =$ 7.2 Hz, -CH_2-C**H$_3$**); 2.02–2.15 (m, 2H, C**H$_2$**-CH_3); 2.42 (s, 3H, Ar-C**H$_3$**); 2.63–2.69 (m, 2H, -C**H$_2$**-CH_3); 2.79–3.01 (m, 4H, -C**H$_2$**CONH & -C**H$_2$**); 3.48–4.03 (m, 5H, -C**H$_2$** & -OC**H**$_3$); 6.87–7.71 (m, 10H, Ar-**H**); 8.17 (7.93*, s, 1H, N=C**H**); 10.51 (s, 1H, indole N-**H**); 11.43 (11.25*, s, 1H, CO-N**H**); ^{13}C-NMR (75 MHz), (DMSO-d_6/TMS) δ ppm: 8.3 (pyran CH_2**C**H_3), 14.9 (indole CH_2**C**H_3), 21.6 (Ar**C**H_3), 24.2 (pyran -**C**H_2CH_2O-), 22.3 (indole **C**H_2CH_3), 31.2 (pyran **C**H_2CH_3), 43.6 (**C**H_2CO), 55.9&56.0 (ArO**C**H_3), 60.5&60.7 (pyran -CH2**C**H2O-), 76.2&76.5 (-CH_2O**C**H-), 107.5, 107.7, 115.8, 119.1, 12.9, 126.5, 127.0, 128.6, 128.7, 128.9, 130.7, 131.7, 134.0, 134.9, 136.7, 137.0, 146.4 (**C**H=N), 150.0& 150.2 (**C**-OSO_2), 166.1&171.9 (**C**=O); Anal. calcd. for $C_{32}H_{35}N_3O_6S.1/2H_2O$: **C:** 64.20, **H:** 5.91, **N:** 7.05, **S:** 5.39. Found: **C:** 64.76, **H:** 6.06, **N:** 7.02, **S:** 5.36; LCMS (ES-API) m/z: 582 $[M+Na]^+$.

4-((2-(6-(2-(3-methoxy-4-(tosyloxy)benzylidene)hydrazine-1-carbonyl)picolinoyl) hydrazinylidene)methyl)-2-methoxyphenyl 4-methylbenzenesulfonate (4g) White solid; yield: 88%; m.p. 263–264 °C; FTIR υ_{max} (cm^{-1}): 3574 (O-H), 3379, 3244 (N-H), 1668, 1583 (C=O & C=N), 1356&1165 (S=O); ^{1}H-NMR (300 MHz), (DMSO-d_6/TMS) δ ppm: 2.44 (s, 6H, C**H$_3$**), 3.61 (s, 6H, ArOC**H$_3$**), 7.23–7.76 (m, 14H, Ar-**H**), 8.27–8.39 (m, 3H, pyridine-**H**), 8.75 (s, 2H, C**H**=N), 12.39 (s, 2H, CON**H**-N=); ^{13}C-NMR (150 MHz), (DMSO-d_6/TMS) δ ppm: 21.6 (2Ar-**C**H_3), 56.1 (2ArO**C**H_3), 110.9, 121.0, 124.4, 126.1, 128.7, 130.3, 132.5, 134.8, 139.4, 140.5, 146.2 (pyridine 2**C**-N), 148.6 (2**C**-OCH_3), 149.3 (2**C**H=N), 152.1 (2**C**-OSO_2), 160.0 (2**C**=O); Anal. calcd. for $C_{37}H_{33}N_5O_{10}S_2.4H_2O$: **C:** 52.66, **H:** 4.90, **N:**8.30, **S:** 7.60. Found: **C:** 52.98, **H:** 5.04, **N:** 8.54, **S:** 7.91; LCMS (ES-API) m/z: 794 $[M+Na]^+$.

4-((2-(2-(2-((2,6-dichlorophenyl)amino)phenyl)acetyl)hydrazinylidene)methyl)-2-methoxyphenyl 4-methylbenzenesulfonate (4h) White solid; yield: 83%; m.p. 224–225 °C; FTIR υ_{max} (cm^{-1}): 3329 (N-H), 1660 (C=O), 1600 (C=N), 1369&1182 (S=O.); ^{1}H-NMR (300 MHz), (DMSO-d_6/TMS) δ ppm: 2.43 (s, 3H, C**H$_3$**), 3.54 (s, 3H, OC**H$_3$**), 4.13 (3.71*, s, 2H, C**H$_2$**CO), 6.27–8.19 (m, 16H, Ar-**H**& N**H**& C**H**=N), 11.89 (11.74*, s, 1H, CO-N**H**); ^{13}C-NMR (150 MHz), (DMSO-d_6/TMS) δ ppm: 21.6&21.6 (Ar-**C**H_3), 35.8&36.0 (**C**H_2CO), 56.0 (Ar- OC**H$_3$**), 111.1, 111.3, 116.1, 120.0, 120.7, 121.0, 121.3, 124.3, 124.4, 125.1, 125.7, 126.0, 127.8, 127.9, 128.6, 129.7, 130.0, 130.9, 131.6, 132.5, 134.7, 137.4, 138.9, 139.2, 143.1, 143.3, 143.5&146.1 (**C**H=N), 146.8, 152.0 (**C**-OSO_2), 168.3, 173.6 (**C**=O). Anal. calcd. for $C_{29}H_{25}Cl_2N_3O_5S$: **C:** 58.20, **H:** 4.21, **N:** 7.02, **S:** 5.36. Found: **C:** 58.20, **H:** 4.59, **N:** 6.96, **S:** 5.39.

4-((2-(4-(thiophene-2-carboxamido)benzoyl)hydrazinylidene)methyl)-2-methoxyphenyl 4-methylbenzenesulfonate (4i) White solid; yield: 88%; m.p. 242–243 °C; FTIR υ_{max} (cm^{-1}): 3315, 3234 (N-H), 1703, 1645 (C=O), 1608 (C=N), 1377&1174 (S=O); ^{1}H-NMR (300 MHz), (DMSO-d_6/TMS) δ ppm: 2.43 (s, 3H, Ar-C**H$_3$**), 3.57 (s, 3H, Ar-OC**H$_3$**), 7.26–8.09 (m, 14H, Ar-**H**), 8.41 (s, 1H, C**H**=N), 10.49 (s, 1H, thiophene-CON**H**), 11.89 (s, 1H, CON**H**); ^{13}C-NMR (75 MHz), (DMSO-d_6/TMS) δ ppm: 21.6 (Ar-**C**H_3), 56.0 (ArO**C**H_3),110.6, 120.7, 124.3, 128.6, 129.0, 130.3, 132.9, 135.1, 139.0, 140.0, 142.5, 146.1, 146.6 (**C**H=N), 152.0 (**C**-OSO_2), 160.6, 163.0 (**C**=O); Anal. calcd. for $C_{27}H_{23}N_3O_6S_2$: **C:** 59.00, **H:** 4.22, **N:** 7.65, **S:** 11.67. Found: **C:** 58.80, **H:** 4.26, **N:** 7.68, **S:** 11.94; LCMS (Q-TOF) m/z: 550 $[M+H]^+$.

4-((2-(4-benzamidobenzoyl)hydrazinylidene)methyl)-2-methoxyphenyl 4-methylbenzenesulfonate (4j) White solid; yield: 79%; m.p. 276–278 °C; FTIR υ_{max} (cm^{-1}): 3336, 3273 (N-H), 1647 (C=O), 1585 (C=N), 1352&1178 (S=O); ^{1}H-NMR (300 MHz), (DMSO-d_6/TMS) δ ppm: 2.43 (s, 3H, C**H$_3$**), 3.57 (s, 3H, Ar-OC**H$_3$**), 7.18–8.00 (m, 16H, Ar-H), 8.42 (s, 1H, C**H**=N), 10.53&11.88 (s, 2H, CON**H**); ^{13}C-NMR (150 MHz), (DMSO-d_6/TMS) δ ppm: 21.6 (Ar-**C**H_3), 56.1 (Ar-O**C**H_3), 110.7, 120.0, 120.7, 124.3, 128.2, 128.4, 128.7, 128.9, 130.3, 132.3, 132.4, 135.1, 135.1, 139.1, 142.9, 146.1 (**C**H=N), 146.7 (**C**-OCH_3), 152.0 (**C**-OSO_2), 163.1 (**C**=O), 166.3 (**C**=O); Anal. calcd. for $C_{29}H_{25}N_3O_6S$. H_2O: **C:** 62.02, **H:** 4.85, **N:** 7.48, **S:** 5.71. Found: **C:** 62.70, **H:** 4.67, **N:** 7.77, **S:** 5.97; LCMS (ES-API) m/z: 567 $[M+H+Na]^+$.

4-((2-((5-(propylthio)-2,3-dihydro-1*H*-benzo[d]imidazol-2-yl) carbamoyl) hydrazinylidene)methyl)-2-methoxyphenyl 4-methylbenzenesulfonate (4k) White solid; yield: 72%; m.p. 182–184 °C; FTIR υ_{max} (cm^{-1}): 3398, 3252 (N-H); 1703 (C=O), 1627 (C=N); 1354&1172 (S=O); ^{1}H-NMR (300 MHz), (DMSO-d_6/TMS) δ ppm: 0.95 (t, 3H, $J =$ 7.2 Hz, C**H$_3$**), 1.48–1.61 (m, 2H, C**H$_2$**), 2.43 (s, 3H, Ar-C**H$_3$**), 2.86 (t, 2H, $J = 7.2$ Hz, C**H$_2$**), 3.60 (s, 3H, OC**H$_3$**), 7.09–7.75 (m, 10H, Ar-**H**); 7.96 (s, 1H, C**H**=N), 10.52 (s, 1H, N**H**CONHN=), 11.29 (s, 1H, benzimidazole N**H**), 11.96 (s, 1H, NHCON**H**N=); ^{13}C-NMR (75 MHz), (DMSO-d_6/TMS) δ ppm: 13.5 (propyl -CH_2-CH_2-**C**H_3), 21.5 (Ar-**C**H_3), 22.5 (propyl -**C**H_2-**C**H_2-CH_3), 37.1 (propyl -**C**H_2-CH_2-CH_3), 56.2 (O**C**H_3),120.6, 123.9, 124.4, 128.7, 130.2, 132.4, 134.8, 138.7, 141.9, 146.0 (**C**H=N), 151.9 (**C**-OSO_2); Anal. calcd. for $C_{26}H_{27}N_5O_5S_2$: **C:** 56.40, **H:** 4.92, **N:** 12.65, **S:** 11.58. Found: **C:** 56.47, **H:** 5.01, **N:** 12.44, **S:** 11.76; LCMS (Q-TOF) m/z: 554 $[M+H]^+$.

4-((2-((4-bromophenyl)sulfonyl)hydrazinylidene)methyl)-2-methoxyphenyl 4-methylbenzenesulfonate (4l) Yellow solid; yield: 82%; m.p. 147–148 °C; FTIR υ_{max} (cm^{-1}):

3234 (N-H), 1599 (C=N), 1346&1151 (SO_2); ^{1}H-NMR (300 MHz), (DMSO-d_6/TMS) δ ppm: 2.42 (s, 3H, C**H$_3$**), 3.52 (s, 3H, Ar-OC**H$_3$**), 7.09–7.87 (m, 13H, Ar-H&C**H**=N), 11.73 (s, 1H, CON**H**-N=); ^{13}C-NMR (150 MHz), (DMSO-d_6/TMS) δ ppm: 21.6 (Ar-**C**H$_3$), 56.1 (Ar-O**C**H$_3$), 111.5, 119.7, 127.6, 128.2, 128.7, 129.7, 130.3, 130.4, 132.4, 132.8, 134.1, 138.5, 139.1, 146.1 (**C**H=N), 146.8 (**C**-OCH$_3$), 151.9 (**C**-OSO$_2$); Anal. calcd. for $C_{21}H_{19}BrN_2O_6S_2$: **C:** 46.76, **H:** 3.55, **N:** 5.19, **S:** 11.89. Found: **C:** 46.81, **H:** 3.45, **N:** 4.65, **S:** 11.31; LCMS (Q-TOF) m/z: 540 $[M+2H]^+$.

4-((2-((4-chlorophenyl)sulfonyl)hydrazinylidene)methyl)-2-methoxyphenyl 4-methyl benzene sulfonate (4m) Dark yellow solid; yield: 87%; m.p. 136–137 °C; FTIR υ_{max} (cm^{-1}): 3252 (N-H); 1583 (C=N); 1357&1172 (S=O); ^{1}H-NMR (300 MHz), (DMSO-d_6/TMS) δ ppm: 2.42 (s, 3H, C**H$_3$**), 3.51 (s, 3H, Ar-OC**H$_3$**), 7.10–7.89 (m, 12H, Ar-H&C**H**=N), 11.74 (s, 1H, CON**H**-N=); ^{13}C-NMR (75 MHz), (DMSO-d_6/TMS) δ ppm: 21.6 (Ar-**C**H$_3$); 56.0 (O**C**H$_3$), 111.5, 119.6, 124.3, 128.1, 128.7, 129.6, 129.9, 130.3, 132.3, 134.1, 138.5, 139.0, 146.5,146.8 (**C**H=N), 151.9 (**C**-OSO$_2$); Anal. calcd. for $C_{21}H_{19}ClN_2O_6S_2$: **C:** 50.96, **H:** 3.84, **N:** 5.74, **S:** 11.91. Found: **C:** 49.82, **H:** 3.87, **N:** 5.66, **S:** 12.96. LCMS (ES-API) m/z: 495 $[M+H]^+$.

4-((2-((4-nitrophenyl)sulfonyl)hydrazinylidene)methyl)-2-methoxyphenyl 4-methylbenzenesulfonate (4n) Yellow solid; yield: 90%; m.p. 104–105 °C; FTIR υ_{max} (cm^{-1}): 3230 (N-H), 1668 (C=N), 1346&1170 (S=O); ^{1}H-NMR (300 MHz), (DMSO-d_6/TMS) δ ppm: 2.42 (s, 3H, C**H$_3$**), 3.53 (s, 3H, Ar-OC**H$_3$**), 7.09–8.46 (m, 12H, Ar-H&C**H**=N), 11.99 (s, 1H, CON**H**-N=); ^{13}C-NMR (75 MHz), (DMSO-d_6/TMS) δ ppm: 21.6 (Ar-**C**H$_3$), 56.1 (Ar-O**C**H$_3$), 111.6, 119.8, 124.3, 125.1, 128.6, 129.3, 130.3, 132.4, 133.9, 139.2, 144.5, 146.1 (**C**-OCH$_3$), 147.4 (**C**H=N), 150.4 (**C**-NO$_2$), 152.0 (**C**-OSO$_2$); Anal. calcd. for $C_{21}H_{19}N_3O_8S_2.2H_2O$: **C:** 46.57, **H:** 3.43, **N:** 7.76, **S:** 11.84. Found: **C:** 46.90, **H:** 3.44, **N:** 7.56, **S:** 11.86; LCMS (ES-API) m/z: 528 $[M+Na]^+$.

Biological assay

Cell culture studies

Human lung adenocarcinoma cell line (A549), human breast cancer cell line (MCF-7), human colorectal adenocarcinoma cell line (HT-29), human prostate cell line (PC-3), human liver cancer cell line (Hep3B), human cervical cancer cell (HeLa) and nontumorigenic mouse embryonic fibroblast cell line (NIH 3T3) were purchased from American Type Culture Collection (ATCC) (Manassas, VA, USA). Cells were cultured in Dulbecco's modified eagle medium (DMEM) (Gibco, Rockville, MD, USA) containing 10% fetal bovine serum (FBS) (Gibco, Rockville, MD, USA) and maintained in a 37 °C, 5% CO_2 incubator. Cell passage was conducted at 80–90% confluence.

Cell viability assay

Cell viability was determined by the MTT assay as described previously [29]. Briefly, cells were seeded into 96-well plates at 10.000 cells and incubated overnight. Then, the cells were treated with compounds (at 10 µM) for 48 h. After the incubation period, MTT was added into each well to for the 4 h at a final concentration of 0.5 mg/mL. The culture medium was then removed and 100 µL of the SDS buffer was added to solubilize the purple formazan product. The colour product of the reaction was quantified by measuring absorbance at a 570 and 630 nm were measured by a microplate reader (Biotek, Winooski, VT).

Apoptosis studies

Annexin V binding, caspase-3 and caspase-9 activation measurement and detection of the loss of mitochondrial membrane potential procedures have been previously described in detail [30]. Following the treatment, cells were centrifuged and resuspended in cold PBS afterwards. After incubation of cells with annexin V for 15 min at room temperature in the dark at room temperature, then centrifuged at $1000 \times g$ for 5 min at room temperature. Fluorescence intensity was measured using a fluorescence Elisa reader. The activity of proteases caspases was detected using the caspase colorimetric assay kits (Millipore, Billerica, MA, USA). To detect caspase activity, cells were lysed in ice-cold lysis buffer. Samples were centrifuged at $10{,}000 \times g$ for 1 min. Subsequently, the supernatants were collected and the protein concentrations were measured by the Bradford method. Samples containing 200 µg protein were incubated with 5 µl of the 4 mM p-nitroanilide (pNA) substrates, (DEVD-pNA for caspase-3 and LEHD-pNA for caspase-9) for 2 h at 37 °C. pNA cleavage was observed spectrophotometrically using an EPOCH microplate reader (Biotek, Winooski, VT, USA) at 405 nm. Data are expressed as fold increase in caspase activity.

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Compliance with ethical standards

Conflict of interest The authors declare no competing interests.

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