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EFFICIENT AND CONVENIENT ROUTE TO THE SYNTHESIS OF SOME NOVEL SULFONATE ESTER-BASED HETEROCYCLES AS ANTITUMOR AGENTS

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Abstract – In the present investigation, simple and straightforward methodology for the preparation of novel thiazolidinone, thiazole, pyridinone, chromene, pyrazole, benzimidazo[1,2-*a*]pyrimidine and thiazolo[3,2-*a*]pyrimidine derivatives bearing sulfonate ester moiety through the reaction of 4-formylphenyl benzenesulfonate (**1**) with some nitrogen nucleophiles such as hydrazine hydrate, thiosemicarbazide and 2-cyanoacetohydrazide is described. The antitumor activities were evaluated according to the protocol of the National Cancer Institute (NCI) *in vitro* disease-oriented human cells screening panel assay against two human tumor cell lines namely; breast cancer MCF-7 and prostate cancer PC3. The results revealed that compounds (**4**), (**7**), (**9**), (**13**) and (**16**) exhibited promising antitumor activity in the two cell lines assay compared with 5-fluorouracil as a reference drug.

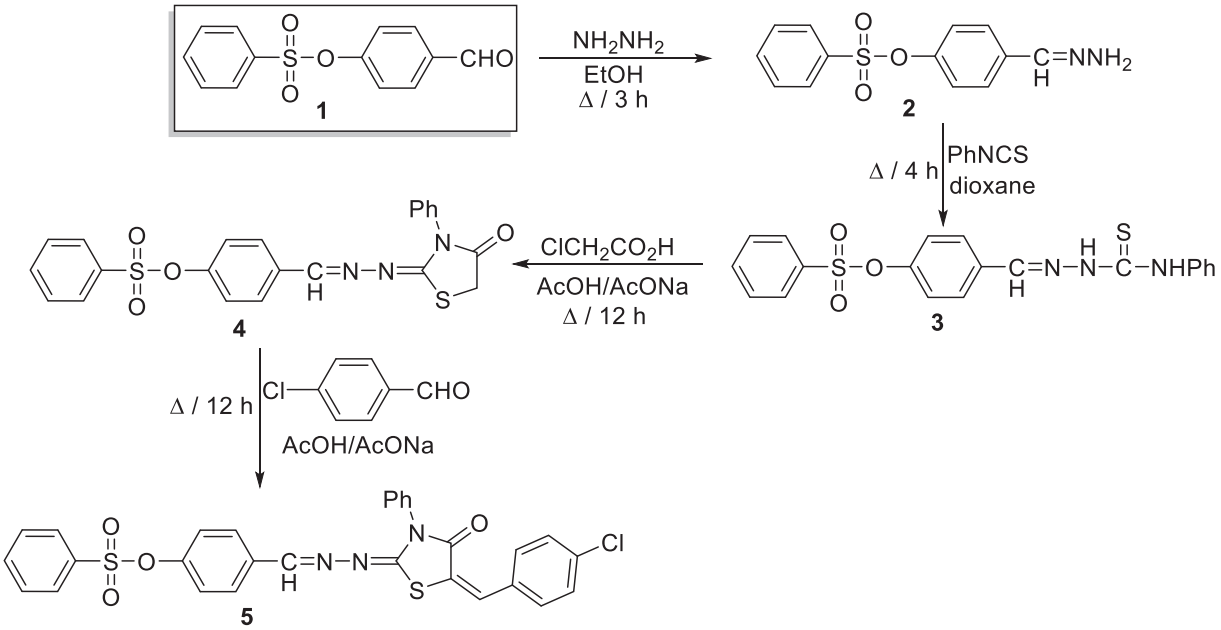
INTRODUCTION

The arylsulfonyloxy is a frequent partner in various heterocyclic systems owing to its widespread of physiological significances.[1-6] It was typically regarded as the important moiety in the synthesis of bioactive compounds which possess insecticidal activity,[7] reduction in liver cholesterol accumulation and plasma[8] and anti-thrombotic activity.[9] Additionally, more than 30 drugs bearing this functional fragment are in pharmaceutical utilities, such as anticonvulsants and antibacterial agents,[10] anticancer and anti-human immunodeficiency virus 1.[11,12] We have been concerned in a program going for the synthesis of novel heterocycles bearing aryl sulfonate ester moiety to be used as potential antimicrobial agents.[13-15]

In the light of this program and because of increased interest in aryl sulfonate moiety, some new thiazolidinone, thiazole, pyridinone, chromene, pyrazole, benzimidazo[1,2-*a*]pyrimidine and thiazolo[3,2-*a*]pyrimidine derivatives bearing sulfonate ester moiety which have not been stated previously were required for the study of biological activity. 4-Formylphenyl benzenesulfonate (**1**) serve as good intermediate to fulfill this target *via* its reactions with some nitrogen nucleophiles.

RESULTS AND DISCUSSION

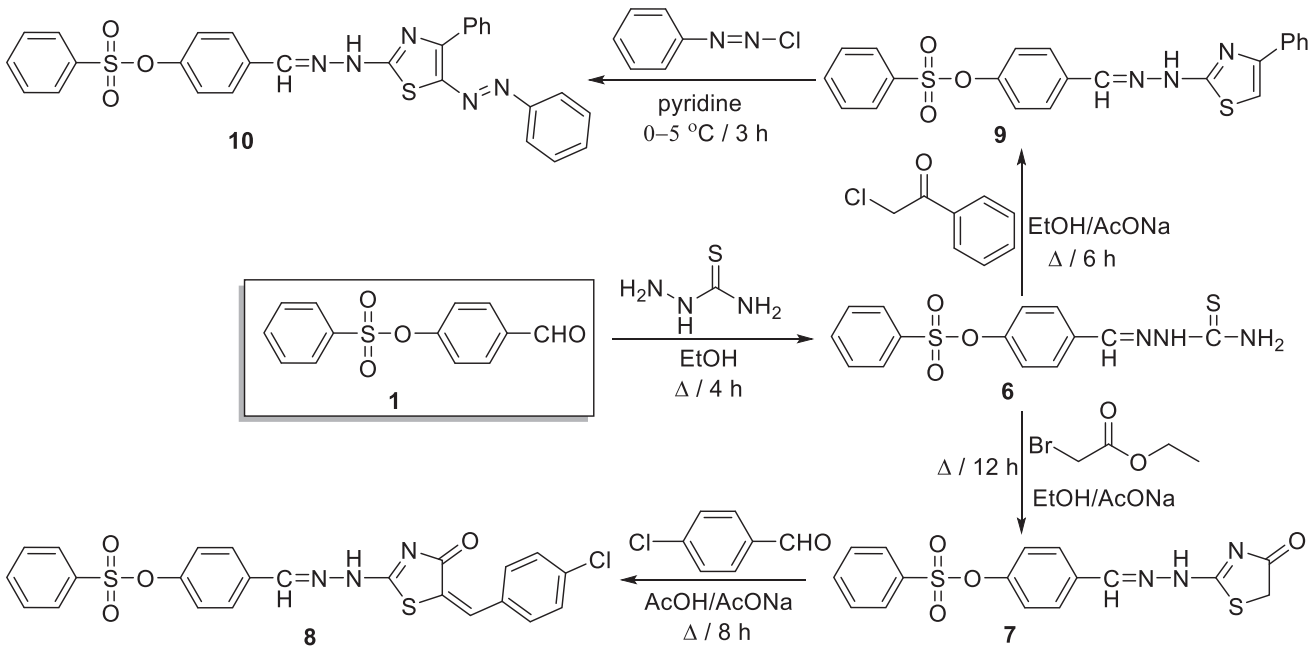
4-Formylphenyl benzenesulfonate (**1**) was prepared in an excellent yield by the reaction of benzenesulfonyl chloride with *p*-hydroxybenzaldehyde in methylene chloride and a catalytic amount of triethylamine at 0-5 ºC according to the method prescribed in literatures.[16,17] 4-(Hydrazonomethyl)phenyl benzenesulfonate (**2**) could be readily obtained through the reaction of 4-formylphenyl benzenesulfonate (**1**) with hydrazine hydrate in ethanol. The absorption band of aldehyde group was lacked in IR spectrum and showed bands at 3427-3347 cm^{-1} corresponding to NH_2 function as well as at 1627 cm^{-1} specific for C=N group. ^1H NMR spectrum lacked signal assignable to aldehyde proton and showed two singlet signals at δ 6.91 and 8.65 ppm for NH_2 and CH protons. Treatment of Schiff's base (**2**) with phenyl isothiocyanate in dioxane under reflux, led to the formation of 4-((2-(phenylcarbamothioyl)hydrazono)methyl)phenyl benzenesulfonate (**3**).



Scheme 1

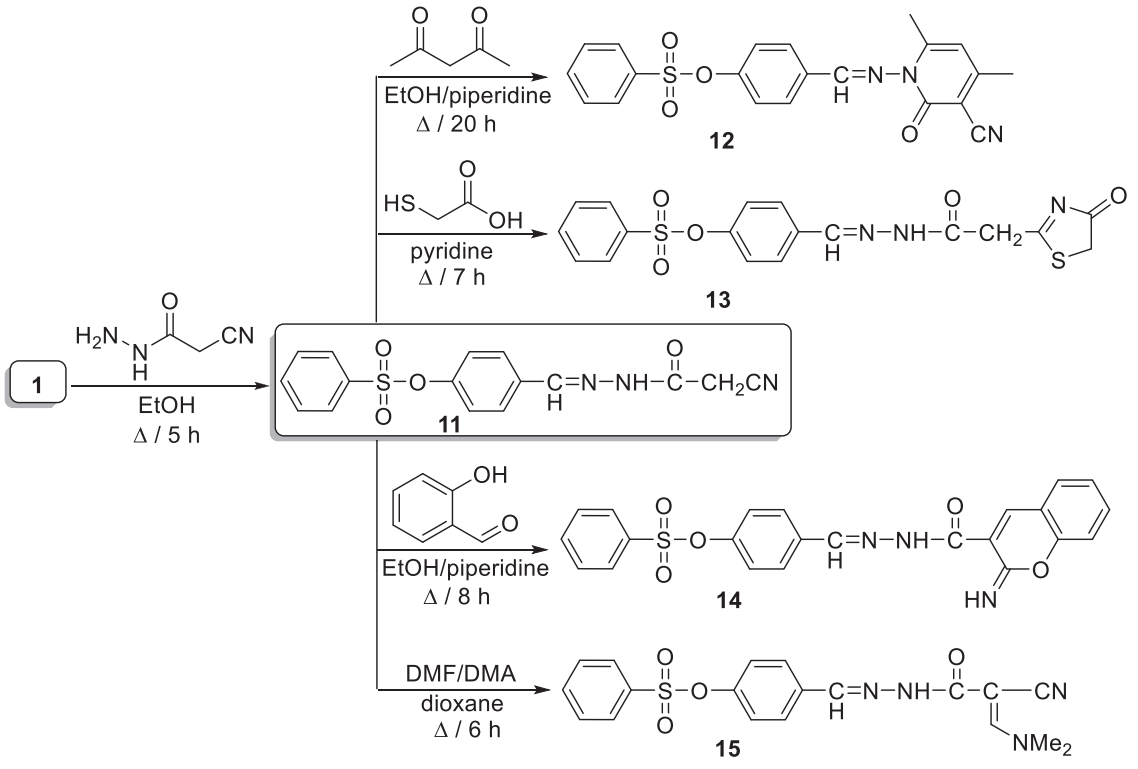
Heating the latter with chloroacetic acid in acetic acid and sodium acetate gave 4-(((4-oxo-3-phenylthiazolidin-2-ylidene)hydrazono)methyl)phenyl benzenesulfonate (**4**). The product of

4 was based on IR spectrum which revealed band at 1708 cm^{-1} specific for cyclic C=O function. Also, ^1H NMR spectrum displayed at δ 4.11 ppm singlet signal for CH_2 protons. Condensation of thiazolidinone (**4**) with 4-chlorobenzaldehyde according to Knoevenagel reaction in acetic acid and fused sodium acetate gave the arylidene analogue (**5**) (Scheme 1). Shifting to Scheme 2, treatment of aldehyde (**1**) with thiosemicarbazide in ethanol yielded the corresponding thiosemicarbazone (**6**). Cyclocondensation of **6** with ethyl bromoacetate in ethanol containing fused sodium acetate gave 4-((2-(4-oxo-4,5-dihydrothiazol-2-yl)hydrazono)methyl)phenyl benzenesulfonate (**7**) based on IR spectrum which appeared absorption band at 1710 cm^{-1} assignable to C=O group. In ^1H NMR spectrum, new singlet signal of CH_2S protons at δ 3.89 ppm was observed and a singlet signal of NH_2 protons at δ 8.04 ppm was disappeared. Condensation of **7** with 4-chlorobenzaldehyde in acetic acid containing fused sodium acetate afforded the arylidene derivative (**8**). When we use phenacyl chloride instead of ethyl bromoacetate afforded the respective 4-((2-(4-phenylthiazol-2-yl)hydrazono)methyl)phenyl benzenesulfonate (**9**). The most wonderful chemical property of thiazole (**9**) is the hydrogen atom at C-5 which undergoes electrophilic substitution reactions.[18] So, 4-((2-(4-phenyl-5-(phenyldiazenyl)thiazol-2-yl)hydrazono)methyl)phenyl benzenesulfonate (**10**) was prepared as highly colored solid compound through coupling of diazonium salt of aniline with thiazole (**9**) in pyridine solution at 0-5 ºC. The appearance of azo group band at 1553 cm^{-1} in IR spectra and the disappearance of signal due to proton at C-5 of thiazole ring in ^1H NMR spectra of the reaction product supported structure (**10**).



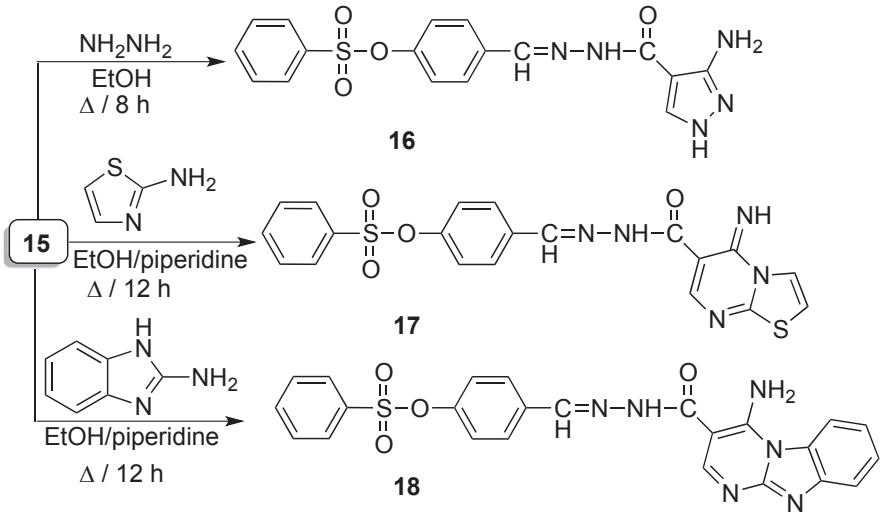
Scheme 2

To additionally investigate the synthetic potential of aldehyde (**1**), we also examined its reactivity with 2-cyanoacetohydrazide in refluxing ethanol to afford 4-((2-(2-cyanoacetyl)hydrazono)methyl)phenyl benzenesulfonate (**11**) (Scheme 3), based on the disappearance of absorption band specific for an aldehyde group in IR spectrum and appearance of CN stretching band at 2265 cm^{-1} and amidic C=O stretching band at 1686 cm^{-1}. Also, the proposed structure was supported using ^{1}H NMR spectrum through three singlet signals at δ 8.14, 4.19 and 11.82 ppm due to CH, CH_2 and NH protons, respectively. The latter product (**11**) was serve as good intermediate for the formation of several polysubstituted heterocycles *via* its reactivity towards a variety of chemical reagents. Treatment of cyanoacetylhydrazono derivative (**11**) with acetylacetone in refluxing ethanolic piperidine solution, afforded 4-(((3-cyano-4,6-dimethyl-2-oxopyridin-1(2*H*)-yl)imino)methyl)phenyl benzenesulfonate (**12**). The presence of two sharp singlet signals at δ 2.25 and 2.35 ppm in ^{1}H NMR spectrum assignable to two Me group supported structure (**12**). Moreover, thiazolidin-4-one (**13**) could be achieved through refluxing of **11** with thioglycolic acid in pyridine. Furthermore, cyclocondensation of **11** with salicylaldehyde in ethanolic solution containing piperidine as base catalyst gave chromene (**14**) as main product. ^{1}H NMR spectrum of (**14**) appeared a singlet signal at δ 8.45 ppm for the chromene H-4. Treatment of **11** with dimethylformamide dimethyl acetal in dioxane gave the enaminonitrile analogue (**15**). New three sharp singlet signals at δ 8.00, 3.29 and 3.22 ppm assignable to methine and *N,N*-dimethylamino protons were observed in ^{1}H NMR spectrum of **15**.



Scheme 3

Enaminonitriles are important precursors for the preparation of heterocyclic compounds possessing diverse biological activities.[19-21] The behavior of the enaminonitrile (**15**) towards some *N*-nucleophiles in this protocol to attain polyfunctionally substituted heterocyclic systems containing a sulfonate moiety of prospect biological interest has been discussed (Scheme 4). 3-Aminopyrazole (**16**) was prepared as a main product through heating the enaminonitrile (**15**) with hydrazine hydrate in ethanol. The pyrazole H-5 appeared as a singlet at δ 7.79 ppm in ^{1}H NMR spectrum. Reaction of enaminonitrile (**15**) with both 2-aminothiazole and 2-aminobenzimidazole in ethanol containing piperidine as base catalyst under reflux, gave the thiazolo[3,2-*a*]pyrimidine (**17**) and benzimidazo[1,2-*a*]pyrimidine (**18**) derivatives, respectively (see experimental).



Scheme 4

PHARMACOLOGY

Cytotoxicity and antitumor evaluation

The synthesized compounds were selected to be evaluated for their *in-vitro* anticancer effect *via* the standard MTT method,[22-25] against two human tumor cell lines namely; breast cancer MCF-7 and prostate cancer PC3. The cell lines were obtained from ATCC *via* the Holding company for biological products and vaccines (VACSERA), Cairo, Egypt. 5-Fluorouracil (5-Fu) was used as a standard anticancer drug for comparison. The results in Table 1 revealed that five of the tested compounds namely; (**4**), (**7**), (**9**), (**13**) and (**16**) exhibited variable degrees of inhibitory activity toward the two tested human tumor cell lines. As for activity against breast cancer MCF-7, the highest cytotoxic activity was displayed by compounds (**9**) and (**16**) which showed the percentage viability IC_{50} at 8.9 and 9.1 μg/mL, respectively. Remarkable inhibitory activity was also demonstrated by compounds (**4**), (**7**) and (**13**). Further interpretation of the results revealed that the other compounds showed weak-moderate anticancer activity

against the same cell line with percentage inhibition range of 31.4-100 μg/mL. On the other hand, the prostate cancer PC3 cell line showed highest sensitivity towards the tested compound (**18**), as its growth was found to be initiated by this compound. However, the best activity was demonstrated by compound (**9**) which have IC_{50} at 8.9 μg/mL. Compounds (**4**), (**7**), (**13**) and (**16**) exhibited remarkable inhibitory activity. The remaining compounds exhibited less inhibitory activity with percentage inhibition range of 34.8-100 μg/mL. Compounds (**10**) and (**12**) showed no cytotoxicity against two cell lines. It is worth mentioning that cyclization of **3** and **6** to thiazolidinone derivatives (**4**) and (**7**) enhanced the antitumor activity against cell lines while the introducing of arylidene moiety to a thiazolidinone ring in position 5 reduced the activity.

Table 1. Cytotoxicity (IC_{50}) of tested compounds on two different cell lines

Compounds	IC_{50} (μg/mL)	
	MCF-7	PC3
5-Fu	3.6	5.1
1	52.1	56.9
2	42.4	66.7
3	49.2	34.8
4	13.6	14.5
5	48.9	49.4
6	31.4	38.8
7	11.5	10.9
8	35.2	42.9
9	8.9	8.9
10	100	>100
11	46.8	55.4
12	100	>100
13	18.5	10.1
14	68.6	48.1
15	37.1	53.7
16	9.1	10.9
17	32.1	58.9
18	74.6	79.2

Also, cyclization of thiosemicarbazone (**6**) to thiazole (**9**) enhanced the antitumor activity while the introducing of phenyldiazenyl moiety to a thiazole ring in position 5 diminished the activity.

On the other hand, transformation of cyanoacetylhydrazono (**11**) to thiazolidin-4-one (**13**) increased the cytotoxic activity while conversion of **11** to pyridinone (**12**), unfortunately produced weak cytotoxic activity.

To conclude, we have discussed a simple and facile straightforward methodology for the synthesis of some new thiazolidinone, thiazole, pyridinone, chromene, pyrazole, benzimidazo[1,2-*a*]pyrimidine and thiazolo[3,2-*a*]pyrimidine derivatives bearing sulfonate ester moiety through the reaction of 4-formylphenyl benzenesulfonate (**1**) with some nitrogen nucleophiles with the hope of discovering new structure leads serving as anticancer agents. The results revealed that compounds (**4**), (**7**), (**9**), (**13**) and (**16**) exhibited promising activity.

EXPERIMENTAL

All melting points were determined on an electrothermal Gallenkamp apparatus (Germany) and are uncorrected. The IR spectra were measured on a Mattson 5000 FTIR Spectrometer (USA) in potassium bromide discs. NMR spectra were measured in DMSO-d_6 as solvent at 300 MHz (^{1}H NMR) and at 75 MHz (^{13}C NMR) on a Varian MercuryVX300 NMR spectrometer using TMS as internal standard and chemical shifts are expressed as δ_{ppm}. The mass spectra were recorded on Finnegan MAT 212 instrument (USA) and the ionizing voltage was 70 ev. Elemental analyses were carried out by the Micro-analytical unit of Faculty of Science, Cairo University, Egypt. All reactions were followed by TLC (silica gel, aluminum sheets 60 F254, Merck).

General procedure for the reaction of 4-formylphenyl benzenesulfonate (1) with some nitrogen nucleophiles. To a solution of **1** (2.62 g, 0.01 mol) in 25 mL EtOH, hydrazine hydrate, thiosemicarbazide or 2-cyanoacetohydrazide (0.01 mol) was added. The reaction mixture was refluxed for 3-5 h then cooled. The precipitated product was filtered and recrystallized from EtOH.

4-(Hydrazonomethyl)phenyl benzenesulfonate (2): yield 2.34 g (85%); yellow crystals; mp 190-192 ºC; IR (KBr) ν_{max}/cm^{-1}: 3427-3347 (NH_2), 2922 (C-H, stretching), 1627 (C=N), 1596 (C=C), 1346 (SO_3); ^{1}H NMR (DMSO-d_6): δ_{ppm}: 8.65 (s, 1H, CH), 7.91-7.16 (m, 9H, Ar-H), 6.91 (s, 2H, NH_2); ^{13}C NMR (DMSO-d_6): δ_{ppm}: 140 (CH), 116, 128, 130, 132, 137, 150 (Ar-C); MS: (*m/z*, %): 276 (M^+, 23.36), 135 (100.00), 107 (5.43), 77 (86.12), 65 (14.22), 51 (33.16). Anal. Calcd for $C_{13}H_{12}N_2O_3S$ (276.31): C 56.51; H 4.38; N 10.14%. Found: C 56.49; H 4.36; N 10.11%.

4-((2-Carbamothioylhydrazono)methyl)phenyl benzenesulfonate (6): yield 2.38 g (71%); yellow crystals; mp 205-207 ºC; IR (KBr) ν_{max}/cm^{-1}: 3426 (NH), 3349-3259 (NH_2), 3022 (C-H, stretching), 1622 (C=N), 1597 (C=C), 1374 (SO_3), 1273 (C=S); ^{1}H NMR (DMSO-d_6): δ_{ppm}: 11.48 (s, 1H, NH), 8.23 (s, 1H,

CH), 8.04 (s, 2H, NH_2), 8.00-7.02 (m, 9H, Ar-H); ^{13}C NMR (DMSO-*d*$_6$): δ_{ppm}: 143 (CH), 180 (C=S), 116, 128, 130, 132, 137, 150 (Ar-C); MS: (*m/z*, %): 335 (M^+, 11.44), 255 (11.32), 140 (24.19), 100 (5.00), 77 (100.00), 64 (12.56), 51 (31.24), 43 (30.97). Anal. Calcd for $C_{14}H_{13}N_3O_3S_2$ (335.40): C 50.14; H 3.91; N 12.53%. Found: C 50.11; H 3.90; N 12.50%.

4-((2-(2-Cyanoacetyl)hydrazono)methyl)phenyl benzenesulfonate (11): yield 2.23 g (65%); orange crystals; mp 241-243 ºC; IR (KBr) ν_{max}/cm^{-1}: 3218 (NH), 2921 (C-H, stretching), 2265 (CN), 1686 (C=O), 1618 (C=N), 1373 (SO_3); ^{1}H NMR (DMSO-*d*$_6$): δ_{ppm}: 11.82 (s, 1H, NH), 8.14 (s, 1H, CH), 7.96-7.07 (m, 9H, Ar-H), 4.19 (s, 2H, CH_2); ^{13}C NMR (DMSO-*d*$_6$): δ_{ppm}: 29 (CH_2), 129 (CN), 145 (CH), 173 (C=O), 116, 128, 130, 132, 137, 150 (Ar-C); MS: (*m/z*, %): 343 (M^+, 16.11), 283 (5.14), 239 (4.78), 167 (4.43), 140 (20.06), 97 (17.26), 77 (100.00), 57 (53.07), 43 (60.45). Anal. Calcd for $C_{16}H_{13}N_3O_4S$ (343.36): C 55.97; H 3.82; N 12.24%. Found: C 55.95; H 3.80; N 12.22%.

Synthesis of 4-((2-(phenylcarbamothioyl)hydrazono)methyl)phenyl benzenesulfonate (3). Phenyl isothiocyanate (1.35 g, 0.01 mol) was added to a boiling solution of compound **2** (2.76 g, 0.01 mol) in dioxane (30 mL). Reaction mixture was refluxed for 4 h and stand overnight at room temperature. The solid obtained was filtered and recrystallized from dioxane; yield 2.51 g (61%); yellow crystals; mp 155-157 ºC; IR (KBr) ν_{max}/cm^{-1}: 3220, 3190 (2 NH), 2922 (C-H, stretching), 1628 (C=N), 1592 (C=C), 1345 (SO_3), 1296 (C=S); ^{1}H NMR (DMSO-*d*$_6$): δ_{ppm}: 11.87 (s, 1H, NH), 10.13 (s, 1H, NH), 8.65 (s, 1H, CH), 7.95-7.16 (m, 14H, Ar-H); MS: (*m/z*, %): 411 (M^+, 11.40), 374 (5.35), 284 (4.19), 266 (6.06), 197 (35.12), 176 (12.34), 140 (16.84), 123 (16.18), 91 (19.49), 77 (100.00), 55 (58.41). Anal. Calcd for $C_{20}H_{17}N_3O_3S_2$ (411.49): C 58.38; H 4.16; N 10.21%. Found: C 58.35; H 4.15; N 10.20%.

Synthesis of 4-(((4-oxo-3-phenylthiazolidin-2-ylidene)hydrazono)methyl)phenyl benzenesulfonate (4). A mixture of **3** (4.11 g, 0.01 mol), chloroacetic acid (1 g, 0.01 mol) and anhydrous sodium acetate (0.82 g, 0.01 mol) in glacial acetic acid (30 mL) was refluxed for 12 h. The reaction mixture was poured into ice-cold water, the solid was filtered off and recrystallized from MeOH; yield 2.48 g (55%); yellow crystals; mp 188-190 ºC; IR (KBr) ν_{max}/cm^{-1}: 2922 (C-H, stretching), 1708 (C=O), 1628 (C=N), 1592 (C=C), 1376 (SO_3); ^{1}H NMR (DMSO-*d*$_6$): δ_{ppm}: 8.65 (s, 1H, CH), 7.95-7.06 (m, 14H, Ar-H), 4.11 (s, 2H, CH_2); ^{13}C NMR (DMSO-*d*$_6$): δ_{ppm}: 29 (CH_2), 145 (CH), 156 (thiazolidine-C2), 175 (C=O), 116, 126, 128, 130, 132, 137, 150 (Ar-C); MS: (*m/z*, %): 451 (M^+, 11.04), 317 (16.92), 286 (10.16), 259 (60.00), 140 (42.54), 76 (100.00), 57 (13.51), 42 (47.07). Anal. Calcd for $C_{22}H_{17}N_3O_4S_2$ (451.52): C 58.52; H 3.80; N 9.31%. Found: C 58.50; H 3.78; N 9.28%.

Synthesis of 4-(((5-(4-chlorobenzylidene)-4-oxo-3-phenylthiazolidin-2-ylidene)hydrazono)methyl)-phenyl benzenesulfonate (5). 4-Chlorobenzaldehyde (0.14 g, 0.001 mol) was added to a solution of **4** (0.45 g, 0.001 mol) in glacial acetic acid (20 mL) containing anhydrous sodium acetate (0.12 g, 0.0015 mol). The mixture was refluxed for 12 h, and cooled to room temperature. The separated solid product

was filtered off and recrystallized from EtOH; yield 0.69 g (83%); yellow crystals; mp 208-210 ºC; IR (KBr) ν_{max}/cm^{-1}: 2922 (C-H, stretching), 1700 (C=O), 1634 (C=N), 1600 (C=C), 1376 (SO_3); ^{1}H NMR (DMSO-d_6): δ_{ppm}: 8.65 (s, 1H, CH), 7.95-7.06 (m, 18H, Ar-H), 7.81 (s, 1H, CH); MS: (*m/z*, %): 575 (M^++1, 9.18), 330 (13.02), 288 (75.42), 242 (34.13), 212 (18.95), 165 (33.55), 97 (12.10), 77 (100.00), 58 (23.12). Anal. Calcd for $C_{29}H_{20}ClN_3O_4S_2$ (574.07): C 60.68; H 3.51; N 7.32%. Found: C 60.66; H 3.50; N 7.30%.

Reaction of thiosemicarbazone (6) with ethyl bromoacetate and phenacyl chloride. A mixture of **6** (1.67 g, 0.005 mol), ethyl bromoacetate or phenacyl chloride (0.005 mol) and anhydrous sodium acetate (1.64 g, 0.02 mol) was refluxed for 6-12 h in 30 mL EtOH. The product obtained after cooling was filtered and recrystallized from EtOH.

4-((2-(4-Oxo-4,5-dihydrothiazol-2-yl)hydrazono)methyl)phenyl benzenesulfonate (7): yield 1.27 g (68%); yellow crystals; mp 218-220 ºC; IR (KBr) ν_{max}/cm^{-1}: 3279 (NH), 2921 (C-H, stretching), 1710 (C=O), 1632 (C=N), 1592 (C=C), 1373 (SO_3); ^{1}H NMR (DMSO-d_6): δ_{ppm}: 11.89 (s, 1H, NH), 8.37 (s, 1H, CH), 7.89-7.11 (m, 9H, Ar-H), 3.89 (s, 2H, CH_2); MS: (*m/z*, %): 375 (M^+, 12.11), 233 (16.22), 133 (11.19), 105 (19.43), 77 (100.00), 51 (31.00), 43 (5.98). Anal. Calcd for $C_{16}H_{13}N_3O_4S_2$ (375.42): C 51.19; H 3.49; N 11.19%. Found: C 51.17; H 3.48; N 11.17%.

4-((2-(4-Phenylthiazol-2-yl)hydrazono)methyl)phenyl benzenesulfonate (9): yield 1.17 g (54%); yellow crystals; mp 233-235 ºC; IR (KBr) ν_{max}/cm^{-1}: 3307 (NH), 2920 (C-H, stretching), 1630 (C=N), 1601 (C=C), 1377 (SO_3); ^{1}H NMR (DMSO-d_6): δ_{ppm}: 12.25 (s, 1H, NH), 8.00 (s, 1H, CH), 7.97-7.02 (m, 15H, Ar-H); MS: (*m/z*, %): 435 (M^+, 11.21), 366 (14.72), 251 (3.80), 237 (15.12), 198 (10.06), 152 (14.99), 120 (73.43), 105 (52.23), 92 (31.09), 77 (64.54), 57 (84.09), 43 (100.00). Anal. Calcd. for $C_{22}H_{17}N_3O_3S_2$ (435.52): C 60.67; H 3.93; N 9.65%. Found: C 60.65; H 3.92; N 9.63%.

Synthesis of 4-((2-(5-(4-chlorobenzylidene)-4-oxo-4,5-dihydrothiazol-2-yl)hydrazono)methyl)phenyl benzenesulfonate (8). A mixture of **7** (0.37 g, 0.001 mol) and 4-chlorobenzaldehyde (0.14 g, 0.001 mol) in 20 mL glacial acetic acid containing anhydrous sodium acetate (0.33 g, 0.004 mol) was refluxed for 8 h. After cooling, the solid obtained was filtered and recrystallized from DMF; yield 0.28 g (58%); orange crystals; mp 247-249 ºC; IR (KBr) ν_{max}/cm^{-1}: 3230 (NH), 2921 (C-H, stretching), 1701 (C=O), 1630 (C=N), 1598 (C=C), 1370 (SO_3); ^{1}H NMR (DMSO-d_6): δ_{ppm}: 9.97 (s, 1H, NH), 8.34 (s, 1H, CH), 8.01 (s, 1H, CH), 7.95-6.86 (m, 13H, Ar-H); MS: (*m/z*, %): 499 (M^++1, 8.14), 378 (18.43), 288 (17.71), 254 (11.16), 188 (34.49), 133 (26.37), 86 (49.06), 77 (100.00). Anal. Calcd. for $C_{23}H_{16}ClN_3O_4S_2$ (497.97): C 55.48; H 3.24; N 8.44%. Found: C 55.46; H 3.23; N 8.42%.

Synthesis of 4-((2-(4-phenyl-5-(phenyldiazenyl)thiazol-2-yl)hydrazono)methyl)phenyl benzenesulfonate (10). The diazonium salt solution of aniline [a solution of sodium nitrite (0.7 g in 10 mL H_2O) was gradually added to a well cooled solution of the aniline (0.01 mol) in conc. HCl (3.0 mL)]

was added with continuous stirring to a cold solution of the thiazole derivative **9** (4.35 g, 0.01 mol) in pyridine (30 mL). Reaction mixture was stand in the ice bath for 3 h and then filtered. The 5-arylazothiazole **9** thus obtained was recrystallized from EtOH; yield 3.23 g (60%); brown crystals; mp 250-252 ºC; IR (KBr) ν_{max}/cm^{-1}: 3315 (NH), 2920 (C-H, stretching), 1618 (C=N), 1598 (C=C), 1553 (N=N), 1371 (SO_3); ^{1}H NMR (DMSO-d_6): δ_{ppm}: 11.95 (s, 1H, NH), 8.03 (s, 1H, CH), 7.97-6.92 (m, 19H, Ar-H); ^{13}C NMR (DMSO-d_6): δ_{ppm}: 144 (CH), 170, 150, 130 (thiazole-C2, C4, C5), 116, 126, 128, 130, 132, 137, 150 (Ar-C); MS: (*m/z*, %): 539 (M^+, 11.44), 447 (3.27), 350 (3.08), 296 (7.66), 226 (10.37), 185 (12.84), 166 (20.62), 98 (14.22), 70 (100.00). Anal. Calcd for $C_{28}H_{21}N_5O_3S_2$ (539.63): C 62.32; H 3.92; N 12.98%. Found: C 62.30; H 3.91; N 12.96%.

Synthesis of 4-(((3-cyano-4,6-dimethyl-2-oxopyridin-1(2*H*)-yl)imino)methyl)phenyl benzenesulfonate (12). A mixture of **11** (0.69 g, 2 mmol) and acetylacetone (0.21 mL, 2 mmol) in EtOH (20 mL) containing a few drops of piperidine (3 drops) was refluxed for 20 h. The solid so obtained upon cooling was filtered off and recrystallized from EtOH; yield 0.52 g (64%); orange crystals; mp 291-293 ºC; IR (KBr) ν_{max}/cm^{-1}: 2923 (C-H, stretching), 2220 (CN), 1666 (C=O), 1618 (C=N), 1596 (C=C), 1373 (SO_3); ^{1}H NMR (DMSO-d_6): δ_{ppm}: 8.07 (s, 1H, CH), 7.98-7.10 (m, 9H, Ar-H), 6.27 (s, 1H, pyridine H-5), 2.35 (s, 3H, CH_3), 2.25 (s, 3H, CH_3); MS: (*m/z*, %): 407 (M^+, 10.16), 286 (8.00), 239 (14.61), 175 (8.08), 134 (12.34), 123 (33.28), 105 (14.19), 76 (100.00), 51 (28.38). Anal. Calcd for $C_{21}H_{17}N_3O_4S$ (407.44): C 61.91; H 4.21; N 10.31%. Found: C 61.90; H 4.20; N 10.28%.

Synthesis of 4-((2-(2-(4-oxo-4,5-dihydrothiazol-2-yl)acetyl)hydrazono)methyl)phenyl benzenesulfonate (13). A mixture of **11** (3.43 g, 0.01 mol) and thioglycolic acid (0.69 mL, 0.01 mol) in dry pyridine (20 mL) was heated under reflux for 7 h, allowed to cool, and poured into cold water (50 mL). The solid product obtained was collected and recrystallized from EtOH; yield 2.17 g (52%); orange crystals; mp 230-232 ºC; IR (KBr) ν_{max}/cm^{-1}: 3189 (NH), 2922 (C-H, stretching), 1693, 1670 (2 C=O), 1629 (C=N), 1596 (C=C), 1375 (SO_3); ^{1}H NMR (DMSO-d_6): δ_{ppm}: 11.80 (s, 1H, NH), 8.65 (s, 1H, CH), 7.90-7.07 (m, 9H, Ar-H), 4.22 (s, 2H, CH_2), 3.73 (s, 2H, CH_2); MS: (*m/z*, %): 417 (M^+, 12.08), 363 (5.56), 295 (11.43), 267 (19.18), 236 (13.04), 211 (5.06), 151 (5.22), 97 (17.49), 71 (100.00), 57 (86.20). Anal. Calcd for $C_{18}H_{15}N_3O_5S_2$ (417.45): C 51.79; H 3.62; N 10.07%. Found: C 51.77; H 3.60; N 10.00%.

Synthesis of 4-((2-(2-imino-2*H*-chromene-3-carbonyl)hydrazono)methyl)phenyl benzenesulfonate (14). To a solution of **11** (0.68 g, 2 mmol) in EtOH (20 mL) containing piperidine (0.5 mL), salicylaldehyde (0.3 g, 2 mmol) was added. The reaction mixture was refluxed for 8 h, then allowed to cool. The precipitate formed was recrystallized from EtOH; yield 0.46 g (52%); orange crystals; mp 220-222 ºC; IR (KBr) ν_{max}/cm^{-1}: 3410, 3270 (2 NH), 2922 (C-H, stretching), 1683 (C=O), 1629 (C=N), 1596 (C=C), 1375 (SO_3); ^{1}H NMR (DMSO-d_6): δ_{ppm}: 11.55 (s, 1H, NH), 9.31 (s, 1H, NH), 8.45 (s, 1H, chromene-H4), 8.08 (s, 1H, CH), 7.90-7.07 (m, 13H, Ar-H); MS: (*m/z*, %): 447 (M^+, 11.13), 355 (26.24),

284 (26.00), 209 (10.03), 192 (72.09), 110 (8.00), 86 (5.71), 71 (100.00). Anal. Calcd for $C_{23}H_{17}N_3O_5S$ (447.47): C 61.74; H 3.83; N 9.39%. Found: C 61.72; H 3.82; N 9.36%.

Synthesis of 4-((2-(2-cyano-3-(dimethylamino)acryloyl)hydrazono)methyl)phenyl benzenesulfonate (15). A mixture of **11** (0.34 g, 10 mmol) and dimethylformamide dimethyl acetal (1.2 g, 10 mmol) in dioxane (30 mL) was refluxed for 6 h. The solid precipitate that formed upon cooling was filtered, washed with petroleum ether (bp 40-60 ºC), and recrystallized from dioxane; yield 0.21 g (53%); yellow crystals; mp 240-242 ºC; IR (KBr) ν_{max}/cm^{-1}: 3425 (NH), 2922 (C-H, stretching), 2191 (CN), 1664 (C=O), 1605 (C=N), 1596 (C=C), 1372 (SO_3); ^{1}H NMR (DMSO-d_6): δ_{ppm}: 10.94 (s, 1H, NH), 8.65 (s, 1H, CH), 8.00 (s, 1H, CH), 7.88-7.06 (m, 9H, Ar-H), 3.29 (s, 3H, CH_3), 3.22 (s, 3H, CH_3); MS: (*m/z*, %): 398 (M^+, 10.50), 380 (4.07), 368 (9.18), 334 (15.77), 275 (11.26), 259 (12.61), 214 (5.73), 175 (6.66), 140 (22.04), 104 (16.20), 95 (10.01), 76 (100.00), 43 (45.75). Anal. Calcd for $C_{19}H_{18}N_4O_4S$ (398.44): C 57.28; H 4.55; N 14.06%. Found: C 57.26; H 4.53; N 14.03%.

Reaction of enaminonitrile (15) with nitrogen nucleophiles. A mixture of the enaminonitrile **15** (0.79 g, 2 mmol) and an equimolar amount of the nitrogen nucleophiles (2 mmol) in 30 mL EtOH containing few drops of piperidine (3 drops in case of 2-aminothiazole or 2-aminobenzimidazole) was refluxed for 8-12 h, then left to cool. The solid deposited was recrystallized from EtOH.

4-((2-(3-Amino-1*H*-pyrazole-4-carbonyl)hydrazono)methyl)phenyl benzenesulfonate (16): yield 0.61 g (79%); yellow crystals; mp 240-242 ºC; IR (KBr) ν_{max}/cm^{-1}: 3430-3360 (NH_2), 3260, 3145 (2 NH), 2923 (C-H, stretching), 1660 (C=O), 1629 (C=N), 1599 (C=C), 1375 (SO_3);^{1}H NMR (DMSO-d_6): δ_{ppm}: 11.88 (s, 1H, NH), 10.92 (s, 1H, NH), 8.65 (s, 1H, CH), 7.79-6.96 (m, 10H, Ar-H), 4.29 (s, 2H, NH_2); MS: (*m/z*, %): 385 (M^+, 13.09), 224 (9.17), 197 (16.00), 159 (14.34), 135 (10.00), 111 (27.23), 97 (51.05), 71 (100.00), 57 (83.37). Anal. Calcd for $C_{17}H_{15}N_5O_4S$ (385.40): C 52.98; H 3.92; N 18.17%. Found: C 52.96; H 3.90; N 18.15%.

4-((2-(5-Imino-5*H*-thiazolo[3,2-*a*]pyrimidine-6-carbonyl)hydrazono)methyl)phenyl benzenesulfonate (17): yield 0.43 g (48%); yellow crystals; mp 260-262 ºC; IR (KBr) ν_{max}/cm^{-1}: 3379, 3188 (2 NH), 2923 (C-H, stretching), 1660 (C=O), 1618 (C=N), 1604 (C=C), 1374 (SO_3); ^{1}H NMR (DMSO-d_6): δ_{ppm}: 11.98 (s, 1H, NH), 10.00 (s, 1H, NH), 8.51 (s, 1H, pyrimidine-H4), 8.45 (s, 1H, CH), 7.88-7.07 (m, 9H, Ar-H), 7.26, 7.64 (d, 2H, J = 4.5, thiazole-H4, H5); MS: (*m/z*, %): 453 (M^+, 8.32), 300 (12.00), 291 (52.05), 140 (5.23), 110 (12.63), 76 (100.00), 63 (14.19), 51 (23.51). Anal. Calcd for $C_{20}H_{15}N_5O_4S_2$ (453.49): C 52.97; H 3.33; N 15.44%. Found: C 52.95; H 3.32; N 15.42%.

4-((2-(4-Aminobenzo[4,5]imidazo[1,2-*a*]pyrimidine-3-carbonyl)hydrazono)methyl)phenyl benzenesulfonate (18): yield 0.47 g (48%); yellow crystals; mp 234-236 ºC; IR (KBr) ν_{max}/cm^{-1}: 3440-3362 (NH_2), 3242 (NH), 2922 (C-H, stretching), 1665 (C=O), 1619 (C=N), 1609 (C=C), 1374 (SO_3); ^{1}H NMR (DMSO-d_6): δ_{ppm}: 11.98 (s, 1H, NH), 8.81 (s, 1H, pyrimidine-H4), 8.63 (s, 1H, CH),

7.98-6.77 (m, 13H, Ar-H), 6.61 (s, 2H, NH_2); MS: (*m/z*, %): 486 (M^+, 8.41), 286 (4.47), 183 (4.09), 176 (100.00), 134 (46.34), 104 (12.42), 77 (38.00). Anal. Calcd for $C_{24}H_{18}N_6O_4S$ (486.51): C 59.25; H 3.73; N 17.27%. Found: C 59.24; H 3.72; N 17.25%.

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