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PII: S0040-4020(18)30210-2

DOI: 10.1016/j.tet.2018.02.052

Reference: TET 29323

To appear in: *Tetrahedron*

Received Date: 5 January 2018

Revised Date: 20 February 2018

Accepted Date: 22 February 2018

Please cite this article as: Mandal PS, Kumar AV, Three-component one-pot synthesis of *N*-arylsulfonyl-2-iminocoumarins, *Tetrahedron* (2018), doi: 10.1016/j.tet.2018.02.052.

Graphical Abstract

Three-Component One-Pot Synthesis of *N*-Arylsulfonyl-2-Iminocoumarins

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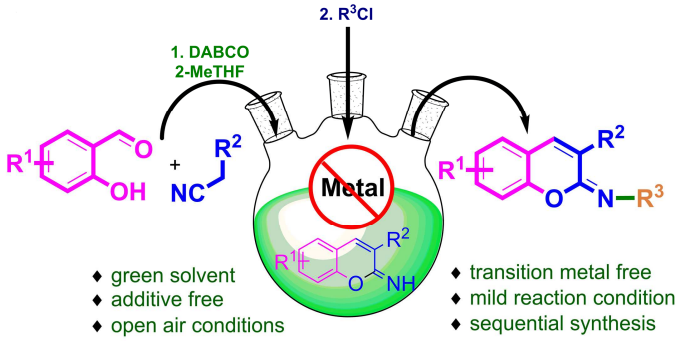

Tetrahedron
journal homepage: www.elsevier.com

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ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

Keywords:
Iminocoumarin
Coumarin
Catalyst-free
DABCO
2-MeTHF

ABSTRACT

A one-pot, synthesis of *N*-arylsulfonyl-2-iminocoumarins is developed at ambient temperature by the reaction of 2-hydroxybenzaldehydes, arylacetonitriles, and aryl sulfonyl chlorides using DABCO as a base in a bio-mass-derived green solvent 2-MethylTHF. A simple telescoped process in which 2*H*-chromen-2-imines are formed in situ by the condensation of 2-hydroxybenzaldehyde and arylacetonitriles. The formed imines are further reacted with arylsulfonyl chlorides in a one-pot approach to obtain the target compounds. This protocol provides access to 3-aryl-*N*-arylsulfonyl-2-iminocoumarins in a practical and environmentally benign way avoiding cumbersome steps of intermediate syntheses and purifications.

Introduction

Coumarin is an important building block that is found in various biologically active molecules and natural products which have diverse applications[1-3] in perfumery [4] and as dyes in laser technology [5] . They also show remarkable biological activities, such as antibacterial,[6] antifungal, [7] anti-HIV,[8] and anti-tumor. [9] Interestingly, iminocoumarin are also important scaffolds in biologically active compounds (Figure 1). Despite several methods for the synthesis of iminocoumarin derivatives, versatile and flexible methodologies to construct iminocoumarin are still desirable. This core is present in two bioactive compounds hyrtimomine A (1) and hyrtimomine B (2) which have been recently isolated from an Okinawan marine sponge *Hyrtios sp.*[10] (Figure 1).Similar to coumarins, iminocoumarins also show different biological activities such as antimalarial and anticancer (Figure 1),[11,12] antimicrobial,[13,14] anti-inflammatory,[15-17] mitogen-activated protein kinase inhibition (MK-2),[18] dynamins I and II GTPase,[19] HIV-1 integrase inhibition,[20] and cell imaging.[21-24] Additionally they are also useful as fluorescent dyes,[25] and sensors for thiols[26] and H_2S.[27]

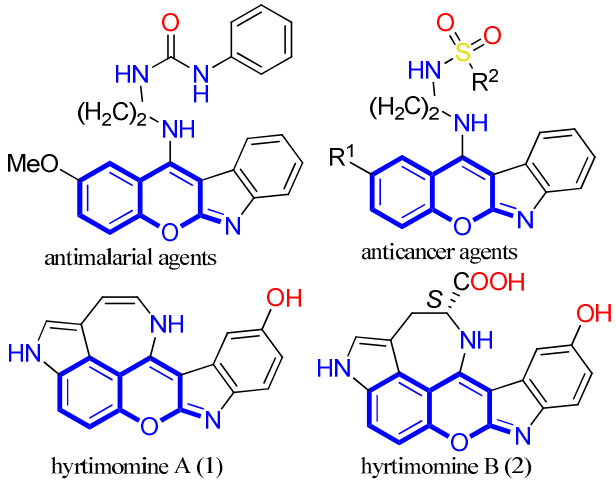


Figure 1 Representative molecules containing the iminocoumarin moiety

Till date, various methods have been reported in the literature for the synthesis of *N*-arylsulfonyl-2-iminocoumarins (a) CuI-catalyzed three-component reaction of an alkyne, an aryl sulfonyl azide and salicyldehyde,[28] or 2-ethynylphenol[29] (b) CuI-mediated three-component reaction of salicylaldehydes, ethynyl phenols, and an aryl sulfonyl azides[30] (c) Cu salt catalyzed reaction of *o*-hydroxybenzonitriles, terminal alkynes, and aryl sulfonyl azides[31](Figure 2). However, several limitations such as harsh reaction conditions along with transition metal catalysts, additive such as tetrabutylammonium iodide (TBAI), requisite of aryl sulfonyl azides which are potent explosives and expensive terminal alkynes hinder their wide usage. Moreover, the use of toxic halogenated solvents such as dichloromethane and chloroform increase the health and environmental risks, and limit the scalability options. The development of sustainable and safe methods for the synthesis of *N*-arylsulfonyl-2-iminocoumarins overcoming the aforementioned inadequacies is highly desirable. Over the recent years "Green Solvents" have received remarkable attention owing to the various advantages.[32-41] At present, the major concern is the toxicity of the existing solvent regime for organic reactions. Even though alternatives such as supercritical fluids, perfluorinated solvents, ionic liquids, etc. have been evaluated, concerns such as availability and biodegradability limit their utility. In this context, 2-Methyl-tetrahydrofuran (2-MeTHF), a renewable resources derived

environmentally benign solvent can be a promising alternative for conventional toxic solvents.[42] Therefore, keeping in mind these advantages, in continuation to our efforts to develop alternate methodologies for iminocoumarins synthesis,[43] we introduce a simple one-pot process wherein, 2-hydroxybenzaldehydes and arylacetonitriles and arylsulfonyl chlorides *via* an *in situ* reaction in presence of a base to directly afford *N*-arylsulfonyl-2-iminocoumarins precluding the need to isolate iminocoumarin.

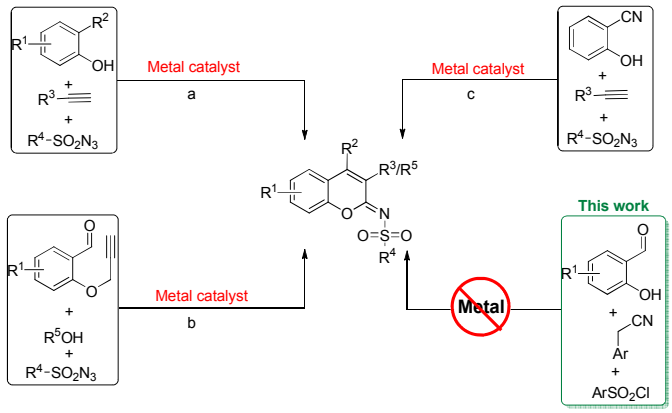
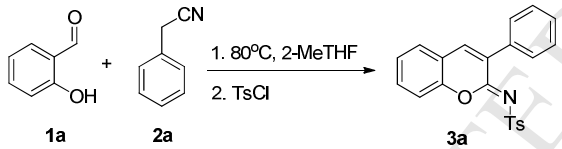


Figure 2. Comparison of previous and our approach

2. Result and discussion

To test the hypothesis, we began the investigation by treatment of 2-hydroxybenzaldehyde **1a** with phenylacetonitrile **2a** and Tosyl chloride (TsCl) in presence of IRA resin OH in toluene, which provided the expected **3a** in 21% yield (entry 1, Table 1).

Table 1. Optimization conditions of the reaction.[a]

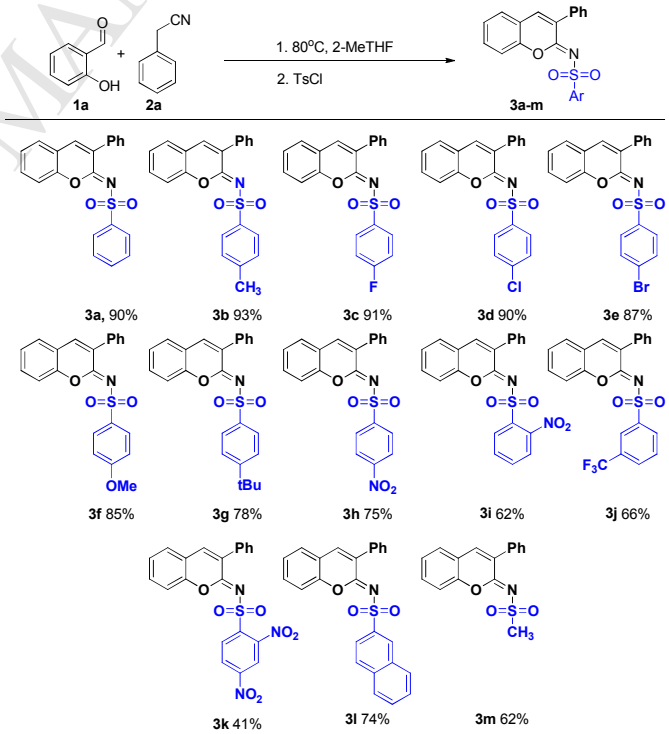


Entry	Base(equiv)	Solvent	Time (h)	Yield [%][b]
1	resin/1.0	toluene	12	21
2	resin/1.0	Cyclohexane	11	35
3	resin/1.0	2-MeTHF	9	42
4	resin/2.0	2-MeTHF	9	55
5	TEA/1.0	2-MeTHF	10	47
6	DMAP/1.0	2-MeTHF	10	68
7	DBU/1.0	2-MeTHF	10	54
8	K_2CO_3/1.0	2-MeTHF	10	51
9	Cs_2CO_3/1.0	2-MeTHF	10	62
10	DABCO /1.0	2-MeTHF	8	79
11	DABCO /0.5	2-MeTHF	8	42
12	DABCO /1.5	2-MeTHF	8	93
13	DABCO /2.0	2-MeTHF	8	85
14	DABCO /3.0	2-MeTHF	8	72
15	-	2-MeTHF	8	-

[a]Reaction condition: **1a** (0.81 mmol), **2a** (0.81 mmol), base (0.60 mmol), 2-MeTHF (5mL), reflux 80°C till aldehyde consumed, after which base (0.60 mmol) Tosyl chloride (TsCl, 1.21 mmol), was added at 0°C. [b]isolated yield.

The formation of **3a** was confirmed by Mass Spectrometry (MS) and NMR spectroscopy. Despite low conversion, this first result showed the feasibility of the envisioned strategy. Encouraged by this, we further examined the same reaction under various conditions to improve the product yield. The use of IRA resin in cyclohexane helped in improving the yield to 35% (entry 2, Table 1). The screening of various bases (resin, DABCO, TEA, DMAP, DBU, K_2CO_3 and Cs_2CO_3) amberlite ira-900 ion-exchange resin, 1,4-diazabicyclo[2.2.2]octane, trimethylamine, 4-dimethylaminopyridine, 1,8-Diazabi43cyclo (5.4.0)undec-7-ene, potassium carbonate, caesium carbonate and solvents such as cyclohexane, toluene and 2-MeTHF (2-Methyltetrahydrofuran). The reaction of **1a** with **2a** revealed that DABCO and 2-MeTHF is the best choice in affording the 79% yield of **3a** (entries 10, Table 1). Additional optimizations showed that the variation in the amount of DABCO employed has little influence on the outcome of the reaction (entries 11 to 14, Table 1). DABCO has afforded excellent yields of iminocoumarin in the first iteration when compared to other bases such as DBU, DMAP, etc. It might be because of the superior nucleophilicity of DABCO when compared to DBU and DMAP,[44] which helps in the activation of tosylchlorides, further making the imine attack more facile. Despite DABCO having lower basicity than DBU and DMAP, its nucleophilicity might be responsible for the tosyl chloride activation. The same was also observed in several other DABCO catalyzed reactions such as Baylis-Hilman and *N*-methylation of Indoles.[45]

Table 2. Scope of arylsulfonyl chlorides ($ArSO_2Cl$).[a,b]

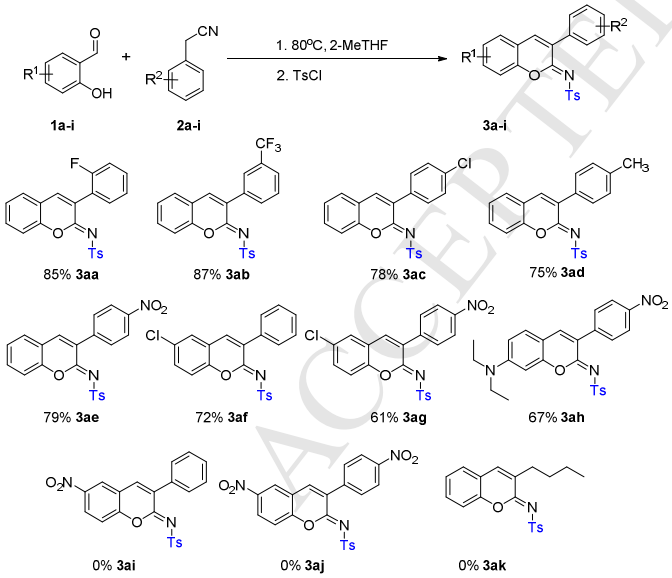


[a]Reaction conditions: **1a-i** (0.81 mmol), **2a-i** (0.81 mmol), DABCO (0.60 mmol) and 2-MeTHF, reflux at 80°C till aldehyde consumed, after which DABCO (0.60 mmol), Tosyl chloride (TsCl, 1.21 mmol) was added at 0°C. [b]isolated yield.

Finally, with these optimized conditions, *i.e.* DABCO/2-MeTHF we examined the substrate scope by varying arylsulfonyl chloride precursors with **1a** and **2a** and the results are depicted in Table 2. The best yields were obtained with phenyl (**3a**, 90%), and the *para* substituted arylsulfonyl chloride derivatives such as 4-Me (**3b**, 93%), 4-F (**3c**, 91%), 4-Cl (**3d**,

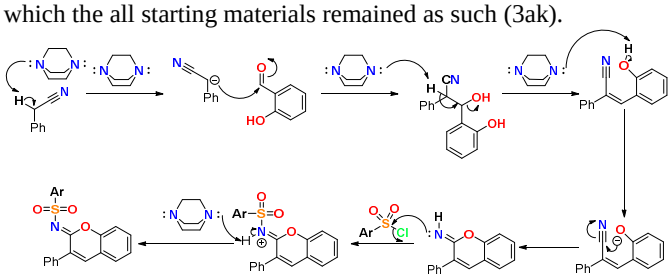
90%) and 4-Br (**3e**, 87%). The yields in the case of arylsulfonyl chloride bearing an electron-donating group such as 4-OMe (**3f**, 87%) and 4-*t*-Bu (**3g** 78%) were good and moderate respectively. The yields of the arylsulfonyl chlorides bearing electron-withdrawing groups such as 4-NO_2 (**3h**, 75%) and 2-NO_2 (**3i**, 62%) were lowered due to the decreased nucleophilicity and steric crowding of the *ortho* substituent respectively. Other arylsulfonyl chloride, such as 3-CF_3 (**3j**, 66%), 2, 4-dinitro, (**3k**, 41%), 2-naphthalene (**3l**, 74%) and methyl sulfonyl group (**3m**, 62%) afforded the products in good to moderate yields. Altogether a wide variety of substrates were successfully synthesized under these reaction conditions. Next, the reactivity of different salicylaldehydes (**1a-i**) and benzylnitriles (**2a-i**) with TsCl was investigated, and the results are summarized in Table 3. It was observed that the aldehydes bearing electron donating group and the nitriles possessing both electron donating and electron withdrawing groups underwent smooth conversions. The reaction of 2-hydroxybezaldehydes with *ortho, meta, para* substituted nitrile substrates such as 2-F (**3aa**, 85%), 3-CF_3 (**3ab**, 87%), 4-Cl (**3ac**, 78%), 4-Me (**3ad**, 75%), and 4-NO_2 (**3ae**, 79%) gave good to moderate product yields. The reaction in the case of 5-Cl-salicylaldehyde with phenylacetonitrile derivative has also successfully afforded the product (**3af**, 72%) in moderate yield. We further screened the reaction of aldehydes possessing electron donating group (5-Cl, 4-*N*,*N*-diethyl) with the nitrile substrates having electron withdrawing group (4-NO_2) for their the products (**3ag**, 61%), (**3ah**, 67%) were obtained in moderate amounts. However, the reactions in the case of both the aldehydes and nitriles substrates possessing electron withdrawing group (NO_2) were found to be non-progressive (meant no-conversion).

Table 3. Scope of substituted aldehyde and nitrile derivative with TsCl.[a,b]



[a]Reaction conditions: **1a-i** (0.81 mmol), **2a-i** (0.81 mmol), DABCO (0.60 mmol) and refluxed at 80°C till aldehyde consumption, after which DABCO (0.60 mmol), Tosyl chloride (TsCl, 1.21 mmol) was added at 0°C. [b]isolated yield.

The reactions in these cases did not proceed at all, wherein all starting materials remained as such (**3ai**, **3aj**). It can be seen that the reaction time was less in the case of unsubstituted aldehydes, whereas the substituted aldehydes took little longer time to complete. Moreover, the reaction with the aliphatic nitrile pentanenitrile, was non-progressive (meant no-conversion) in which the all starting materials remained as such (3ak).

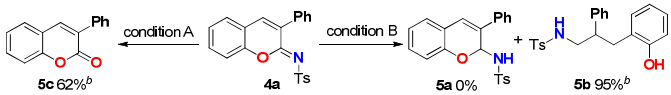


Scheme 1. Proposed mechanistic pathway.

Based on the previous reports[46,47] and substrate study, we propose a plausible mechanistic pathway for the three component one-pot knoevenagel adducts formation, followed by the *in situ* cyclization to iminocoumarins and their further *N*-tosylation under metal-free conditions (Scheme 1).

Having completed the substrate scope and mechanistic aspects of the reaction, we further extended our study to the synthesis of 2-(3-aminopropyl) phenol derivative. The precursor **4a** containing imino group was subjected to reduction by using $NaBH_4$ in MeOH solvent at 0 °C, wherein the starting material was consumed in 3h. We expected the formation of the cyclic eneaminal compound as shown **5a** in Scheme 2, but to our surprise the reaction afforded an amine derivative of phenol (**5b**) *i.e.* *N*-(3-(2-hydroxyphenyl)-2-phenylpropyl)-4-methylbenzene sulfonamide. Interestingly, literature survey showed that these compounds are not synthesized by the conventional iminocoumarin route. Also the tosyl group was hydrolyzed by using PTSA/H_2O to form 3-phenyl-2*H*-chromen-2-one (**5c**) in 62% yield. Thus, these results show that the synthesized imino-benzenesulfonamides compounds could be useful starting materials for the synthesis of coumarins as well as aminopropyl phenol compounds.

Scheme 2. Functionalization of *N*-Arylsulfonyl-2-Iminocoumarin [a]



[a]Reaction Condition A: PTSA/H_2O, 70°C, 16h; Condition B: $NaBH_4$/ MeOH, 0°C to rt, 3h [b]isolated yield.

3. Conclusion

In conclusion, we have established a practical and efficient transition metal-free methodology for the synthesis of *N*-arylsulfonyl-2-iminocoumarins derivative from aryl aldehydes/nitriles/TsCl with and DABCO in 2-MeTHF as green solvent. The sequential synthetic approach described here is operationally simple and requires no isolation of the less stable iminocoumarin intermediates. The environmental and economic advantages derived from the use of such a benign solvent are clear in terms of safety, cost and innocuousness. The results showed that various aldehydes and nitrile derivatives including sterically hindered substrates could react effectively with TsCl to afford the desired products in moderate to excellent yields. Additionally, the synthesized *N*-arylsulfonyl-2-iminocoumarins derivatives can be precursors for the less available 2-(3-aminopropyl) phenol derivatives.

4. Experimental

4.1. General information

NMR spectra were recorded with tetramethylsilane as the internal standard. TLC was performed on glass-backed silica plates. Column chromatography was performed using silica gel (200-300 mesh) eluting with ethyl acetate and petroleum ether. ^{1}H-NMR spectra were recorded at 400 MHz, and ^{13}C- NMR spectra were recorded at 100MHz. Chemical shifts (δ) are reported in ppm downfield from $CDCl_3$ (δ = 7.26 ppm) or DMSO-D_6 (*δ* = 2.49 ppm) for ^{1}H-NMR and relative to the central $CDCl_3$ resonance (δ = 77.0 ppm) or DMSO-D_6 (δ = 39.5 ppm) for ^{13}C-NMR spectroscopy. Coupling constants (*J*) are given in Hz. Commercial grade solvents were dried and purified by standard procedures as specified in Purification of Laboratory Chemicals.

4.2. General procedure for the synthesis of Chroman-Benzene sulfonamides.

To a Solution of aldehyde (0.81 mmol), base (0.60), arylacetonitrile (0.81 mmol) in 2-MeTHF (3 mL) was reflux for 8 h. The progress of reaction was monitored by TLC analysis. After complete conversion of both the starting material, the reaction mixture was cooled to 0 °C to it add base (0.60 mmol), and TsCl derivatives (1.22 mmol) was added. The reaction completed within 15-60 min. After completion of the reaction, the organic phase was concentrated under reduced pressure and the solid residue was fractioned in ethyl acetate (20 mL) and water (10 mL) thrice. The combined organic phases were dried on anhydrous Na_2SO_4 and solvent was removed in vacuum. The crude residue was purified by column chromatography with ethyl acetate/petroleum ether.

*4.2.1(Z)-N-(3-Phenyl-2H-chromen-2-ylidene)benzene sulfonamide **3a***[48]

The obtained residue after work up was purified by column chromatography over silica gel using EtOAc/petroleum ether (10:90) to furnish the pure compound **3a** 100 mg scale reaction (296 mg, 90%) as off green solid. Physical state: off yellow solid, m.p.: 162-163°C; IR (*ν*/cm^{-1}): 3070, 1632, 1543, 1310, 1131, 1088, 765, 686; ^{1}H-NMR (400 MHz, $CDCl_3$) *δ*: 8.05 (d, *J* = 6.9 Hz, 2H), 7.71 (s, 1H), 7.62 – 7.43 (m, 8H), 7.41 – 7.31 (m, 4H); ^{13}C-NMR (100 MHz, $CDCl_3$) *δ*: 152.26, 139.70, 134.32, 132.28, 131.95, 130.10, 129.05, 129.01, 128.56, 128.24, 128.11, 127.09, 125.76, 119.76, 116.47; LCMS Mass Chemical Formula: $C_{21}H_{16}NO_3S$ [M + H]+: 362.08; Found: 362.15.

*4.2.2 (Z)-4-Methyl-N-(3-phenyl-2H-chromen-2- ylidene) benzene sulfonamide **3b***[28]

The obtained residue after work up was purified by column chromatography over silica gel using EtOAc/petroleum ether (10:90) to furnish the pure compound **3b** 100 mg scale reaction (285 mg, 93%) as yellow solid, m.p.: 194-195°C; IR (*ν*/cm^{-1}): 3065, 2922, 1635, 1628, 1558, 1305, 1182, 1088, 863; ^{1}H-NMR (400 MHz, $CDCl_3$) *δ*: 7.93 (d, *J* = 8.0 Hz, 2H), 7.69 (s, 1H), 7.62 – 7.49 (m, 4H), 7.46 (d, *J* = 8.1 Hz, 1H), 7.42 – 7.31 (m, 4H), 7.27 (d, *J* = 8.0 Hz, 2H), 2.39 (s, 3H).; ^{13}C-NMR (100 MHz, $CDCl_3$) *δ*: 157.36, 152.25, 143.00, 139.59, 139.21, 134.35, 131.88, 130.07, 129.16, 129.05, 128.96, 128.22, 128.13, 127.22, 125.71, 119.75, 116.40, 21.52.; LCMS Mass Chemical Formula: $C_{22}H_{18}NO_3S$ [M + H]$^{+}$: 376.10 ; Found: 376.15.

*4.2.3 (Z)-4-Fluoro-N-(3-phenyl-2H-chromen-2-ylidene) benzene sulfonamide: **3c***

The obtained residue after work up was purified by column chromatography over silica gel using EtOAc/petroleum ether (10:90) to furnish the pure compound **3c** 100 mg scale reaction (280 mg, 91%) as yellow solid, m.p.154-155 ^{0}C; IR (*ν*/cm^{-1}): 3080, 1670, 1556, 1493, 1307, 1286, 757.; ^{1}H-NMR (400 MHz, $CDCl_3$) *δ*: 8.10 – 7.99 (m, 2H), 7.73 (s, 1H), 7.62 – 7.52 (m, 4H), 7.48 (d, *J* = 8.1 Hz, 1H), 7.44 – 7.32 (m, 4H), 7.14 (t, *J* = 8.3 Hz, 2H).; ^{13}C-NMR (100 MHz, $CDCl_3$) *δ*: 166.11, 163.59, 157.74, 152.20, 139.97, 138.24, 134.24, 132.08, 131.39, 129.96, 129.81, 129.72, 129.05, 129.01, 128.50, 128.45, 128.26, 128.22, 125.89, 119.75, 116.44, 115.86, 115.64.; HRMS Mass Chemical Formula: $C_{21}H_{15}FNO_3S$ [M + H]$^{+}$: 380.0751; Found: 380.0746.

*4.2.4 (Z)-4-Chloro-N-(3-phenyl-2H-chromen-2-ylidene) benzene sulfonamide **3d***

The obtained residue after work up was purified by column chromatography over silica gel using EtOAc/petroleum ether (10:90) to furnish the pure compound **3d** 100 mg scale reaction (293 mg, 90%) as yellow solid, m.p.160-161^{0}C; IR (*ν*/cm^{-1}): 3063, 1622, 1540, 1446, 1310, 1153, 1083, 767.; ^{1}H-NMR (400 MHz, $CDCl_3$) *δ*: 7.96 (d, *J* = 8.0 Hz, 2H), 7.73 (s, 1H), 7.56 (dd, *J* = 10.8, 5.5 Hz, 4H), 7.46 (dd, *J* = 16.0, 8.2 Hz, 3H), 7.41 – 7.33 (m, 4H).; ^{13}C-NMR (100 MHz, $CDCl_3$) *δ*: 157.87, 152.20, 140.72, 140.06, 138.65, 134.21, 132.12, 129.95, 129.06, 129.00, 128.84, 128.56, 128.27, 128.23, 125.92, 119.76, 116.46.; HRMS Mass Chemical Formula: $C_{21}H_{15}ClNO_3S$ [M + H]$^{+}$: 396.0456; Found: 396.0435.

*4.2.5 (Z)-4-Bromo-N-(3-phenyl-2H-chromen-2-ylidene) benzene sulfonamide: **3e***

The obtained residue after work up was purified by column chromatography over silica gel using EtOAc/petroleum ether (10:90) to furnish the pure compound **3e** 100 mg scale reaction (313 mg, 87%) as yellow solid, m.p. 195-196°C; IR (*ν*/cm^{-1}): 3056, 1622, 1540, 1447, 1310, 1083, 1151, 768.; ^{1}H-NMR (400 MHz, $CDCl_3$) *δ*: 7.89 (d, *J* = 8.5 Hz, 1H), 7.74 (s, 1H), 7.64 – 7.52 (m, 3H), 7.48 (d, *J* = 8.2 Hz, 1H), 7.42 – 7.33 (m, 2H).; ^{13}C-NMR (100 MHz, $CDCl_3$) *δ*: 157.90, 152.21, 141.24, 140.07, 134.20, 132.13, 131.81, 129.97, 129.08, 129.00, 128.67, 128.28, 128.22, 1127.16, 125.92, 119.76, 116.49; LCMS Mass Chemical Formula: $C_{21}H_{15}BrNO_3S$ [M + H]$^{+}$: 439.99; Found: 442.10.

*4.2.6 (Z)-4-Methoxy-N-(3-phenyl-2H-chromen-2- ylidene) benzene sulfonamide: **3f***

The obtained residue after work up was purified by column chromatography over silica gel using EtOAc/petroleum ether (15:85) to furnish the pure compound **3f** 100 mg scale reaction (272 mg, 85%) as white solid, m.p.165-166°C; IR (*ν*/cm^{-1}): 3072, 1624, 1545, 1495, 1308, 1295, 1149, 1084, 766.; ^{1}H-NMR (400 MHz, $CDCl_3$) *δ*: 8.04 – 7.91 (m, 2H), 7.67 (s, 1H), 7.61 – 7.43 (m, 5H), 7.41 – 7.27 (m, 4H), 6.97 – 6.89 (m, 2H), 3.82 (s, 3H).; ^{13}C-NMR (100 MHz, $CDCl_3$) *δ*: 162.63, 157.12, 152.28, 139.43, 134.40, 133.93, 131.84, 130.16, 129.34, 129.04, 128.95, 128.59, 128.22, 128.09, 125.67, 119.77, 116.43, 114.19, 113.70, 55.52.; HRMS Mass Chemical Formula: $C_{22}H_{18}NO_4S$ [M + H]$^{+}$: 392.0951; Found: 392.0947.

4.2.7 (Z)-4-(tert-Butyl)-N-(3-phenyl-2H-chromen-2-ylidene) benzene sulfonamide: ***3g***

The obtained residue after work up was purified by column chromatography over silica gel using EtOAc/petroleum ether (10:90) to furnish the pure compound **3g** 100 mg scale reaction (265 mg, 78%) as off white solid, m.p. 240-241°C; IR (ν/cm^{-1}): 3063, 2968, 1627, 1548, 1316, 1153, 1082, 766.; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.96 (d, J = 8.5 Hz, 1H), 7.69 (s, 1H), 7.64 – 7.58 (m, 1H), 7.50 (qd, J = 15.1, 8.4 Hz, 3H), 7.42 – 7.29 (m, 2H), 1.31 (s, 5H).; ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 157.39, 155.98, 152.28, 139.58, 139.14, 134.40, 131.86, 130.14, 129.07, 128.98, 128.25, 128.09, 126.95, 125.69, 125.57, 119.77, 116.47, 35.08, 31.09.; HRMS Mass Chemical Formula: $C_{25}H_{24}NO_3S$ [M + H]$^+$: 418.1471; Found: 418.1466.

4.2.8 (Z)-4-Nitro-N-(3-phenyl-2H-chromen-2-ylidene) benzene sulfonamide: ***3h***

The obtained residue after work up was purified by column chromatography over silica gel using EtOAc/petroleum ether (20:80) to furnish the pure compound **3h** 100 mg scale reaction (250 mg, 75%) as yellow white solid, m.p. 160-161°C; IR (ν/cm^{-1}): 3054, 1628, 1549, 1522, 1302, 1088, 852, 645, 764.; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 8.31 (d, J = 8.2 Hz, 2H), 8.17 (d, J = 8.3 Hz, 2H), 7.80 (s, 1H), 7.59 (dt, J = 19.1, 7.8 Hz, 5H), 7.40 (s, 4H).; ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 158.68, 152.19, 149.75, 147.90, 140.72, 134.05, 132.44, 129.83, 129.23, 128.97, 128.35, 128.19, 126.20, 123.90, 119.78, 116.63; HRMS Mass Chemical Formula: $C_{21}H_{15}N2O_5S$ [M + H]$^+$: 407.0696; Found: 407.0691.

4.2.9 (Z)-2-Nitro-N-(3-phenyl-2H-chromen-2-ylidene) benzene sulfonamide: ***3i***

The obtained residue after work up was purified by column chromatography over silica gel using EtOAc/petroleum ether (20:80) to furnish the pure compound **3i** 100 mg scale reaction (205 mg, 62%) as pale brown solid, m.p.164-165°C; IR (ν/cm^{-1}): 3062, 1622, 1536, 1454, 1324, 1127, 1154, 760.; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 8.30 (dd, J = 7.6, 1.6 Hz, 1H), 7.78 – 7.73 (m, 2H), 7.72 – 7.63 (m, 2H), 7.62 – 7.51 (m, 5H), 7.42 – 7.33 (m, 6H).; ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 157.92, 152.12, 148.07, 140.46, 135.74, 134.05, 133.16, 132.14, 132.07, 130.33, 129.97, 129.02, 128.99, 128.35, 128.21, 125.98, 124.60, 119.78, 116.46.; HRMS Mass Chemical Formula: $C_{21}H_{15}N2O_5S$ [M + H]$^+$: 407.0696; Found: 407.0691.

4.2.10 (Z)-N-(3-Phenyl-2H-chromen-2-ylidene)-3-(trifluoromethyl) benzenesulfonamide: ***3j***

The obtained residue after work up was purified by column chromatography over silica gel using EtOAc/petroleum ether (15:85) to furnish the pure compound **3j** 100 mg scale reaction (230 mg, 66%) as brown solid, m.p.130-131°C; IR (ν/cm^{-1}): 3069, 1626, 1557, 1456, 1326, 1295, 1126, 1100, 756, 692.; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 8.34 (s, 1H), 8.19 (d, J = 8.0 Hz, 1H), 7.77 (s, 2H), 7.60 (dd, J = 22.0, 8.2 Hz, 5H), 7.52 (d, J = 8.2 Hz, 1H), 7.38 (d, J = 13.9 Hz, 4H).; ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 158.29, 152.23, 143.34, 140.33, 134.11, 132.26, 130.16, 129.97, 129.40, 129.15, 128.99, 128.87, 128.33, 128.26, 126.05, 124.41, 124.37, 119.78, 116.55.; HRMS Mass Chemical Formula: $C_{22}H_{15}F_3NO_3S$ [M + H]$^+$: 430.0719; Found: 430.0709.

4.2.11 (Z)-2,4-Dinitro-N-(3-phenyl-2H-chromen-2-ylidene) benzene sulfonamide ***3k***[26]

The obtained residue after work up was purified by column chromatography over silica gel using EtOAc/petroleum ether (40:60) to furnish the pure compound **3k** 100 mg scale reaction (150 mg, 41%) as brown solid, m.p. 243-244°C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 8.85 (d, J = 0.9 Hz, 1H), 8.67 (d, J = 1.6 Hz, 2H), 8.36 (s, 1H), 7.87 – 7.80 (m, 1H), 7.68 (dd, J = 7.9, 1.5 Hz, 3H), 7.46 (dq, J = 7.0, 5.6 Hz, 5H).; ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 159.00, 152.04, 150.58, 148.37, 143.76, 139.04, 134.47, 133.62, 133.20, 129.91, 129.66, 129.48, 128.78, 128.53, 127.72, 127.14, 120.74, 120.36, 116.16, 40.66, 40.45, 40.24, 40.03, 39.82, 39.61, 39.40.

4.2.12 (Z)-N-(3-phenyl-2H-chromen-2-ylidene) naphthalene-2-sulfonamide: ***3k***

The obtained residue after work up was purified by column chromatography over silica gel using EtOAc/petroleum ether (10:90) to furnish the pure compound **3k** 100 mg scale reaction (250 mg, 74%) as white solid, m.p.172-173°C; IR (ν/cm^{-1}): 3063, 1623, 1538, 1445, 1306, 1149, 1127, 764, 647.; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 8.60 (s, 1H), 8.05 – 7.99 (m, 1H), 7.92 (t, J = 8.0 Hz, 2H), 7.86 (d, J = 7.4 Hz, 1H), 7.70 (s, 1H), 7.64 – 7.44 (m, 7H), 7.42 – 7.28 (m, 4H).; ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 157.56, 152.28, 139.71, 139.11, 134.72, 134.34, 132.06, 131.95, 130.11, 129.20, 129.07, 129.00, 128.73, 128.43, 128.24, 128.09, 127.81, 127.18, 125.74, 122.88, 119.77, 116.49.; HRMS Mass Chemical Formula: $C_{25}H_{18}NO_3S$ [M + H]$^+$: 412.1002; Found: 412.0994.

4.2.13 (Z)-N-(3-Phenyl-2H-chromen-2-ylidene) methane sulfonamide: ***3l***[28]

The obtained residue after work up was purified by column chromatography over silica gel using EtOAc/petroleum ether (05:95) to furnish the pure compound **3l** 100 mg scale reaction (155 mg, 62%) as white solid, m.p.152-154°C; IR (ν/cm^{-1}): 3032, 2930, 1624, 1558, 1550, 1305, 1139, 954, 767.; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.23 (d, J = 7.3 Hz, 1H), 7.86 (s, 1H), 7.70 (d, J = 7.3 Hz, 2H), 7.55 – 7.39 (m, 6H), 3.19 (s, 3H).; ^{13}C NMR (100 MHz, $CDCl_3$) δ: 147.32, 135.41, 133.74, 131.72, 129.80, 129.39, 129.21, 128.00, 127.85, 126.22, 122.88, 117.23, 115.23, 38.23.

4.2.14 (Z)-N-(3-(2-Fluorophenyl)-2H-chromen-2-ylidene)-4-methylbenzenesulfonamide: ***3aa***

The obtained residue after work up was purified by column chromatography over silica gel using EtOAc/petroleum ether (10:90) to furnish the pure compound **3aa** 100 mg scale reaction (275 mg, 85%) as yellow solid, m.p.164-165°C; IR (ν/cm^{-1}): 3062, 2922, 1629, 1547, 1317, 1146, 1082, 750.; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.91 (d, J = 6.9 Hz, 2H), 7.70 (s, 1H), 7.57 (t, J = 7.3 Hz, 1H), 7.50 (d, J = 7.5 Hz, 1H), 7.44 (d, J = 6.9 Hz, 2H), 7.34 (dd, J = 7.0, 5.2 Hz, 2H), 7.26 (d, J = 7.2 Hz, 2H), 7.20 – 7.06 (m, 2H), 2.38 (s, 3H).; ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 161.09, 158.62, 156.84, 152.50, 142.99, 141.63, 139.11, 132.30, 131.38, 130.80, 129.12, 128.27, 127.22, 125.76, 124.92, 123.93, 122.22, 119.26, 116.55, 115.95, 115.74, 21.52; HRMS Mass Chemical Formula: $C_{22}H_{17}FNO_3S$ [M + H]$^+$: 394.0908; Found: 394.0903.

*4.2.15(Z)-4-Methyl-N-(3-(3-(trifluoromethyl)phenyl)-2H-chromen-2-ylidene)benzenesulfonamide : **3ab***

The obtained residue after work up was purified by column chromatography over silica gel using EtOAc/petroleum ether (20:80) to furnish the pure compound **3ab** 100 mg scale reaction (371 mg, 87%) as pale brown solid, m.p.175-176°C; IR (ν/cm^{-1}): 3056, 2852, 1627, 1557, 1303, 1152, 1085, 694.; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.93 – 7.82 (m, 3H), 7.81 – 7.73 (m, 2H), 7.66 – 7.46 (m, 5H), 7.37 (t, J = 7.4 Hz, 1H), 7.27 (d, J = 7.5 Hz, 2H), 2.39 (s, 3H).; ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 156.82, 152.45, 143.15, 140.15, 139.05, 135.12, 132.47, 132.38, 129.22, 128.79, 128.61, 128.30, 126.98, 125.99, 125.95, 125.89, 125.65, 125.61, 119.42, 116.69, 21.51.; HRMS Mass Chemical Formula: $C_{23}H_{17}F_3NO_3S$ $[M + H]^+$: 444.0876; Found: 444.0876.

*4.2.16 (Z)-N-(3-(4-Chlorophenyl)-2H-chromen-2-ylidene)-4-methylbenzenesulfonamide : **3ac***

The obtained residue after work up was purified by column chromatography over silica gel using EtOAc/petroleum ether (20:80) to furnish the pure compound **3ac** 100 mg scale reaction (263 mg, 78%) as white solid, m.p.161-162°C; IR (ν/cm^{-1}): 3070, 2592, 1628, 1557, 1489, 1293, 1139, 1088, 835.; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.92 (d, J = 7.2 Hz, 2H), 7.79 (d, J = 7.2 Hz, 2H), 7.68 (s, 1H), 7.53 (dd, J = 12.9, 5.7 Hz, 3H), 7.45 (d, J = 8.3 Hz, 1H), 7.31 (dd, = 25.6, 8.1 Hz, 5H).; ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 157.06, 152.29, 143.19, 139.66, 139.00, 135.04, 132.75, 132.17, 130.37, 129.66, 129.24, 128.88, 128.48, 128.20, 127.22, 126.42, 125.83, 119.57, 116.47, 21.55.; HRMS Mass Chemical Formula: $C_{22}H_{17}ClNO_3S$ $[M + H]^+$: 410.0612; Found: 410.0592.

*4.2.17 (Z)-4-Methyl-N-(3-(p-tolyl)-2H-chromen-2-ylidene)benzene sulfonamide : **3ad***

The obtained residue after work up was purified by column chromatography over silica gel using EtOAc/petroleum ether (20:80) to furnish the pure compound **3ad** 100 mg scale reaction (240 mg, 75%) as pale brown solid, m.p.196-197°C; IR (ν/cm^{-1}): 3080, 1622, 1540, 1451, 1301, 1150, 1085, 818, 749.; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.94 (d, J = 8.2 Hz, 2H), 7.67 (s, 1H), 7.59 – 7.42 (m, 5H), 7.37 – 7.26 (m, 3H), 7.19 (d, J = 7.9 Hz, 2H), 2.38 (d, J = 8.0 Hz, 6H).; ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 157.49, 152.18, 142.95, 139.26, 139.05, 139.02, 131.69, 131.45, 130.07, 129.16, 128.95, 128.92, 128.00, 127.26, 125.64, 119.86, 116.40, 21.53, 21.29.; HRMS Mass Chemical Formula: $C_{23}H_{20}NO_3S$ $[M + H]^+$: 390.1158; Found: 390.1139.

*4.2.18 (Z)-4-Methyl-N-(3-(4-nitrophenyl)-2H-chromen-2-ylidene) benzenesulfonamide : **3ae***

The obtained residue after work up was purified by column chromatography over silica gel using EtOAc/petroleum ether (20:80) to furnish the pure compound **3ae** 100 mg scale reaction (272 mg, 79%) as yellow solid, m.p.197-198°C; IR (ν/cm^{-1}): 3111, 2851, 1591, 1517, 1448, 1339, 1166, 1086, 881.; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 8.28 (d, J = 8.9 Hz, 2H), 8.09 (d, J = 7.0 Hz, 1H), 7.68 (d, J = 8.9 Hz, 2H), 7.62 (s, 1H), 7.55 (d, J = 8.3 Hz, 2H), 7.52 – 7.38 (m, 2H), 7.27 (d, J = 8.1 Hz, 1H), 7.12 (d, J = 8.1 Hz, 2H), 2.32 (s, 3H).; ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 148.26, 148.06, 147.77, 146.05, 139.54, 138.59, 132.63, 131.51, 130.19, 128.84, 128.33, 127.79, 127.15, 126.66, 124.25, 124.00, 116.13, 111.54, 21.67.; HRMS Mass Chemical Formula: $C_{22}H_{17}N_2O_5S$ $[M + H]^+$: 421.0853; Found: 421.0863.

4.2.19 *(Z)-N-(6-Chloro-3-phenyl-2H-chromen-2-ylidene)-4-methylbenzenesulfonamide* : **3af**

The obtained residue after work up was purified by column chromatography over silica gel using EtOAc/petroleum ether (15:85) to furnish the pure compound **3af** 100 mg scale reaction (190 mg, 72%) as yellow solid, m.p.162-163°C; IR (ν/cm^{-1}): 3066, 1640, 1510, 1450, 1324, 1120, 1085, 756.; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.89 (d, J = 8.2 Hz, 2H), 7.61 – 7.52 (m, 2H), 7.47 (dd, J = 5.1, 2.2 Hz, 1H), 7.38 (dd, J = 10.7, 7.7 Hz, 2H), 7.26 (d, J = 8.2 Hz, 1H), 2.38 (s, 3H).; ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 150.55, 143.17, 139.00, 137.98, 133.94, 131.72, 131.36, 130.98, 129.26, 129.22, 129.01, 128.29, 127.23, 127.11, 120.82, 117.88, 21.54.; HRMS Mass Chemical Formula: $C_{22}H_{17}ClNO_3S$ $[M + H]^+$: 410.0612; Found: 410.0589.

*4.2.20 (Z)-N-(6-chloro-3-(4-nitrophenyl)-2H-chromen-2-ylidene)-4-methylbenzene sulfonamide : **3ag***

The obtained residue after work up was purified by column chromatography over silica gel using EtOAc/petroleum ether (35:65) to furnish the pure compound **3ag** 100 mg scale reaction (179 mg, 61%) as yellow solid, m.p.189-190°C; IR (ν/cm^{-1}): 3096, 2942, 1592, 1468, 1342, 1191, 1084, 841.; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: δ 8.29 (dd, J = 8.6, 3.2 Hz, 2H), 8.03 (d, J = 2.3 Hz, 1H), 7.91 – 7.82 (m, 1H), 7.68 (d, J = 8.7 Hz, 2H), 7.54 (dd, J = 19.4, 5.8 Hz, 3H), 7.46 – 7.30 (m, 1H), 7.17 (dd, J = 16.8, 8.4 Hz, 2H), 2.33 (s, 3H).; ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 148.29, 147.95, 146.58, 146.33, 140.22, 139.07, 137.05, 133.58, 132.33, 131.27, 130.31, 129.49, 128.57, 128.36, 126.82, 125.24, 124.31, 123.69, 118.10, 115.57, 112.84, 21.69.; HRMS Mass Chemical Formula: $C_{22}H_{15}ClN_2NaO_5S$ $[M + Na]^+$: 477.0282; Found: 477.0282.

*4.2.21 (Z)-N-(7-(diethylamino)-3-(4-nitrophenyl)-2H-chromen-2-ylidene)-4-methylbenzenesulfonamide : **3ah***

The obtained residue after work up was purified by column chromatography over silica gel using EtOAc/petroleum ether (35:65) to furnish the pure compound **3ah** 100 mg scale reaction (170 mg, 67%) as orange solid, m.p.185-168°C; IR (ν/cm^{-1}): 2889, 1615, 1572, 1406, 1373, 1265, 1169, 1072, 841.; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 8.19 (dd, J = 12.8, 9.1 Hz, 3H), 7.57 (dd, J = 32.8, 8.6 Hz, 4H), 7.37 (s, 1H), 7.11 (d, J = 8.2 Hz, 2H), 6.60 (dd, J = 9.2, 2.6 Hz, 1H), 6.44 (d, J = 2.6 Hz, 1H), 3.37 (q, J = 7.1 Hz, 4H), 2.27 (s, 3H), 1.17 (t, J = 7.1 Hz, 6H).; ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 151.11, 150.90, 146.88, 145.79, 141.38, 138.01, 131.83, 129.99, 129.49, 128.30, 125.58, 124.06, 117.95, 113.00, 110.16, 105.84, 102.70, 44.84, 21.60, 12.45.; HRMS Mass Chemical Formula: $C_{26}H_{26}N_3O_5S$ $[M + H]^+$: 492.1588; Found: 492.1591.

*4.2.22 N-(3-(2-hydroxyphenyl)-2-phenylpropyl)-4-methylbenzene sulfonamide: **5b***

The compound **4a** (200 mg) was dissolved in MeOH (25 mL) and cooled to 0 °C on an ice-water bath. $NaBH_4$ (0.180 g, 5.3 mmol) was then added in portion to the reaction mixture and stirred at 0 °C for 3 hours. Then, solvent was evaporated under reduced pressure and residue partitioned between ethyl acetate (50 mL) and water (30 mL). Water layer was separated and ethyl

acetate layer was washed with brine (1 x 10 mL), dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The obtained residue was purified by column chromatography over silica gel using EtOAc/petroleum ether (20:80) to furnish the pure compound *N*-(3-(2-hydroxyphenyl)-2-phenylpropyl)-4-methyl benzene sulfonamide **5b** (193 mg, 95%) as white solid, m.p.165-166°C; IR (ν/cm^{-1}): 3450, 3314, 1591, 1454, 1315, 1152, 1089.; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 9.27 (s, 1H), 7.58 – 7.53 (m, 2H), 7.43 (s, 1H), 7.32 (d, J = 7.9 Hz, 2H), 7.22 (t, J = 7.2 Hz, 2H), 7.17 – 7.11 (m, 3H), 6.92 (dd, J = 7.6, 1.5 Hz, 1H), 6.74 (ddd, J = 14.0, 7.8, 1.3 Hz, 2H), 6.58 – 6.52 (m, 1H), 3.17 – 3.08 (m, 1H), 3.00 – 2.85 (m, 3H), 2.67 (dd, J = 13.6, 8.0 Hz, 1H), 2.37 (s, 3H).; ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 155.64, 143.32, 142.85, 137.89, 130.90, 129.96, 129.76, 128.48, 128.32, 127.33, 126.94, 126.60, 126.24, 126.08, 118.92, 115.20, 48.05, 45.17, 34.42, 21.42.; HRMS Mass Chemical Formula: $C_{22}H_{24}NO_3S$ $[M + H]^+$: 382.1471: Found: 382.1493.

4.2.23 3-Phenyl-2H-chromen-2-one: ***5c***[49]

The **4a (**100mg, 0.26mmol) and *p*-Toluenesulfonic acid (PTSA) (190 mg, 0.40 mmol) was dissolved in 5mL of distilled water. The reaction mixture was reflux at 70 °C for 16 hour. Then, solvent was evaporated under reduced pressure and residue partitioned between ethyl acetate (50 mL) and water (30 mL). Water layer separated and ethyl acetate layer was washed with brine (1 x 10 mL), dried over Na_2SO_4 and evaporated under reduced pressure. The obtained residue was purified by column chromatography over silica gel using EtOAc/petroleum ether (05:95) to furnish the pure compound (37 mg, 63%) as a white solid, m.p. 139-140°C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.80 (s, 1H), 7.72 – 7.67 (m, 2H), 7.51 (dd, J = 12.9, 4.6 Hz, 2H), 7.47 – 7.34 (m, 4H), 7.29 (td, J = 7.6, 0.8 Hz, 1H).

Acknowledgments

PSM is grateful to UGC-BSR, Department of Chemistry, Institute of Chemical Technology (ICT) for the research fellowship. AVK is thankful to DST, Govt. of India for the INSPIRE Faculty Award [IFA12-CH-40] and research funding. We also thank the Department of Pharmaceutical Sciences and Technology, ICT, for the NMR analysis.

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Supplementary Material

^{1}H and ^{13}C NMR, Mass spectra of all the compounds.