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Full Length Article

Synthesis and evaluation of N-(Substituted phenyl)-2-(3-substituted) sulfamoyl) phenyl) acetamide derivatives as anticancer agents

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ABSTRACT

A series of molecules containing sulfonyl and amide coupling structure were developed, synthesized and evaluated. Total 21 compounds having sulfonamide and amide groups are synthesized. The structures of the synthesized compounds were elucidated and confirmed by ^{1}H NMR, ^{13}C NMR, Mass spectrum and the purity was checked through HPLC analysis. All synthesized compounds (**4a–4u)** were tested for their *in vitro* anticancer activity against a series of different cell lines like A549 (Lung Cancer cell), HeLa (Cervical), MCF-7 (Breast Cancer cell) and Du-145 (Prostate Cancer cell) respectively. The results of the anticancer activity revealed that most of the tested compounds showed moderate to good anticancer activity. Compounds **4d, 4**k and **4**s show promising anticancer activity in different cell lines.

Introduction

The fused ring nucleus having sulfonamide and amide coupling is an important constituent for an enormous variety of therapeutic agents, including anticancer, antiproliferative, antimalarial, antifungal and antibacterial agents [1–5]. The sulphonamide act as matrix metalloproteinase inhibitors it is a significant pharmacophore and its coupling with other rings could provide new biologically active compounds [6]. Lately, the applications of amide coupled with naphthoyl rings were found to show antimicrobial agents and biofilm inhibitors [7]. The compounds like some esters and amide coupled compounds act as anti-inflammatory drugs as cyclooxygenase-2-inhibitors [8] while some act as antimalarials [9]. The sulfonamide coupled with pyrimidine shows antimicrobial and anticancer activities [10]. Inhibitors of 5-Lipoxygenase [11], Yersinia enteroclitica Y opH tyrosine phosphatase inhibitors [12], antimalassezia [13], antiamoebic and antimalarial activities [14], inhibitor of phosphodiesterase type 4 [15], antihypertensive [16]. Some sulfonamides linked compounds act as hepatitis-C virus as nonstructural protein 3 protease inhibitors [17].

The sulfonamide coupled with thiourea shows antiinflammatory and antimicrobeal activities [18]. Some dihydropyrazole sulfonamide derivatives act as potential COX-1/COX-2 inhibitors [19]. Literature revealed some chromone-based sulfonamide derivatives shows carbonic anhydrase inhibition and cytotoxic activity [20], while the heterocyclic sulfonamides act as sphingosine 1-phosphate receptor 1 (S1P1) antagonists [21].

Following a wide literature exploration, it was observed that, different coupling of sulfonamide and amide compounds shows different activities like carbonic anhydrase inhibitors [22], Antimycobacterial [23], some sulfonamides act as sphingosine-1-phosphate (S_1P_1) receptor [24]. 11-beta-hydroxysteroid dehydrogenase type 1 (11β-HSD_1) inhibitors for the treatment of metabolic disorders [25], sulfonamide-1,2,4-triazoles, 1,3,4-thiadiazoles and 1,3,4-oxadiazoles, as potential antibacterial and antifungal agents [26]. The structurally related compounds having sulfonamide and amide linkage in combinations derivatives show selectively SIRT-2 inhibiting activity [27].

From above references it is clear that sulfonamide and amide coupled with different group compounds show considerable varied activities. All above references indicate that the probability of potent anticancer activity of the derivatives containing benzene sulfonamide and phenyl amide coupled compound increases considerably. So we have synthesized compounds having benzene sulfonamide and phenyl amide compounds which coupled at *meta* positions of benzene to each other. We have also developed simplified reaction conditions for all the steps so we can avoid costly reagents, tedious purifications, and all the synthesized compounds also have good purity. We here report the synthesis of new substituted sulfonamide derivatives (Scheme 1) with the aim of investigating their anticancer activity. The synthetic methods adopted for the preparation of the title compounds (**4a-4u)** [28] are depicted in the scheme presented below.

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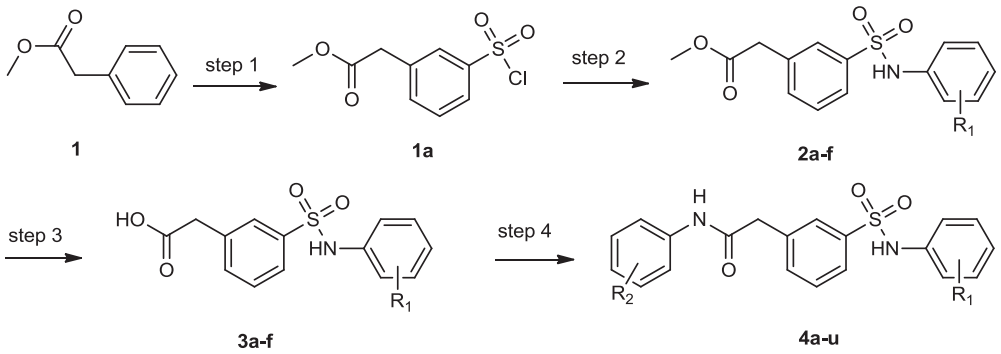

Scheme 1. Synthesis of N-(Substituted phenyl)-2-(3-substituted) sulfamoyl) phenyl) acetamide derivatives **(4a-4u)**.

Reagents and conditions: (step 1) Chlorosulfonic acid, DCM 0 °C-rt; (step 2) substituted amine, pyridine, DCM, 0 °C -rt; (step 3) Li(OH), THF, EtOH, H_2O, rt; (step 4) substituted amine, EDCI, DIPEA, DCM, rt.

	R_1	R_2		R_1	R_2
4a	2-CH_3	2,4-CH_3	**4l**	2-CH_3-CH_2	4-$C(CH_3)_3$
4b	2-CH_3-CH_2	2,4-CH_3	**4m**	2-CF_3	2-$C(CH_3)_3$
4c	2-CF_3	2,4-CH_3	**4n**	2-$C(CH_3)_3$	2-$C(CH_3)_3$
4d	2-$C(CH_3)_3$	2,4-CH_3	**4o**	Indoline	2-$C(CH_3)_3$
4e	Indoline	2,4-CH_3	**4p**	2,4-CH_3	2-CH_3
4f	2-CH_3	2-CH_3, 4-Cl	**4q**	2,4-CH_3	2-CH_3-CH_2
4g	2-CH_3-CH_2	2-CH_3, 4-Cl	**4r**	2,4-CH_3	2-OCH_3
4h	2-CF_3	2-CH_3, 4-Cl	**4s**	2-CH_3,4-$C(CH_3)_3$	2-CH_3
4i	2-$C(CH_3)_3$	2-CH_3, 4-Cl	**4t**	2-CH_3,4-$C(CH_3)_3$	2-CH_3-CH_2
4j	Indoline	2-CH_3, 4-Cl	**4u**	2-CH_3,4-$C(CH_3)_3$	2-OCH_3
4k	2-CH_3	4-$C(CH_3)_3$			

From above (Scheme 1, Table 1 & 2 See supporting information) here we have optimized the condition for aromatic chlorosulfonation in the presence of ester group. The reactivity changes according to the equivalent of chlorosulfonic acid used. We have carried out 10 different combinations and optimized the reaction condition which reduces the efforts of tedious work up and purifications of intermediate for first time. For all the reactions we have kept time constant. It is confirmed that when we use neat excess of chlorosulfonic acid without solvent there is 60% formation of required product (entry 10), then we have used excess chlorosulfonic acid with DCM then yield is 40% (entry 9). From above these two conditions it is clear that we have to use chlorosulfonic acid in equivalents along with in neat and in DCM solvent conditions.

The varied results are shown in Table 1. The (entries 1, 2, 3 and 4) shows there is formation product along with side products, the yields are 30%–55%. When we consider (entries 5, 6, 7 and 8) the yields are increasing from 40% to 80% when we used equivalent amount of chlorosulfonic acid. Mainly there is formation of product and less side products in (entries 5–8). But in (entries 1–4) there is formation of multiple spots on TLC, but in entries 5 to 8 the TLC profile was much more promising. The yields are isolated yields after series of reactions optimization and the condition 8 works (entry 8) well for given compound. By using this method the work up is easy we have to evaporate reaction mixture under reduced pressure and obtained gummy material which is washed with excess of hexane and it is crystallized from 20% ethyl acetate: hexane mixture to obtain white solid which is used further for sulfonamide coupling reaction. In entries 1 to 4 the side product is 4-substituted sulfonyl chloride compound obtained along with polar junk material, which required purification by column chromatography so the yields are less, but in latter case purification not required pure compound obtained by crystallization which is not possible in earlier entries, the gummy material remains as such.

In Scheme 2 and Scheme 3 first we have optimized the reaction solvent and base, from initial screening we have finalized DCM as the solvent and pyridine as the base that we have tabulated in Table 2. From Table 2 it is confirmed that when we used equivalents of pyridine and DCM the yield is 90% Table 4 entries 5.

There are many reports for the formations of sulfonamide so initially we have screened different bases by taking DCM and THF as solvents. In entry 5 with 2.5 equiv. of pyridine and in DCM the yield is 70% from entries 1 to 4 the yield ranges from 30% to 60%, in entries 6–10 the yield is 25%–60% also the reaction time for all entries is from 6 to 16 h. Time monitored on the bases on consumption of starting material. We have faced isolation problem in all the cases, like extraction needed for all the examples and obtained compounds are not cleaner so need to modify the yields. In entry 5 we have optimize work up condition so that we have to avoid rigorous extractions. In Table 3 we have varied the equivalents of pyridine and we have come to conclude that if we use equivalent volumes of pyridine along with DCM solvent then yield is 90% (entry 5). We have used pyridine as base and modified the

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