SYNTHESIS AND ANTICANCER EVALUATION OF NEW BENZENESULFONAMIDE DERIVATIVES

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A highly efficient protocol was developed for the synthesis of 3-(indoline-1-carbonyl)-N-(substituted)benzenesulfonamide compounds with excellent yields. The in vitro anticancer activity of the new 3-(indoline-1-carbonyl)-N-(substituted)benzenesulfonamide derivatives against A549 (lung cancer cell), HeLa (cervical), MCF-7 (breast cancer cell) and Du-145 (prostate cancer cell) cell lines were studied. Most of the tested compounds showed anticancer activity (IC_{50} values ranged between 1.98 and 9.12 µM against different cell lines).

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INTRODUCTION

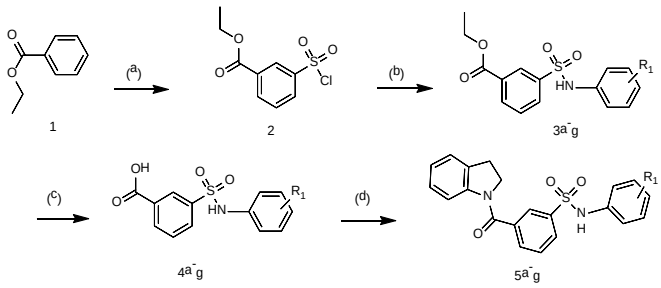
Antibiotic-resistant bacteria are rapidly emerging worldwide.[1] The indole derivatives are key structural features commonly found in biologically active natural products[2,3] as tryptophan,[4] tryptamine[5] and auxin.[6] It has been reported that sharing of the indole 3-carbon in the formation of spiroindoline derivatives profoundly enhances the biological activity of the formed compounds.[7] Moreover, some of the compounds containing benzenesulfonamide moiety also show a broad spectrum of important biological properties such as elastase inhibition,[8] carbonic anhydrase inhibition,[9] *Clostridium histolyticum* collagenase inhibition[10] as well as herbicides and plant growth regulator effect.[11]

Sulfonamides are common motifs in many drugs and medicinal compounds and play an essential role in their bioactivity.[12] Common drugs such as glibenclamide,[13] sultiame,[14] and COX-II inhibitors like Piroxicam,[15] Ampiroxicam,[16] and Celecoxib[17] containing a sulfonyl moiety. The sulfonamides have attracted increasing attention for their excellent biological activity[18-20] including antitumor, antibacterial, thrombin inhibition and antifungal activities.[21-23]

In continuation of our previous work on triazoles, pyrimidine, thiazoles and thiazolidinones of pharmaceutical interest[24,25] we report here the synthesis and anticancer activity of several new 3-(indoline-1-carbonyl)-N-(substituted)benzenesulfonamide derivatives.

RESULTS AND DISCUSSION

We have synthesized new indole derivatives containing sulfonamide linkage. The synthetic methods for the preparation of the N-(substituted phenyl)-3-(indoline-1-carbonyl)benzenesulfonamide derivatives **(5a-g)** are presented at Scheme 1. We have screened peptide coupling conditions in (Table 1) to obtain better yield, excellent purity, shorter reaction time, avoiding costly reagents and mainly reproducibility of yields



Scheme 1 Synthesis of N-(substituted phenyl)-3-(indoline-1-carbonyl)benzenesulfonamides. **3a-5a**: R^1=2-methyl; **3b-5b**: R^1=2-ethyl; **3c-5c**: R^1=2-CF_3, **3d-5d**: 2-t-Bu; **3e-5e**: R^1=indoline, **3f-5f**: R^1=2-Me, 4-t-Bu; **3g-5g**: R^1=H. **Reagents and conditions:** (a) sulfonyl chloride, dichloromethane (DCM) 0 ^{0}C-rt; (b) substituted amine, pyridine, DCM, 0 ^{0}C-rt; (c) lithium hydroxide (LiOH), tetrahydrofuran (THF), water (H_2O), rt; (d) Indoline, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDCI), diisopropylethyl-amine (DIPEA), DCM, rt.

The synthesis of compound **2** was done by treatment of**1** with sulfonyl chloride at 0 ^{0}C in DCM for 60 min and room temperature for 1 h. The reaction mixture was evaporated under reduced pressure and the obtained gummy material was washed with an excess of n-hexane. Recrystallization using 20 % ethyl acetate: n-hexane mixture gave pure **2** as yellow solid

Table 1. Optimization of peptide coupling reactions (**5a-g**)

Coupling Reagent	Base	Solvent	Time, h	Yield, %
HATU (1.1 equiv)	TEA (1.2 equiv)	DMF	14	57
HATU (1.1 equiv)	DIPEA (1.2 equiv)	DMF	14	55
PyBOP (1.1 equiv)	TEA (1.2 equiv)	THF	14	45
PyBOP (1.1 equiv)	DIPEA (1.2 equiv)	THF	14	50
EDCI (1.5 equiv)	TEA (2.5 equiv.)	DMF	14	62
HOBt (1.5 equiv)				
EDCI (1.5 equiv)	DIPEA (2.5 equiv)	DMF	14	72
HOBt (1.5 equiv)				
EDCI (1.5 equiv)	TEA (4 equiv)	DMF	14	78
HOBt (1.5 equiv)	DIPEA (4 equiv)	DMF	14	67
T3P (1.2 equiv)	TEA (2.5 equiv)	DCM	10	50
T3P (1.2 equiv)	DIPEA (2.5equiv)	DCM	10	60
EDCI (1.5 equiv)	DIPEA (2.5 equiv)	DCM	10	95
Acid (1 equiv) and Indoline (1.2 equiv)				

PyBOP=benzotriazol-1-yl-oxytripyrrolidinophosphonium hexafluorophosphate;TEA=triethylamine; HATU=1-[bis(dimethylamino)-methylene]-1H-1,2,3-triazolo[4,5-*b*]pyridinium 3-oxid hexafluorophosphate; EDCI=1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide, HOBt=hydroxybenzotriazole, T3P=propylphosphonic anhydride; DIPEA=diisopropylethylamine; DMF-dimethyformamid; DCM-dichloromethane; THF-tetrahydrofuran

Table 2. In vitro anticancer screening of the synthesized compounds **4a-4g** and **5a-5g** against A549, HeLa, MCF-7 and Du-145 cell lines. Data are expressed as IC_{50} (µM) ± SD (*n* = 3)

Compound	A549	HeLa	MCF-7	Du-145
4a	1.98±0.12	3.83±0.16	3.52±0.06	3.86±0.16
4b	2.81±0.13	2.92±0.08	2.32±0.22	3.82±0.12
4c	4.81±0.12	6.32±0.04	4.32±0.06	3.73±0.12
4d	2.82±0.11	1.99±0.22	2.36±0.12	3.52±0.11
4e	3.86±0.08	4.38±0.06	3.63±0.12	6.52±0.22
4f	2.72±0.11	3.87±0.08	4.12±0.06	3.86±0.22
4g	3.14±0.14	3.98±0.12	4.86±0.11	4.57±0.11
5a	8.48±0.14	9.12±0.08	7.82±0.08	9.12±0.06
5b	3.82±0.08	4.13±0.12	3.13±0.11	3.52±0.08
5c	4.13±0.12	5.16±0.08	6.12±0.12	4.52±0.11
5d	2.06±0.12	2.12±0.08	2.52±0.16	5.12±0.08
5e	2.52±0.11	3.52±0.11	4.48±0.08	4.08±0.11
5f	4.48±0.08	4.98±0.11	5.17±0.22	5.18±0.18
5g	2.73±0.08	2.12±0.12	2.12±0.08	2.12±0.04
5-Fluorouracil	1.61±0.12	1.72±0.18	1.81±0.10	1.89±0.12

The synthesis of compounds **3a-3g** was performed with sulfonamide coupling using variously substituted amines and compound **2** in the presence of pyridine as base and DCM as solvent at room temperature for 4 h. The reaction mass was treated with cold 2 M aq. HCl and the precipitated solids were washed with cold diethyl ether and pentane. The white solids **(3a-3g)** yield was varied between 85 and 95 %. The compounds **4a-4g** were prepared with hydrolysis of the compounds **3a-3g** using lithium hydroxide, tetrahydrofuran and water at room temperature for 10 h. Washing under basic conditions and acidifying led to the desired products as white solids with the required purity. The compounds **4a-4g** yield was varied between 80 and 85 %.

In order to synthesize compounds **5a-5g,** a series of coupling reagents and bases, and various solvents and reaction times were tested. We have varied the molar ratio of reagents and bases used to get better yield and purity in order to avoid column purifications (Table 1).

Using 1-[bis(dimethylamino)methylene]-1H-1,2,3-triazo-lo[4,5-*b*]py-ridinium 3-oxid hexafluorophosphate (HATU) as coupling reagent and DMF as solvent and triethylamine (TEA) and diisopropylethylamine (DIPEA) as bases, after 14 h, the yield of the product was 57 and 55 %, respectively. Using benzotriazol-1-yl-oxytripyrrolidino-phosphonium hexafluorophosphate (PyBOP) as coupling reagent and THF solvent, and TEA and DIPEA as a base, the obtained yields were 45 and 50%, respectively. 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDCI) and hydroxybenzotriazole (HOBt) as coupling reagents with DMF as a solvent, with 2.5 and 4 equiv. of TEA and DIPEA as bases for 14 h, gave 62, 78, and 72 and 67 % yields, respectively. Propylphosphonic anhydride (T3P) as coupling reagent with TEA and DIPEA as bases in DCM gave 50 and 60 % yield, respectively. When EDCI (1.5 equiv) was used together with DIPEA (2.5 equiv) in DCM, the yields were 95 %. Working up does not require column chromatography, no costly reagents are required.

The IC_{50} values for **4a-4g** and **5a-5g** are presented in Table 2, where all compounds exhibit moderate to a good activity toward cancer cell lines compared to 5-fluorouracil as a positive control. In the case of the human lung cancer cell line (A549) compounds **4a, 4b, 4d, 4f, 5d** and **5g** were the most potent with IC_{50} values ranging from 1.98-2.82 µM. The **4b, 4d, 5d** and **5g** compounds showed activity against HeLa cell line (IC_{50} = 1.99-2.92 µM), while in case of the MCF-7 breast cancer cell line, the most potent compounds were **4d, 5d** and **5g** withIC_{50}values of 2.12-2.52 µM. Lower activity was observed for the synthesized compounds on the Du-145 prostate cancer cell line, where the most potent candidate was the compounds **5g** with an IC_{50} value of 2.12 µM.

Generally, the lung (A549) and cervical (HeLa) cancer cell lines were the most sensitive toward the synthesized compounds. Regarding broad-spectrum anticancer activity reveals that compounds **4b, 4d** and **5g** were the most active, showing effectivity toward all four cell lines. The structure-activity relationship (SAR) showed that less hindered substitutions like methyl and ethyl groups at ortho and para position of aromatic rings increase the anticancer activity at all four cell lines, while ortho trifluoromethyl and indole groups decrease the anticancer activity. Despite steric hindrances, **4b**, **4d, 5d** and **5g** show promising anticancer activity due to electron donating substituents, and generally, the compounds with electron donating groups on the aromatic ring have more considerable anticancer activity than the compounds with electron withdrawing groups.

EXPERIMENTAL PART

Sulfonyl chloride and various solvents were commercially available. The chemicals were purchased from Sigma-Aldrich and Avra labs. Reaction courses were monitored by TLC on silica gel precoated F254 Merck plates. Developed plates were examined with UV lamps (254 nm). IR spectra were recorded on an FT-IR (Bruker). Melting points were recorded on SRS Optimelt, melting point apparatus and are uncorrected. The ^{1}H and ^{13}C NMR spectra were recorded on a 400 MHz Varian NMR spectrometer with DMSO-d_6 solvent. The chemical shifts are reported as δ ppm units (TMS). The following abbreviations are used; singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m) and broad (br). mass spectra were taken with Micromass-Quattro-II of water mass spectrometer.

General experimental procedure for the synthesis of N-(substituted phenyl)-3-(indoline-1-carbonyl)benzenesulfonamides (5a-5g)

Preparation of ethyl 3-(chlorosulfonyl)benzoate (2)

To a stirred solution of ethyl benzoate (10 g, 67 mmol) in DCM (25 mL) cooled to 0 ^{0}C, chlorosulfonic acid (9 g, 73 mmol) was added dropwise and the mixture was stirred for 1h at the same temperature followed by stirring at room temperature for further 1 h. After completion of reaction, the reaction mixture was evaporated under reduced pressure and the obtained gummy material was washed with excess of hexane and crystallized from 20 % ethyl acetate:hexane mixture to obtain ethyl 3-(chlorosulfonyl)benzoate **(2)** as white solid which is used further for sulfonamide coupling reaction, Yield 54 g (81 %).

Preparation of ethyl 3-(N-(o-tolyl)sulfamoyl)benzoate (3a)

To a stirred solution of ethyl 3-(chlorosulfonyl)benzoate **(2)** (3 g, 10.1 mmol) in DCM (5 ml), pyridine (5 ml) was added and the mixture was stirred at room temperature for 10 min. The reaction mixture was cooled to 0 ºC and 2-methylaniline (1.6 g, 15.16 mmol) was added dropwise followed by stirring at room temperature for 3 h. The reaction was monitored by TLC and LCMS, after completion of the reaction the reaction mixture was poured into cold 2 M aqueous HCl (10 ml) and stirred the mixture for 30 min. The obtained solid was filtered and washed with an excess of water, cold diethyl ether (10 ml) and cold pentane (10 ml). Ethyl 3-(N-(o-tolyl)sulfamoyl)benzoate (**2)** was obtained as white solid. Yield 2.8 g (90 %).

Preparation of 3-(N-(o-tolyl)sulfamoyl)benzoic acid (4a)

To a stirred solution of ethyl 3-(N-(o-tolyl)sulfamoyl)benzoate (**3a)** (2 g, 5.40 mmol) in THF (10 ml), water (2 ml) and lithium hydroxide (0.377 g, 18.2 mmol) were added and the reaction mixture was stirred for 4 h. The progress of the reaction was monitored by TLC and LC-MS. After the completion of the reaction, the reaction mixture was evaporated under reduced pressure with obtaining a gummy material. After adding 10 ml of water, the mixture was extracted with diethyl ether (10 ml). The pH of the collected aqueous layer was adjusted to 4 by 6 M aq. HCl. A precipitate was formed, and the mixture was stirred for 30 min. The obtained solid was filtered off, washed it with an excess of water, cold diethyl ether (10 ml) and cold pentane (10 ml) to obtain the desired 3-(N-(o-tolyl)sulfamoyl)benzoic acid (**4a)** as white solids. Yield 1.6 g (90 %)

N-(substituted phenyl)-3-(indoline-1-carbonyl)benzenesulfonamide (5a)

The compound 3-(N-(o-tolyl)sulfamoyl)benzoic acid (**4a**) (0.2 g, 0.65 mmol) was treated with EDCI (0.188 g, 0.98 mmol) and DIPEA (0.34 ml, 1.96 mmol) in DCM (10 ml). Then 2,4-dimethylaniline (0.238 g, 1.96 mmol) was added and the mixture was stirred at room temperature for 4 h. The reaction was monitored with TLC. 10 ml of cold water was added and the mixture was stirred for 10 min, then extracted with 10 ml of DCM. The collected organic layer was washed with 1 M aqueous HCl and brine (10 ml). Evaporating the organic layer, the compound **5a** was obtained with 90 % purity**.** Purification was done by washing with 5:95 % of DCM:hexane mixture, when the solid obtained was further washed with cold diethyl ether (20 ml) and cold pentane (20 ml).

3-(Indoline-1-carbonyl)-N-(o-tolyl)benzenesulfonamide (5a)

White solid (0.242 g, 92 %). LC-MS m/z (%): 393 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.70 (s, 1H), 8.26 (s, 1H), 8.22 (d, J=7.6 Hz, 1H), 7.81 (d, J=8 Hz, 1H), 7.7 (d, J=8 Hz, 1H), 7.18-7.13 (m, 4H), 7.1 (d, J=7.6 Hz, 2H), 6.95-6.92 (m, 2H), 3.60 (t, 2H), 3.16 (t, 2H), 2.14 (s, 3H). HPLC-98.50 % RT-5.68 min. ^{13}C NMR ($CDCl_3$, 100 MHz): 17.65, 27.79,

51.54, 126.09, 126.38, 126.40, 126.43, 126.58, 129.23, 129.42, 130.82, 130.89, 131.38, 133.42, 133.62, 134.27, 134.65, 135.40, 135.41, 135.45, 141.09, 163.93.

N-(2-Ethylphenyl)-3-(indoline-1-carbonyl)benzenesulfonamide (5b)

White solid, (0.240 g, 92 %) LC-MS *m/z* (%): 406 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.70 (s, 1H), 8.27 (s, 1H), 8.22 (d, *J*=8 Hz, 1H), 7.84 (d, *J*=8 Hz, 1H), 7.71 (t, *J*=7.6 Hz, 1H), 7.21-7.13 (m, 4H), 7.08-7.01 (m, 4H), 3.63 (t, 2H), 3.08 (t, 2H), 2.16 (q, 2H), 0.96 (t, 3H). HPLC-99.53% RT-9.21 min. ^{13}C NMR ($CDCl_3$, 100 MHz): 14.39, 18.80, 27.57, 53.18, 111.2, 120.3, 122.3, 124.5, 126.15, 126.23, 126.62, 126.63, 126.66, 129.34, 129.46, 131.36, 133.44, 133.67, 133.88, 135.46, 140.52, 141.13, 164.0.

3-(Indoline-1-carbonyl)-N-(2-(trifluoromethyl)phenyl)benzenesulfonamide (5c)

White solid, (0.240 g, 94 %). LC-MS *m/z* (%): 446 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.16 (s, 1H), 8.34 (s, 1H), 8.26 (d, *J*=7.2 Hz, 1H), 7.96 (d, *J*=7.6 Hz, 1H), 7.79 (d, 2H), 7.58 (t, *J*=8 Hz, 1H), 7.49 (t, *J*=7.8 Hz, 1H), 7.18 (d, *J*=8 Hz, 1H), 7.08-7.01 (m, 4H), 3.63 (t, 2H), 3.08 (t, 2H), HPLC-96.65%RT-4.89 min. ^{13}C NMR ($CDCl_3$, 100 MHz): 27.74, 52.51, 111.55, 115.07, 119.55, 125.6, 127.08, 127.09, 127.54, 128.58, 128.59, 129.23, 129.57, 130.86, 131.51, 133.29, 133.39, 133.59, 133.88, 135.36, 139.51,164.87.

N-(2-(tert-butyl)phenyl)-3-(indoline-1-carbonyl)benzenesulfonamide (5d)

White solid (0.240 g, 92 %), LC-MS *m/z* (%): 434 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.16 (s, 1H), 8.32 (s, 1H), 8.24 (d, *J*=7.2 Hz, 1H), 7.94 (d, *J*=7.6 Hz, 1H), 7.77 (d, 2H), 7.54 (t, *J*=8 Hz, 1H), 7.45 (t, *J*=7.8 Hz, 1H), 7.16 (d, *J*=8 Hz, 1H), 7.06-7.02 (m, 4H), 3.61 (t, 2H), 3.06 (t, 2H), 1.43 (s, 9H). HPLC-99.33% RT-6.18 min. ^{13}C NMR ($CDCl_3$, 100 MHz): 27.65, 31.3, 53.79, 51.54, 126.09, 126.38, 126.40, 126.43, 126.58, 129.23, 129.42, 130.82, 130.89, 131.38, 133.42, 133.62, 134.27, 134.65, 135.40, 135.41, 135.45, 141.09, 163.93.

Indolin-1-yl(3-(indolin-1-ylsulfonyl)phenyl)methanone (5e)

White solid (0.244 g, 94 %). LC-MS m/z (%): 404 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.26 (s, 1H), 8.22 (d, J=7.6 Hz, 1H), 7.81 (d, J=8 Hz, 1H), 7.7 (t, J=8 Hz, 1H), 7.20-7.15 (m, 4H), 7.06-7.02 (m, 4H), 4.11 (t, 2H), 3.65 (t, 2H), 3.11 (t, 2H), 3.06 (t, 2H). HPLC-97.99 %. RT-8.42 min. ^{13}C NMR ($CDCl_3$, 100 MHz): 26.65, 27.79, 42.40, 51.54, 111.23, 126.09, 126.38, 126.40, 126.43, 126.58, 129.23, 129.42, 130.82, 130.89, 131.38, 133.42, 134.27, 134.65, 135.40, 135.41, 135.45, 141.09, 163.93.

N-(4-(tert-butyl)-2-methylphenyl)-3-(indoline-1-carbonyl)-benzenesulfonamide (5f)

White solid (0.238 g, 90 %), LC-MS *m/z* (%): 448 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.62 (s, 1H), 8.27 (s, 1H), 8.23 (d, *J*=7.2 Hz, 1H), 7.87 (d, *J*=7.6 Hz, 1H), 7.73 (d, *J*=7,6 Hz, 1H), 7.29 (d, *J*=8.4 Hz, 2H), 7.06-7.02 (m, 4H), 6.83 (d, *J*=8.4 Hz, 1H), 3.61 (t, 2H), 3.05 (t, 2H), 2.04 (s, 3H), 1.21 (s, 9H). HPLC-98.67% RT-7.43 min. ^{13}C NMR ($CDCl_3$, 100 MHz): 27.65, 31.79, 34.21, 52.33, 111.56, 120.19, 123.17, 125.17, 126.03, 126.29, 126.32, 126.34, 127.64, 129.3, 129.49, 131.24, 131.95, 133.85, 135.35, 139.56, 141.42, 148.88, 151.78, 163.81.

3-(Indoline-1-carbonyl)-N-phenylbenzenesulfonamide (5g)

(0.244 g, 94 %) as White solid, LC-MS *m/z* (%): 378 (M+H). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.72 (s, 1H), 8.28 (s, 1H), 8.24 (d, *J*=7.6 Hz, 1H), 7.85 (d, *J*=8 Hz, 1H), 7.70 (d, *J*=8 Hz, 1H), 7.16-7.13 (m, 5H), 7.06-7.02 (m, 4H), 3.61 (t, 2H), 3.05 (t, 2H). HPLC-93.70% RT-7.58 min.^{13}C NMR ($CDCl_3$, 100 MHz): 27.34, 53.63, 119.40, 122.34, 125.63, 126.03, 126.12, 126.29, 126.71, 126.84, 128.2, 129.01, 129.37, 129.53, 129.94, 130.31, 133.87, 135.11, 136.24, 140.41, 165.03.

Anticancer activity

The synthesized compounds were evaluated for their *in vitro* anticancer activity against human lung cancer cell line (A549), cervical (HeLa) cancer cell line, breast cancer cell line (MCF-7) and prostate cell line (DU-145) using 5-fluorouracil as reference drug.[26] The IC_{50} value which corresponds to the concentration required for 50% inhibition of cell viability was determined.

Briefly, cells are grown in 96‐well plates in suspension and then were exposed for 48 hours to four serial concentrations of 1×10^{-7}, 1×10^{-6}, 1×10^{-5}, 1×10^{-4} and 1×10^{-3} M of each compound. Following this, cells were fixed and stained with protein binding SRB stain. Excess stain is washed out and the bound stain was solubilized, and the absorbance was measured at 492 nm in a plate reader. The concentration of the compounds that inhibited 50 % of the net cell growth was calculated from the dose-response curve obtained for each test compound and cell line. IC_{50} values were presented in micromolar (μM) concentration. 5‐Fluorouracil (5‐Fu) was used as positive control for the comparison of cytotoxicity of synthesized compounds. Assays were performed in triplicate on three independent experiments and their mean

CONCLUSION

An effective method was developed which provides easy access to new N-(substituted phenyl)-3-(indoline-1-carbonyl)benzenesulfonamide (**5a-g**) analogs. The mild reaction conditions, good to excellent yields, easiness of workup and the available substrates make the reactions to be attractive for the preparation of this compound class. The compounds (**4b, 4d, 5d** and**5g**) show potent anticancer activity in all the four cell lines tested.

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REFERENCES

[1]Walsh, C. T., Wencewicz, T. A., Prospects for new antibiotics: a molecule-centered perspective. *J. Antibiot.*,**2013**, *67*, 7. https://doi.org/10.1038/ja.2013.49

[2]Alvarez, M., Salas, M., Joule, J.A., Marine, Nitrogen-containing Heterocyclic Natural Products-Structures and Syntheses of Compounds Containing Indole Units, *Heterocycles*,**1991**, *32(7)*, 1391. https://doi.org/10.3987/rev-91-429

[3]Ruiz-Sanchis, P., Savina, S.A., Albericio, F., Alvarez, M., Structure, bioactivity and synthesis of natural products with hexahydropyrrolo[2,3-*b*]indole, *Chem. Eur. J*.,**2011**, *17(5)*, 1388.https://doi.org/10.1002/chem.201001451

[4]Mantle, P.G., The role of tryptophan as a biosynthetic precursor of indole-diterpenoid fungal metabolites: continuing a debate, *Phytochemistry*,**2009**, *70(1)*, 7.

https://doi.org/10.1016/j.phytochem.2008.11.004

[5]Jones, R. S. G., Tryptamine: a neuromodulator or neurotransmitter in mammalian brain, *Prog Neurobiol***1982**, *19(1-2)*, 117. https://doi.org/10.1016/0301-0082(82)90023-5

[6]Folkes, L.K., Wardman, P., Oxidative activation of indole-3-acetic acids to cytotoxic species- a potential new role for plant auxins in cancer therapy. *Biochem Pharmacol*, **2001**, *61(2)*, 129. https://doi.org/10.1016/S0006-2952(00)00498-6

[7]Abdel-Rahman, A.H., Keshk, E.M.; Hanna, M.A.; El-Bady, S.M., *Bioorg. Med. Chem.*,**2004**, *12(9)*, 2483. https://doi.org/10.1016/j.bmc.2003.10.063

[8]Scozzafava, A., Owa, T., Mastrolorenzo, A., Supuran, C.T., Anticancer and antiviral sulfonamides, *Curr. Med. Chem.*,**2003**, *10*, 925.

https://doi.org/10.2174/0929867033457647

[9]Scozzafava, A., Briganti, F., Ilies, M.A., Supuran, C. T., Carbonic anhydrase inhibitors: synthesis of membrane-impermeant low molecular weight sulfonamides possessing in vivo selectivity for the membrane-bound versus cytosolic isozymes, *J. Med. Chem.*,**2000**, *43*, 292. https://doi.org/10.1021/jm990479+

[10]Scozzafava, A., Supuran, C.T., Protease inhibitors. Part 8: synthesis of potent Clostridium histolyticum collagenase inhibitors incorporating sulfonylated L-alanine hydroxamate moieties, *Bioorg. Med. Chem.*,**2000**, *8*, 637. https://doi.org/10.1016/S0968-0896(99)00316-8

[11]Levitt, G., Agricultural sulfonamides, U. S. Patent No. US4383113, **1983**.

[12]Drews, J., Drug discovery: a historical perspective, *Science*. **2000**, *287*, 1960. https://doi.org/10.1126/science.287.5460.1960

[13]Wells, G. J., Tao, M., Josef, K.A., Bihovsky, R., 1,2-Benzothiazine 1,1-dioxide P(2)-P(3) peptide mimetic aldehyde calpain I inhibitors.*J. Med. Chem.*,**2001**, *44*, 3488.

https://doi.org/10.1021/jm010178b

[14]Brooke, E.W., Davies, S.G., Mulvaney, W. A., Synthesis and in vitro evaluation of novel small molecule inhibitors of bacterial arylamine N-acetyltransferases (NATs), *Bioorg. Med. Chem. Lett*.,**2003**, *13*, 2527.https://doi.org/10.1016/S0960-894X(03)00484-0

[15]Bihovsky, R., Tao, M., Mallamo, J. P., Wells, G. J.,1,2-Benzothiazine 1,1-dioxide alpha-ketoamide analogues as potent calpain I inhibitors, *Bioorg. Med.Chem. Lett*.,**2004**, *14*, 1035.https://doi.org/10.1016/j.bmcl.2003.11.037

[16]Zia-ur-Rehman, M., Choudary, J. A., Ahmad, S.; Siddiqui, H. L., Synthesis of potential biologically active 1,2-benzothiazin-3-yl-quinazolin-4(3H)-ones, *Chem. Pharm. Bull*.,**2006**, *54*, 1175.

[17]Hendricks, R. T., Spencer, S. R., Blake, J. F.,3-Hydroxyisoquinolines as inhibitors of HCV NS5b RNA-dependent RNA polymerase, *Bioorg. Med. Chem. Lett*.,**2009**, *19*, 410.https://doi.org/10.1016/j.bmcl.2008.11.060

[18]Kwon, Y., Song, J., Lee, H., Kim, E.Y., Lee, K., Lee, S.K., Kim, S., Design, Synthesis, and Biological Activity of Sulfonamide Analogues of Antofine and Cryptopleurine as Potent and Orally Active Antitumor Agents.*J. Med. Chem*.,**2015**, *58*, 7749.https://doi.org/10.1021/acs.jmedchem.5b00764

[19]Sławinski, J., Szafranski, K., Vullo, D., Supuran, C.T., Carbonic anhydrase inhibitors. Synthesis of heterocyclic 4-substituted pyridine-3-sulfonamide derivatives and their inhibition of the human cytosolic isozymes I and II and transmembrane tumor-associated isozymes IX and XII, *Eur. J. Med. Chem*.**2013**, *69*, 701.https://doi.org/10.1016/j.ejmech.2013.09.027

[20]Mirjafary, Z., Ahmadi, L., Moradi, M., Saeidian, H., A copper(II)–thioamide combination as a robust heterogeneous catalytic system for green synthesis of 1,4-disubstituted-1,2,3-triazoles under click conditions, *R. S. C. Adv*.,**2015**, *5*, 78038.https://doi.org/10.1039/C5RA16581D

[21]Pingaew, R., Prachayasittikul, V., Mandi, P., Nantasenamat, C., Prachayasittikul, S., Ruchirawat, S., Prachayasittikul, V., Synthesis and molecular docking of 1,2,3-triazole-based sulfonamides as aromatase inhibitors. *Bioorg. Med. Chem.* **2015**, *23*, 3472.https://doi.org/10.1016/j.bmc.2015.04.036

[22]Wang, X. L., Wan, K., Zhou, C. H., Synthesis of novel sulfanilamide-derived 1,2,3-triazoles and their evaluation for antibacterial and antifungal activities. *Eur. J. Med. Chem.*,**2010**, *45*, 4631.https://doi.org/10.1016/j.ejmech.2010.07.031

[23]Zhang, Z., Jeyakkumar, P., Kumar, K. V., Zhou, C. H., Synthesis of novel sulfonamide azoles via C–N cleavage of sulfonamides by azole ring and relational antimicrobial study. *New. J. Chem*., **2015**, *39*, 5776. https://doi.org/10.1039/C4NJ01932F

[25](a) Pansare, D. N., Shelke, R. N., Pawar, C. D., A facile synthesis of (Z)-2-((5-(4-chlorobenzylidene)-4-oxo-4,5-dihydrothiazol-2-yl)amino)substituted acid using microwave irradiation and the conventional method. *Lett. Org. Chem.*, **2017,** *14(7)*, 517. https://doi.org/10.2174/1570178614666170524142722; (b) Pansare, D. N., Shelke, R. N., Shinde, D. B., A facial synthesis and anticancer activity of (Z)-2-((5-(4-nitrobenzylidene) -4-oxo-4,5-dihydrothiazol-2-yl)amino) substituted acid, *J. Het. Chem.*, **2017**, *54(6)*, 3077. https://doi.org/10.1002/jhet.2919 ; (c) Pansare, D. N., Shinde, D. B., A facile synthesis of novel series (Z)-2-((4-oxo-5-(thiophen-2-yl methylene)-4,5-dihydro thiazol-2-yl)amino) substituted acid, *J. Saudi. Chem. Soc*., **2017**, *21*, 434. https://doi.org/10.1016/j.jscs.2015.10.005 ; (d) Pawar, C. D., Chavan, S.L., Pawar, U. D., Pansare, D. N., Deshmukh, S. V., Shinde, D. B., Synthesis, anti-proliferative activity, SAR and Kinase inhibition studies of thiazol-2-yl-substituted sulfonamide derivatives, *J. Chin. Chem. Soc*., **2018,** https://doi.org/10.1002/jccs.201800312; (e) Pawar, C. D., Pansare, D. N., Shinde, D. B., (Substituted)-benzo[*b*]thiophene-4-carboxamide synthesis and antiproliferative activity study, *Lett. Drug. Des. Disc*., **2018,** https://doi.org/10.2174/1570180815666181004114125 ;

[26](a) Pawar, C. D., Pansare, D. N., Shinde, D. B., Synthesis of new 3-(substituted phenyl)-N-(2-hydroxy-2-(substituted phenyl)ethyl)-N-methylthiophene-2-sulfonamide derivatives as antiproliferative agents, *Eur. J. Chem.*, **2018**, *9(1)*, 13. https://doi.org/10.5155/eurjchem.9.1.13-21.1669;

(b) Pawar, C. D., Pansare, D. N., Shinde, D. B., Synthesis and antiproliferative activity of 3-(substituted)-4,5,6,7-tetrahydro-6-(substituted)-1H-pyrazolo[3,4-c]pyridine derivatives, *Eur. J. Chem.,* **2017**, *8(4),* 400. https://doi.org/10.5155/eurjchem.8.4.400-409.1645

[27]Skehan, P., Storeng, R., Scudiero, D., Monks, A., McMohan, J., Vistica, D., Warrem, J. T., Bokesch, H., Kenney, S., Boyd, M. R., New colorimetric cytotoxicity assay for anticancer-drug screening, *J. Natl. Cancer. Inst.*, **1990**, *82*, 1107.

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