One Pot Synthesis of Some Novel Sulfonamide Derivatives Containing -NH2 Group: Spectral Characterization and Biological Evaluation

Hajira Rehman1,*, Abdul Qadir M1, Hazoor Ahmad Shad2,3, and Zafar Iqbal Khan4

1Institute of Chemistry, University of the Punjab, Lahore, Pakistan
2Department of Chemistry, University of Sargodha, Pakistan
3Department of Chemistry, Postgraduate College Jhang, Pakistan
4Department of Botany, University of Sargodha, Sargodha, Pakistan

Abstract
A series of sulfonamide derivatives HR1-HR5 were synthesized in one step reaction (nucleophilic substitution reaction SN2). Structures of new products were confirmed by elemental and spectral analysis i.e., FTIR, UV, 1H NMR, 13C NMR, EIS-MS. In-vitro, antibacterial and anti-fungal activity of newly synthesized compounds was investigated against two bacterial strains: Escherichia coli and Staphylococcus aureus and two fungal strains: Aspergillum flavous and Aspergillum niger. It was found that among all tested compounds HR2 showed good antibacterial activity with MIC 1.13 × 10^-3 and 1.54 × 10^-3 for S. aureus and E. coli respectively. While HR4 showed good antifungal activity with inhibition zone 25.2 ± 0.12 mm (MIC: 71.2 × 10^-3 mol/L) and 17.1 ± 55.5 mm (MIC: 98.9 × 10^-3 mol/L) against A. flavous and A. niger respectively. Developed compounds were also screened for their In-vitro antioxidant activity by DPPH radical scavenging assay. All compounds showed moderate activity but potential activity with 15.75% at 6 mM was exhibited by compound HR2.

Keywords: Antibacterial activity; Antifungal activity; p-Toluene sulfonamides; Sulfonamide

Introduction
Sulfonamides have commercialized applications as antibacterial antibiotic agents as they inhibit activity of enzyme dihydropteroate synthase (DHPS) [1] and prevent synthesis of folic acid (Vitamin B9), which is an essential intermediate for life of bacteria. So sulfonamides and their derivatives are used as antibiotics medicines [2]. Apart from this application as an antibacterial agent, various sulfonamide derivatives are known to inhibit many enzymes such as Serine protease [3-5], cyclooxygenase [6], matrix metalloproteinase [7] and carbonic anhydrase [8-11]. Moreover their widespread potential values have led to discovery of various therapeutic applications in cancer chemotherapy, hypoglycemia, diuretics [12] and anti-impotence agent Viagra [13]. They have also received a considerable attention due to their diverse biological activities as HIV protease [14,15] and as an antitumor [16]. In recent year, novel sulfonamides were synthesized such as doriperiens with brand name doribax which is an injectable antibiotic [17]. Other developed sulfonamides drugs such as AZA (acetazolamide) and MZA (metahacetazoamides) are widely used mainly as anti-glaucoma agents and also used for therapy of some other diseases [18-20]. Ester derivatives of sulfonamides are well known as cell proliferation inhibitor [21]. Newer sulfonamides and their derivatives have also got more attraction in the field of medicine [22,23]. On other hand disease causing organisms when treated with routine antibiotic become must resistance with appearance of some additional species as per mutation. So synthesis of novel sulfonamides and their derivatives have got much attention from researcher because of their widespread applications in the field of medical chemistry and medicine science [24,25]. Most practical and different method for the synthesis of sulfonamides (Scheme 1) involves sulfonation of amines and alcohols [26] in presence of some base such as Pyridine, triethylamine, or some metal hydroxides or carbonates.

In present study, we have synthesized five new sulfonamides (HR1-HR5) (Figure 1) derivatives by reaction of amine -NH2 group containing drug and p-toluene sulfonyl chloride. These -NH2 group containing drugs are cefotixin, ciprofloxacin, frusamide, amlodepine and indapamide respectively. These synthesized compounds not yet reported which is a strong evidence of their novelty. Synthesized compounds were biologically evaluated by using the bacterial and two fungal strains such as Escherichia coli, Staphylococcus aureus, Aspergillum niger and Aspergillum flavous.

Experimental

Chemistry
Chemicals used in present work were of analytical grade and used without further purification to synthesize desired compounds. Chemicals were obtained from E-Merck (Germany) and BDH (UK). Grade 1 quality water (0.01 μS/cm) was prepared in our own laboratory. 1H NMR spectra were developed on Bruker spectrometer 400 MHz.

Finnegan MAT 112 mass spectrometer was used for recording MS data. Elementary analysis of compound was conducted by using Elmer elemental analyzer. Gallen kamp MP70 was used to determine the m.p. For recording infrared spectra, Cary 630 Agilent FIFIR was used. Absorption spectra were conducted on PGFT90+UV-VIS spectrometer. Pre-coated TLC silica plates (Merck, Germany) were used for purification and to confirm the progress of the synthesized compounds.

General procedure for synthesis of compounds
For the preparation of sulfonamide derivatives (HR1-HR5), a proficient method based on Hinsberg Test was used i.e., sulfonation of primary, secondary amine in presence of base resulting in nucleophilic attack by amine. Tosylchloride was used for sulfonation and Na₂CO₃ for the preparation of sulfonamide derivatives.

*Corresponding author: Hazoor Ahmad Shad, Department of Chemistry, University of Sargodha, Pakistan, Tel: +923323177994; E-mail: hazoozahmad@gmail.com

Received September 15, 2016; Accepted September 26, 2017; Published September 29, 2017

Citation: Rehman H, Abdul Qadir M, Shad HA, Khan ZI (2017) One Pot Synthesis of Some Novel Sulfonamide Derivatives Containing -NH2 Group: Spectral Characterization and Biological Evaluation. Med Chem (Los Angeles) 7: 252-256. doi: 10.4172/2161-0444.1000465

Copyright: © 2017 Rehman H, et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.
Figure 1: New sulphonamides (HR1-HR5).

Results

Spectral characterization of sulphonamides

(6R,7R)-3-(acetoxyethyl)-7-((Z)-2-(methylaminooxy)-2-(4-methylphenylsulfonyl)thiazol-4-yl)acetamido)-8-oxo-5-thia-1-azabicyclo [4.2.0] oct-2-ene-2-carboxylic acid (HR1): Yield: 82%, Colour: off white, m.p. (decomp.): 185°C. FTIR (cm⁻¹): 3442.7, 2923.8, 1738.9, 1159.48 (S=O str), 1054.3 (C-N str), 1642.1 (C=O), 814.0 (-OH). ¹HNMR (DMSO-d6, ppm): 11.08 (1H, s, -COOH), 8.68 (1H, s, -CH=COOH), 7.85-7.87 (2H, d, J = 8.1, -ArH), 7.40-7.44 (2H, d, J = 8.3, -ArH), 5.63 (2H, s, -OCH₂-), 3.92 (3H, s, -OCOCH₃). ¹³C NMR (δ, ppm): (170.27), (167.47), (164.52), (163.78), (161.73), (151.39), (149.47), (137.41), (136.82), (130.32), (129.38), (129.38), (129.78), (129.79), (129.23), (63.27), (62.31), (60.69), (56.85), (24.23), (21.84), (20.92). MS (m/z, ESI): Calcd. for C₂₃H₂₃N₅O₉S₃ (609.05): C: 45.31; H: 3.80; N: 14.49; Found: C: 45.13; H: 3.98; N: 14.49.

(6R,7R)-2-(4-Chloro-2-((furan-2-ylmethyl)amino)-5-(N-tosylsulfamoyl)benzoic acid (HR3): Yield: 75%, Colour: Yellow, M.p. (decomp.): 240°C. FTIR (cm⁻¹): 3442.7, 2932.8, 1730.1 (C=O), 1155.3 (S=O str), 1050 (C-S str), 3368.2 (-OH). ¹HNMR (DMSO-d6, ppm): 11.08 (1H, s, -COOH), 8.09-8.12 (1H, d, J = 6.0, -NHCO), 7.82-7.84 (2H, d, J = 8.2, -NH), 7.62 (1H, s, -C=CH₂), 7.40-7.44 (2H, d, J = 8.3, -ArH), 5.52-5.54 (1H, d, J = 6.1, -NHCH₂CO-), 5.11-5.16 (1H, d, J = 6.9, -SCH-), 4.79 (2H, s, -OCH₂-), 4.02 (1H, s, -NHSO₂-), 3.92 (3H, s, -OCH₃), 3.19-3.23 (1H, d, J = 7.1, -CH₂-, 3.08-3.10 (1H, d, J = 7.0, -CH₂-), 2.35 (3H, s, -ArCH₃), 2.27 (3H, s, -COCH₃). ¹³C NMR (δ, ppm): (170.27), (167.47), (164.52), (163.78), (161.73), (151.39), (149.47), (137.41), (136.82), (130.32), (129.38), (129.38), (129.72), (129.79), (129.78), (129.23), (63.27), (62.31), (60.69), (56.85), (24.23), (21.84), (20.92). MS (m/z, ESI): Calcd. for C₂₃H₂₃N₅O₉S₃ (609.05): C: 45.31; H: 3.88; Found: C: 45.13; H: 3.81; N: 14.45.

1-cyclopropyl-6-fluoro-4-oxo-7-(4-tosylpiperazin-1-yl)-1,4-dihydroquinoline-3-carboxylic acid (HR2): Yield: 75%, Colour: Yellow, M.p. (decomp.): 240°C. FTIR (cm⁻¹): 3442.7, 2932.8, 1730.1 (C=O), 1155.3 (S=O str), 1050 (C-S str), 3368.2 (-OH). ¹HNMR (DMSO-d6, ppm): 11.08 (1H, s, -COOH), 6.84 (1H, s, -CH=COOH), 6.41-6.44 (1H, d, J = 7.1, -NCH-), 3.19-3.23 (1H, d, J = 7.2, -NCH₂-, 2.35 (3H, s, -ArCH₃), 1.83-2.05 (2H, dq, J = 7.2-8.3, -CHCH₂CH₃), 1.11-1.37 (2H, dq, J = 7.2-8.3, -CHCH₂CH₃). ¹³C NMR (δ, ppm): (170.27), (167.47), (164.52), (163.78), (161.73), (151.39), (149.47), (137.41), (136.82), (130.32), (129.38), (129.38), (129.78), (129.79), (129.78), (129.23), (63.27), (62.31), (60.69), (56.85), (24.23), (21.84), (20.92). MS (m/z, ESI): Calcd. for C₂₃H₂₃N₅O₉S₃ (609.05): C: 45.31; H: 3.88; Found: C: 45.13; H: 3.81; N: 14.45.

Antimicrobial activity

Luria-Bertani broth was used as Growth media as it is highly supportive in bacterial growth [27]. In order to make media, 4.0 g of Tryptone, 2.0 g of yeast extract and 4.0 g of sodium chloride were added in 400 ml distilled water. The pH value of media was kept at 7. The media was then sterilized in autoclave at 125°C for 30 min. Sample solutions, in 5-50 µg concentration range, were prepared. For each bacterial strain, three test tubes were prepared i.e., S. aureus and E. coli. In above autoclaved tubes, 2 mL of LB Broth and 20 µL of bacterial strain were added, followed by the addition of stocks of 5 µL, 10 µL, 20 µL containing 5.0 µg, 12.5 µg and 50 µg. Then these tubes were incubated at 37°C for 72 h. At 600 nm, OD of each medium and mixture was stirred 2 h. Precipitates were filtered and purified by using preparatory TLC. The media was then sterilized in autoclave at 125°C for 30 min at 120°C and cooled at 50°C and inoculated with 0.5 McFarland standard. Then Agar medium was then poured into all assay plates 9 cm in diameter and were allowed to cool down until solidified. Equidistance four wells 6 mm in diameter were cut out of agar upon solidification. 6 µL of medium, containing synthesized compounds, was added into these wells. Incubation of plates was done at 27°C for 48 h. For each compound, MIC values in µg/mL and zone of inhibition in mm were measured, comparing it with standard antibiotic isoniazid (ISC) in concentration 1.0 µg/mL in each plate as positive control. Results are mentioned in the Table 1.

Antioxidant activity

In-vitro antioxidant activity of synthesized compounds, using DPPH, was evaluated by a reported method [33]. In order to produce precise results, all compounds were run in triplicate. Trolox was used for standard curve. Relative concentrations of compounds were determined using R value, and scavenging percentage that directly represents the antioxidant activity was calculated using formula i.e.,

\[ \text{Inhibition\%} = \left( \frac{1 - \text{sample}_{530}}{\text{blank}_{530}} \right) \times 100 \]

Results are given in Table 2.

Results

Spectral characterization of sulphonamides

Citation: Rehman H, Abdul Qadir M, Shad HA, Khan ZI (2017) One Pot Synthesis of Some Novel Sulphonamide Derivatives Containing -NH₂ Group: Spectral Characterization and Biological Evaluation. Med Chem (Los Angeles) 7: 252-256. doi: 10.4172/2161-0444.1000465
A series of five sulfonamides were synthesized using efficient method based on Hinsberg Test and details of reaction conditions are explained in experimental section. The compounds HR1, HR2 and HR5 were obtained in excellent yield (above 75%) while the compounds HR3 and HR4 were obtained in good yield (above 62%). Conformation of compounds was done by elemental analysis and measurement of absorption maximum (λ_{max}) provided the justification. The physiochemical and analytical data of synthesized sulfonamides are presented in Table 3. The synthesized compounds were characterized by FT-IR; the characteristics band at 1148-1155.5 cm⁻¹ of S=O stretching and 1048-1055 cm⁻¹ for (C-N) and 813-814 cm⁻¹ (C-S) and 930-958.9 cm⁻¹ (S-N) for all compounds reveals the formation of sulfonamides. In HR1 and HR2, peaks of Ar-CH₃ were explained in experimental section. The compounds HR1, HR2 and HR5 were obtained in excellent yield (above 75%) while the compounds HR3 and HR4 were obtained in good yield (above 62%). Conformation of compounds was done by elemental analysis and measurement of absorption maximum (λ_{max}) provided the justification. The physiochemical and analytical data of synthesized sulfonamides are presented in Table 3. The synthesized compounds were characterized by FT-IR; the characteristics band at 1148-1155.5 cm⁻¹ of S=O stretching and 1048-1055 cm⁻¹ for (C-N) and 813-814 cm⁻¹ (C-S) and 930-958.9 cm⁻¹ (S-N) for all compounds reveals the formation of sulfonamides. In HR1 and HR2, peaks of Ar-CH₃ were explained in experimental section.
found in their concerned region i.e., 2.34-2.36 ppm. In HR1 there is a stereo-centre i.e., -CH$_2$H$_2$S-, both protons attached to carbon atom are in different environment. That’s why they couple with each other to give their own doublets. A broad triplet was found in HR2 due to a six member ring containing two nitrogen atoms i.e., -N$_2$(CH$_3$)$_2$ - at 3.19-3.30 ppm. In HR3 and HR4, -ArCH$\equiv$ peaks were recorded at 2.37 and 2.36 ppm respectively. In both compounds chemical shift values of -ArH which are in the vicinity of chlorine containing carbon were shifted to the downfield side due to electron withdrawing inductive effect of -Cl atom than other -ArH. In case of HR4 there is an ethyl group which is directly attached to the ester group. Methyl group (-CH$_3$) showed its triplet at 1.31-1.37 ppm and methylene group (-CH$_2$-) showed its quartet at 4.20-4.29 ppm. In HR5 there are two -CH$_2$ groups, one group is aromatic methyl and second group is attached to a five member ring. Their peaks were found at 2.35 ppm and 1.25-1.27 ppm respectively. Similarly, chemical shift values of -ArH in -Cl containing ring has been shifted to down field side than other aromatic protons. This shifting is due to the high electronegativity of chlorine atom and its electron withdrawing effect. Developed compounds were also screened for their antioxidant and antimicrobial activities. All exhibited moderate activity but potential activity with 15.75% at 6 mM was shown by compound HR2. Compounds HR4 and HR2 exhibited good activities against fungal strain A. flavus almost comparable with the reference Isocoumarin. MIC values and zone of inhibition are presented in Table 1.

**Conclusion**

In conclusion, sulfonamides derivatives of five novel compounds, HR1-HR5, were synthesized and their antioxidant, antimicrobial and cytotoxicity test were also done. Remarkable antioxidant activity of concerned compounds guided and motivated us about their possible clinical significance. Antimicrobial activity was not so pronounced. Compound HR4 showed remarkable antifungal results, but compound HR2 was found to have potential antioxidant activity. However they did not give so pronounced cytotoxic effects.

**Acknowledgements**

Hajira Rehman gratefully acknowledges the cooperation of Director, Institute of Chemistry University of Punjab, Lahore, Pakistan for providing me lab facilities. I am also thankful to HEC Pakistan for providing financial support to carry out this project.

**Conflict of Interest**

Authors declare that there is no conflict of interest regarding the publication of this paper.

**References**

1. Brown GM (1971) The Biosynthesis of Pteridines. Advances in Enzymology and Related Areas of Molecular Biology 35: 35-77.
2. Massah AR, Adibi H, Khodarahmn H, Abiri R, Majooni MB, et al. (2008) Synthesis, in vitro antibacterial and carbonic anhydrase II inhibitory activities of N-acylsulfonamides using silica sulfuric acid as an efficient catalyst under both solvent-free and heterogeneous conditions. Bioorganic Medicinal Chemistry 16: 5465-5472.
3. Casini J, Antel F, Abbate A, Scozzafava S, David H, et al. (2003) Identification of 3, 4-Dihydropyrroloquinoline-2 (1H) -sulfonamides as Potent Carbonic Anhydrase Inhibitors: Synthesis, Biological Evaluation, and Enzyme- Ligand X-ray Studies. Bioorganic Medicinal Chemistry Letters 13: 841-845.
4. Thiry A, Dogme JM, Supuran CT, Masereel B (2008) Current Pharmaceutical Design 14: 661-671.
5. Gitto R, Agnello S, Ferro S, De Luca L, Vullo D, et al. (2010). Journal of Medicinal Chemistry 53: 2401-2408.
6. Supuran CT, Casini A, Scozzafava A (2003) Protease inhibitors of the sulfonamide type: anticancer, antiinflammatory, and antiviral agents. Medicinal Research Reviews 23: 535-556.
7. Cheng XC, Wang Q, Fang H, Xu WF (2008) Role of sulfonamide group in matrix metalloproteinase inhibitors. Current Medicinal Chemistry 15: 368-373.
8. Kuang R, Epp JB, Ruan S, Yu H, Huang P, et al. (1999) Therapeutic potential of sulfamides as enzyme inhibitors. Journal of the American Chemical Society 121: 8128-8129.
9. Groutas WC, He S, Kuang R, Ruan S, Tu J, et al. (2001) Bioorganic Medicinal Chemistry 9: 1543-1548.
10. Zhong J, Gan X, Allston KR, Lai Z, Yu H, et al. (2004) J Comb Chem 6: 556-563.
11. Winum JY, Scozzafava A, Montero JL, Supuran CT (2006) Medicinal Research Reviews 26: 767-792.
12. Maren TH (1967) Carbonic anhydrase: Chemistry, physiology, and inhibition. Physiological Reviews 47: 595-781.
13. Supuran CT, Innocenti A, Mastrolorenzo A, Scozzafava A (2004) Antiviral sulfonamide derivatives. Mini-Reviews in Medicinal Chemistry 4: 169-200.
14. Markgren PO, Schau W, Hamalainen M, Karlen A, Hallberg A, et al. (2002) Relationships between structure and interaction kinetics for HIV-1 protease inhibitors. Journal of Medicinal Chemistry 2: 5430-5439.
15. Stranix BR, Sauve G, Bouzide A, Coté A, Sévigny JY, et al. (2004) Lysine sulfonamides as novel HIV- protease inhibitors: Rapsoni -dihedral-oued. Bioorganic Medicinal Chemistry Letters 14: 3971-3974.
16. Crespo R, De Bravo MG, Colinas PA, Bravo RD (2010) In vitro antitumor activity of N-glycosyl sulfonamides. Bioorganic Medicinal Chemistry Letters 20: 6469-6474.
17. Brown SD, Traczewski MM (2005) Synthesis and antibacterial activity of sulfonamides. SAR and DFT Studies. Journal of Antimicrobial Chemotherapy 55: 944-949.
18. Supuran CT, Scozzafava A (2002) Applications of carbonic anhydrate inhibitors and activators in therapy. Expert Opinion on Therapeutic Patents 12: 217-242.
19. Supuran CT, Scozzafava A (2001) Carbonic Anhydrase Inhibitors. Current Medicinal Chemistry - Immunology Endocrine & Metabolic 1: 61-97.
20. Supuran CT, Scozzafava A (2000) Carbonic anhydrase inhibitors and their therapeutic potential. Expert Opinion on Therapeutic Patents 10: 575.
21. Das B, Reddy VS, Reddy MR (2004) An efficient and selective tosylation of alcohols with p-toluenesulfonylic acid. Tetrahedron Letters 45: 6717-6719.
22. Chohan ZH, Hazoor A, Shad S (2008) Structural elucidation and biological significance of 2-hydroxy-1-naphthaldehyde derived sulfonamides and their first row d-transition metal chelates. Journal of Enzyme Inhibition and Medicinal Chemistry 23: 369-379.
23. Chohan ZH, Hazoor AS, Faiiz-ul-Hassan N (2009) Synthesis, characterization and biological properties of sulfonamide-derived compounds and their transition metal complexes. Applied Organometallic Chemistry 23: 319-328.
24. Chohan ZH, Hazoor AS, Moulay H, Youssoufi Y, Hadda TB (2010) Some new biologically active metal-based Sulfonamide. European Journal of Medicinal Chemistry 45: 2893-2901.
25. Chohan ZH, Hazoor AS (2011) Sulfonamide-derived compounds and their transition metal complexes: synthesis, biological evaluation and X-ray structure of 4-bromo-2-[E]-[4-[3,4-dimethylisoxazol-5-yl]-sulfonyl][phenyl] iminomethyl] phenolate. Applied Organometallic Chemistry 25: 591-600.
26. Caddick D, Wilden JD, Judd BB (2004) Direct synthesis of sulfonamides and activated sulfonate esters from sulfonic acids. Journal of Organic Chemistry 126: 1024-1042.
27. Sezonov G, Joselevau-Pelti D, Dari R (2007) Escherichia coli physiology in Luria-Bertani broth. Journal of Bacteriology 189: 8746-8749.
28. Magalha S, Camero T (1997) Susceptibility of Candida albicans ‘invitro’ mediante los pozos de difusión. Boletín de la Sociedad Venezolana de Microbiología 18: 16-20.
29. Magalha S, Camero T (1998) Pruebas de sensibilidad de Candida albicans frente a los de usocomercial. Boletín de la Sociedad Venezolana de Microbiología 18: 16-20.
30. Magalha S, Mata S, Camero T (1999) Determinacion de lasenibilidad antifúngica a los de usocomercial. Boletín de la Sociedad Venezolana de Microbiología 18: 16-20.
32. Magaldi S, Mata S, Hartung C (2001) In vitro susceptibility to fluconazole of Candida spp. isolates comparing three different methods. J Mycol Med 1: 123-126.

33. Mohammed H (2009) Natural and synthetic flavonoid derivatives with potential antioxidant and anticancer activities.