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Synthesis of some new sulfonamides derived from Anthraquinone

Dr. Ayman Ramadan and Dr. Kamal Khoudari

Department of chemistry, Faculty of Science, Aleppo University, Syria

***Abstract*:** *A convenient, simple, eco-friendly, economical and efficient one-pot synthesis of new sulfonamide compounds derived from anthraquinone is described. The reaction occurs between anthraquinone-2-sulfonyl chloride (resulted by chlorosulfonation of anthraquinone) and some aminobenzene derivatives (4-aminophenol, 4-chloroaniline and 1,4-Diaminobenzne) in the presence of Potassium carbonate as base and water as solvent at room temperature within a short reaction times, gives the corresponding sulfonamides in good to excellent yields. The structures of the new sulfonamides confirmed by spectral analysis techniques (FT-IR, ESI-MS).*

Keywords: Anthraquinone, Chlorosulfonation, Sulfonamide, FT-IR, Mass spectrum.

1. Introduction

Sulfonamides are basis of several drug groups, known as sulfa drugs. Any compound that has sulfonamide moiety (SO_2NH_2) in its structure is referred to as sulfonamide. They comprise substantial class of pharmaceutical drugs, containing various kinds of pharmacological agents which exhibit a wide spectrum of biological activities such as having antitumor [1], antibacterial [2] antiviral agents, anti VIH protease inhibitor [3], anti-inflammatory [4], antifungal [5], antiprotozoal [6] anticonvulsant agents [7], diuretic [8] and hypoglycemic [9]. Furthermore, sulfonamides are employed as herbicides [10], pesticides [11] and surfactants [12].

More recently, sulfonamides have been found to be potent cysteine protease inhibitors, which could possibly extend their therapeutic applications to include conditions such as Alzheimer's disease, arthritis and cancer [13].

Sulfonamides are mostly used to treat the bacterial infectious cells because they do not significantly affect the antigenic properties of the infective organism or the development of specific antibodies [14]. Bacteria have liability to acquire resistance against sulfonamides by changing their cell wall permeability, enhancing essential metabolites production, or increasing production of enzyme [15]. As a result of wide range of activity and importance, there are several available methods for the preparation of sulfonamides. The development of simple, efficient, eco-friendly and economically viable processes in organic synthesis of sulfonamides is an urgent need.

The most typical method for the synthesis involves reaction between primary or secondary amines with a sulfonyl chloride in presence of organic or inorganic bases but the nucleophilicity of amines may vary depending on the groups attached to it. In general, primary amines are highly reactive, whereas secondary amines show very low to almost nil reactivity [16]. This synthesis method represents the simplest and direct pathway to obtain sulfonamides, wherein the sulfonamide yield is high [17].

Over the decades researchers reported use of neat pyridine or its combination with polar solvents for the preparation of sulfonamides of primary amines *e.g.*, Youn *et al.* reported preparation of sulfonamide using aryl primary amine and aryl sulfonyl chloride employing pyridine as a base at (0-25) °C. They have observed 100% yield when aniline is used as a primary amine and benzene sulfonyl chloride or 4-nitrobenzyl sulfonyl chloride as sulfonylation agent. Quantitative yield also reported for reaction between *p*-toluidine and tosylchloride [18]. Triethylamine is also commonly used in the synthesis of sulfonamides. Behmadi *et al*. reported synthesis of heteroaryl sulfonamides by condensation diamines containing a pyridine ring with sulfonyl chlorides to give corresponding disulfonamides using Tetrahydrofuran as solvent and triethyl amine as base [19].

Use of inorganic base like potassium carbonate was also explored in sulfonylation reaction by Pranab *et al.* where the researchers achieved up to 78% yield when reactions were carried out in PEG-400 solvent. The developed protocol was convenient due to heterogeneous reaction mass where base can be easily separated from reaction mass by filtration. Recovery and reuse of PEG-400 is another advantage of the reported method from economic and environmental aspect [20]. Rebecca and coworkers reported poor yield (only 44%) when strong inorganic base like sodium hydroxide was employed for the

sulfonamide synthesis reaction. In a magnetic stirrer acid chloride and amine were mixed together. Addition of 10% NaOH was done in portions and the reaction mixture stirred for 1 h at RT to produce *N*-phenylbenzene sulfonamide. The main intension of the study was to prepare unalkylated benzene sulfonanilides to check rearrangement of the same to sulfones [21].

Sulfonamide synthesis by reaction between aqueous solution of primary amine and sulfonyl chloride at RT using sodium carbonate as a base was reported by Soukaina *et al*. A new benzene sulfonamide derivatives were synthesized by a simple method in aqueous media under dynamic pH control is adopted for synthesis of sulfonamides. The research group prepared series of sulfonamide-4-substituted-1, 2, 3-trizolyl nucleosides and evaluated their activity against tumor cell lines *RCC4* and *MDA-MB-231* [22]. Amidine and benzene sulfonamides derivatives were synthesized and evaluated biologically by Waseem *et al.* The pH of the reaction mixture was strictly monitored and maintained at (8–10) at regular intervals during the experimental reaction using Na_2CO_3 solution (1M) [23].

The chemical importance of the synthesis of the sulfonamides is distinguish between types of amines(primary, secondary and tertiary amines) by means of what is known as a Hinberg's test. In this test, the amine is shaken well with Hinsberg reagent in the presence of aqueous alkali (either KOH or NaOH). A reagent containing an aqueous sodium hydroxide solution and benzenesulfonyl chloride is added to a substrate. A primary amine will form a soluble sulfonamide salt. Acidification of this salt then precipitates the sulfonamide of the primary amine. A secondary amine in the same reaction will directly form an insoluble sulfonamide. A tertiary amine will not react with the sulfonamide but is insoluble. After adding dilute acid this insoluble amine is converted to a soluble ammonium salt. In this way the reaction can distinguish between the three types of amines [24]. The synthesis of sulfonamides can also be used for the protection of primary and secondary amines [25] and for the analytical derivatization purposes, *e.g.* anthraquinone-2-sulfonyl chloride reacts in one-step quantitatively with series of aliphatic amines to form stable sulfonamides, which are readily amenable to analysis by normal phase and reversed phase HPLC was reported by Feng *et al*. [26]. The synthesis of a new sulfonamide derivatives from natural products such as anthraquinones is an important idea that has been focused on in this research.

2. Materials and Methods

2.1. Materials

4-Aminophenol, 1,4-diaminobenzene, 4-Chloroaniline, Anthraquinone, chlorosulfonic acid, Potassium carbonate, and HCl were of analytical grade obtained from from Sigma-Aldrich.

2.2. Apparatus

Infrared device type FT -IR-4100 from the Japanese company JASCO, Liquid Chromatograph HPLC-MS with UV Detector Connected with Mass Spectrometer from Japan Shimadzu Type LC-20AD, Heating device with a magnetic stirrer Produced by Sybron of America, Model. SP1842, Atlas syringe pump – LabMakelaar

2.3. General Description for Synthesis of Sulfonamides

A simple method in aqueous media under dynamic pH control is adopted for synthesis of sulfonamides. Filtration after acidification is involved for isolation of products. All the amines were weighed accurately and suspended in water by constant stirring using magnetic stirrer. The pH of the reaction contents was strictly monitored and maintained at (8-10) at regular intervals during the experimental reaction using K_2CO_3 solution (1M). When anthraquinone-2-sulfonyl chloride was accurately weighed and added carefully into the above solution. The reaction was carried in round bottom flask equipped with magnetic stirrer. The course of reaction was examined by the change in pH value due to formation of HCl by the consumption of sulphonyl chloride during the reaction. The completion of reaction occurs when the pH value is not changed. Then the pH was adjusted at (2-3) using HCl solution (2M). The precipitates formed were filtered through Whatman filter washed with water and dried to afford the required compound. No further purification was needed.

2.4. Synthesis of anyhrquinone-2-sulfony chloride as intermediate compound

The reaction of chlorosulfonation is carried out in a 100ml two-hole flask equipped with a magnetic stirrer. Anthraquinone (25mmol, 5.2g) placed in the flask and chlorosulfonic acid (250mmol, 16.6ml) added to it with extreme caution in a small batches by drip funnel. The flask is connected to a refluxed distillation device and provided from the top with a hose to a vessel containing an alkaline aqueous solution to absorb the non-condensing chlorosulfonic acid vapors, which releases strongly during the reaction. The mixture of reaction is stirred by a magnetic stirrer and heated for 30min, the chlorosulfonic acid boils at 152 °C. After the time has elapsed, the flask is cooled down and 25g of ice

is added to it, mixed well and left to settle for ten minutes, then the reaction product (anthraquinone-2-sulfonyl chloride) is filtered by a Büchner funnel. The sediment is washed well with cold distilled water to get rid of the traces of acid, then the precipitate is left to dry in the air first, then inside a desiccator filled with anhydrous calcium chloride granules to obtain the compound as a yellow solid. The synthesis reaction of anyhrquinone-2-sulfony chloride is shown in Figure (1)

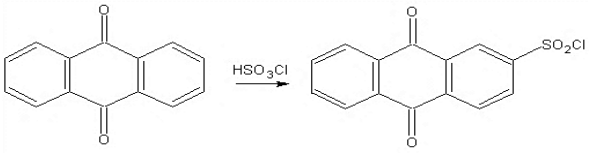

Figure 1. Synthesis of anyhrquinone-2-sulfony chloride

2.5. Synthesis of 2-[N-(*para* hydroxyl phenyl)sulfonamide]anthraquinone

The solid mixture of 4-aminophenol (3.2mmol, 0.349g) and anyhrquinone-2-sulfony chloride (3.2mmol, 1g) was suspended in 25 ml water. The pH of the suspension was adjusted and was maintained at (8-10) by adding 1mol/l K_2CO_3 aqueous solution at room temperature using a syringe pump equipped with a pH controller. It took 90min for the reaction to complete. HCl (2M) was added to adjust pH= 2.0. The precipitate was collected by filtration, washed with water and dried to afford the compound as a red solid. The synthesis reaction of new sulfonamide derivative is shown in Figure (2)

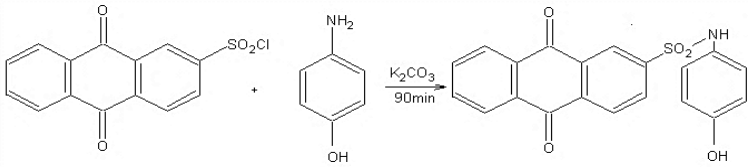

Figure 2. Synthesis of 2-[N-(*para* hydroxyl phenyl)sulfonamide]anthraquinone

2.6. Synthesis of 2-[N-(*para* chloro phenyl)sulfonamide]anthraquinone

The solid mixture of 4-chloroaniline (3.2mmol, 0.408g) and anthraquinone-2-sulfonyl chloride (3.2mmol, 1g) was suspended in 25 ml water. The pH of the suspension was adjusted and maintained at (8-10) by adding 1M K_2CO_3 aqueous solution at room temperature using a syringe pump equipped with a pH controller. It took 2 hours for the reaction to complete. HCl (2M) was added to adjust pH=2.0. The precipitate was collected by filtration, washed with water and dried to afford the compound as a green solid. The synthesis of new sulfonamide derivative is shown in Figure (3)

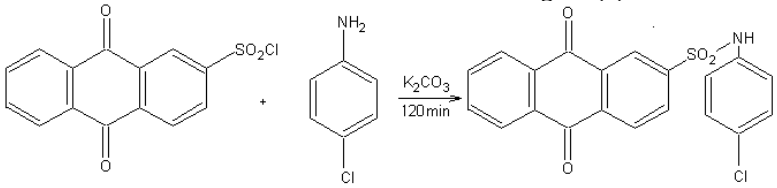

Figure 3. Synthesis of 2-[N-(*para* amino phenyl)sulfonamide]anthraquinone

2.7. Synthesis of 2-[N-(*para* amino phenyl)sulfonamide]anthraquinone

The solid mixture of 1,4-diaminobenzene (3.2mmol, 0.346g) and anthraquinone-2-sulfonyl chloride (3.2mmol, 1g) was suspended in 25 ml water. The pH of the suspension was adjusted and was maintained at (8-10) by adding 1M K_2CO_3 aqueous solution at room temperature using a syringe pump equipped with a pH controller. It took 90min for the reaction to complete. HCl (2M) was added to adjust pH=2. The precipitate was collected by filtration, washed with water and dried to afford the compound as a dark violet solid. The synthesis of new sulfonamide derivative is shown in Figure (4)

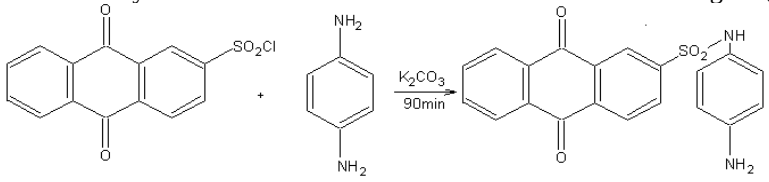

Figure 4. Synthesis of 2-[N-(*para* amino phenyl)sulfonamide]anthraquinone

3. Results and Discussion

3.1. Spectroscopic and Physical Data

Anyhrquinone-2-sulfony chloride:

$C_{14}H_7ClO_4S$; Yellow Solid, Yield (23.75mmol, 7.284g, 95%); Mp:193-194°C; FTIR (KBr): 3043cm^{-1} (C-H str. aromatic), 1380cm^{-1} and 1177cm^{1} (S=O str. in sulfonylchlorides), 1687cm^{-1} (C=O Diaryl str.), 1584cm^{-1} (C=C aromatic str.), 925cm^{-1}, 813cm^{-1} and 701cm^{-1} (C-H aromatic bend); ESI-MS: *m/z* = 306 [M_w].FTIR and mass spectrums of the new sulfonamide compound are shown in figure (5) and (6).

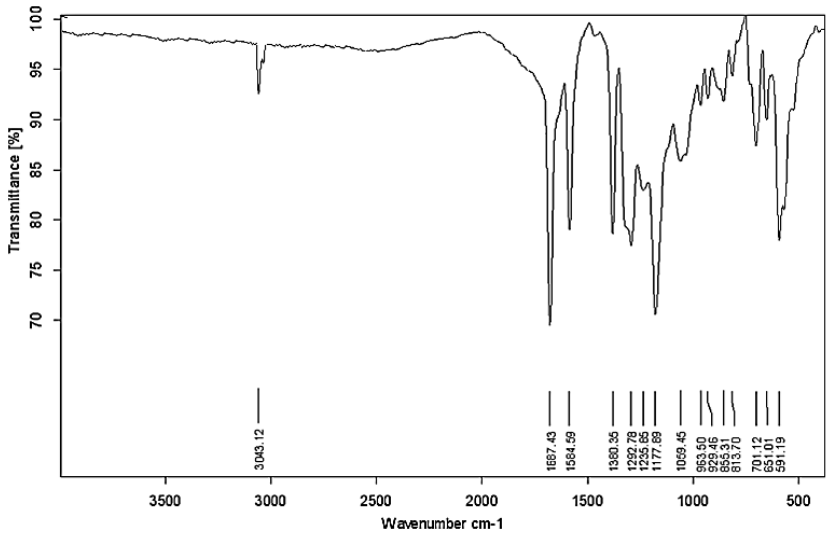

Figure 5. FTIR Spectrum of Anyhrquinone-2-sulfony chloride

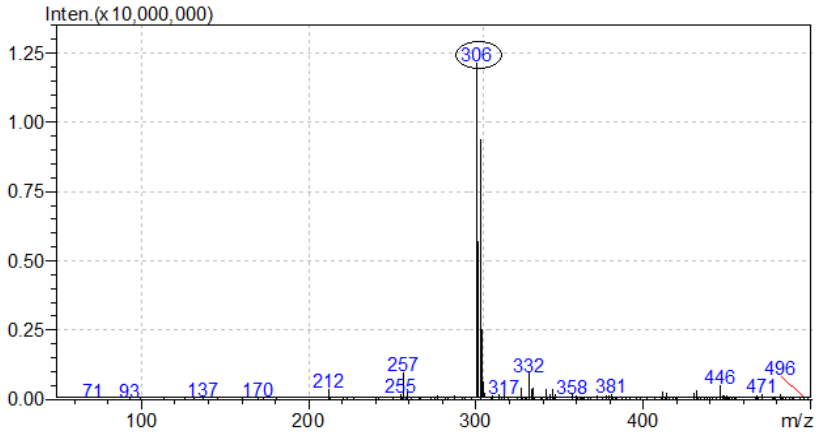

Figure 6. Mass Spectrum of Anyhrquinone-2-sulfony chloride

2-[N-(*para* hydroxyl phenyl)sulfonamide] anthraquinone

$C_{20}H_{13}NO_5S$; Red Solid; Yield (2.976mmol, 1.127g, 93%); Mp:189–190°C; FTIR (KBr): 3432cm^{-1} (O-H str.), 3364cm^{-1} (N-H str.), 1158cm^{-1} (S=O Sym. str.), 1331cm^{-1} (S=O Asym. str.), 1677cm^{-1} (C=O Diaryl str.), 1587cm^{-1} and 1490cm^{-1} (C=C aromatic str.), 1290cm^{-1} (O-H bond.) 824cm^{-1} and 702cm^{-1} (C-H aromatic bend); ESI-MS: *m/z* = 378 [M_w-1]. FTIR and mass spectrums of the new sulfonamide compound are shown in figure (7) and (8)

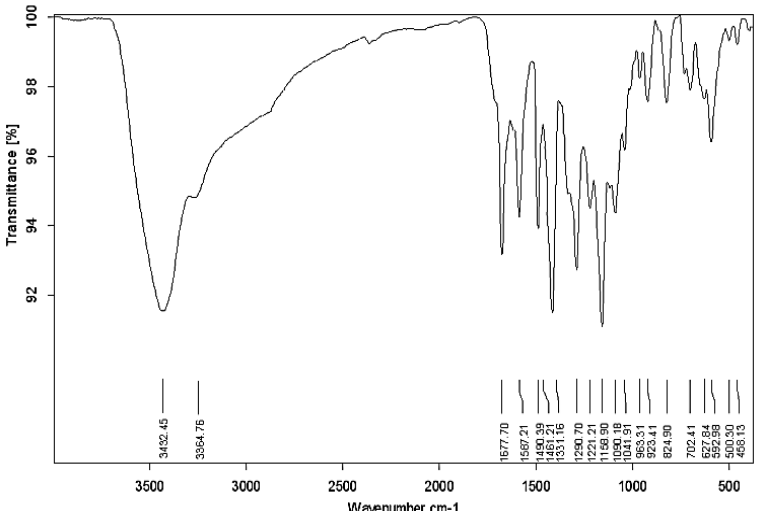

Figure 7. FTIR Spectrum of 2-[N-(*para* hydroxyl phenyl)sulfonamide] anthraquinone

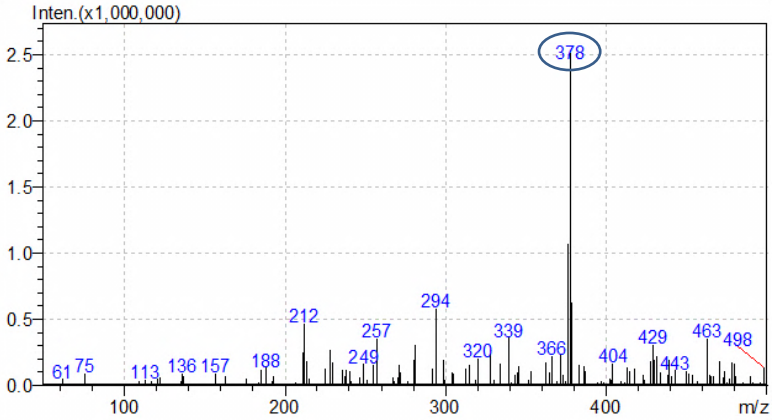

Figure 8. Mass Spectrum of 2-[N-(*para* hydroxyl phenyl)sulfonamide] anthraquinone

2-[N-(*para* chloro phenyl)sulfonamide]anthraquinone

$C_{20}H_{12}NO_4SCl$; Green Solid, Yield (2.592mmol, 1.030g, 81%); Mp:177–178°C; FTIR (KBr): 3332cm^{-1} (N-H str.), 1158cm^{-1} (S=O Sym. str.), 1341cm^{-1} (S=O Asym. str.), 1677cm^{-1} (C=O Diaryl str.), 1090cm^{-1} (C-Cl str.), 1584cm^{-1} and 1490cm^{-1} (C=C aromatic str.), 923cm^{-1}, 824cm^{-1} and 702cm^{-1} (C-H aromatic bend); ESI-MS: *m/z* = 397 [M_w , ^{35}Cl : 2/3] and 399 [M_w , ^{37}Cl : 1/3].

FTIR and mass spectrums of the new sulfonamide compound are shown in figure (9) and (10)

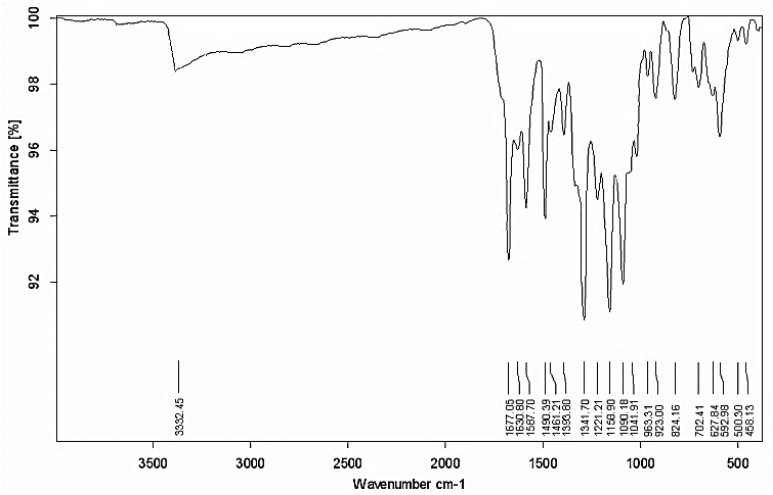

Figure 9. FTIR Spectrum of 2-[N-(*para* chloro phenyl)sulfonamide] anthraquinone

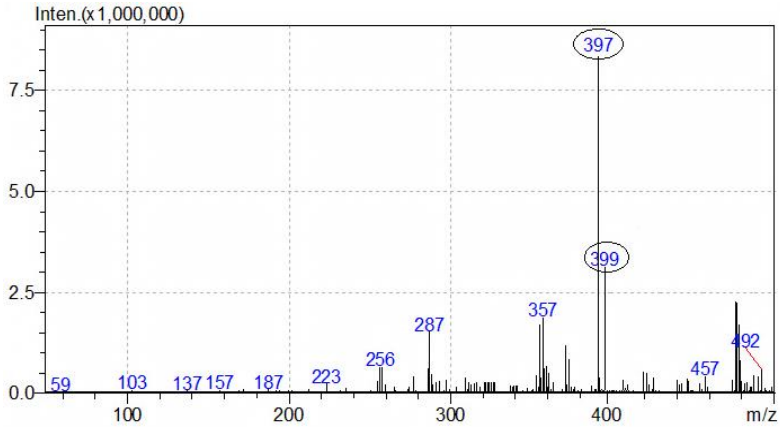

Figure 10. Mass Spectrum of 2-[N-(*para* chloro phenyl)sulfonamide] anthraquinone

2-[N-(*para* amino phenyl)sulfonamide]anthraquinone

$C_{20}H_{14}N_2O_4S$, Dark violet solid; Yield (2.752mmol, 1.040g, 86%); Mp:202–203°C; FTIR (KBr): 3331cm^{-1} and 3291cm^{-1}(N-H str.), 1680cm^{-1}(N-H bend.), 1150cm^{-1} (S=O Sym. str.), 1345cm^{-1} (S=O Asym. str.), 1680cm^{-1} (C=O Diaryl str.), 1589cm-1 and 1490cm^{-1} (C=C aromatic str.), 923cm^{-1}, 826cm-1 and 704cm^{-1} (C-H aromatic bend); ESI-MS: *m/z* = 379 [M_w+1].

FTIR and mass spectrums of the new sulfonamide compound are shown in figure (11) and (12)

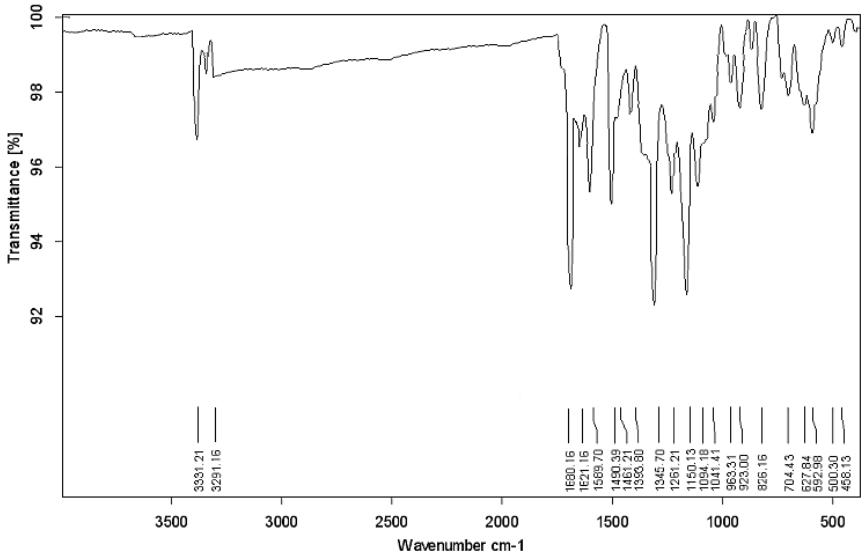

Figure 11. FTIR Spectrum of 2-[N-(*para* amino phenyl)sulfonamide] anthraquinone

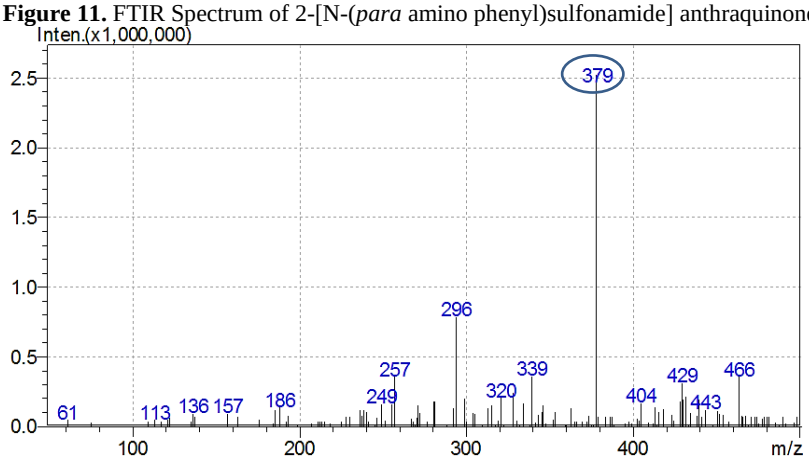

Figure 12. Mass Spectrum of 2-[N-(*para* amino phenyl)sulfonamide] anthraquinone

4. Conclusion

In this article, three new sulfonamides derived from anthraquinone have been synthesized by reaction between anthraquinone-2-sulfonyl chloride (resulted by chlorosulfonation of anthraquinone) and some of aminobenzene derivatives. The identification of new sulfonamides have been done by IR and Mass spectroscopy. This method of synthesis offers several noteworthy advantages, including high yields of products and easy work-up in combination with stability, economical, cleaner and greener conditions, non-toxicity, mild reaction conditions, easy preparation, and cheapness of the catalysts are the main advantages of this method. Moreover, this method has the ability to tolerate a wide variety of substitutes in aromatic compounds.

Acknowledgements

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References

1. T. Owa, T. Nagasu, **Novel sulphonamide derivatives for the treatment of cancer**, *Expert Opinion on Therapeutic Patents*, 10(11), 2000, 1725–1740.
2. C. T. Supuran, A. Scozzafava, A. Casini, **Carbonic anhydrase inhibitors**, *Medicinal Research Reviews*, 23(2), 2003, 146–189.
3. J. B. McMahon, R. J. Gulakowsky, O. S. Weislow, R. J. Schultz, V. L. Narayanan, D. J. Clanton, R. Pedemonte and others, **Diarylsulfones, a new chemical class of nonnucleoside antiviral inhibitors of human immunodeficiency virus type 1 reverse transcriptase**, *Antimicrob, Agents, Chemother*, 1993, 37, 754.
4. A. Scozzafava, T. Owa, A. Mastrolorenzo, **Anticancer and antiviral sulfonamides,** *Curr. Med. Chem*., 2003, 10, 925.
5. R. Ezabadi, C. Camoutsis, , P. Zoumpoulakis, , A. Geronikaki, M. Soković, J. Glamočilija, , A. Čirič, **Sulfonamide-1,2,4-triazole derivatives as antifungal and antibacterial agents: synthesis, biological evaluation, lipophilicity, and conformational studies,** *Bioorg. Med. Chem.* 2008, 16, 1150.
6. K. hibale, , H. Haupt, , H. Kendrick, V. Yardley, A. Saravanamuthu, A. H. Fairlamb, S. L. Croft, **Antiprotozoal and cytotoxicity evaluation of sulfonamide and urea analogues of quinacrine**, *Bioorg Med. Chem. Lett*. 2001, 11, 2655.
7. A. Kleeman, J. Engel, B. K. Reichert, **Pharmaceutical Substances; Synthesis, Patents and Applications, 3rd ed.**,*Thieme: Stuttgart*, 1999
8. C. Supuran, C. Conroy,T. Maren, **Carbonic anhydrase inhibitors: synthesis and inhibitory properties of 1,3,4-thiadiazole-2,5-bissulfonamide**, *European Journal of Medicinal Chemistry*,.31(11), 1996, 843–846.
9. A. E. Boyd III, **Sulfonylurea receptors, ion channels, and fruit flies**, *Diabetes*, 37(7), 1988, 847–850.
10. T. W. Jabusch , R. S. Tjeerdema, **Chemistry and Fate of Triazolopyrimidine Sulfonamide Herbicides**, *Rev Environ Contam Toxicol* 193: 2008, 31–52.
11. E. Kissa, **Fluorinated Surfactants and Repellents, In Surfactant Science Series**, 97; *Marcel Dekker*: New York, 2001.
12. 1H. J. Lehmler, **Synthesis of environmentally relevant fluorinated surfactants-a review**, *Chemosphere* 58, 2005, 1471.
13. W. R. Roush, S. L. Gwaltney, J. Cheng, K. A. Scheidt, J. H. McKerrow, E. Hansell, **Vinyl Sulfonate Esters and Vinyl Sulfonamides: Potent, Irreversible Inhibitors of Cysteine Proteases,** *J. Am. Chem. Soc*., 120, 1998, 10994.
14. Z. Zhong, X. Ji, R. Xing et al., **The preparation and antioxidant activity of the sulfanilamide derivatives of chitosan and chitosan sulfates**, *Bioorganic & Medicinal Chemistry*,15(11), 2007, 3775–3782.
15. R. E. Clopton and A. Smith, **Efficacy of oral sulfadimethoxine against two gregarine parasites, Protomagalhaensia granulosae and Gregarina cubensis (Apicomplexa: Eugregarinida), infecting the Death's Head cockroach, Blaberus discoidalis**, *Journal of Parasitology*, 88(4), 2002, 786–789.
16. T.C. Das, S.A. Quadri1, M. Farooqui, **Recent advances in synthesis of sulfonamides: A review**, *Chemistry & Biology Interface*, 2018, 8(4), 194-204.
17. A. Kolaczek, I. Fusiarz, J. Lawecka, D. Branowska, **Biological activity and synthesis of sulfonamide derivatives: a brief review**, *Chemik*, 68(7), 2014, 620-628.
18. S. W. Youn, T. Y. Ko, Y. H. Jang, **Palladium-Catalyzed Regioselective Synthesis of 3-Arylindoles from N-Ts-Anilines and Styrenes.**, *Angew. Chem. Int. Ed.*, 2017, 56, 6636-6640.
19. H. Behmadi, S.M. Saadatia, M. Roshania, M. Ghaemyb, **Synthesis of new disulfonamides from different substituted diamino pyridines**, *Ecl. Quím., São Paulo*, 34(3), 2009, 27-31.
20. P. J.Das, B. Sharma, **A Convenient and Benign Synthesis of Sulphonamides in PEG-400**, *Asian J. Chem*., 27(1), 2015, 189-191.
21. N. Rebecca, M. James, Z. Muray, **Triflic acid–catalyzed rearrangement of unalkylated benzene sulfonanilides**, *Synth. Commun*., 46, 2016, 949-955.
22. A. Saukaina, D. Maeva, D. Mohsine, D. Luc, O. Khalid, R. Guillaume, **Synthesis and anti-cancer activities of new sulfonamides 4-substituted-triazolyl nucleosides**, *Bioorg. Med. Chem. Lett*., 27, 2017, 1989-1992.
23. M. A. Qadir, M. Ahmed, H. Aslam, S. Waseem, M. I. Shafiq, **Amidine Sulfonamides and Benzene Sulfonamides: Synthesis and Their Biological Evaluation**, *Hindawi Publishing Corporation*, Volume 2015, Article ID 524056, 8 pages.
24. R. L. Shriner, R. C. Fuson, and D. Y. Curtin, **The systematic identification of organic compounds**, *John Wiley & Sons, Inc., Journal of the American Pharmaceutical Association (Scientific ed.)*, 45(6), 1956, 435.
25. T. W Greene, P. G. M. Wuts, **Protective Groups in Organic Synthesis**, *J. Med. Chem.*, 1999, 42, 25, 5285.
26. F. Feng, B. Uno, M Goto, Z .Zhang, D. An, **Anthraquinone-2-sulfonyl chloride: A new versatile derivatization reagent-synthesis mechanism and application for analysis of amines,** *Talanta* 57(3), 2002, 481-490.