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Synthesis, antimicrobial and QSAR studies of novel benzenesulfonamide derivatives

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Novel benzenesulfonamide derivatives have been synthesized and characterized by various spectroscopical and analytical techniques, such as, FT-IR, UV-Vis, and NMR, and elemental analysis. The derivatives synthesized have been tested for *in vitro* antimicrobial activities against several microorganisms using the disc diffusion method, wherein a broad spectrum of activity has been observed with inhibition zones in the range 10–32 mm. Photoluminescence properties have been evaluated and a QSAR investigation on the compounds synthesized has been carried out to reveal correlations between various physicochemical parameters and antimicrobial activity.

Keywords: Benzenesulfonamide, antimicrobial activity, QSAR studies, fluorescence

Research on cannabinoids continues to advance, where one direction is geared towards structural changes in the dibenzopyran motif of the progenitor compound tetrahydrocannabinol (THC) to target various needs. Studies of cannanbinoids for ophthalmic applications followed the discovery of ocular cannabinoid receptors[1,2]. While sulfonamide type compounds have been shown to have ophthalmic properties, specifically, antiglaucomal[3,4], they are also analgesic[5], and potential antiulcer agents[6], and tumor suppressants[7,8].

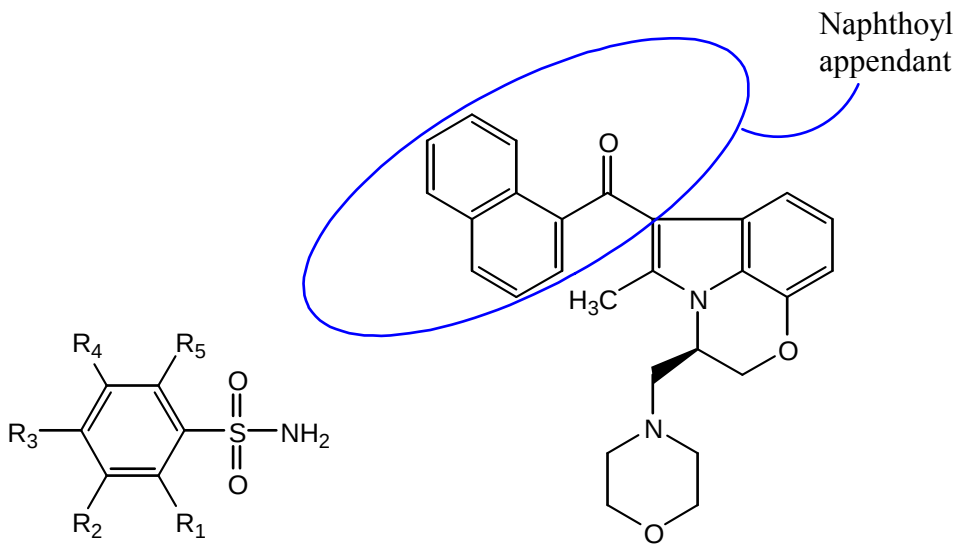
In an earlier study, we reported the synthesis of new thiadiazolic sulfonamides[9], where antimicrobial activities and fluorescence measurements were carried out, and evaluations were presented. Encouraged by the successful synthesis earlier, work herein was extended to synthesize other sulfonamides, and includes the QSAR HOMO and LUMO elements of study, to yield more useful information. Further, these new molecules may be used as appendages to be incorporated into much larger molecular structures. As discussed in the earlier paper, the design of these benzenesulfonamides stems from the structure of the compound aminoalkylindole WIN 55,212-2 (Figure 1), a potent CB_1 cannabinoid[10], such that its naphthoyl appendant was utilized. A sulfonamide unit, specifically a benzenesulfonamide was combined with this naphthoyl group, as sulfonamides are known to belong to the sulfa-type class of compounds that have an important role in medicinal chemistry[11]; the general structure of benzenesulfonamides is given in Figure 1. Additionally, though sulfonamides are known for their antiglaucomal carbonic anhydrase inhibition[12,13], their mechanism of action is still unclear, which thus remains a focus of research.

Fluorescence characteristics of the target compounds were also studied as they may have considerable fluorescence signals that may be utilized to serve in medical diagnostics as possible biotherapeutic aids. Such structural combinations may lead to compounds having enhanced biological properties, and may be possible candidates for treatment of glaucoma, and the development of antimicrobial drugs.

Results and Discussion

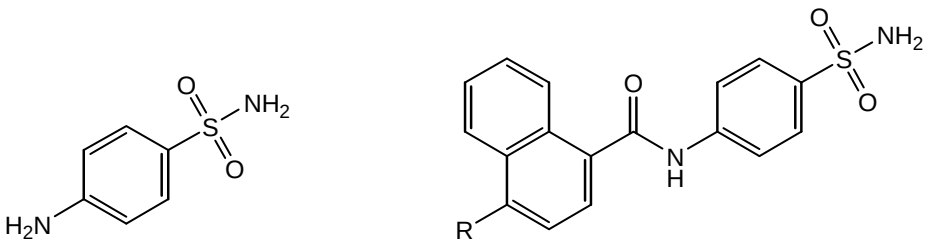
Chemistry

The synthesis and study of (4-alkyl-1-naphthoyl-amino)-benzenesulfonamides are presented. These derivatives showed chain elongation from the methyl through the butyl alkyl chain length. The 4-alkyl group was incorporated *via* 4-alkylnaphthoic acid moieties, synthesized following a method described



1 **2**

Figure 1 — General structure of benzenesulfonamides (**1**) and structure of WIN 55,212-2 (**2**)



3 **4a-d** R: R = CH_3-, CH_3CH_2-, $CH_3CH_2CH_2$-, $CH_3CH_2CH_2CH_2$-

Figure 2 — Sulfanilamide (**3**) and the prepared benzenesulfonamide derivatives (**4a-d**)

previously[14]. Figure 2 provides the structures of the benzenesulfonamide derivatives prepared in this study.

Antimicrobial evaluation

The *in vitro* antimicrobial studies are presented in Table I.

Structures **3**, **4c** and **4d** were shown to be effective, where compound **3** was the reference sulfanilamide. Streptomycin had greater activity than derivatives **4a** and **4b**, and lower activity than **4c** and **4d**. Derivatives **4a** and **4b**, being less lipophilic than **4c** and **4d**, showed no activity against any bacteria. The yeast *Saccharomyces cerevisiae* gave no activity. Thiadiazolic sulfonamides synthesized earlier[9], also revealed the same trend, where the corresponding propyl and methyl derivatives showed the greatest activities, and which were higher than both streptomycin and their respective reference compound.

QSAR physicochemical evaluations

QSAR analyses of the derivatives were undertaken to determine the structural features that influenced the observed antimicrobial activity. The effect of lipophilicity on inhibitory activity was examined. The lipophilicity parameter, known as the partition coefficient logP, influences the biological properties of compounds[15]. It is a quantitative descriptor that aids in the design of new biologically active molecules, as it allows for analysis of the permeability of bioactive compounds through apolar cell membranes. QSAR molecular descriptors logP, the Eigen values of HOMO and LUMO, and molecular weight, volume and refractivity of the synthesized compounds, abbreviated as, MW, MV and MR, respectively, were calculated. Selected descriptor values are given in Table II. The physicochemical data collected for thiadiazolic sulfonamides synthesized

Table I — Summary of the antimicrobial activities

Compd	Zone of inhibition (diameter, mm)				
	Gram (−)	Gram (+)			Yeast
	E. coli	*B. cereus*	*B. megaterium*	*E. fecalis*	*S. cereviciae*
Streptomycin[a]	9	14	17	15	−
3	22	16	10	12	−
4a	−	−	−	−	−
4b	−	−	−	−	−
4c	28	20	14	16	−
4d	32	30	22	18	−

[a] Standard compound
[b] 80 μg mg/ per disk
−: Ineffective

Table II — Some QSAR data of compounds synthesized and eigen values of HOMO and LUMO

Compd	logP	MW	MV (Å^3)	MR (Å^3)	HOMO (eV)	LUMO (eV)	ΔE (eV)	Total Energy (eV)	Dipole Moment, μ (D)
3	−1.98	172.20	497.84	47.76	−9.305	−0.657	8.648	1931.71	6.502
4a	−0.77	340.40	928.43	103.99	−9.127	−0.924	8.203	−3769.88	3.519
4b	−0.37	354.42	976.52	108.59	−9.134	−0.921	8.213	−3919.42	3.294
4c	0.02	368.45	1029.72	113.20	−9.129	−0.922	8.207	−4068.96	3.323
4d	0.42	382.48	1082.29	117.80	−9.132	−0.930	8.202	−4218.50	3.482

earlier were reported[9]. Studies herein include HOMO and LUMO parameters for new benzenesulfonamide derivatives.

Lipophilicity increased from the 4-methyl derivative through to the 4-butyl derivative. Likewise, in a similar fashion, the antimicrobial activities for these structures increased, with no antimicrobial activity for the 4-methyl and 4-ethyl analogues, and the highest activity for the 4-butyl analogue. A dependency between lipophilicity and antimicrobial activity was revealed, as confirmed by the observed antimicrobial activity above.

As MV of the structures increased, the *in vitro* antimicrobial activities increased with both the bulky 4-alkyl group and naphthoyl group affecting antimicrobial activities. MR is used for relating chemical structures with their behaviour. Table II shows MR increasing with increasing lipophilicity, therefore, as MR increased, the antimicrobial activities also increased. Chain length increases of the 4-alkyl group results in an increase in the hydrophobic portion of the derivatives, and thus an increase in lipophilicity. As derived by the Meyer-Overton Theory of Anesthesia[16,17], log P is a measure of hydrophobicity which is important for the penetration and distribution of drugs, and thus for the interaction with receptors, where receptors are prevalent in a hydrophobic environments. The 4-alkyl groups of increasing size, and the naphthoyl sub-unit cause an increase in hydrophobicity, and thus affect antimicrobial activities.

HOMO-LUMO and electronic dipole analyses

The HOMO and LUMO energies of the compounds were computed. The difference in energy between these levels is known as the HOMO/LUMO energy gap and is a valuable indicator of the stability molecular structures[18,19]. The greater the energy gap, the greater the stability for further reaction. Thus, it can be noted that alkyl substitution leads to stable derivatives **4a-d**, of essentially the same energy.

Low-energy conformations of the synthesized compounds were utilized for studying the HOMO and LUMO frontier molecular orbitals. After Woodward and Hoffman, Fukui revealed that the progress of chemical reactions rely on the HOMO and LUMO orbitals[18,19], where the electron localization of HOMO and availability of LUMO directs the reaction, and the respective gap gives an insight into the molecular stability. A study of the synthesized derivatives showed that the derivatives, in general, gave HOMOs located over the naphthyl ring, carbonyl group, C-N of the amide bond, and the C1 and C2 of the chain of the molecule (for the methyl derivative just C1 of the chain of the molecule), and LUMOs located over the naphthyl and benzene rings of the molecule. Therefore, the HOMO-LUMO interaction was such that electron density transfer occurred to the naphthyl

and benzene rings. The HOMO LUMO energy gap was low (≈ 8 eV) and thus this showed the charge transfer interactions occurred within the molecules. Further it was found that for compound **4a** 61 of 112 molecular orbitals were occupied, with the HOMO and LUMO calculated as −9.127 and −0.924 eV, respectively. Compound **4b** gave 64 of 118 molecular orbitals occupied with its HOMO and LUMO at −9.134 and −0.921 eV, respectively. Derivative **4c** showed 67 of 124, with its HOMO and LUMO orbitals at −9.129 and −0.922, respectively. Compound **4d** had 70 of 130 molecular orbitals occupied with the HOMO and LUMO orbitals at −9.132 and −0.930 eV, respectively. It can be seen from Table II that electron donation increases from **4a** to **4d**, due to 4-alkyl group elongation, hence the band gap reductions.

Fluorescence measurements

Photoluminescence is regularly used in medical diagnostics in the treatment of various infectious diseases. Physicochemical characteristics of the derivatives synthesized may allow them to be considered as potential fluorimeric analytical reagents. Excitation and emission spectra were recorded for sulfanilamide (**3**) and benzenesulfonamide derivative (**4a-d**) solutions, excited at 259 nm. Fluorescence investigations for thiadiazolic sulfonamides synthesized earlier was also studied and reported[9].

Figure 3 displays the photoluminescence spectra of the resulting synthesized molecules in $CHCl_3$ solvent.

Structure **3** revealed the maximum photoluminescent intensity at 379 nm wavelength and full-width half-maximum as being 105 nm. A photoluminescence quantum efficiency of 32% and an excited-state lifetime of 2.98 ns were observed for structure **3**. Benzenesulfonamide derivatives **4a-d** had higher photoluminescence intensity and quantum yields than that of starting molecule **3**. This is because upon derivatization, larger cyclic molecular structures designed and thus electron rich molecules formed more readily and emission was observed efficiently. The introduction of more *para* electron donating groups onto rings brings about photoluminescence intensity increases for maximum peaks and shifts to higher emission wavelengths. Larger molecular structures revealed high quantum efficiency as a result of possessing a considerable amount of delocalization of π electrons throughout the molecular system. It is well known that electron rich cyclic molecular arrays, with more π bonds, cause greater fluorescence emission intensity. When electron rich cyclic molecules of the benzenesulfonamides result, delocalization of electrons and/or transfer of energy from the excited state of the derivatives increases, hence the non-radiated transition of the benzene-sulfonamides excited state decreases, and the ultimate fluorescence emission increases. Table III summarizes the photoluminescence data for sulfanilamide (**3**) and the benzenesulfonamides **4a-d**.

Experimental Section

Reagents and solvents were purchased from Sigma-Aldrich (Sigma-Aldrich ChemieGmbH, Münich,

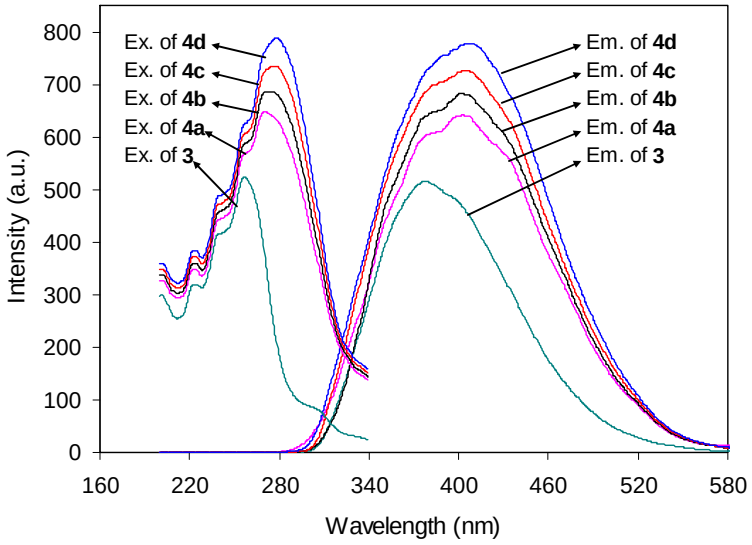


Figure 3 — Photoluminescence spectra of sulfanilamide (**3**) and the benzenesulfonamides **4a-d** in $CHCl_3$ with excitation at 259 nm

Table III — Photoluminescence data for sulfanilamide (3) and benzenesulfonamides 4a-d

Compd	λ_{max} Ex (nm)	In Ex	λ_{max} Em (nm)	In Em	ϕ_f (%)	τ_f (ns)
3	259 (224;233;265)	518	379 (359;402)	514	32	2.98
4a	273 (225;235;253)	646	405 (351;380;434)	641	38	3.56
4b	276 (225;235;254)	685	407 (358;381;435)	679	40	3.73
4c	279 (226;236;255)	731	409 (359;385;436)	724	42	3.90
4d	281 (226;236;256)	781	412 (385;437)	773	44	4.09

Maximum excitation wavelength (λ_{max} Ex); maximum excitation intensity (In Ex); maximum emission wavelength (λ_{max} Em); maximum emission intensity (In Em); quantum yield (ϕ_f); excited-state lifetime (τ_f).

Germany), and Merck Chemical (Merck, Darmstadt, Germany) companies, and used without further purification, unless reactions called for dry conditions whereby drying and distillations procedures were carried out.

Melting points were measured with Electrothermal 9200 apparatus (Thermo Fisher Scientific, Dubuque, IA, USA). NMR spectra (Varian Mercury Plus 300 MHz spectrometer, Varian, Inc. MA, USA) were recorded for solutions in $CDCl_3$. C, H, N, and S content were examined by CHNS Analyzer (Thermo Scientific FLASH 2000, Thermo Scientific, MA, USA). Mass spectra were recorded using AB Sciex 3200 QTrap LC-MS-MS in the electrospray mode (AB Sciex, Framingham, MA, USA). IR spectra were obtained using a Perkin-Elmer Spectrum 100 FT-IR with Universal ATR Sampling Accessory (Perkin-Elmer, MA, USA). Spectrophotometry and absorption spectra using a PG Instruments Ltd T80+ UV/VIS Spectrometer (PG Instruments, UK). Excitation and emission properties were investigated using a luminescence spectrometer (Perkin-Elmer LS55) (Perkin-Elmer, MA, USA).

Determination of antimicrobial activity

The *in vitro* antimicrobial activities were assessed using the agar diffusion method according to the reported procedure[9]. Diameters of the zones of inhibition were obtained in mm, where repetitions were carried out to get values in triplicate.

Calculation of QSAR molecular descriptors

QSAR studies were followed in order to evaluate the relationships between physiochemical parameters and biological activities. QSAR descriptors were obtained using HyperChem[20]. Optimized structures were collected using the Molecular Mechanics Force Field (MM+) element of HyperChem, and were further refined using the PM3 semi-empirical method. QSAR data for the compounds studied were collected, together with the Eigen values of HOMO and LUMO.

General procedure for the preparation of derivatives 4a–d

Benzenesulfonamide derivatives **4a–d** were synthesized following a previously published method[9], and column chromatography was used for purification using appropriate solvent systems.

(4-Methyl-1-naphthoylamino)-benzenesulfonamide, 4a: Yield 68%. Yellow oil. FT-IR: 3312, 3242 (-NH_2, amine; -NH, amide), 2958 (C-H, arom.), 2926 (C-H, alkane), 1725 (C=O, carbonyl), 1600 (C=C, arom., N-H bend), 1120 (C-N), 959 (C-H, OOP), 746 cm^{-1} (N-H, OOP); UV-Vis (CH_2Cl_2) λ_{max}: 234, 276, 314 nm; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.80 (s, 3H, -CH_3), 5.00 (s, 1H, N-H), 6.98 (s, 2H, -NH_2), 7.50-7.59 (m, 4H, Ar-H), 7.62-7.74 (m, 4H, Ar-H), 8.12 (d, J = 8.3 Hz, 1H, Ar-H), 8.35 (d, J = 8.2 Hz, 1H, Ar-H); ESI-MS: *m/z* 341 $[M+H]^+$. Anal. Calcd for $C_{18}H_{16}N_2O_3S$: C, 63.51; H, 4.74; N, 8.23; S, 9.42. Found: C, 63.62; H, 4.68; N, 8.19; S, 9.48%.

(4-Ethyl-1-naphthoylamino)-benzenesulfonamide, 4b: Yield 65%. Yellow oil. FT-IR: 3310, 3240 (-NH_2, amine, -NH, amide), 2958 (C-H, arom.), 2927 (C-H, alkane), 1724 (C=O, carbonyl), 1600 (C=C, arom., N-H bend), 1121 (C-N), 960 (C-H, OOP), 743 cm^{-1} (N-H, OOP); UV-Vis (CH_2Cl_2) λ_{max}: 238, 284, 306 nm; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.41 (t, J = 7.2 Hz, 3H, -CH_3), 3.21 (q, J = 7.5 Hz, 2H, -CH_2), 5.00 (s, 1H, N-H), 6.98 (s, 2H, -NH_2), 7.50-7.60 (m, 4H, Ar-H), 7.68-7.79 (m, 4H, Ar-H), 8.19 (d, J = 8.1 Hz, 1H, Ar-H), 8.38 (d, J = 8.2 Hz, 1H, Ar-H); ESI-MS: *m/z* 355 $[M+H]^+$. Anal. Calcd for $C_{19}H_{18}N_2O_3S$: C, 64.39; H, 5.12; N, 7.90; S, 9.05. Found: C, 64.36; H, 5.33; N, 7.98; S, 9.17%.

(4-Propyl-1-naphthoylamino)-benzenesulfonamide, 4c: Yield 65%. Yellow oil. FT-IR: 3310, 3240 (NH_2, amine, -NH, amide), 2958 (C-H, arom.), 2927 (C-H, alkane), 1725 (C=O, carbonyl), 1600 (C=C, arom., N-H bend), 1121 (C-N), 960 (C-H, OOP), 746 cm^{-1} (N-H, OOP); UV-Vis (CH_2Cl_2) λ_{max}: 238, 274, 298 nm; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.22 (t, J = 7.3 Hz, 3H, -CH_3), 1.38-1.46 (m, 2H, -CH_2), 3.18 (t, J = 7.4 Hz, 2H, -CH_2), 5.00 (s, 1H, N-H), 6.98 (s, 2H, NH_2), 7.44-7.55 (m, 4H, Ar-H), 7.68-7.78 (m, 4H, Ar-H), 8.18 (d, J = 8.1 Hz, 1H, Ar-H), 8.36 (d, J = 8.2 Hz, 1H, Ar-H); ESI-MS: *m/z* 369 $[M+H]^+$. Anal. Calcd for $C_{20}H_{20}N_2O_3S$: C, 65.20; H, 5.47; N, 7.60; S, 8.70. Found: C, 65.22; H, 5.51; N, 7.55; S, 8.88%.

(4-Butyl-1-naphthoylamino)-benzenesulfonamide, 4d: Yield 60%. Yellow oil. FT-IR: 3310, 3240 (NH_2, amine, -NH, amide), 2958 (C-H, arom.), 2927 (C-H, alkane), 1728 (C=O, carbonyl), 1600 (C=C, arom., N-H bend), 1120 (C-N), 960 (C-H, OOP), 748 cm^{-1} (N-H, OOP); UV-Vis (CH_2Cl_2) λ_{max}: 238, 274, 298 nm; ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.83 (t, J = 7.2 Hz, 3H, -CH_3), 1.20-1.31 (m, 2H, -CH_2), 1.38-1.45 (m, 2H, -CH_2), 3.21 (t, 2H, -CH_2), 5.04 (s, 1H, N-H), 7.00 (s, 2H,-NH_2), 7.51-7.60 (m, 4H, Ar-H), 7.70-7.79 (m, 4H, Ar-H), 8.22 (d, J = 8.2 Hz, 1H, Ar-H), 8.34 (d, J = 8.1 Hz, 1H, Ar-H); ESI-MS: *m/z* 383 $[M+H]^+$. Anal. Calcd for $C_{21}H_{22}N_2O_3S$: C, 65.95; H, 5.80; N, 7.32; S, 8.38. Found: C, 65.88; H, 5.76; N, 7.40; S, 8.62%.

Conclusions

New benzenesulfonamide derivatives were synthesized, where these structures bear both the naphthoyl moiety of a potent cannabinoid, and the sulfanilamide unit of typical aromatic sulfonamide antiglaucoma agents. QSAR investigations included the HOMO and LUMO values, and their respective quantitative and qualitative effects on *in vitro* antimicrobial activities were asssessed. A photoluminescence study of the synthesized derivatives was performed and evaluated. The novel derivatives showed higher photoluminescence intenties and efficiencies than that of the reference molecule sulfanilamide.

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