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Synthesis and Structural Determination of Several Sulfonamides Synthesized From Nitrovanillin

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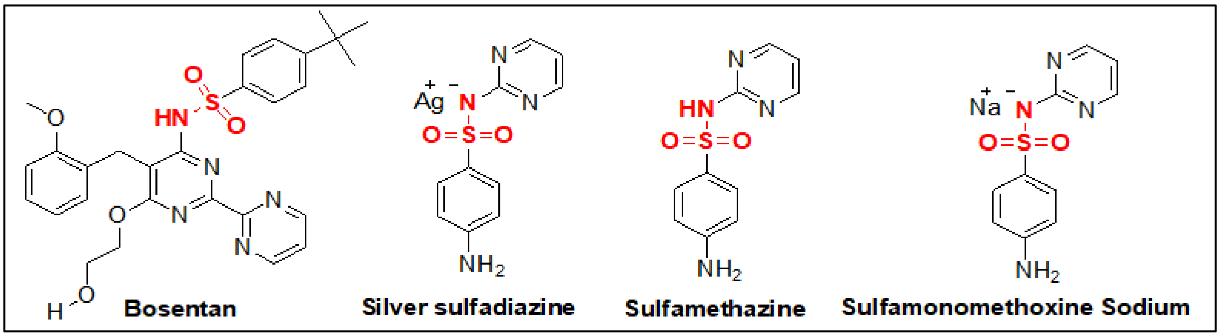
Abstract: In this study, five sulfonamide derivatives **7a1, 7a2, 7a3, 7a4,** and **7a5**, were successfully synthesized from nitrovanillin as the starting material using simple and efficient methods through six reaction stages. Among these synthesis stages, two steps were assisted by microwave irradiation, which significantly reduced the reaction time and improved the yield compared to traditional organic synthesis methods. The structures of the five sulfonamides were accurately determined using modern spectroscopic techniques, including NMR and MS.

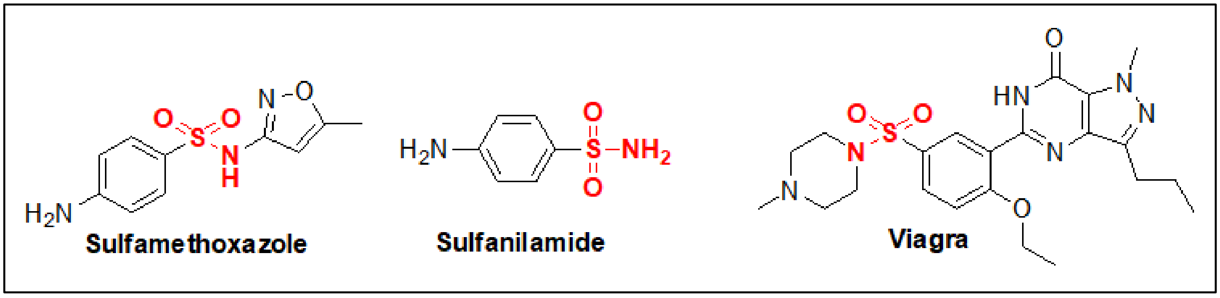
Keywords: Nitrovanillin, sulfonamide, microwave.

INTRODUCTION

Sulfonamides are a class of antibiotics characterized by a distinctive chemical structure and represent the first group of antimicrobial agents to be introduced into clinical practice. Several sulfonamides have been widely used to treat a variety of diseases, such as the antihypertensive agent bosentan [Kanda, Y. *et al*., 2001]; sulfa antibacterial drugs including sulfamethoxazole, silver sulfadiazine, sulfamethazine, and sulfamonomethoxine sodium [Stokes, S. S. *et al*., 2012]; antiparasitic agents [Chibale, K. *et al*., 2001]; and the vaginal antifungal agent sulfanilamide [Ezabadi, I. R. *et al*., 2008]. In addition, certain sulfonamide derivatives are employed as carbonic anhydrase inhibitors [Vullo, D. *et al*., 2013].

Sulfonamides have also demonstrated efficacy in the treatment of urinary tract, gastrointestinal, and ocular infections, burns, ulcerative colitis [Block, J., & Beale, J. M. 2003], rheumatoid arthritis [Levin, J. I. *et al*., 2002], and erectile dysfunction in males, exemplified by the phosphodiesterase-5 inhibitor sildenafil, more commonly known by its trade name Viagra [Kim, D. K. *et al*., 2001], as well as obesity [Hu, B. *et al*., 2001]. Recently, several sulfonamide derivatives have been investigated and applied as adjunctive therapies for COVID-19 (ramatroban) [Ackermann, M. *et al*., 2020], AIDS (darunavir) [Jain, A. *et al*., 2016], and Alzheimer's disease (avagacestat) [Coric, V. *et al*., 2012].





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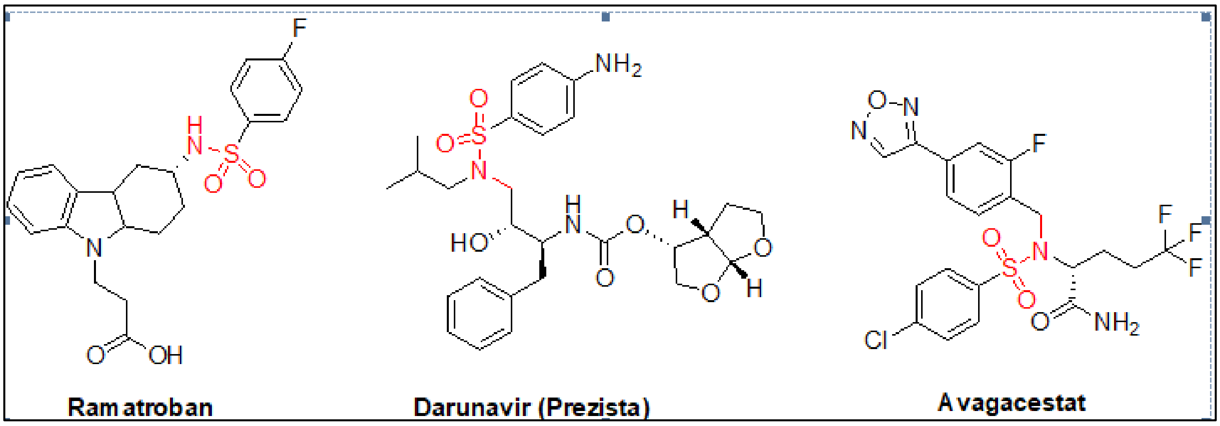


The simplest method for synthesizing sulfonamide derivatives involves the reaction of primary or secondary amines with sulfonyl chlorides in the presence of an organic or inorganic base. Among these, primary amines exhibit high reactivity, whereas secondary amines show very low or nearly negligible reactivity [Das, T. C. *et al*., 2018]. In this study, we present a simple and efficient approach for the synthesis of several sulfonamide derivatives via the reaction of primary aromatic amines derived from nitrovanillin (a type of *o*-aminophenol) with various benzenesulfonyl chlorides. The structures of the resulting sulfonamide derivatives were unambiguously elucidated using modern spectroscopic techniques, including NMR and MS.

MATERIALS AND METHODS

Chemicals and Instrumentation

Solvents and chemicals required for the experimental procedures were purchased from Sigma-Aldrich, Merck Corp., and Aladdin, or sourced from suppliers in Vietnam and China.

Spectroscopic measurements were performed at the Institute of Chemistry, Vietnam Academy of Science and Technology. ESI–MS spectra were recorded on an LTQ Orbitrap XL mass spectrometer equipped with an electrospray ionization (ESI) source, operating in both positive and negative ion modes to detect [M+H]$^+$ and [M−H]$^-$ ions, using CH_3OH as the solvent. Nuclear magnetic resonance (NMR) spectra were acquired on a Bruker Avance spectrometer, using DMSO as the solvent at room temperature; ^{1}H NMR spectra were recorded at 600 MHz and ^{13}C NMR spectra at 125 MHz.

Melting points were determined using a Gallenkamp melting point apparatus at the laboratory of Hong Duc University. An Electrolux microwave oven (800 W, 2015, Vietnam) was employed in certain stages of the experimental procedures.

Synthesis of Compounds

The compounds were synthesized according to Scheme 1 and the procedures reported in the literature [Hoan, D. Q. *et al*., 2019; Mai, N. T. N. *et al*., 2024].

Synthesis of 4-((E)-(4-chlorophenylimino)methyl)-2-methoxy-6-nitrophenol (2a)

A mixture of 5-nitrovanillin 1a (0.40 g, 2 mmol) and *p*-chloroaniline (0.32 g, 2.5 mmol) was dissolved in 10 mL of DMF in a 50 mL beaker, followed by the addition of 5–6 drops of acetic acid as a catalyst. The reaction mixture was subjected to microwave irradiation at a medium power of 400W for 6–8 min. To avoid overheating that could lead to solvent evaporation and decomposition of the reactants, the irradiation time was divided into intervals of 30–45 s. The resulting solid product was recrystallized from 96% ethanol to afford brown crystals, designated as 2a (0.49 g, 80%, mp = 196°C).

Synthesis of 4-((4-chlorophenylamino)methyl)-2-methoxy-6-nitrophenol (3a)

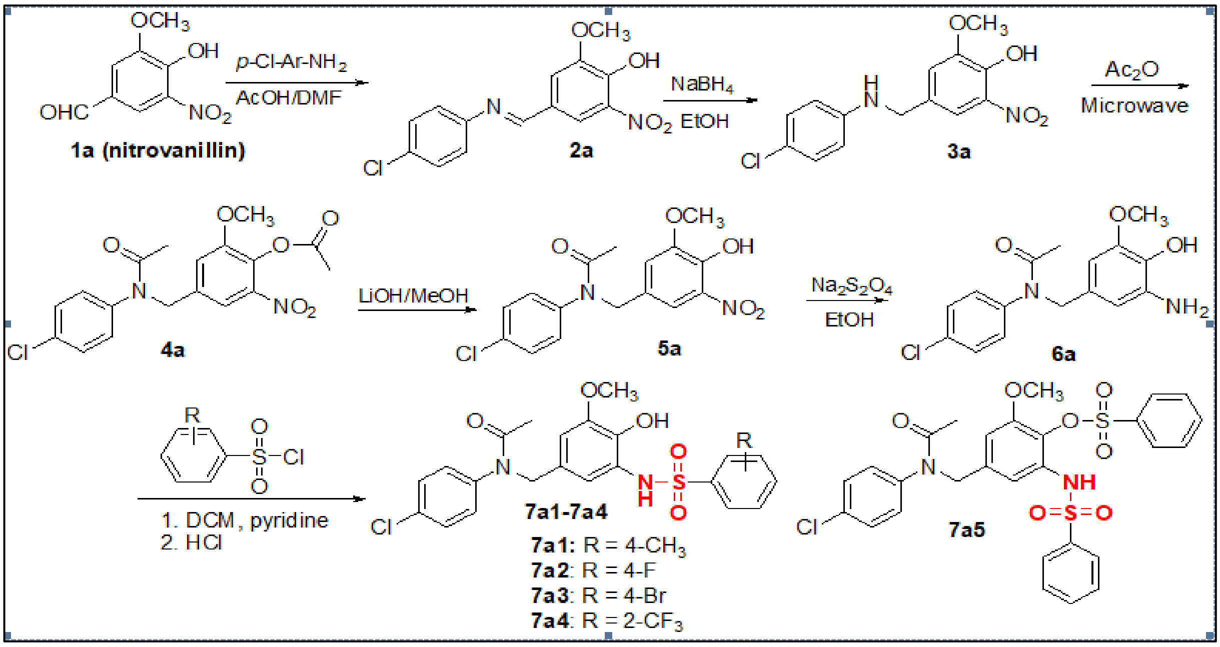
A mixture of 2a (0.306 g, 1 mmol) and ethanol (20 mL) was heated in a 100 mL round-bottom flask until complete dissolution of 2a. Sodium borohydride ($NaBH_4$, 0.30 g, 8.0 mmol) was then added slowly to the reaction mixture over 10 min, followed by stirring at room temperature for an additional 15 min to complete the reaction. Subsequently, 50 mL of cold water was added, and the mixture was neutralized with 5% HCl solution to pH 5–6. An orange precipitate formed, which was filtered and washed several times with distilled water to give compound 3a (0.28 g, 90%, mp = 186°C).

Synthesis of 4-((N-(4-chlorophenyl)acetamido)methyl)-2-methoxy-6-nitrophenyl acetate (4a)

Compound 3a (0.308 g, 1 mmol) was thoroughly mixed with acetic anhydride (2 mL) in a 100 mL glass beaker. The beaker was sealed and subjected to microwave irradiation for 7 min. The progress of the reaction was monitored by TLC until complete consumption of the starting material. The resulting solid was recrystallized from 96% ethanol to afford pale yellow needle-shaped crystals, designated as 4a (0.37 g, 95%, mp = 196°C).

N-(4-hydroxy-3-methoxy-5-nitrobenzyl)-N-(4-chlorophenyl)acetamide (5a)

A mixture of 4a (0.078 g, 0.2 mmol), LiOH (0.048 g, 2 mmol), and 10 mL of a methanol/H_2O solvent mixture (4:1, v/v) was refluxed for 30 min. The reaction progress was monitored by TLC until complete consumption of the starting material. The reaction mixture was then neutralized with 5% HCl solution to pH 5–6. The precipitated solid was filtered and recrystallized from an ethanol/H_2O solvent system (1:2, v/v) to yield pale yellow needle-shaped crystals of compound 5a (0.33 g, 92%, mp = 196 °C).



Scheme 1. Synthesis of sulfonamide derivatives from nitrovanillin

N-(3-amino-4-hydroxy-5-methoxybenzyl)-N-(4-chlorophenyl)acetamide (6a)

Compound 5a (0.351 g, 1 mmol) was completely dissolved in 10 mL of ethanol at 80°C. Sodium dithionite ($Na_2S_2O_4$, 1.1 g, 6 mmol) was then added portionwise to the reaction mixture, which was subsequently heated and stirred for approximately 8 h until the color changed from reddish orange to milky white, at which point the reaction was terminated. The progress of the reaction was monitored by TLC until complete consumption of the starting material.

The reaction mixture was hot-filtered to remove insoluble solids, and the filtrate was concentrated under reduced pressure to remove approximately half of the solvent. Subsequently, 50 mL of cold water was added to the remaining solution, resulting in the formation of white needle-shaped crystals. The solid was filtered and dried to afford compound 6a (0.24 g, 75%, mp = 186°C).

Synthesis of sulfonamides 7a1, 7a2, 7a3, 7a4, and 7a5

Compound 6a (0.32 g, 1.0 mmol) was placed in a 100 mL round-bottom flask containing 15 mL of dichloromethane (DCM). The mixture was stirred and heated at 50 °C until complete dissolution of 6a. The corresponding sulfonyl chlorides (1.0 mmol, or 2.0 mmol for the synthesis of 7a5) were then added to the reaction mixture. Subsequently, 5–6 drops of pyridine were introduced, and the mixture was stirred at room temperature for 3 h.

The reaction progress was monitored by TLC using a hexane/ethyl acetate solvent system (1:3, v/v). After completion, the reaction mixture was acidified with 1 M HCl to pH 6–7 and extracted to remove the aqueous inorganic layer. The organic phase was evaporated to dryness, and the residue was recrystallized from absolute ethanol to afford needle-shaped crystals of the sulfonamide products, designated as 7a1–7a5. The reaction yields ranged from 70% to 85%.

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7a1, *N*-(4-hydroxy-3-methoxy-5-(tosylamino)benzyl)-*N*-(4-chlorophenyl)acetamide), 0.33g, 70%, mp: 252-253°C); ^{1}H NMR (500 MHz, DMSO-d_6) *δ (ppm):* H2 (6,47 (s, 1H); H6 (6,64 (s, 1H), H7 (3,63 (s, 3H); H8 (4,68 (s, 2H); H10 (1,79 (s, 3H); H12 (7,29 (d, *J* = 7,0, 1H); H13 (7,58 (d, *J* = 7,0, 1H); H15 (7,58 (d, *J* = 7,0, 1H); H16 (7,29 (d, *J* = 7,0, 1H); H18 (7,38 (d, *J* = 7,0, 1H); H19 (7,06 (d, *J* = 6,5, 1H); H21 (7,06 (d, *J* = 6,5, 1H); H22 (7,38 (d, *J* = 7,0, 1H); H23 (2,32 (s, 3H); NH 9,11 (s, 1H); OH (8,77 (s, 1H). ^{3}C NMR (125 MHz, DMSO-d_6) *δ (ppm)*: C1 (129,5); C2 (115,3); C3 (124,4); C4 (137,9); C5 (147,5); C6 (108,6); C7 (55,7); C8 (51,1); C9 (168,8); C10 (22,3); C11 (142,7); C12 (129,2); C13 (126,6); C14 (137,5); C15 (126,6); C16 (129,2); C17 (131,9); C18 (129,8); C19 (127,2); C20 (141,2); C21 (127,2); C22 (129,8); C23 (20,2). ESI-MS *m/z*: 475,2(100%) và 476,6 (33,3%) $[M+H]^+$ ($C_{23}H_{24}ClN_2O_5S$ 475 corresponding to ^{35}Cl và 477 corresponding to ^{37}Cl).

7a2, *N*-(4-hydroxy-3-methoxy-5-(4-fluorobenzenesulfonylamino)benzyl)-*N*-(4-chlorophenyl)acetamide 0.36g, 75%, mp: 246-247°C); ^{1}H NMR (500 MHz, DMSO-d_6) *δ (ppm):* H2 (6,53 (s, 1H); H6 (6,62 (s, 1H); H7 (3,65 (s, 3H); H8 (4,70 (s, 2H); H10 (1,80 (s, 3H); H12 (7,12 (d, *J* = 7,0, 1H); H13 (7,42 (d, *J* = 7,0, 1H); H15 (7,42 (d, *J* = 7,0, 1H); H16 (7,12 (d, *J* = 7,0, 1H); H18 (7,73 (m, 1H); H19 (7,33 (t, *J* = 7,5, 1H); H21 (7,33 (t, *J* = 7,5, 1H); H22 (7,73 (m, 1H); NH (9,33 (s, 1H); OH (8,78 (s, 1H); ^{3}C NMR (125 MHz, DMSO-d_6) *δ (ppm)*: C1 (127,2); C2 (116,5); C3 (123,9); C4 (138,7); C5 (147,5); C6 (109,1); C7 (55,8); C8 (51,1); C9 (168,9); C10 (22,3); C11 (141,2); C12 (129,8); C13 (129,2); C14 (132,0); C15 (129,2); C16 (129,8); C17 (138,7); C18 (129,5); C19 (116,0); C20 (163,1); C21 (115,8); C22 (129,6); ESI-MS *m/z*: 479,2 $[M+H]^+$ ($C_{22}H_{21}ClFN_2O_5S$ 479 amu).

7a3, *N*-(4-hydroxy-3-methoxy-5-(4-bromobenzenesulfonylamino)benzyl)-*N*-(4-chlorophenyl)acetamide (0.43g, 80%, mp: 256-257°C); ^{1}H NMR (500 MHz, DMSO-d_6) *δ (ppm):* H2 (6,53 (s, 1H); H6 (6,61 (s, 1H); H7 (3,65 (s, 3H); H8 (4,70 (s, 2H); H10 (1,80 (s, 3H); H12 (7,10 (d, *J* = 7,0, 1H); H13 (7,42 (d, *J* = 7,0, 1H); H15 (7,42 (d, *J* = 7,0, 1H); H16 (7,10 (d, *J* = 7,0, 1H); H18 (7,73 (d, *J* = 7,5, 1H); H19 (7,61 (t, *J* = 7,0, 1H); H21 (7,61 (t, *J* = 7,0, 1H); H22 (7,73 (d, *J* = 7,5, 1H); NH (9,46 (s, 1H); OH (8,89 (s, 1H). ^{3}C NMR (125 MHz, DMSO-d_6) *δ (ppm)*: C1 (127,2); C2 (116,5); C3 (123,7); C4 (138,7); C5 (147,6); C6 (109,2); C7 (55,7); C8 (54,6); C9 (168,9); C10 (18,5); C11 (141,1); C12/C16 (128,8); C13/C15 (129,2); C14 (131,9); C17(138,7); .C18/C22 (126,6/126,3); C19/C21 (116,5); C20 (147,6); ESI-MS *m/z*: 539,2 (50%) và 541,2 (50%) $[M+H]^+$ ($C_{22}H_{21}ClBrN_2O_5S$ 539 corresponding to^{79}Br và 541 corresponding to ^{81}Br).

7a4 *N*-(4-hydroxy-3-methoxy-5-(2-(trifluoromethyl)benzenesulfonylamino)benzyl)-*N*-(4-chlorophenyl)acetamide (0.45g, 85%, mp: 283-284°C); ^{1}H NMR (500 MHz, DMSO-d_6) *δ (ppm):* H2 (6,63 (s, 1H); H6 (6,55 (s, 1H); H7 (3,67 (s, 3H); H8 (4,69 (s, 2H); H10 (1,76 (s, 3H); H12 (7,09 (d, *J* = 7,0, 1H); H13 (7,37 (d, *J* = 7,0, 1H); H15 (7,37 (d, *J* = 7,0, 1H); H16 (7,09 (d, *J* = 7,0, 1H); H19 (7,98 (d, *J* = 7,5, 1H); H20 (7,81 (t, *J* = 7,0, 1H); H21 (7,76 (t, *J* = 7,0, 1H); H22 (7,97 (d, *J* = 7,5, 1H); NH (9,40 (s, 1H); OH (9,01 (s, 1H). ^{13}C NMR (125 MHz, DMSO-d_6) *δ (ppm)*: C1 (127,4); C2 (116,1); C3 (123,8); C4 (138,4); C5 (147,6); C6 (109,1); C7 (55,8); C8 (51,1); C9 (168,8); C10 (22,2); C11 (141,3); C12 (129,8); C13 (129,2); C14 (132,0); C15 (129,2); C16 (129,8); C19 (130,5); C20 (133,0); C21 (132,7); C22 (128,2).

7a5 *N-(4-benzenesulfonyloxy-3-methoxy-5-(benzenesulfonylamino)benzyl)-N-(4-chlorophenyl)acetamide* (0.48g, 78%, mp: 287-288°C); ^{1}H NMR (500 MHz, DMSO-d_6) *δ (ppm):* H2 (6,56 (s, 1H); H6 (6,49 (s, 1H); H7 (3,33 (s, 3H); H8 (4,66 (s, 2H); H10 (1,75 (s, 3H); H12 (6,94 (d, *J* = 7,8, 1H); H13 (7,40 (d, *J* = 7,8, 1H); H15 (7,40 (d, *J* = 7,8, 1H); H16 (94 (d, *J* = 7,8, 1H); H18/H22 (7,8, m); H19/H20/H21 (7,81, m); H19'/H20'/H21' (7,65, m); H18'/H22' (7,62, m); NH (9,76 (s, 1H); ^{3}C NMR (125 MHz, DMSO-d_6) *δ (ppm)*: C1 (127,9); C2 (113,7); C3 (128,8); C4 (130,2); C5 (152,0); C6 (109,0); C7 (55,5); C8 (51,1); C9 (169,0); C10 (22,2); C11 (141,1); C12/C16 (129,4); C13/C15 (129,1); C14 (131,6); C17/C17'(136,2/132,8); .C18/C22 (127,9); C18'/C22' (129,3); C19/C20/C21 (126,7); C19'/C20'/C21' (126,5); C20/C20' (134,4/140,0). ESI-MS *m/z*: 601,2 (100%) $[M+H]^+$ ($C_{28}H_{26}ClN_2O_7S_2$ 601).

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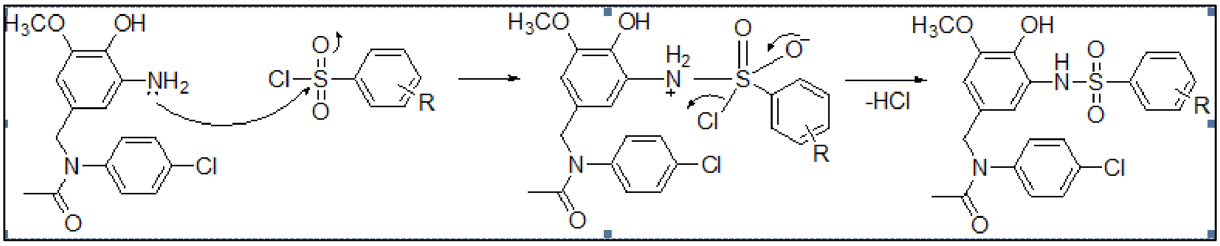
RESULTS AND DISCUSSION

Synthesis of the Compounds

The transformation of nitrovanillin (1a) into the *N*-acetyl derivative 5a involves a series of straightforward organic synthetic reactions. Among these, two key transformation steps were improved by the application of microwave irradiation (the synthesis of 2a and 4a), which significantly shortened the reaction times and enhanced the reaction yields compared with conventional reflux methods. The reduction of the *o*-nitrophenol-type compound (5a) to the corresponding *o*-aminophenol (6a) was also systematically investigated in order to identify the optimal solvent and reducing agent [Mai, N. T. N. *et al*., 2024].

The sulfonamide derivatives (7a1–7a5) were successfully synthesized via the reaction of various benzenesulfonyl chlorides with the primary aromatic amine (6a) in the presence of pyridine. The proposed reaction mechanism is illustrated as follows [Hameed, A. D. *et al*., 2021].



Scheme 2. Proposed reaction mechanism for the formation of sulfonamide derivatives

Structural Elucidation

The proton and carbon signals were assigned based on detailed analysis of the ^{1}H and ^{13}C NMR spectra in combination with HMBC correlations, with reference to the literature [Silverstein, R. M., & Bassler, G. C. 1962]. Compound 7a1 was selected as a representative example to present the detailed spectroscopic analysis for structural determination, while the structures of the remaining compounds were elucidated in an analogous manner. For convenience in spectral assignment, the carbon and hydrogen atoms of 7a1 were numbered according to the structures shown in Figures 1 and 2.

According to the proposed structure, compound 7a1 has the molecular formula $C_{23}H_{23}ClN_2O_5S$ (M = 474 amu for ^{35}Cl and 476 amu for ^{37}Cl), corresponding to the $[M+H]^+$ ion with the formula $C_{23}H_{24}ClN_2O_5S$ (m/z = 475 and 477). The (+) ESI–MS spectrum (Figure 1) exhibits a peak at m/z = 475.2 (100%) and a peak at m/z = 476.5 (33.3%), which correspond to the natural isotopic abundance of ^{35}Cl and ^{37}Cl, respectively. These results confirm that the molecular formula of compound 7a1 is consistent with the initially proposed structure.

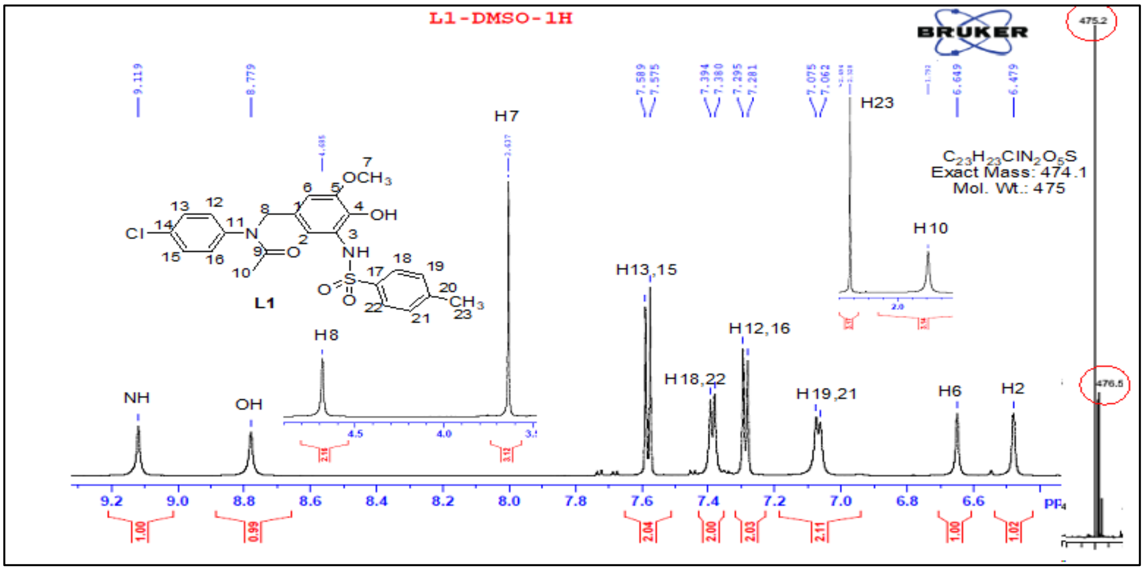


Figure 1. Partial ^{1}H NMR and (+) ESI–MS spectra of compound 7a1

The ^{1}H NMR spectrum of compound 7a1 exhibits all expected resonance signals corresponding to non-equivalent protons. The signals of the aliphatic protons (H7, H8, H10, and H23) appear in the region $\delta < 5$ ppm. Specifically, the signals of H10 and H23 are observed as singlets integrating for 3H at $\delta = 1.79$ ppm and $\delta = 2.52$ ppm, respectively. The signal of H7 is also a singlet integrating for 3H at $\delta = 3.63$ ppm; due to the attachment of H7 to an oxygen atom with high electronegativity, its resonance is shifted downfield. The signal of H8 appears as a singlet integrating for 2H at $\delta = 4.68$ ppm.

The protons of the NH and OH groups are readily assigned: the NH proton appears as a singlet integrating for 1H at $\delta = 9.11$ ppm, while the OH proton also appears as a singlet integrating for 1H at $\delta = 8.77$ ppm. These assignments were further confirmed by two-dimensional HMBC spectroscopy.

The spectral region between $\delta = 6–8$ ppm corresponds to aromatic protons. Based on chemical shifts, signal multiplicities, and spin–spin coupling constants, the aromatic protons can be assigned as follows. The signals of the amine-derived moiety (originating from nitrovanillin), namely H13/H15 and H12/H16, were assigned by comparison with the key intermediate 6a and show only minor changes relative to 6a, as they are located far from the site of structural modification. The signals of H2 and H6 are shifted downfield relative to compound 6a due to the conversion of the NH_2 group into a sulfonamide; these protons still appear as singlets at $\delta = 6.64$ ppm and $\delta = 6.47$ ppm, respectively.

In the benzenesulfonyl moiety, the signals of H19 and H21 are chemically equivalent and appear as doublets integrating for 2H at $\delta = 7.06$ ppm (d, J = 6.5 Hz), arising from mutual *ortho* coupling. Similarly, the signals of H18 and H22 appear as doublets at $\delta = 7.38$ ppm (d, J = 7.0 Hz, 2H) due to *ortho* coupling between these protons. Protons H19/H21 are located closer to the electron-donating group and therefore resonate at a higher field (lower chemical shift) than H18/H22.

The ^{13}C NMR spectrum of compound 7a1 shows fewer carbon resonance signals than the actual number of carbon atoms present in the molecule, which can be attributed to accidental overlap of some carbon signals with identical or very similar chemical shifts. Based solely on chemical shift values, only the aliphatic carbons (C7, C8, C10, and C23) and the carbonyl carbon (C9) can be unambiguously assigned. The assignment of aromatic carbon signals requires analysis of the HMBC spectrum of compound 7a1.

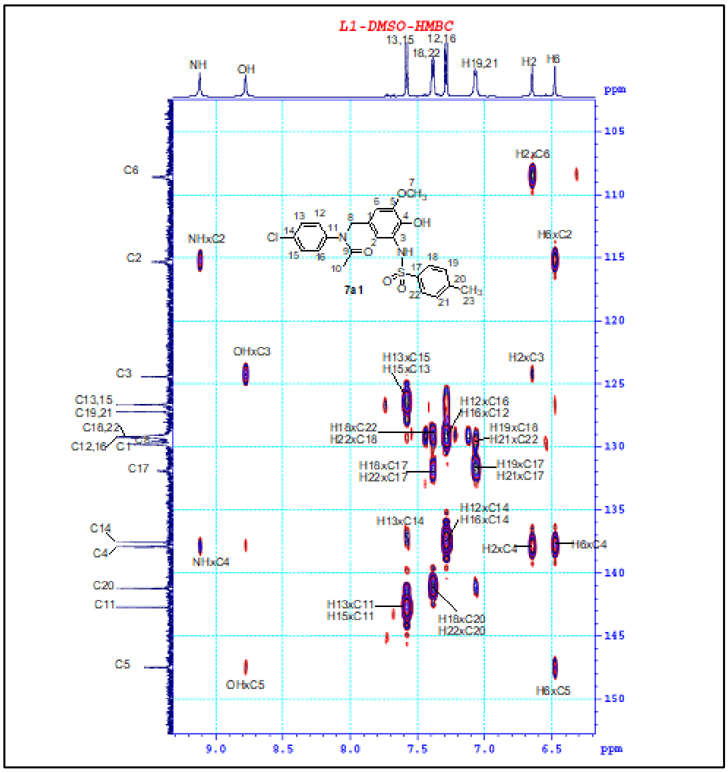


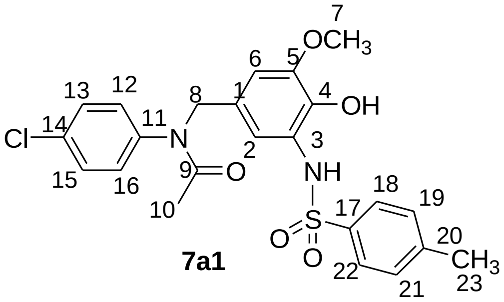
Figure 2. HMBC spectrum of sulfonamide 7a1

The HMBC spectrum of sulfonamide 7a1 is shown in Figure 2. Based on the cross-peaks corresponding to C–H correlations over two to four bonds, the resonance signals of individual aromatic carbons can be unambiguously assigned. From the cross-peaks of H2, the signal of C6 can be deduced, while the cross-peaks of H6 allow the assignment of C2; in addition, H6 shows a correlation with C5, from which the resonance of C5 can be assigned. Both H2 and H6 exhibit cross-peaks with C4, enabling the assignment of C4.

From the cross-peaks of H13 and H15, the signals of C13 and C15 can be assigned, whereas the cross-peaks of H12 and H16 correspond to C12 and C16. Protons H13, H15, H12, and H16 all show correlations with C17, allowing the assignment of the resonance signal of C17. The signals of the NH and OH protons can also be clearly distinguished, as the NH proton exhibits two cross-peaks with C2 and C4, whereas the OH proton shows only a single cross-peak with C3.

Using a similar approach, the resonance signals of all carbon atoms in sulfonamide 7a1 can be reliably assigned. The results of the spectroscopic analysis of sulfonamide 7a1 are summarized in Table 1.

Table 1. Spectroscopic data for sulfonamide 7a1

 **7a1**				
^{1}H NMR		^{13}C NMR		HMBC x: có vân giao với
Proton	δ (ppm), J (Hz)	Carbon	δ (ppm)	
-	-	C1	129,5	-
H2	6,47 (s, 1H)	C2	115,3	H2 x C4, C6
-	-	C3	124,4	-
-	-	C4	137,9	-
-	-	C5	147,5	-
H6	6,64 (s, 1H)	C6	108,6	H5 x C2, C4
H7	3,63 (s, 3H)	C7	55,7	H7 x C5
H8	4,68 (s, 2H)	C8	51,1	H8 x C2, C6, C11, C9
-	-	C9	168,8	-
H10	1,79 (s, 3H)	C10	22,3	H10 x C9
-	-	C11	142,7	-
H12	7,29 (d, J = 7,0, 1H)	C12	129,2	H12 x C16, C14
H13	7,58 (d, J = 7,0, 1H)	C13	126,6	H13 x C15, C11
-	-	C14	137,5	-
H15	7,58 (d, J = 7,0, 1H)	C15	126,6	H15 x C13, C11
H16	7,29 (d, J = 7,0, 1H)	C16	129,2	H16 x C12, C14
-	-	C17	131,9	-
H18	7,38 (d, J = 7,0, 1H)	C18	129,8	H18 x C20, C22
H19	7,06 (d, J = 6,5, 1H)	C19	127,2	H19 x C17, C21
-	-	C20	141,2	-
H21	7,06 (d, J = 6,5, 1H)	C21	127,2	H21 x C17, C19
H22	7,38 (d, J = 7,0, 1H)	C22	129,8	H22 x C18, C20
H23	2,32 (s, 3H)	C23	20,2	H23 x C20
NH	9,11 (s, 1H)	-	-	NH x C2, C4
OH	8,77 (s, 1H)	-	-	OH x C3, C5

CONCLUSION

Starting from nitrovanillin, five new sulfonamide derivatives (7a1, 7a2, 7a3, 7a4, and 7a5) were successfully synthesized using conventional organic synthetic methods, with improvements at selected stages through the application of microwave irradiation. The use of microwave-assisted synthesis contributed to reduced reaction times and improved overall efficiency.

The structures of the synthesized sulfonamide derivatives were unambiguously established by modern spectroscopic techniques, including ^{1}H NMR, ^{13}C NMR, HMBC, and mass spectrometry (MS).

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