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ABSTRACT

The sulfonylation reaction of various aliphatic, alicyclic, aromatic, and hetero-aromatic amines with *p*-acetamidobenzenesulfonyl chloride has been investigated using different types of base catalysis under varied reaction conditions. Mg–Al hydrotalcite, characterizable as an inexpensive, reusable, and green solid catalyst, was found to be the most efficient catalyst, when the reaction is carried out in a minimum volume of solvent (acetone). The reaction was found to be accelerated drastically with the support of ultrasound irradiation, affording the sulfonamides in yields better or equivalent to those obtained under the longer lasting conventional stirring conditions.
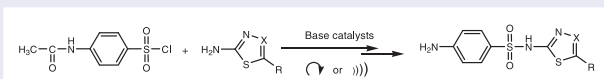
1. Introduction

Sulfonamides (general formula: R^1-SO_2-NR^2R^3), the amides of sulfonic acids, can be classified as un-substituted ($R^2 = R^3 = H$), mono-substituted ($R^3 = H$), or di-substituted (R^2, $R^3 \neq H$) sulfonamides, depending on the number of groups attached to nitrogen. They make up the oldest group of synthetic anti-microbacterial compounds that has been procured and developed during more than 80 years. The first sulfonamide recognized to have anti-microbacterial efficiency, *i.e.* Prontosil (4-[(2,4-diaminophenyl)azo]benzenesulfonamide) was discovered in 1932; however, its mode of biological action by releasing the actually active compound sulfanilamide (4-aminobenzenesulfonamide) was not perceived for next 20 years.[1,2] Sulfonamides have been used intensively as antibacterial agents,[3–6] carbonic anhydrase inhibitors (CAs) and COX-II inhibitors,[7,8] cysteine protease inhibitors,[9,10] and pharmaceuticals

agents for many other categories of disease.[11–14] Today sulfa drugs have been replaced considerably by safer and more powerful antibiotics; however, they are still used exclusively against urinary tract infections.[3,15] From a chemical point of view, the sulfonamides have frequently been regarded as the most convenient and efficient form for preservation of amines because of their stability, combined with the fact that the amines can be regenerated easily by desulfonylation under mild reaction conditions.[16–19]

Since derivatives of sulfanilamide (4-aminobenzenesulfonamide) are structurally related to the *p*-aminobenzoic acid analogs (components necessary for the synthesis of folic acid in bacteria), the corresponding sulfa drugs have been prepared analogously by reaction of *p*-acetamidobenzenesulfonyl chloride with ammonia or other relevant amines, to give the desired sulfonamides. Subsequent convenient base catalyzed hydrolysis of the *p*-acetamido-groups yields the desired sulfa drug without severe consequences for the survival of the sulfonamide group.[3]

A great number of methods for the synthesis of sulfonamides have been developed using a variety of starting materials, *e.g.* sulfonic acids,[20–23] sulfonic acid esters,[24–27] and sulfonyl chlorides.[28–41] Other synthetic routes to sulfonamides depend on the electrochemical oxidation of amine derivatives in the presence of arenesulfinic acid,[42–46] and the direct conversion of thiols into sulfonamides by treatment successively with hydrogen peroxide, thionyl chloride, and the pertinent amine.[47]

Evidently, the base-catalyzed sulfonylation of amines by means of sulfonyl chlorides has been the preferred method of choice owing to its efficiency and simplicity, whether by use of homogeneous organic base catalysts such as pyridine,[13,28] triethylamine,[6,29,30] 1,8-diaza-bicyclo[5.4.0]undec-7-ene (DBU),[31] and other amine reagents,[32,33] or by use of various heterogeneous catalysts found to be excellent alternatives because of the easy isolation of the product,[34–37] as well as with respect to the renewal of the catalytic activity.[38–41]
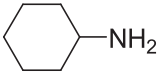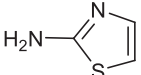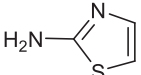
On this background and with sympathy for the principles of green chemistry,[48,49] we found it relevant to investigate the reactivity of *p*-acetamidobenzenesulfonyl chloride (a most pertinent sulfonyl chloride, *cf.* statement above) toward a selection of aliphatic, alicyclic, aromatic, and hetero-aromatic amines. Mg–Al hydrotalcite was chosen as the primary heterogeneous catalyst to be tested in comparison with KF/alumina as well as some organic catalysts [triethylamine and 4-dimethylaminopyridine (DMAP)] owing to the inexpensiveness, stability, and large applications of Mg–Al hydrotalcite in organic syntheses.[50–53] Furthermore, the effect of using ultrasound irradiation was also taken into consideration as a green source of energy supply.[48,49]

2. Result and discussion

At the beginning of this research work, the solvent-free reactions of *p*-acetamido-benzenesulfonyl chloride with cyclohexylamine and 2-aminothiazole were respectively tested. However, incomplete reaction conversion and moderate yields of the sulfonamides forced us to turn our attention to survey a qualified solvent for these reactions. The results demonstrated that acetone appeared to be the best solvent in competition with acetonitrile, dioxane, ethyl acetate, and dichloromethane.

The sulfonylation of amines liberates hydrogen chloride during the reaction, therefore two equivalents of the amine must be used. In general, because the amine component is

Table 1. Influence of the nature of the base catalyst on the yields of the *p*-acetamido-benzenesulfonamides obtained by the reactions of *p*-acetamidobenzenesulfonyl chloride with cyclohexylamine and 2-aminothiazole, respectively under specified reaction conditions.[a]

Entry	Amine (mmol)	Catalyst (mmol)	Time (h)	Yield (%)[b]
1		None	3	56
2		Mg–Al hydrotalcite (0.4)	4	81
3		Mg–Al hydrotalcite (0.4)[c]	0.75	86
4		KF/alumina (1)[c]	0.75	60
5		None	4	27
6		Mg–Al hydrotalcite (0.4)	4	73
7		KF/alumina (2)	4	52
8		Triethylamine (2)	4	53
9		4-Dimethylaminopyridine (DMAP) (2)	4	52
10		Mg–Al hydrotalcite (0.4) and triethylamine (2)	4	73
11		Mg–Al hydrotalcite (0.8)	4	71

[a]The reaction of *p*-acetamidobenzenesulfonyl chloride (2 mmol) with cyclohexylamine or 2-aminothiazole dissolved in acetone (1.5 mL) was performed under stirring at room temperature.
[b]Yield of isolated product.
[c]The reaction was assisted by ultrasound irradiation.

valuable, sulfonamide synthesis is often carried out using one equivalent of the amine plus a corresponding amount of an inexpensive base. A selected variety of catalysts were tested for the sulfonylation of cyclohexylamine (**2a**) and 2-aminothiazole (**2f**) by an equimolar amount of *p*-acetamidobenzenesulfonyl chloride (**1**) in acetone solution at room temperature under magnetic stirring or ultrasound irradiation (Table 1). Finally, Mg–Al hydrotalcite was selected as the supporting base catalyst owing to its good influence on the yield of the sulfonamide products.
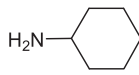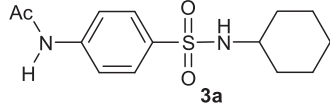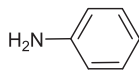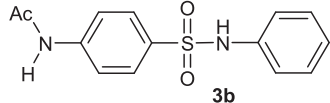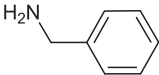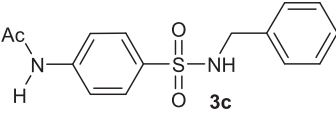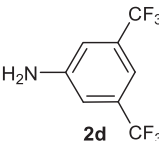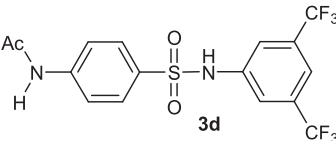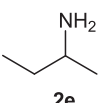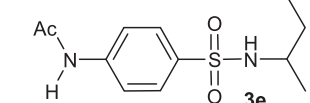
The introductory experiments also disclosed that the two amines (cyclohexylamine and 2-aminothiazole) react differently with equimolar amounts of *p*-acetamidobenzene-sulfonyl chloride: cyclohexylamine undergoes a monosulfonylation reaction, whereas 2-aminothiazole apparently preferably undergoes a double sulfonylation reaction. Further experiments disclosed quite clearly that aliphatic, alicyclic, and also the aromatic amine 3,5-bis(trifluoromethyl)aniline react with an equimolar amount of *p*-acetamidobenzenesulfonyl chloride in a minimum amount of acetone (solvent) and in the presence of the solid catalyst Mg–Al hydrotalcite to form exclusively the corresponding monosulfonylated amines, *i.e.* the corresponding *p*-acetamidobenzenesulfonamides (Scheme 1, Table 2).

On the other hand, the medicinal importance of hetero-aromatic sulfonamides (the 'sulfa drugs' [54]) made us curious to investigate also the conversion of the three hetero-aromatic amines (2-aminothiazole, 2-amino-5-methylthiazole, and 2-amino-5-methylthio-1,3,4-thiadiazole) into the corresponding sulfonamides under the same reaction conditions as described above. Surprisingly, but in accord with the above-mentioned observation concerning the sulfonylation of 2-aminothiazole, all three hetero-aromatic
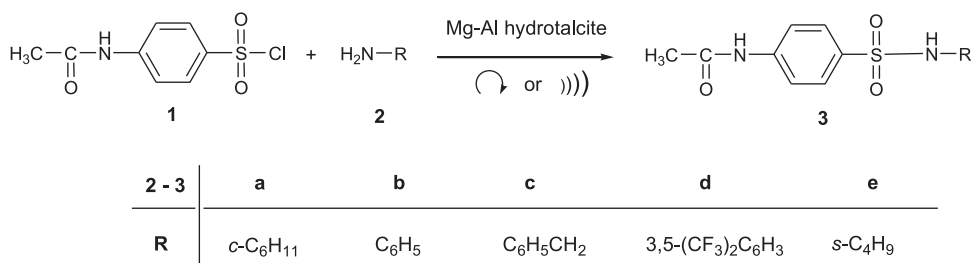
Scheme 1. Monosulfonylated products obtained from the reaction of *p*-acetamidobenzenesulfonyl chloride with aliphatic, cyclic, and aromatic amines.

Table 2. Yields of monosulfonylated compounds from the reaction of *p*-acetamidobenzenesulfonyl chloride with aliphatic, alicyclic, and aromatic amines.[a]

Entry	Amine	Product	Yield (%)[b] (Time)[c]	
			Method A[a]	Method B[a]
1	2a	3a	91 (6)	92 (0.25)
2	2b	3b	59 (6)	71 (0.5)
3	2c	3c	63 (6)	76 (0.5)
4	2d	3d	51 (6)	56 (0.5)
5	2e	3e	54 (6)	63 (0.5)

[a]The reaction of *p*-acetamidobenzenesulfonyl chloride (2 mmol) with amine (2 mmol) catalyzed by Mg–Al hydrotalcite (0.4 mmol, 0.24 g) dissolved in acetone (1.5 mL) was performed under magnetic stirring at room temperature (Method A) or under ultrasound irradiation (Method B).
[b]Yield of isolated product.
[c]Time = reaction time in hours.

amines underwent exclusively the double sulfonylation reaction to form as the only product, the 2-[bis-(*p*-acetamidobenzenesulfonyl)amino]-hetero-aromatic compounds **3f**, **3g** and **3h**, respectively, in fair yields (Scheme 2, Table 3).
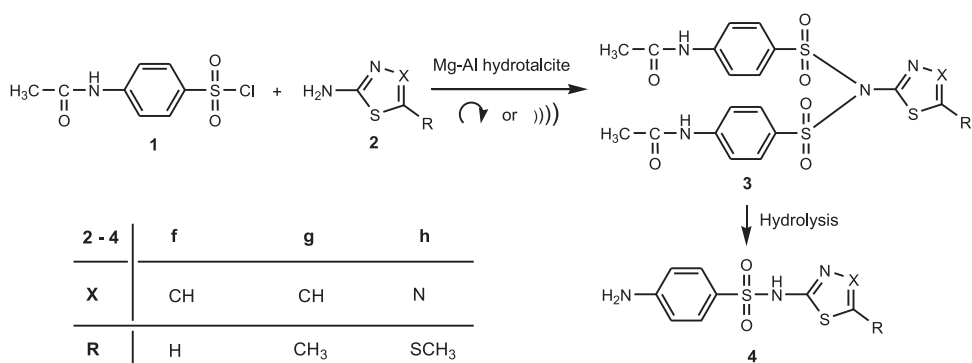
Scheme 2. Synthetic pathway of sulfanilamides from *p*-acetamidobenzenesulfonyl chloride and hetero-aromatic amines.

2 - 4	f	g	h
X	CH	CH	N
R	H	CH$_3$	SCH$_3$

Table 3. Yields of disulfonylated compounds from the reaction of *p*-acetamidobenzenesulfonyl chloride and hetero-aromatic amines.[a]

			Yield (%)[b] (Time)[c]	
Entry	Amine	Product	Method C[a]	Method D[a]
1	2f	3f	71 (0.5)	74 (0.17)
2	2g	3g	74 (4)	77 (1.25)
3	2h	3h	39 (5)	40 (3.25)

[a]The reaction of *p*-acetamidobenzenesulfonyl chloride (2 mmol) with amine (1 mmol) catalyzed by Mg–Al hydrotalcite (0.8 mmol, 0.48 g) dissolved in acetone (1.5 mL) was performed under magnetic stirring at room temperature (Method C) or under ultrasound irradiation (Method D).
[b]Yield of isolated products.
[c]Time = reaction time in hours.

Evidently, either monosulfonylation or disulfonylation can take place, depending on the nature of the amine. The formation of a mixture of the two types of product was never observed. It was therefore concluded that, in the case of the disulfonylation reaction, a previous monosulfonylation reaction must have occurred, leading to a monosulfonylated

$$R^2 - SO_2 - Cl \quad + \quad H_2N - R^1 \quad \longrightarrow \quad R^2 - SO_2 - NH - R^1 \quad + \quad HCl \qquad \text{Eq. (1)}$$

$$Mg\text{-}Al\ HT \quad + \quad HCl \quad \longrightarrow \quad Mg\text{-}Al\ HTH^+ \quad + \quad Cl^{\ominus} \qquad \text{Eq. (2)}$$

$$R^2 - SO_2 - NH - R^1 \quad + \quad Mg\text{-}Al\ HT \quad \longrightarrow \quad R^2 - SO_2 - \overset{\ominus}{N} - R^1 \quad + \quad Mg\text{-}Al\ HTH^+ \qquad \text{Eq. (3)}$$

$$R^2 - SO_2 - Cl \quad + \quad R^2 - SO_2 - \overset{\ominus}{N} - R^1 \quad \longrightarrow \quad \begin{array}{c} R^2 - SO_2 \\ \diagdown \\ N - R^1 \\ \diagup \\ R^2 - SO_2 \end{array} \quad + \quad Cl^{\ominus} \qquad \text{Eq. (4)}$$

$$2\ R^2 - SO_2 - Cl \quad + \quad H_2N - R^1 \quad + \quad 2\ Mg\text{-}Al\ HT \quad \longrightarrow \quad \begin{array}{c} R^2 - SO_2 \\ \diagdown \\ N - R^1 \\ \diagup \\ R^2 - SO_2 \end{array} \quad + \quad 2\ Mg\text{-}Al\ HTH^+ \quad + \quad 2\ Cl^{\ominus}$$
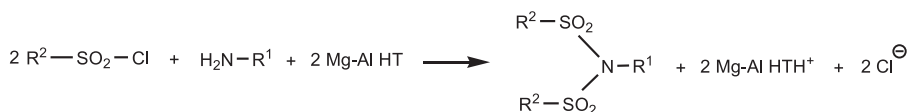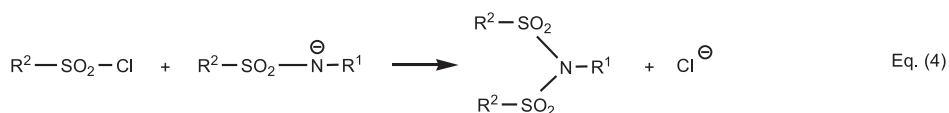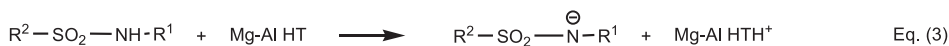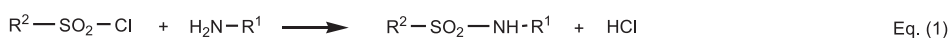
Scheme 3. A plausible mechanism for the double sulfonylation of the hetero-aromatic amines (**2f–2h**) using Mg–Al hydrotalcite.

species being more reactive toward sulfonylation than the hetero-aromatic amine itself. This species can be derived only from the monosulfonylated hetero-aromatic amine $R^2\text{-}SO_2\text{-}NH\text{-}R^1$ (*cf.* Scheme 3), where R^1 is the hetero-aromatic group. A recent investigation of the acidities of *p*-aminobenzenesulfonylated hetero-aromatic amines has demonstrated that the hydrogen atom attached to nitrogen is quite acidic (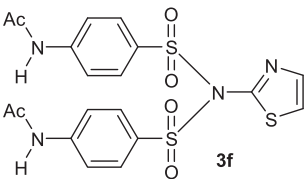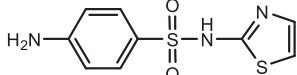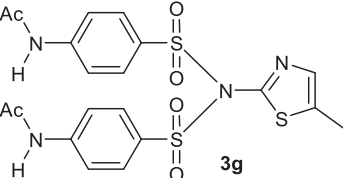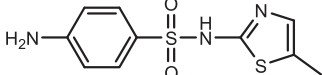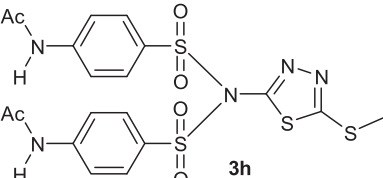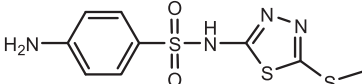pK_a-values ranging from 5.2 to 7.4).[54] In the presence of the solid base catalyst Mg–Al hydrotalcite, the monosulfonylated hetero-aromatic amine is likely to be transformed into the anionic species $R^2\text{-}SO_2\text{-}N^-\text{-}R^1$, which will be a more aggressive species toward the sulfonyl chloride than the hetero-aromatic amine, and therefore give rise to the formation of the observed disulfonylated product (Scheme 3).

It should be noticed that the sulfonylation reactions of the hetero-aromatic amines were constantly monitored by TLC (thin layer chromatography) as well as by the analysis of the crude products by HPLC (high-performance liquid chromatography). In no case even traces of a monosulfonylated hetero-aromatic amine could be detected.

Altogether five simple amines and three hetero-aromatic amines were subjected to sulfonylation by *p*-acetamidobenzenesulfonyl chloride in a minimum amount of acetone, using two different methods. In the first series of sulfonylation reactions, where the mixture of reactants was simply stirred magnetically at room temperature (Method A), fair to high yields were obtained in all cases. The next series of the sulfonylation was performed as described in Method A, but under the assistance of ultrasound irradiation replacing the magnetic stirring (Method B). Although the yields of the products were only slightly improved, the reaction times were shortened considerably in comparison with those under the magnetic stirring method. Due to cavitation collapse in a liquid near a solid surface, high pressure and high temperature are generated shortly and hit the surface of Mg–Al hydrotalcite particles to cause the renewal of its reactive surface area, reduction in Mg–Al hydrotalcite particle size and great enhancement of mixing.[48]

In the hydrolysis step of the *p*-acetamido-groups by means of a base catalyst, *e.g.* the disulfonylated products formed were easily transformed into desired monosulfonylated

Table 4. Yields of sulfanilamides from the base-catalyzed hydrolysis of disulfonylated compounds (**3f–3h**).[a]

Entry	Disulfonylated compounds	Product	Yield (%)[b]
1	**3f**	**4f**	75
2	**3g**	**4g**	79
3	**3h**	**4h**	70

[a]Optimized hydrolysis reaction were performed with disulfonylated compounds (1 mmol) and 10% sodium hydroxide solution (5 mL) for 45 min under stirring reflux at 75°C.
[b]Yield of isolated products.

products in high yield (Table 4). A series of experiments were performed with traditional base catalytic solutions, *e.g.* aqueous saturated sodium carbonate solution or 10% of sodium hydroxide solution under conventional heating at 65°C, 75°C, 85°C and 95°C, or with solid base catalysts in solvent-free conditions, *e.g.* Mg–Al hydrotalcite or potassium fluoride absorbed on alumina under the assistance of microwave irradiation at 100°C. Finally, sodium hydroxide solution was selected for the hydrolysis of disulfonylated hetero-aromatic amines (**2f, 2 g, 2 h**) owing to its good effects on the yield of desired monosulfonylated products.

With the advantages of Mg–Al hydrotalcite on reactive enhancement, simple handling, cheaper operation, and easy product isolation, the reusability of Mg–Al hydrotalcite was paid attention to be examined. The Mg–Al hydrotalcite collected after filtration from the previous reaction was washed with aqueous saturated sodium carbonate solution for 1 h at room temperature, subsequently heated in oven at 100°C for 2 h, and obtained with 97% of recycled yield. The structure of recovered catalyst was comparable with that of the fresh Mg–Al hydrotalcite by the X-ray diffraction (XRD) pattern. The recycled Mg–Al hydrotalcite was used for the sulfonylation of 2-aminothiazole with *p*-acetamidobenzenesulfonyl chloride as that of the optimized experiment presented in Entry 1, Table 3. The catalytic efficiency of Mg–Al hydrotalcite did not drop significantly even after seven runs of being reused and recycled (Figure 1).
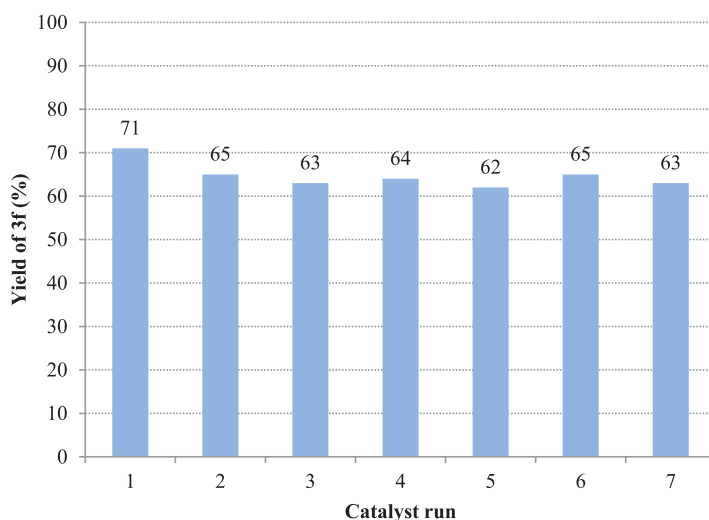
Figure 1. Reusability of Mg–Al hydrotalcite (0.8 mmol, 0.48 g) in the sulfonylation of 2-aminothiazole (1 mmol) with *p*-acetamidobenzenesulfonyl chloride (2 mmol) dissolved in acetone (1.5 mL) under half-an-hour magnetic stirring.

3. Experimental design

3.1. Instrumentation and chemicals

3.1.1. Instrumentation

The reactions were carried out by means of a magnetic stirrer IKA Ret Basic C, speeding at 250 rpm and a BRANSON 1510 ultrasonic bath, operating at frequency 40 kHz. The progress of reaction was monitored by TLC on 60 F_{254} aluminum plates (Merck) with detection by UV light. ^1H NMR (500 MHz) and ^{13}C NMR (125 MHz) spectra were recorded on a Brüker Advance DPX 500 MHz spectrometer in DMSO with TMS as the internal standard. HPLC/ESI (high-performance liquid chromatography/electrospray ionization) analyses were performed on a TSQ 7000 (Thermo-Finnigan) instrument. Melting points were determined on a Büchi B-545 melting point apparatus.

3.1.2. Chemicals

All commercially available chemicals used were from Aldrich and analyzed for authenticity and purity by GC/MS (gas chromatography/mass spectrometry) before being used.

3.2. Typical procedures

3.2.1. The sulfonylation of aliphatic, cyclic, and aromatic amines (2a–2e) under magnetic stirring (Method A)

A solution of the simple amine (2 mmol) in acetone (1.5 mL) was added into a 10 mL round flask containing Mg–Al hydrotalcite (0.4 mmol, 0.24 g) and *p*-acetamidobenzenesulfonyl chloride (2 mmol, 0.467 g). The reaction mixture was then stirred for six hours at room temperature (Method A, Table 2). After reaction completion, the reaction mixture was

extracted with acetone (8 × 5 mL) and filtered to collect the solid base catalyst for recy-cling and reuse. The filtrate was concentrated *in vacuo*, and then the residue after solvent removal was washed with hot distilled water (70–80°C) to remove completely remain-ing *p*-acetamido-benzenesulfonyl chloride or amine. The crude product was filtered, and purified by recrystallization in ethanol/water to afford compounds (**3a–3e**) as white solid.

3.2.2. The sulfonylation of aliphatic, cyclic, and aromatic amines (2a–2e) under ultrasound irradiation (Method B)

A solution the simple amine (2 mmol) in acetone (1.5 mL) was added into a 10 mL round flask containing Mg–Al hydrotalcite (0.4 mmol, 0.24 g) and *p*-acetamidobenzenesulfonyl chloride (2 mmol, 0.467 g). The reaction mixture was then irradiated ultrasonically for the necessary period of reaction time (Method B, Table 2). After reaction completion, the reaction mixture was worked up as in Method A.

3.2.3. The sulfonylation of hetero-aromatic amines (2f–2h) under magnetic stirring (Method C)

A solution of the hetero-aromatic amine (1 mmol) in acetone (1.5 mL) was added into a 10 mL round flask containing also Mg–Al hydrotalcite (0.8 mmol, 0.48 g) and *p*-acetamido-benzenesulfonyl chloride (2 mmol, 0.467 g). The reaction mixture was then stirred magnet-ically for a specific period of time at room temperature (Method C, Table 3). After reaction completion, the reaction mixture was worked up as in Method A.

3.2.4. The sulfonylation of hetero-aromatic amines (2f–2h) under ultrasound irradiation (Method D)

A solution of the heterocyclic amine (1 mmol) in acetone (1.5 mL) was added into a 10 mL round flask containing Mg–Al hydrotalcite (0.8 mmol, 0.48 g) and *p*-acetamidobenzenesulfonyl chloride (2 mmol, 0.467 g). The flask was placed into an ultra-sound bath where the mixture of reactants was exposed to ultrasound irradiation for a specific period of time (Method B, Table 3). After reaction completion, the reaction mixture was worked up as described for Method A.

3.2.5. Hydrolysis of disulfonylated compound (3f–3h)

A round-bottom flask (10 mL volume) was charged with the disulfonylated compound (**3f–3h**) (1 mmol) and 10% aqueous sodium hydroxide (5 mL). The mixture was then immersed in a preheated oil bath, heated to 75°C, and simultaneously stirred for 45 min. After reaction completion, the resulting mixture was cooled to room temperature and acid-ified by HCl aqueous solution (10%) until the mixture had pH 5. The pH of the mixture was subsequently adjusted to just basic (checked by litmus) by adding solid sodium acetate, and then this mixture was heated to boiling and filtered. The resulting filtrate was cooled slowly first to room temperature and then further to 0°C in an ice bath. The final prod-uct (**4f–4h**) was isolated by filtration as a yellowish solid and purified by re-crystallization in ethanol/water or by flash column chromatography (7–8 g silica gel, Davisil, grade 710, 4–20 μm, 6 Å, 99%) using as eluent a mixture of dichloromethane and ethyl acetate (5:5 $^v/_v$).

3.3. Spectroscopic data

The identity and purity of all products reported were confirmed by ^{1}H-NMR, ^{13}C-NMR and HSQC spectroscopy, as well as by GC/MS or HPLC/MS. Since the derivatives of *p*-acetamidobenzenesulfonamide are a large group and NMR spectroscopic data for 11 sulfonamides synthesized have not been well characterized spectroscopically, for which reason full details of both the ^{1}H-NMR spectra and the ^{13}C-NMR spectra are presented below.

3.3.1. N-cyclohexyl 4-(acetamido)benzenesulfonamide (3a)

^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm) = 10.26 (s, 1H), 7.74 (d, 2H, J = 9 Hz), 7.72 (d, 2H, J = 9 Hz), 7.45 (d, 1H, J = 7.5 Hz), 2.89 (s, 1H), 2.08 (s, 3H), 1.54–1.56 (m, 4H), 1.41–1.43 (m, 1H), 0.99–1.14 (m, 5H).[55] MS (*m/z*): 253 [M]$^{\cdot+}$, 198, 134, 98, 43.

3.3.2. N-phenyl 4-(acetamido)benzenesulfonamide (3b)

^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm) = 10.27 (s, 1H), 10.13 (s, 1H), 7.69 (d, 2H, J = 9.5 Hz), 7.67 (d, 2H, J = 9 Hz), 7.21 (t, 2H, J = 7 Hz), 7.07 (d, 2H, J = 8.5 Hz), 7.00 (t, 1H, J = 7.5 Hz), 2.05 (s, 3H). MS (ESI$^+$): *m/z* 308.11 ([M+NH$_4$]$^+$, 100%), 291.08([M+H]$^+$, 49%).

3.3.3. N-benzyl 4-(acetamido)benzenesulfonamide (3c)

^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm) = 10.30 (s, 1H), 7.99 (t, 1H, J = 6.5 Hz), 7.75 (d, 2H, J = 9.5 Hz), 7.73 (d, 2H, J = 9 Hz), 7.20–7.30 (m, 5H), 3.95 (d, 2H, J = 6.5 Hz), 2.09 (s, 3H).[20] MS (ESI$^+$): *m/z* 322.11 ([M+NH$_4$]$^+$, 100%), 305.10 ([M+H]$^+$, 80%).

3.3.4. N-(3,5-bis(trifluoromethyl)phenyl) 4-(acetamido)benzenesulfonamide (3d)

M.p = 210–212°C (literature M.p = 211°C).[56] ^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm) = 11.12 (s, 1H), 10.35 (s, 1H), 7.75 (s, 4H), 7.72 (s, 1H), 7.64 (s, 2H), 2.05 (s, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ (ppm) = 169.1, 143.7, 140.0, 131.8, 131.2, 128.0, 122.8, 118.8, 118.5, 116.5–116.7, 24.0. MS (ESI$^-$): *m/z* 424.84 ([M-H]$^-$, 81%), 228.11 (100%), 227.03 (85%), 226.06 (45%).

3.3.5. N-(sec-butyl) 4-(acetamido)benzenesulfonamide (3e)

^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm) = 10.27 (s, 1H), 7.74 (d, 2H, J = 9 Hz), 7.71 (d, 2H, J = 9 Hz), 7.34 (d, 1H, J = 8 Hz), 3.01 (hept, 1H, J = 7 Hz), 2.08 (s, 3H), 1.28 (quint, 2H, J = 7 Hz), 0.85 (d, 3H, J = 7 Hz), 0.69 (t, 3H, J = 7 Hz). MS(ESI$^+$): *m/z* 288.13 ([M+NH$_4$]$^+$, 100%), 271.11 ([M+H]$^+$, 90%).

3.3.6. N,N-bis(4-acetamidobenzenesulfonyl)-2-aminothiazole (3f)

M.p = 127–130°C (literature M.p = 127–129°C).[57] ^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm) = 10.44 (s, 1H), 10.26 (s, 1H), 7.82 (d, 2H, J = 9 Hz), 7.68 (d, 1H, J = 5 Hz), 7.67 (d, 2H, J = 9 Hz), 7.63 (d, 2H, J = 9 Hz), 7.47 (d, 2H, J = 9 Hz), 6.97 (d, 1H, J = 5 Hz), 2.12 (s, 3H), 2.08 (s, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ (ppm) = 169.3, 168.9, 163.8, 145.7, 143.2, 133.8 (2C), 130.8, 126.9, 123.2, 118.3, 118.2, 107.7, 24.2, 24.1. MS (ESI$^+$): *m/z* 517.11 ([M+Na]$^+$, 100%), 495.14 [M+H]$^+$, 72%), 198 (16%).

3.3.7. N,N-bis(4-acetamidobenzenesulfonyl)-2-amino-5-methylthiazole (3g)

Decomposed at 205°C. ^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm) = 10.43 (s, 1H), 10.25 (s, 1H), 7.81 (d, 2H, J = 9 Hz), 7.68 (d, 2H, J = 9 Hz), 7.62 (d, 2H, J = 9 Hz), 7.50 (d, 1H, J = 1.5 Hz), 7.47 (d, 2H, J = 9 Hz), 2.20 (d, 3H, J = 1.5 Hz), 2.12 (s, 3H), 2.08 (s, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ (ppm) = 169.3, 168.9, 163.2, 145.6, 143.2, 133.9, 130.6, 127.2, 126.9, 119.0, 118.8, 118.3 (2C), 24.2, 24.1, 12.2. MS (ESI^{+}): m/z 509.60 ([M+H]$^{+}$, 12%), 198.03 (100%).

3.3.8. N,N-bis(4-acetamidobenzenesulfonyl)-2-amino-5-methylthio-1,3,4-thiadiazole (3h)

De-composed at 173°C. ^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm) = 10.31 (s, 1H), 10.00 (s, 1H), 7.70–7.75 (m, 4H), 7.50–7.54 (m, 4H), 2.64 (s, 3H), 2.07 (s, 3H), 2.04 (s, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ (ppm) = 168.9, 168.3, 166.8, 155.1, 142.9, 142.6, 139.5, 135.5, 126.9, 126.1, 118.6, 117.9, 24.1, 24.0, 15.3. MS (ESI^{+}): m/z 541.81 ([M+H]$^{+}$, 8%), 198.06 (100%).

3.3.9. 2-(4-aminobenzenesulfonylamido)thiazole (4f)

M.p = 202–203°C (literature M.p = 202–203°C).[58,59] ^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm) = 12.40 (s, 1H), 7.44 (d, 2H, J = 9 Hz), 6.74 (d, 1H, J = 4.5 Hz), 6.56 (d, 2H, J = 9 Hz), 5.83 (s, 2H).[60] ^{13}C NMR (125 MHz, DMSO-d_6) δ (ppm) = 167.9, 152.2, 128.0, 127.7, 124.2, 112.5, 107.4.[61] MS (ESI^{+}): m/z 255.99 ([M+H]$^{+}$, 8%), 156.07 (100%), 92.22 (43%).

3.3.10. 2-(4-aminobenzenesulfonylamido)-5-methylthiazole (4g)

M.p = 247–249°C (literature M.p = 247°C).[62] ^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm) = 12.07 (s, 1H), 7.42 (d, 2H, J = 8.5 Hz), 6.90 (d, 1H, J = 1.5 Hz), 6.56 (d, 2H, J = 8.5 Hz), 5.82 (s, 2H), 2.16 (d, 3H, J = 1.5 Hz). ^{13}C NMR (125 MHz, DMSO-d_6) δ (ppm) = 167.2, 152.1, 128.2, 127.6, 119.9, 119.0, 112.5, 12.1. MS (ESI^{+}): m/z 269.94 ([M+H]$^{+}$, 12%), 156.05 (100%), 92.21 (31%).

3.3.11. 2-(4-aminobenzenesulfonylamido)-5-methylthio-1,3,4-thiadiazole (4h)

M.p = 199–201°C (literature M.p = 198°C).[63] ^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm) = 7.41 (d, 2H, J = 8.5 Hz), 6.58 (d, 2H, J = 8.5 Hz), 2.63 (s, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ (ppm) = 165.8, 154.4, 152.7, 127.7, 126.9, 112.6, 15.2. MS (ESI^{+}): m/z 302.84 ([M+H]$^{+}$, 7%), 156.05 (100%), 92.21 (22%).

4. Conclusion

An environmentally benign pathway to prepare common sulfonamides has been developed. Mg–Al hydrotalcite is commercially available, cheap, easy to store, and can be recycled many times without any remarkable loss of activity. Moreover, ultrasound irradiation has good effects on the yields of sulfonamide products within a shorter reaction time.

Disclosure statement

No potential conflict of interest was reported by the authors.

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References

[1] Hawking F, Lawrence JS. The sulfonamides. London: H.K. Lewis & Co., Ltd; 1950.
[2] Lawrence JS, Francis J. The sulphonamides and antibiotics in man and animals. London: H.K. Lewis & Co., Ltd; 1953.
[3] McMurry J. Organic chemistry. 8th ed. Belmont, CA: Brooks/Cole; 2012. p. 967–968.
[4] Zani F, Vicini P. Antimicrobial activity of some 1,2-Benzisothiazoles having a benzenesulfon-amide moiety. Arch Pharm (Weinheim). 1998;331:219–223.
[5] Vardanyan RS, Hruby VJ. Synthesis of essential drugs. Amsterdam: Elsevier; 2006. p. 486–499.
[6] Narasaiah T, Rao DS, Ramana KV, Adam S, Raju CN. Synthesis of new sulfonamide derivatives of tryptamine and their antimicrobial activity. Der Pharma Chemica. 2012;4:1582–1590.
[7] Scozzafava A, Mastrolorenzo A, Supuran CT. Carbonic anhydrase inhibitors and activators and their use in therapy. Expert Opinion Therapeutic Patents. 2006;16(12):1627–1664.
[8] Supuran CT. Carbonic anhydrases: novel therapeutic applications for inhibitors and activators. Nat Rev Drug Discov. 2008;7:168–181.
[9] Supuran CT, Casini A, Scozzafava A. Protease inhibitors of the sulfonamide type: anticancer, antiinflammatory, and antiviral agents. Med Res Rev. 2003;23:535–558.
[10] Shahripour AB, Plummer MS, Lunney EA, Sawyer TK, Stankovic CJ, Connolly MK, Rubin JR, Walker NPC, Brady KD, Allen HJ, Talanian RV, Wong WW, Humblet C. Structure-based design of caspase-1 inhibitor containing a diphenyl ethersulfonamide. Bioorg Med Chem Lett. 2001;11:2779–2782.
[11] Scozzafava A, Owa T, Mastrolorenzo A, Supuran CT. Anticancer and antiviral sulfonamides. Curr Med Chem. 2003;10:925–953.
[12] Masereel B, Rolin S, Abbate F, Scozzafava A, Supuran CT. Carbonic anhydrase inhibitors: anti-convulsant sulfonamides incorporating valproyl and other lipophilic moieties. J Med Chem. 2002;45:312–320.
[13] Siddiqui N, Arshad MF, Khan SA, Ahsan W. Sulfonamide derivatives of thiazolidin-4-ones with anticonvulsant activity against two seizure models: synthesis and pharmacological evaluation. J Enzyme Inhib Med Chem. 2010;25:485–491.
[14] Namba K, Zheng X, Motoshima K, Kobayashi H, Tai A, Takahashi E, Sasaki K, Okamoto K, Kakuta H. Design and synthesis of benzenesulfonanilides active against methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant *Enterococcus*. Bioorg Med Chem. 2008;16:6131–6144.
[15] Brun-Pascaud M, Chau F, Garry L, Farinotti R, Derouin F, Girard P.-M. Altered trimethoprim-sulfamethoxazole ratios for prophylaxis and treatment of toxoplasma gondii and pneumocystis carinii dual infections in rat model. J Acq Immun Def Synd. 1996;13:201–207.
[16] Wuts PGM, Greene TW. Greene's protective groups in organic synthesis. 4th ed. Hoboken, NJ: John Wiley & Son; 2007. p. 851–868.
[17] Sun P, Weinreb SM. tert-Butylsulfonyl (Bus), a new protecting group for amines. J Org Chem. 1997;62:8604–8608.
[18] Pak CS, Lim DS. Deprotection of 2-pyridyl sulfonyl group from pyridine-2-sulfonamides by magnesium in methanol. Synth Commun. 2001;31:2209–2214.
[19] Milburn RR, Snieckus V. orthor-Anisylsulfonyl as a protecting group for secondary amines: mild Ni0-catalyzed hydrodesulfonylation. Angew Chem Int Ed. 2004;43:892–894.

[20] De Luca L, Giacomelli G. An easy microwave-assisted synthesis of sulfonamides directly from sulfonic acids. J Org Chem. 2008;73:3967–3969.

[21] Caddick S, Wilden JD, Judd DB. Direct synthesis of sulfonamides and activated sulfonate esters from sulfonic acids. J Am Chem Soc. 2004;126:1024–1025.

[22] Shaabani A, Soleimani E, Rezayan AH. A novel approach for the synthesis of alkyl and aryl sulfonamides. Tetrahedron Lett. 2007;48:2185–2188.

[23] Pandit SS, Pandit VU, Bandgar BP. Rapid and efficient synthesis of sulfonamides from sulfonic acid and amines using cyanuric chloride-DMF adduct. J Sulfur Chem. 2008;29:619–622.

[24] Bornholdt J, Fjære KW, Felding J, Kristensen JL. Heterocyclic pentafluoro-phenylsulfonate esters as shelf stable alternatives to sulfonyl chlorides. Tetrahedron. 2009;65:9280–9284.

[25] Caddick S, Wilden JD, Bush HD, Wadman SN, Judd DB. A new route to sulfonamides via intermolecular radical addition to pentafluoro-phenylvinylsulfonate and subsequent aminolysis. Org Lett. 2002;4:2549–2551.

[26] Caddick S, Wilden JD, Judd DB. Observations on the reactivity of pentafluorophenylsulfonate esters. Chem Commun. 2005;(21):2727–2728.

[27] Wilden JD, Geldeard L, Lee CC, Judd DB, Caddick S. Trichlorophenol (TCP) sulfonate esters: a selective alternative to pentafluorophenol (PFP) esters and sulfonyl chlorides for the preparation of sulfonamides. Chem Commun. 2007;(10):1074–1076.

[28] Yasuhara A, Kameda M, Sakamoto T. Selective monodesulfonylation of N,N-disulfonylarylamines with tetrabutylammonium fluoride. Chem Pharm Bull. 1999;47:809–812.

[29] McNulty J, Nair JJ, Capretta A. A synthesis of sulfonamide analogs of platensimycin employing a palladium-mediated carbonylation strategy. Tetrahedron Lett. 2009;50:4087–4091.

[30] Reddy NS, Rao AS, Chari MA, Kumar VR, Jyothy V, Himabindu V. Synthesis and antibacterial activity of sulfonamide derivatives at C-8 alkyl chain of anacardic acid mixture isolated from a natural product cashew nut shell liquid (CNSL). J Chem Sci. 2012;124:723–730.

[31] Jagrut VB, Waghmare RA, Mane RA, Jadhav WN. An improved synthetic route for the synthesis of sulfonamides. Int J Chem Tech Res. 2011;3:1592–1595.

[32] Carvalho EFA, Calvete MJF, Tomé AC, Cavaleiro JAS. Synthesis of sulfonamide-substituted phthalocyanines. Tetrahedron Lett. 2009;50:6882–6885.

[33] Jafarpour M, Rezaeifard A, Golshani T. A green, catalyst-free method for the synthesis of sulfonamides and sulfonylazides. Phosphorus Sulfur. 2011;186:140–148.

[34] Kim J-G, Jang DO. Mild and efficient Indium metal catalyzed synthesis of sulfonamides and sulfonic esters. Synlett. 2007;(16):2501–2504.

[35] Meshram GA, Patil VD. A simple and efficient method for sulfonylation of amines, alcohols and phenols with cupric oxide under mild conditions. Tetrahedron Lett. 2009;50:1117–1121.

[36] Meshram GA, Patil VD. Zinc oxide catalyzed efficient synthesis of sulfonamides under mild conditions. Int J Chem Sci. 2009;7:1948–1956.

[37] Reddy MBM, Pasha MA. Cs_2CO_3 catalyzed rapid and efficient conversion of amines into sulfonamides;Alcohols and phenols into sulfonic esters. Phosphorus Sulfur. 2011;186:1867–1875.

[38] Jafarpour M, Rezaeifard A, Aliabadi M. Catalytic activity of silica gel in the synthesis of sulfonamides under mild and solvent-free conditions. Appl Catal, A: General. 2009;358:49–53.

[39] Mokhtar M, Saleh TS, Ahmed NS, Al-Thabaiti SA, Al-Shareef RA. An eco-friendly the sulfonylation of amines using stable and reusable Zn–Al-hydrotalcite solid base catalyst under ultrasound irradiation. Ultrason Sonochem. 2011;18:172–176.

[40] Zarchi MAK, Aslani M. Convenient Synthesis of sulfonamides from amines and p-toluenesulfonyl chloride mediated by crosslinkedpoly(4-vinylpyridine). J Appl Polym Sci. 2012;124:3456–3462.

[41] Muthayala MK, Chhikara BS, Parang K, Kumar A. Ionic liquid-supported synthesis of sulfonamides and carboxamides. ACS Comb Sci. 2012;14:60–65.

[42] Nematollahi D, Mehdipour E, Zeinodini-Meimand A, Maleki A. Chemical and electrochemical oxidative coupling of N,N-dialkyl-p-phenylenediamines and arylsulfinic acids. Synth Sulfonamide Derivatives Tetrahedron Lett. 2010;51:6447–6450.

[43] Varmaghani F, Nematollahi D, Mallakpour S, Esmaili R. Electrochemical oxidation of 4-substituted urazoles in the presence of arylsulfinic acids: an efficient method for the synthesis of new sulfonamide derivatives. Green Chem. 2012;14:963–967.

[44] Nematollahi D, Varmaghani F, Saremi M. Electrochemical oxidation of 1,2-dihydropyridazine-3,6-dione in the presence of arylsulfinic acids: a green method for the synthesis of new sulfonamides. J Electrochem Soc. 2013;160:G93–G95.

[45] Beiginejad H, Nematollahi D. Electrochemical synthesis of sulfonamide derivatives based on the oxidation of 2,5-diethoxy-4-morpholinoaniline in the presence of arylsulfinic acids. J Org Chem. 2014;79:6326–6329.

[46] Nematollahi D, Davarani SSH, Mirahmadpour P, Varmaghani F. A facile electrochemical method for the synthesis of new sulfonamide derivatives of potential biological significance. Chinese Chem Lett. 2014;25:593–595.

[47] Bahrami K, Khodaei MM, Soheilizad M. Direct conversion of thiols to sulfonyl chlorides and sulfonamides. J Org Chem. 2009;74:9287–9291.

[48] Mason TJ, Lorimer JP. Sonochemistry: theory, applications and uses of ultrasound in chemistry. West Sussex: Ellis Horwood; 1988. p. 64–98.

[49] Ahluwalia VK, Kidwai M. New trends in green chemistry. New Delhi: Anamaya Publishers; 2004. p. 5–14.

[50] Fernandes CI, Nunes CD, Vaz P. Clays in organic synthesis – preparation and catalytic applications. Curr Org Synth. 2012;9(5):670–694.

[51] Morales-Serna JA, Jaime-Vasconcelos MA, García-Ri1os E, Cruz A, Angeles-Beltrán D, Lomas-Romero L, Negrón-Silva GE, Ca1rdenas J. Efficient activity of magnesium–aluminium hydrotalcite in the synthesis of amides. RSC Adv. 2013;3:23046–23050.

[52] Nishimura S, Takagaki A, Ebitani K. Characterization, synthesis and catalysis of hydrotalcite-related materials for highly efficient materials transformations. Green Chem. 2013;15:2026–2042.

[53] Baskaran T, Christopher J, Sakthivel A. Progress on layered hydrotalcite (HT) materials as potential support and catalytic materials. RSC Adv. 2015;5:98853–98875.

[54] Boreen AL, Arnold WA, Mcneill K. Photochemical fate of sulfa drugs in the aquatic environment: sulfa drugs containing five-membered heterocyclic groups. Environ Sci Technol. 2004;38:3933–3940.

[55] Baraldi PG, Moorman AR, Borea PA. Novel adenosine a3 receptor agonists. WO 2005028489 A2. March 31, 2005.

[56] Behnisch R, Klarer J, Mietzsch F. Benzene sulphonic acid derivatives and manufacture thereof. US Patent. No. 2,248,911. July 8, 1941.

[57] Deliwala CV, Ganapathi K, Shirsat MV. Chemotherapy of bacterial infections. X. 2-acetsulphanilimido-3-acetsulphanilylthiazolone and 2-diacetsulphanilylamido-thiazole. A new route to sulphathiazole. Proc Indian Acad Sci – Sect A. 1943;18(6):360–363.

[58] Hartmann M, Cueni F, Druey J. Sulphonamides and process of making same. US. Patent No. 2,386,852. October 16, 1945.

[59] Lott WA, Bergeim FH. 2-(p-Aminobenzenesulfonamido)-thiazole: a new chemotherapeutic agent. J Am Chem Soc. 1939;61:3593–3594.

[60] AIST: Spectral Database for Organic Compounds (SDBS). Available from: http://sdbs.db.aist.go.jp/sdbs/cgi-bin/cre_index.cgi

[61] WSS: Spectral data were obtained from Wiley Subscription Services, Inc. (US).

[62] Jensen KA, Thorsteinsson T. Sulfanilyl derivatives of heterocyclic amines. II. Thiazole and thiazoline derivatives. Dansk Tidsskrift Farmaci. 1941;15:41–77.

[63] Guha PC, Das-Gupta DB. Sulfanilamides. I. N1-Thiadiazolylsulfanilamides. J Indian Chem Soc. 1945;22:79–81.