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Synthesis and antimicrobial evaluation of urea and thiourea derivatives of sulfonic acid

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ABSTRACT

4-Ureido-bezenesulfonic acids and 4-thioureido-benzenesulfonic acids have been synthesized by reaction of differently substituted ureas and thioureas with sulfanilic acid in presence of H_2O as green solvent using microwave irradiations. The structure of the compounds has been confirmed by IR, ^1H NMR, mass and elemental analysis. All the synthesized compounds have been screened for their antibacterial and antifungal activities using micro broth dilution assay.

Keywords: 4-Ureido-benzenesulfonic acids, sulfanilic acid, microwave irradiations antibacterial, antifungal.

INRODUCTION

Sulfonic acid and its derivatives constitute an important class of organosulfur compounds widely used as detergents/surfactants, dyes, pharmaceuticals and acid catalyst [1]. Substituted sulfonic acid derivatives are known to posses diverse pharmacological activities such as antibacterial [2], antitubercular [3], diuretic [4], cytotoxic [5], antiviral [6], enzyme inhibition [7], anticonvulsant [8] and antiinflammatory [9].

Sulfonamide derivatives or Sulfa drugs constitute a broad spectrum of chemotherapeutic agents such as antibacterial [10], antifungal [11], antiprotozoal [12], antiviral [13] and antihypertensive agents [14]. Different varieties of drugs containing sulfonamide functionality are in clinical use to treat allergies [15], obesity [16], cancer [17], diabetes [18], Alzheimer's disease [19] and rheumatoid arthritis [20].

Ureas and thioureas are significant organic compounds having a number of applications in industries, laboratories, automobiles, medicines, fertilizers, herbicides, insecticides, plant growth regulators and urinetharapy. Different urea and thiourea derivatives are known to posses various pharmacodynamic applications as antibacterial [21], antifungal [22], anticancer [23], antiinflammatory [24], antiviral [25], potent inhibitors of influenza virus neuraminidase [26], antihyperglycaemic [27], anti-melanoma [28], antitubercular [29] peptidomimetics [30], diuretics [31], antagonists of human vanilloid VR1 receptors [32], cytokinin analogous [33], and inhibitors of Murine receptor A and Murine receptor B [34].

With the increased frequency of antimicrobial drug resistance in recent times, there is a continuous need for developing newer and more effective chemotherapeutic agents. Diverse phamacological profiles of urea, thiourea and sulfanilic acid derivatives have created our interest in exploring the reaction of different ureas and thioureas with sulfanilic acid and to evaluate the antimicrobial potential of synthesized compounds.

MATERIALS AND METHODS

Melting points were determined in open capillaries and are uncorrected. All reagents were purchased from Sigma-Aldrich and used without further purification. The reactions were carried out in a Synthwave 402 Prolabo microwave reactor with an open system of reaction vessel (freq. 2450 MHz) and were examined by analytical thin layer chromatography (TLC) performed on glass plates precoated with silica gel G as supplied by Sisco Research Laboratories (SRL). Elemental analyses were obtained microanalytically from SAIF, Punjab University, Chandigarh on a Thermo Scientific (FLASH 2000) CHN Elemental Analyser . IR spectra were recorded on FT Infra-Red Spectrometer Model Nicolet IS50 (Thermo Scientific) with KBr pellets. ^{1}H-NMR spectra in DMSO-d_6 solution were recorded on Bruker Avance Π 400 MHz Spectrometer using Tetramethylsilane (TMS) as internal standard and Mass spectra on Thermo Scientific TSQ 8000 Gas chromatograph-Mass Spectrometer.

Synthesis of 4-Ureido-benzenesulfonic acid (3a)

Sulfanilic acid (0.173 g, 1mmol) and Urea (0.06 g, 1mmol) were taken in a 10 mL pyrex beaker. The reaction mixture was thoroughly mixed with the addition of 2-3 drops of water and then exposed to microwave irradiations at 180-190 °C. The progress of the reaction was monitored by TLC (CCl_4: Ethylacetate/3:1) after interval of every 10 sec. The reaction was found to be completed in 3 min. The reaction mixture was diluted with water and the solid thus separated out was filtered, washed with water and recrystallized from ethanol to give 4-Ureido-benzenesulfonic acid in 85 % yield.

4-Ureido-benzenesulfonic acid (3a): M.P. 243-244 °C; Anal. Calc. for $C_7H_8N_2O_4S$ (216): C, 38.88; H, 3.70; N, 12.96; Found: C, 39.13; H, 4.13; N, 11.99 %; FT IR (KBr, υ in cm^{-1}): 3200 (N-H), 3090 (C-H_{Ar}), 1634 (C=O), 1575 (N-H_{bend}), 1423 (C-N), 1319 (S=O_{Asy}), 1158 (S=O_{Sym}), 668 (S-O); ^{1}H NMR (DMSO-d_6, δ ppm): 8.54 (br, 1H, NH); 7.54-7.27 (m, 4H, Ar-H); 5.81 (br, 1H, OH); 5.38 (br, 2H, NH_2); GC-MS (m/z): 216 (M^+), 218 (M+2), 172, 150, 108, 86, 66, 52.

4-(3-Methyl-ureido)-benzenesulfonic acid (3b): M.P.-can't be determined due to hygroscopic nature of the compound; Anal. Calc. for $C_8H_{10}N_2O_4S$ (230): C, 41.73; H, 4.35; N, 12.17; Found: C, 42.31, H, 4.21, N, 12.48 %; FT IR (KBr, υ in cm^{-1}): 3390 (N-H), 3062 (C-H_{Ar}), 1633 (C=O), 1557 (N-H_{bend}), 1410 (C-N), 1312 (S=O_{Asy}), 1169 (S=O_{Sym}), 686 (S-O); ^{1}H NMR (DMSO-d_6, δ ppm): δ 8.82 (br, 1H, NH); 8.12 (br, 1H, NH) δ 7.56 (d, *J* 8.2 Hz, 2H, Ar-H); 7.07 (d, *J* 8.2 Hz, 2H, Ar-H); 5.48 (br, 1H, OH); 2.10 (d, *J* 4.7 Hz, 3H, CH_3); GC-MS (m/z): 230 (M^+), 232 (M+2), 172, 108, 86, 66, 57.

4-(3-Ethyl-ureido)-benzenesulfonic acid (3c): M.P. 174-175 °C; Anal. Calc. for $C_9H_{12}N_2O_4S$ (244): C, 44.26; H, 4.92; N, 11.47; Found: C, 43.05; H, 5.50; N, 12.01 %; FT IR (KBr, υ in cm^{-1}): 3350 (N-H), 3095 (C-H_{Ar}), 1633 (C=O), 1570 (N-H_{bend}), 1398 (C-N), 1378 (S=O_{Asy}), 1161 (S=O_{Sym}), 686 (S-O); ^{1}H NMR (DMSO-d_6, δ ppm): δ 8.93 (br, 1H, NH); 7.71 (br, 1H, NH) δ 7.60-7.58 (m, 2H, Ar-H); 6.96-6.94 (m, 2H, Ar-H); 5.73 (br, 1H, OH); 3.04 (q, 2H, CH_2); 1.02 (t, 3H, CH_3); GC-MS (m/z): 244 (M^+), 246 (M+2), 216, 108, 81, 66, 52.

4-(3-Butyl-ureido)-benzenesulfonic acid (3d): M.P. 220-221 °C; Anal. Calc. for $C_{11}H_{16}N_2O_4S$ (272): C, 48.53; H, 5.88; N, 10.29; S 11.77; Found: C, 48.29; H, 5.78; N, 11.73; S, 12.53 %; FT IR (KBr, υ in cm^{-1}): 3359 (N-H), 3063 (C-H_{Ar}), 1674 (C=O), 1574 (N-H_{bend}), 1420 (C-N), 1339 (S=O_{Asy}), 1160 (S=O_{Sym}), 686 (S-O); ^{1}H NMR (DMSO-d_6, δ ppm): δ 8.85 (br, 1H, NH); 8.21 (br, 1H, NH) δ 7.70 (d, *J* 8.36 Hz, 2H, Ar-H); 7.19 (d, *J* 8.36 Hz, 2H, Ar-H); 5.95 (br, 1H, OH); 2.99-2.96 (m, 2H, CH_2); 1.39-1.24 (m, 4H, -C_2H_4-); 0.92-0.86 (t, 3H, CH_3); GC-MS (m/z): 272 (M^+), 274 (M+2), 216, 172, 156, 108, 84, 65, 52.

4-(-3-Trimethylsilyl-ureido)-benzenesulfonic acid (3e): M.P. 232-233 °C; Anal. Calc. for $C_{10}H_{16}N_2O_4Ssi$ (288): C, 41.66; H, 5.55; N, 9.72; Found: C, 41.01; H, 4.91; N, 10.18 %; FT IR (KBr, υ in cm^{-1}): 3408 (N-H), 3217 (C-H_{Ar}), 1652 (C=O), 1548 (N-H_{bend}), 1465 (C-N), 1359 (S=O_{Asy}), 1159 (S=O_{Sym}), 609 (S-O);^{1}H NMR (DMSO-d_6, δ ppm): δ 11.21 (br, 1H, NH); 8.63 (br, 1H, NH); 7.54 (d, *J* 8.4 Hz, 2H, Ar-H); 7.37 (d, *J* 8.4 Hz, 2H, Ar-H); 5.38 (br, 1H, OH); GC-MS (m/z): 288 (M^+), 290 (M+2), 172, 152, 108, 86, 66, 55.

4-(3-Cyclohexyl-ureido)-benzenesulfonic acid (3f): M.P. 238-244 °C; Anal. Calc. for $C_{13}H_{18}N_2O_4S$ (298): C, 52.35; H, 6.04; N, 9.39; S, 10.74; Found: C, 52.80; H, 6.22; N, 10.32; S, 11.07 %; FT IR (KBr, υ in cm^{-1}): 3327 (N-H), 3037 (C-H_{Ar}), 1627 (C=O), 1576 (N-H_{bend}), 1435 (C-N),1311 (S=O_{Asy}), 1120 (S=O_{Sym}), 684 (S-O); ^{1}H NMR (DMSO-d_6, δ ppm): δ 9.16 (br, 1H, NH); 8.22 (br, 1H, NH) 7.73 (d, *J* 8.4 Hz, 2H, Ar-H); 7.26 (d, *J* 8.4 Hz, 2H, Ar-H); 5.57 (br, 1H, OH); 3.38-3.33 (m, 1H, Cyclohexyl-H); 1.77-1.73 (m, 4H, Cyclohexyl-H); 1.66-1.62 (m, 4H, Cyclohexyl-H); 1.54-1.51 (m, 2H, Cyclohexyl-H); GC-MS (m/z): 298 (M^+), 300 (M+2), 172, 126, 108, 86, 66, 52.

4-Thioureido-benzenesulfonic acid (3g): M.P. 241-242 °C; Anal. Calc. for $C_7H_8N_2O_3S_2$ (232): C, 36.45; H, 3.45; N, 12.06; S, 27.58; Found: C, 36.08; H, 4.05; N, 12.10; S, 27.76 %; FT IR (KBr, υ in cm^{-1}): 3406 (N-H), 3016 (C-H_{Ar}), 1574 (N-H_{bend}), 1496 (C=S), 1403 (C-N), 1300 (S=O_{Asy}), 1177 (S=O_{Sym}), 629 (S-O); ^{1}H NMR (DMSO-d_6, δ ppm): δ 9.83 (br, 1H, NH); 7.75 (d, *J* 8.4 Hz, 2H, Ar-H) 7.39 (d, *J* 8.4 Hz, 2H, Ar-H); 5.74 (br, 1H, OH); 5.18 (s, 2H, NH_2); GC-MS (m/z): 232 (M^+), 234 (M+2), 156, 108, 86, 66.

4-(3-Methyl-thioureido)-benzenesulfonic acid (3h): M.P.-cannot be determined due to hygroscopic nature of the compound; Anal. Calc. for $C_8H_{10}N_2O_3S_2$ (246): C, 39.02; H, 4.06; N, 11.38; S, 26.02; Found: C, 38.62; H, 4.69; N, 11.79; S, 27.18 %; FT IR (KBr, υ in cm^{-1}): 3363 (N-H), 3080 (C-H_{Ar}), 1580 (N-H_{bend}), 1483 (C=S), 1406 (C-N), 1299 (S=O_{Asy}), 1178 (S=O_{Sym}), 632 (S-O); ^{1}H NMR (DMSO-d_6, δ ppm): δ 8.18 (br, 1H, NH); 7.93 (br, 1H, NH) δ 7.37 (d, *J* 8.4 Hz, 2H, Ar-H); 6.56 (d, *J* 8.4 Hz, 2H, Ar-H); 5.35 (br, 1H, OH); 2.40 (s, 3H, CH_3); GC-MS (m/z): 246 (M^+), 248 (M+2), 172, 152, 121, 108, 93, 76, 66.

4-(3-Ethyl-thioureido)-benzenesulfonic acid (3i): 163-164 °C; Anal. Calc. for $C_9H_{12}N_2O_3S_2$ (260): C, 41.54; H, 4.62; N, 10.76; S, 24.62; Found: C, 41.67; H, 4.83; N, 10.26; S, 25.63 %; FT IR (KBr, υ in cm^{-1}): 3461 (N-H), 3022 (C-H_{Ar}), 1574 (N-H_{bend}), 1496 (C=S), 1403 (C-N), 1361 (S=O_{Asy}), 1196 (S=O_{Sym}), 614 (S-O); ^{1}H NMR (DMSO-d_6, δ ppm): δ 8.93 (br, 1H, NH); 8.18 (br, 1H, NH); 7.28 (d, *J* 7.8 Hz, 2H, Ar-H); 6.73 (d, *J* 8.0 Hz, 2H, Ar-H); 5.35 (br, 1H, OH); 3.24 (q, 2H, CH_2); 1.05 (t, 3H, CH_3); GC-MS (m/z): 260 (M^+), 262 (M+2), 232, 187, 172, 108, 77, 66, 52.

Antibacterial Activity

All the synthesized compounds were evaluated for their antibacterial activity against two gram positive bacteria *Staphylococcus aureus* (MTCC 3160), *Bacillus cereus* (MTCC 10085) and two gram negative bacteria *Escherichia coli* (MTCC 433) and *Salmonella enterica* (MTCC 27853) obtained from Institute of Microbial Technology, Chandigarh. The cultures were maintained in Luria broth from Himedia Chemicals Labrotories, India. Ciprofloxacin was used as standard drug for anti-bacterial assay. The MIC values of standard drug and synthesized compounds were determined by modified Resazurin Micro broth Dilution Assay [35]. The compounds were dissolved in dimethyl sulphoxide to prepare stock solutions. A volume of 90.0 µl of stock concentration of drug or synthesized compound was added to 96-well microtitre plate (Tarsons) containing 90.0 µl of Luria Bertini broth and then two fold serial dilution was carried out. A volume of 10.0 µl of bacterial culture was added to each well and incubated at 37 °C for 16 h. After incubation, 10.0 µl of freshly prepared resazurin solution (1 mg/ml) was added to each well and again incubated for 2 h and then observed for any colour change. Growth of bacteria changes the blue dye resazurin to a pink coloured compound, resorufin. The pink colour indicates positive growth and blue indicates growth inhibition.

Antifungal Activity

The antifungal activity of compounds was studied by modified Micro broth Dilution Assay [36] against two fungal strains *Aspergillus fumigatus* (ITCC 4517) and *Aspergillus niger* (ITCC 5405). The standard drug used for antifungal assessment was fluconazole. Aspergillus species cultures were grown on Sabouraud Dextrose (SD) agar at 37 ^oC until sporulation occurs i.e. for 4-5 days. The spores were then harvested in Sabouraud Dextrose (SD) broth from 96 h cultures and by plating serial dilutions on Sabouraud Dextrose agar plates the numbers of Colony Forming Units (CFU) per ml were determined. Autoclaved Sabouraud Dextrose broth (90 µl) was added to the well of 96 culture plates. These plates were incubated at 37 °C and examined microscopically after 48 h for the growth of Aspergillus mycelia. Suitable control wells treated with fluconazole and without any treatment were also included in the experiment. The compound was considered to be active if the wells appear clear without any visible growth of Aspergillus and the result were expressed as Minimum Inhibitory Concentration (MIC).

***In Silico* ADMET analysis**

A number of physicochemical properties of the synthesized compounds were evaluated using Molinspiration software in order to determine their pharmacokinetics in human body i.e. absorption, distribution, metabolism, excretion and toxicity (ADMET). Different physicochemical properties evaluated are: molecular weight, volume, number of heavy atoms, polar surface area, Milog P (partition coefficient), number of hydrogen donors and acceptors and number of rotable bonds. The properties are further investigated for drug likeliness (i.e. the compatibility of compound to act as orally active drug) by Lipinski's rule [37] in combination with Veber filter [38] and Ghose filter [39].

Lipinski's rule

- More than 5 hydrogen bond donors should not be present (the total number of nitrogen–hydrogen and oxygen–hydrogen bonds).
- More than 10 hydrogen bond acceptors should not be present (all nitrogen or oxygen atoms).
- Molecular mass should be less than 500 daltons.

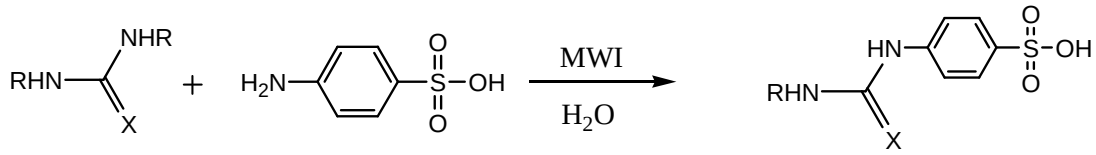
- An octanol-water partition coefficient, log P should not be greater than 5.
- No more than one number of violations.

Veber Filter
- Rotatable bond count should be less than or equal to 10
- Polar surface area (PSA) should be less than or equal to 140 $Å^2$.

Ghose Filter
- Molecular weight should be between 160 to 480 daltons.
- Molar refractivity should be in range 40 to 130 m^3mol^{-1}.
- Total number of atoms should be 20 to 70.

RESULTS AND DISCUSSION

We report herein the synthesis of urea and thiourea derivatives of sulfonic acid in the presence of water as solvent under microwave irradiations **(Scheme 1).**



Ureas/Thioureas (1a-i) | Sulfanilic acid (2) | 4-Ureido/thioureido-benzenesulfonic acids (3a-i)

X= O, S
R= H, Alkyl, Cyclohexyl, Trimethylsilyl

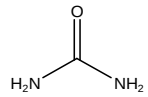
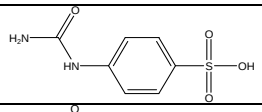
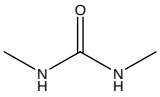
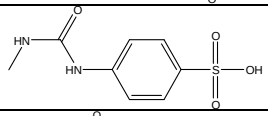
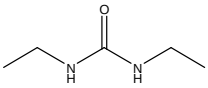
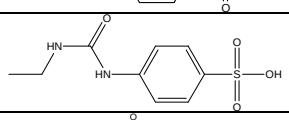
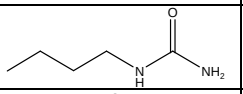
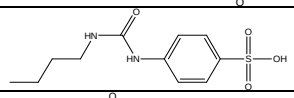
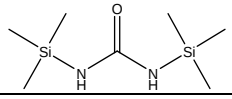
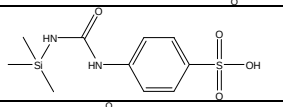
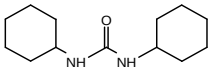
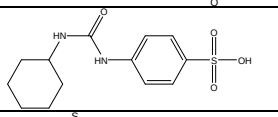
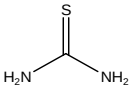
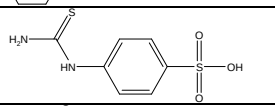
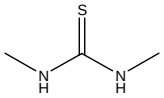
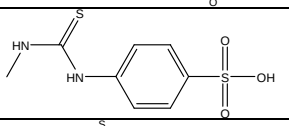
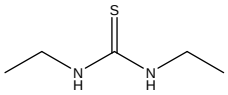
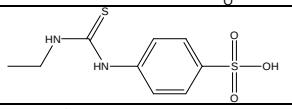
Scheme 1

The title compounds were synthesized by the reaction of Sulfanilic acid with differently substituted ureas and thioureas. The reactants were finely mixed with few drops of water at room temperature and then subjected to microwave irradiations at around 180-190 °C. The progress of the reaction was monitored by TLC using ethyl acetate and carbon tetrachloride as eluent (3:1). 4-Ureido/Thioureido-benzenesulfonic acids **(3a-i)** were synthesized in good yields in few minutes and the products were obtained by simply adding water to the reaction mixture **Table 1**.

The titled compound 4-Ureido-benzenesulfonic acid, in its IR exhibited a band in the region 3200 for N-H stretching, 3090 for aromatic C-H stretching, 1634 for C=O stretching, 1575 for N-H bending, 1423 for C-N stretching, 1319 for S=O asymmetric stretching, 1158 for S=O symmetric stretching, 668 for S-O stretching. In the ^{1}H NMR spectra, the compound exhibited a singlet at δ 8.54 due to NH proton, a multiple at δ 7.54-7.27 due to four aromatic protons, a singlet at δ 5.81 due to OH proton and a singlet at δ 5.38 due to two NH_2 protons. In the Mass spectra, the molecular ion peaks was found at m/z 216 and the base ion peak was found at m/z 172. Correspondingly peaks were also noticed at m/z values of 150, 108, 86, 66, and 52. The mass and elemental analyses data was found in agreement with the proposed structure of the synthesized compound i.e. 4-Ureido-benzenesulfonic acid.

Similarly, the method of structure elucidation was extended to rest of the synthesized compounds of the series. The IR, ^{1}H NMR, mass spectra and elemental analyses data of the synthesized compounds were found to be in good agreement with the proposed structures.

Table 1 Synthesis of 4-Ureido/thioureido-benzenesulfonic acids in the presence of water under MW irradiations

Entry	Reactants	Product	Time (min)	Yield[a] (%)
3a			3	85
3b			1	80
3c			2	78
3d			4	75
3e			5	77
3f			8	70
3g			2	75
3h			1	78
3i			2	78

[a]Yields are of pure product isolated.

Antimicrobial Evaluation:

All the synthesized compounds exhibited moderate to good antibacterial activity against both gram positive and gram-negative bacteria. Compound **3c**, **3d** displayed best activity against all the gram positive and gram negative bacterial strains. Compound **3c**, **3d** and **3i** exhibited significant activity against S. *aureus*.

Antifungal activity results of synthesized compounds revealed that compound **3b**, **3c, 3g, 3h** and **3i** exhibited good antifungal activity against A. *fumigates* and A. *niger* as compared to other compounds . Results are gathered in **Table 2**.

Table 2 Antimicrobial potential evaluation [MIC (mg/ml)] of sulfonic acid derivatives

Entry	Gram positive bacteria		Gram negative bacteria		Fungi	
	S. aureus	*B. cereus*	*E. coli*	*S. enterica*	*A. fumigatus*	*A. niger*
	MTCC 3160	MTCC 10085	MTCC 433	MTCC 27853	ITCC 4517	ITCC 5405
3a	20	20	20	20	20	20
3b	10	10	5	5	10	10
3c	5	10	10	10	10	10
3d	5	5	10	10	20	20
3e	20	20	20	20	20	20
3f	20	20	10	10	20	20
3g	10	10	20	20	10	10
3h	10	10	10	10	10	10
3i	5	10	10	10	10	10
Fluconazole	-	-	-	-	125 µg/mL	62.5µg/mL
Ciprofloxacin	62.5µg/mL	125µg/mL	125µg/mL	125µg/mL	-	-

Results of *In Silico* ADMET Analysis:

All the synthesized sulfonic acid derivatives were further evaluated by *In Silico* ADMET Analysis excluding **3e** as the compound does not shows satisfactory activity against any bacterial or fungal strains. In the ADMET analysis,

all the compounds examined have molecular weight in the range of 216 to 298 daltons and log P value in the range of -2.03 to 0.34. A molecular weight of less than 500 daltons and log P of less than 5 indicate lipophilicity the compound and predicts its intestinal absorption and transcellular transport. Number of rotable bonds less than equal to 10 and PSA of less than equal to 140 $Å^2$ is a measure of good oral bioavailability of drug. Number of hydrogen donor less than five is a measure of good absorption of drug in the body as hydrogen bond donors are generally involved in different phases of metabolism. Low Log P value combined with high TPSA is a measure of low toxicity of compound. Hence the synthesized compounds possess good drug likeliness score as the physicochemical properties of these compounds were found to be good agreement with the Lipinski's rule in combination with Veber filter and Ghose filter. Results are summarized in **Table 3**.

Table 3 Calculated physiological properties of sulfonic acid derivatives

Entry	miLogP	TPSA	nAtoms	n ON	nOHNH	n violation	N rotb.	Volume	MW
3a	-1.94	109.49	14	6	4	0	2	166.17	216.22
3b	-1.56	95.50	15	6	3	0	2	183.84	230.25
3c	-1.19	95.50	16	6	3	0	3	200.64	244.27
3d	-0.12	95.50	18	6	3	0	5	234.25	272.33
3f	0.34	95.50	20	6	3	0	3	257.28	298.36
3g	-2.03	92.42	14	5	4	0	3	175.04	232.29
3h	-1.66	78.42	15	5	3	0	4	192.72	246.31
3i	-1.28	78.42	16	5	3	0	5	209.52	260.34

CONCLUSION

A series of 4-Ureido/thioureido-benzenesulfonic acids was synthesized with excellent yields under clement conditions as no organic solvent was used throughout the reactions and products are isolated using simple workup procedures. All the synthesized compounds were screened for their antimicrobial activity and some of them exhibited moderate to good antibacterial and antifungal activities and satisfactory drug likeliness scores.

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