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Design and Synthesis of a Series of 3-Aminobenzenesulfonamide Derivatives and Their Screening for Antimicrobial and Cytotoxic Activity

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ABSTRACT

A series of 3-aminobenzenesulfonamide derivatives with a 3-*N*-substituted side chains that contain ureas, thioureas or cyclic amines was designed, synthesized and assayed for antibacterial, anti-candidal and cytotoxic activity. The synthesized compounds exhibited minimal antibacterial activity but showed good anti-candidal activity, especially compounds **2a**, **2d**, **2e**, **3a**, **3d**, **4b**, **4c**, **4d**, **4j**, **4k**, **4l** and **4m** with MIC values ranging from 16-64 µg/mL. The thiourea and urea (compounds **2a-f** and **3a-d**), but not the cyclic amine derivatives (compounds **4a-m**), exhibited significant cytotoxic activity against brine shrimp.

Keywords: Urea, Thiourea, Benzenesulfonamide, Cyclic Amine, Anti-Candidal, Brine Shrimp.

INTRODUCTION

Antimicrobial agents are among the largest groups of clinically available medicinal agents. One of the most important issues prompting the continuous development of new antimicrobial agents is the emergence of microbial resistance(1-5). Development of new antimicrobials with chemical scaffolds that are structurally different from the clinically used ones might help in delaying the emergence of resistant. In an effort to identify such new scaffolds, a library of compounds that were synthesized in our laboratory were screened for their antimicrobial activity, (unpublished work). Among screened compounds, compound **1** shown in Figure (1), exhibited promising anti-candidal activity (64 µg/ mL). The simplicity of the scaffold has prompted us to design and synthesize a series of chemically related compounds and screen them for possible antimicrobial and cytotoxic activity. All the reported compounds in this work are *N*-acylated derivatives of 3- amino - *N*-methylbenzenesulfonamide with the general structures **2**, **3** and **4** as depicted in Figure (1).

RESULTS AND DISCUSSION

Chemistry

As shown in scheme 1, commercially available 3-nitrobenzenesulfonyl chloride was treated with excess 40% aqueous solution of methylamine to afforded 3-nitro-*N*-methylbenzenesullfonamide which was then reduced using iron metal and ferrous sulfate ($Fe/FeSO_4$)(6,7) in water/ethanol as a solvent system to afford the desired amine **(5)** in an overall yield of 74%.

Compounds **2a-f**, were synthesized starting from compound **5** as shown in Table 1. Upon the addition of the appropriate isocyanate or isothiocyanate to compound **5** dissolved in chloroform, a precipitate formed

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immediately. After completion of the reaction, the mixture was filtered and the solid was crystallized from ethanol to afford the pure compounds in yields ranging from 52 to 85%.

Synthesis of compounds **3a-d** started by reacting compound **5** with chloroacetyl chloride in a biphasic mixture of water and ethyl acetate in the presence of sodium bicarbonate as a base. The α-chloracetamide **6** was then transformed to the corresponding α-aminoacetamide **7** using Gabriel synthesis(8, 9) as shown in scheme 2. Crystallization from methanol afforded the desired hydrochloride salt in modest yield (59 %). As shown in Table (2), the salt **7** was treated with the appropriate isocyanate or isothiocyanate in the presence of triethylamine in chloroform or DMF. Water was added to the reaction mixture and then was extracted with ethyl acetate. Evaporation of the solvent followed by crystallized afforded compounds **(3a-d)** in relatively low yields (31-58%).

For synthesis of compounds **4a-m** the α-chloroacetylamino **6** was dissolved with the appropriate amine in acetone or acetonitrile in the presence of potassium or sodium carbonate as a base (10). The target tertiary amines were obtained in moderate to very good yields (60-86%) after crystallization from appropriate solvent as summarized in Table (3).

Microbiological and Cytotoxic Evaluation

All the synthesized compounds were assayed for their antibacterial and anti-candidal activity and for cyctotoxicity against brine shrimp. The antibacterial activity was determined according to the macrodilution method of the NCCLS (National Committee for Clinical Laboratory Standards) (11-13) against three standard bacterial strains, *Staphylococcus aureus* (ATCC 29213), *Escherichia coli* (ATCC 25922) and *Pseudomonas aeruginosa* (ATCC 27853). In addition, the compounds were evaluated against one *Candida albicans* clinical isolate. The Brine Shrimp Lethality Test (BSLT) was performed according to published procedures (14, 15). The screening results are summarized in Table (4).

The synthesized compounds showed no or very low antibacterial activity. Only two compounds showed antibacterial activity equal to 128 μg/mL, compound **4j** against *S. aureus* and compound **4h** against *E. coli*. These activities are in the ranges reported for some sulfonamides, e.g. sulfadiazine and sulfadimidine (16).

On the other hand, many of the synthesized compounds showed promising activity against *C. albicans*. The most potent compounds (MIC ≤ 64 μg/mL) were **2a**, **2d**, **2e**, **3a**, **3d**, **4b**, **4c**, **4d**, **4j**, **4k**, **4l** and **4m** and it is evident that the activity is not confined to any particular series. With regard to ureas and thioureas, compounds containing unsubstituted phenyl rings (**3a**, **3b** and **1**) which contained the extra acetyl spacer were two to more than 8 times more active than their shorter analogs (**2a**, **2b** and **2f**). While, the activity of the tolyl ureas were relatively similar in both groups (**2d**, **2e** and **3c**, **3d**). With regard to cyclic amines, with the exception of **4e** and **4f**, monobasic cyclic amines showed acceptable activities compared to similarly-sized dibasic piperazine derivatives. This is obvious when comparing **4b**, **4c** and **4d** (MIC's = 32 μg/mL) to **4g**, **4h** and **4i** (MIC's >512 μg/mL). This might be due to the higher extent of ionization and/or to the higher polarity of the unionized from of the dibasic piperazinyl compounds. *N*-Alkyl substituted piperazines (**4g**, **4f** and **4i**) possess much less anti-candidal activity compared to *N*-aryl or *N*-benzyl substituted cyclic amines (**4j**, **4k** and **4i**), i.e. lipophilicity and/or bulkiness may play a favorable role in drug-target interaction. Compound **4m** showed the best activity in this assay. This is most likely due to the fact that it contains an imidazole ring that is reported to be the ferric ion chelating group responsible for the antifungal action of many commercially available azole antifungal agents such as miconazole (17).

With regard to Brine Shrimp Lethality Test, LC_{50} values > 1000 μg/mL are considered inactive, while values < 5 μg/mL are considered as highly active. It is evident that ureas and thioureas are potent cytotoxic agents. This data is highly encouraging to further test these compounds for anticancer and pesticidal activity using the proper cell lines and assays.

All the reported data in this work is considered preliminary and detailed and precise SAR cannot be drawn. Yet, these results can identify some lead compounds for the development of new anti-candidal agents. Indeed, compound **4m** was chosen to undergo further structural modification to improve its anti-candidal activity.

Experimental

Bulk solvents were purchased through local vendors. Reagent grade and fine chemicals were obtained mainly from Aldrich Chemical Company, USA (www.sigmaaldrich.com), ACROS Chemicals, Belgium (www.acros.com) and Scharlau Chemical, Spain (www.scharlau.com). Melting points were determined using a digital Stuart Scientific melting point apparatus and are uncorrected. Electron impact (EI) mass spectra were obtained using Shimadzu QP5050A GS-MS, Japan. IR spectra were recorded on Nicolet Avatar 360 FT-IR, USA using KBr disks. ^{1}H NMR and ^{13}C NMR spectra were obtained using a Bruker Avance Ultrashield 400 MHz instrument, Switzerland; and are reported in ppm relative to automatic calibration to the residual proton peak of the solvents used namely $CDCl_3$ or DMSO-d_6. TLC analysis was performed on Albet Aluminum TLC plates, Spain, (Aluminum, Silica 60, UV_{254}).

***N*-methyl-3-aminobenzenesulfonamide (5).** To 60 g of 3-nitrobenzenesulfonyl chloride (0.271 mol), 200 mL of 40% methylamine aqueous solution (2.57mol) was added gradually while stirring. The reaction mixture was allowed to stir for 10 minutes, then a precipitate began to form and the reaction was stopped after 15 min after which the reaction mixture was filtered and the pale yellow solid was washed with water. Then the crude product was dissolved in water:ethanol (150:200 mL) with heating and to the solution, a mixture of 76.14 g (1.37 mol) iron powder and 75.3 g (0.271 mol) ferrous sulfate were added slowly and the reaction was maintained at reflux for 24 hr. The reaction mixture was then filtered while hot and the solvent was evaporated and solid residue was washed with ether then crystallized from dichloromethane/ether to obtain 37.3 g of a shiny light brown crystals (74%). 94-95 (m.p); IR (KBr) 3454, 3399, 3262, 1631, 1598, 1302, 1153 cm^{-1}; MS (EI) *m/z* 186.05 (M^{+}); ^{1}H NMR (DMSO-d_6) δ 2.4 (d, *J* = 5 Hz, 3H), 5.57 (bs, 2H), 6.78 (ddd, *J* = 1.8, 8 Hz, 1H), 6.87 (ddd, *J* = 0.85, 1.8, 8 Hz, 1H), 6.97 (t, *J* = 1.8 Hz, 1H), 7.20 (m, 2H); ^{13}C NMR (DMSO-d_6) δ 29.09, 111.72, 113.82, 117.67, 130.01, 140.10, 149.76.

Compound 2a-2f, general procedure: To 1.0 g (5.4 mmol) of **5** dissolved in 25 mL chloroform, an appropriate amount of the isocyanate or isothiocyanate was added and the reaction mixture was allowed to stir at room temperature for 24 hr. The reaction was filtered and the solid was crystallized from ethanol to afford the desired product.

***N*-Methyl-3-(3-phenyl-thioureido)benzenesulfonamide (2a).** 1.12 g (8.25 mmol) of phenylisothiocyanate; 1.1 g of a pale yellow solid (64%). 150-156 °C (m.p); IR (KBr) 3295, 1660, 1328, 1155 cm^{-1}; GC-MS (EI) *m/z* 321.2 (M^{+}); ^{1}H NMR (DMSO-d_6) δ 2.45 (d, *J* = 3.6Hz, 3H), 7.16 (t, *J* = 8 Hz, 1H), 7.36 (t, *J* = 7.6 Hz, 2H), 7.51 (m, 4H), 7.55 (t, *J* = 8 Hz, 1H) 7.74 (d, *J* = 8 Hz, 1H), 7.98 (s, 1H), 10.01 (s, 2H). ^{13}C NMR (DMSO-d_6) δ 29.06, 115.97, 116.29, 119.31, 120.16, 121.99, 123.37, 129.11, 130.11, 138.49, 139.73, 140.17, 140.97, 152.87.

***N*-Methyl-3-(3-phenyl-ureido)-benzenesulfonamide (2b)**. 0.65 g (5.5 mmol) of phenylisocyanate; 1.30 g of a white solid (79%). 167-167.5 °C (m.p); IR (KBr) 3402, 3358, 3205, 1694, 1318, 1163 cm^{-1}; GC-MS (EI) m/z 305.1 (M^{+}); ^{1}H NMR (DMSO-d_6) δ 2.42 (s, 3H), 6.98 (t, *J* = 7.3 Hz, 1H), 7.28 (t, *J* = 7.6 Hz, 2H), 7.35 (d, *J* = 7.6 Hz, 1H), 7.47 (m, 4H), 7.56 (d, *J* = 8 Hz, 1H), 8.29 (s, 1H), 8.76 (s, 1H), 9.07 (s, 1H). ^{13}C NMR (DMSO-d_6) δ 29.14, 116.39, 119.90, 120.18, 122.10, 122.62, 129. 28, 130.12, 139.81, 140.23, 140.93, 152.88.

***N*-Methyl-3-(3-benzoyl-thioureido)-benzenesulfonamide (2c)**. 0.9 g (5.5 mmol) of benzoylisothiocyanate; 1.50 g of a yellow solid (79%). 175-177 °C (m.p); IR (KBr) 3358, 3190, 3025, 1593, 1322, 1158 cm^{-1}; GC-MS (EI) m/z 349.1 (M^{+}); ^{1}H NMR (DMSO-d_6) δ 2.39 (d, *J* = 4 Hz, 3H), 7.54 (m, 3H), 7.65 (m, 3H), 7.89 (bs, 1H), 7.98 (d, *J* = 8 Hz, 2H), 8.19 (s, 1H), 11.67 (s, 1H). ^{13}C NMR (DMSO-d_6) δ 29.17, 123.17, 124.67, 129.69, 130.18, 132.55, 133.67, 139.16, 140.00, 168.57, 180.01.

***N*-Methyl-3-[3-(*m*-tolyl)-ureido]-benzenesulfonamide (2d).** 1.1 g (8.25 mmol) of *m*-tolylisocyanate; 1.35 g of white solid (79%). 189-189.7 °C (m.p); IR (KBr) 3399, 3351, 3161, 1691, 1299, 1156 cm^{-1}; GC-MS (EI) m/z 319.2 (M$^+$); ^{1}H NMR (DMSO-d_6) δ 2.29 (s, 3H), 2.44 (d, J = 5 Hz, 3H), 6.82 (d, J = 7.6 Hz, 1H), 7.17 (t, J = 7.6 Hz, 1H), 7.24 (d, J = 8 Hz, 1H), 7.33 (s, 1 H), 7.36 (d, J = 7.6, 1H), 7.44 (q, J = 5 Hz, 1H), 7.5 (t, J = 7.7 Hz, 1H), 7.56 (d, J = 8 Hz, 1H), 8.07 (s, 1H), 8.65 (s, 1H), 9.02 (s, 1H). ^{13}C NMR (DMSO-d_6) δ 21.66, 29.06, 115.98, 116.30, 119.32, 120.16, 121.99, 123.37, 129.12, 130.11, 138.49, 139.63, 140.18, 140.97, 152.80.

***N*-Methyl-3-[3-(*p*-tolyl)-ureido]-benzenesulfonamide (2e).** 1.1 g (8.25 mmol) of *p*-tolylisocyanate; 1.45 g of white solid (85%). 200-201 °C (m.p); IR (KBr) 3401, 3357, 3212, 1692, 1294, 1160 cm^{-1}; GC-MS (EI) m/z 319.2 (M$^+$); ^{1}H NMR (DMSO-d_6) δ 2.25 (s, 3H), 2.44 (d, J = 5.2 Hz, 3H), 7.10 (d, J = 8 Hz, 2H), 7.35 (d, J = 8 Hz, 3H), 7.44 (q, J = 5.2 Hz, 1H), 7.49 (t, J = 8 Hz, 1H), 7.57 (d, J = 8 Hz, 1H), 8.05 (s, 1H), 8.62 (s, 1H), 9.02 (s, 1H). ^{13}C NMR (DMSO-d_6) δ 20.79, 29.06, 116.27, 118.92, 120.08, 121.96, 129.67, 131.51, 137.22, 140.16, 140.93, 152.85.

***N*-Methyl-3-(3-benzyl-thioureido)-benzenesulfonamide (2f).** 0.82 g (5.5 mmol) of benzylisothiocyanate; 1.40 g of an off-white solid (78%). 112-112.9 °C (m.p); IR (KBr) 3284, 3028, 1541, 1318, 1152 cm^{-1}; GC-MS (EI) m/z 335.1 (M$^+$); ^{1}H NMR (DMSO-d_6) δ 2.43 (d, J = 4.9 Hz, 3H), 4.74 (d, J = 5.3 Hz, 2H), 7.26 (dt, J = 4, 8.5, 1H), 7.35 (m, 4H), 7.43 (q, J = 4.9, 1H), 7.46 (d, J = 7. 7.52 (t, J = 7.8 Hz, 1H), 7.71 (d, J = 7.9 Hz, 1H), 7.99 (s, 1H), 8.35 (s, 1H), 9.85 (s, 1H). ^{13}C NMR (DMSO-d_6) δ 29.10, 47.60, 121.38, 122.21, 126.81, 127.47, 128.81, 129.85, 139.84, 140.69, 181.48.

***N*-methyl-3-(2-chloroacetylamino)-benzenesulfonamide (6):** To a biphasic system made of 150 mL water containing 18.52 g (0.22 mol) sodium bicarbonate and 400 mL ethyl acetate, 22.5 g (0.121 mol) of **5** was added to the reaction flask. Then a solution of 12.8 mL (17.7 g, 0.157 mmol) chloroacetyl chloride in 150 mL ethyl acetate was added dropwise and the mixture was allowed to stir for 2 hr at room temperature. The layers were then separated and the aqueous layer was extracted twice with ethyl acetate and the combined organic layers were concentrated to half volume and allowed to cool to room temperature to afford 30.2 g (95%) of a light brown solid. 105-106 °C (m.p), IR (KBr) 3313, 3182, 1685, 1592, 1322, 1158 cm^{-1}; GC-MS (EI) m/z 261.9 (M$^+$); ^{1}H NMR (DMSO-d_6) δ 2.41 (d, J = 4Hz, 3H), 4.27 (s, 2H), 7.48 (m, 2H), 7.56 (t, J = 8Hz, 1H), 7.76 (dt, J = 8Hz, 2Hz, 1H), 8.12 (s,1H), 10.63 (s, 1H); ^{13}C NMR (CDCl$_3$) δ 29.03, 43.95, 117.76, 122.24, 130.37, 139.53, 140.24, 165.61.

1-[3-(*N*-methylaminosulfonyl)phenyl]-aminoacetyl-2-ammonium chloride (7). To 30.2 g (0.115 mol) of **6** in 114 mL DMF, 42.23 g (0.23 mol) potassium phthalimide was added, and the mixture was maintained at 150 °C for 2 hr. The reaction was then allowed to cool to about 80°C and 250 mL of 28 % acetic acid solution was added and the mixture was placed in the refrigerator overnight. The formed solid was filtered, washed with water and then suspended in 300 mL of 95% ethanol. The alcoholic mixture was heated to reflux, then 8.0 g (160 mmol) hydrazine hydrate was added to it and reflux was maintained for 2 hr. Again, the mixture was allowed to cool and 21 mL of 12 M HCl was added to it and the new mixture was maintained at reflux for another 1.5 hr. Finally, the reaction was allowed to cool to room temperature and filtered. The filtrate was then evaporated to dryness and the residue was crystallized from methanol/water to yield 18.5 g of a white solid (58.5 %). GC-MS (EI) m/z 243 (M$^+$); IR (KBr) 3187, 3078, 1683, 1320, 1140 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 2.40 (s, 3H), 2.49 (s, 2H), 7.47-7.58 (m, 3H), 7.80 (d, J = 8 Hz, 1H), 8.17 (s, 1H), 8.34 (s, 3H), 11.24 (s, 1H). ^{13}C NMR (DMSO-d_6) δ 29.11, 41.43, 117.55, 122.12, 123.03, 130.36, 139.38, 140.30, 165.69.

***N*-methyl-3-(2-[3-phenyl-thioureido]acetylamino)-benzenesulfonamide (3a).** To 1.0 g (3.6 mmol) of **7** suspended in 15mL chloroform, 0.4 g (3.6 mmol) triethylamine and 0.27 g (3.6 mmol) phenylisothiocyanate were added and the reaction mixture was allowed to stir at room temperature for 2 hr. Then, water was added to the reaction and layers were separated. The aqueous layer was extracted with ethyl acetate and the combined organic layers were washed with 1N HCl and dried over MgSO$_4$. Solvents were evaporated and the solid residue was crystallized from ethanol/ether to yield 0.79 g of an off-white solid (58%). 185.5-187.2 °C (m.p); IR (KBr) 3319, 1689, 1597, 1529, 1307, 1255, 1152, 1083 cm^{-1}; GC-MS (EI) m/z 377.9 (M$^+$); ^{1}H NMR (DMSO-d_6) δ 2.41 (d, *J* = 5.2 Hz, 3H), 4.37 (d, *J* = 4.8 Hz, 2H), 7.13 (t, *J* = 7.6 Hz, 1H), 7.34 (t, *J* = 8 Hz, 2H), 7.46 (m, 4H), 7.54 (t, *J* = 8 Hz, 1H), 7.77 (d, *J* = 7.6 Hz, 1H), 7.88 (t, *J* = 5 Hz, 1H), 8.15 (s, 1H), 9.92 (s, 1H), 10.45 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 29.06, 48.10, 117.49, 121.66, 122.96, 123.46, 124.93, 129.26, 130.28, 139.41, 139.93, 140.27, 168.42, 181.19.

***N*-methyl-3-(2-[3-phenyl-ureido]acetylamino)-benzenesulfonamide (3b).** To 0.5 g (1. 8 mmol) of **7** suspended in 15mL chloroform, 0.41 g (4 mmol) triethylamine and 0.26 mL (0.24 g, 2 mmol) phenylisocyanate were added and the reaction mixture was allowed to stir at room temperature for 1 hr. Then, water was added to the reaction and layers were separated. The aqueous layer was extracted with ethyl acetate and the combined organic layers were washed with 1N HCl and dried over $MgSO_4$. Solvents were evaporated and the solid residue was crystallized from methanol to yield 0.4 g of white solid (58%). 157.7-159.4 °C (m.p); IR (KBr) 3281, 1649, 1595, 1312, 1156 cm^{-1}; GC-MS (EI) m/z 362.1 (M$^+$); ^{1}H NMR (DMSO-d_6) δ 2.41 (d, *J* = 4 Hz, 3H), 3.95 (d, *J* = 5.6 Hz, 2H), 6.44 (t, *J* = 5.6 Hz,, 1H), 6.89 (td, *J* = 6 Hz, 0.8 Hz, 1H), 7.21 (t, *J* = 7.2 Hz, 2H), 7.42 (m, 4H), 7.54 (t, *J* = 8 Hz, 1H), 7.79 (d, *J* = 8 Hz, 1H), 8.13 (d, *J* =1.2 Hz, 1H), 8.81 (s, 1H), 10.35 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 29.06, 43.82, 117.59, 118.16, 118.57, 121.61, 122.30, 123.08, 129.16, 130.24, 140.15, 140.75, 155.82, 169.64.

***N*-methyl-3-(2-[3-(*m*-tolyl)-ureido]-acetylamino)-benzenesulfonamide (3c).** To 1.0 g (3.6 mmol) of **7** dissolved in 10 mL DMF, 0.4 g (3.6 mmol) of triethylamine and 0.48 g (3.6 mmol) *m*-tolylisocyanate were added and the reaction mixture was allowed to stir at room temperature for 2hr. Water was added to the reaction and the mixture was extracted with ethyl acetate and combined organic layers were washed with 1N HCl and dried over $MgSO_4$. Solvent was evaporated and the residue was crystallized from ethanol/ethyl acetate to yield 0.61 g of a white solid (45%). 169.2-171.0 °C (m.p); IR (KBr) 3334, 3257, 3079, 1684, 1633, 1551, 1332, 1157, 1085 cm^{-1}; GC-MS (EI) m/z 376.1 (M$^+$); ^{1}H NMR (DMSO-d_6) δ 2.25 (s, 3H), 2.43 (d, *J* = 4.8 Hz, 3H), 3.69 (d, *J* = 5.6 Hz, 2H), 6.44 (t, *J* = 5.4 Hz, 1H), 6.73 (d, *J* = 7.6 Hz, 1H), 7.11 (t, *J* = 7.6 Hz, 1H), 7.19 (d, *J* = 8 Hz, 1H), 7.25 (s, 1H), 7.45 (m, 2H), 7.55 (t, *J* = 8 Hz, 1H), 7.80 (d, *J* = 8 Hz, 1H), 8.15 (s, 1H), 8.74 (s, 1H), 10.36 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 21.69, 29.05, 43.80, 115.34, 117.47, 118.68, 121.59, 122.47, 122.98, 129.00, 130.25, 138.28, 139.85, 140.16, 140.66, 155.80, 169.57.

***N*-methyl-3-(2-[3-(*p*-tolyl)-ureido]-acetylamino)-benzenesulfonamide (3d).** To 1.0 g (3.6 mmol) of **7** dissolved in 10 mL DMF, 0.4 g (3.6 mmol) triethylamine and 0.48 g (3.6 mmol) *p*-tolyl isocyanate were added and the reaction mixture was allowed to stir at room temperature for 2hr. Water was added to the reaction and the mixture was extracted with ethyl acetate and combined organic layers were washed with 1N HCl and dried over $MgSO_4$. Solvent was evaporated and the residue was crystallized from ethanol/water to yield 0.42 g of a white solid (31%). 160.8-162.3 °C (m.p); IR (KBr) 3335, 3259, 3079, 1683, 1634, 1552, 1332, 1157, 1086 cm^{-1}; GC-MS (EI) m/z 376.1 (M$^+$); ^{1}H NMR (DMSO-d_6) δ 2.21 (s, 3H), 2.41 (d, *J* = 4.1 Hz, 3H), 3.93 (d, *J* = 5.3 Hz, 2H), 6.46 (t, *J* = 5.3 Hz, 1H), 7.01 (d, *J* = 7.9 Hz, 2H), 7.27 (d, *J* = 7.9 Hz, 2H), 7.43 (m, 2H), 7.53 (t, *J* = 8 Hz, 1H), 7.77 (d, *J* = 8 Hz, 1H), 8.13 (s, 1H), 8.74 (s, 1H), 10.35 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 21.68, 29.05, 43.82, 115.25, 117.56, 118.59, 121.59, 122.48, 122.98, 129.00, 130.24, 138.28, 139.85, 140.24, 140.65, 155.80, 169.65.

Compounds 4a-4m, general procedure: To **6** and the appropriate amine dissolved in acetonitrile or acetone, potassium carbonate or sodium carbonate was added and the reaction mixture was allowed to stir at room temperature for 24 hr. The reaction mixture was diluted with ethyl acetate, and washed with water and organic layer was separated and dried over $MgSO_4$. The solvent was evaporated, and the solid residue was crystallized from the appropriate solvent(s) to afford the desired product.

***N*-methyl 3-(2-pyrrolidinoacetylamino)-benzenesulfonamide (4a).** 2.0 g (7.6 mmol) of **6**, 0.57 g (8.0 mmol) pyrrolidine, 35 mL acetonitrile and 1.1 g (7.8 mmol) potassium carbonate. Crystallization from ethyl acetate yielded 1.40 g of an off-white solid (68%). 146.3-148.1 °C (m.p); IR (KBr) 3120, 2975, 1665, 1528, 1327, 1162 cm^{-1}; GC-MS (EI) m/z 297.1 (M^{+}); ^{1}H NMR (DMSO-*d*$_6$) δ 1.72-1.75 (m, 4H), 2.41 (s, 3H), 2.56-2.59 (m, 4H), 3.25 (s, 2H), 7.41-7.44 (m, 2H), 7.51 (t, *J* = 8 Hz, 1H), 7.84 (d, *J* = 4 Hz, 1H), 8.19 (t, *J* = 2.2 Hz, 1H), 10.04 (s, 1H); ^{13}C NMR (DMSO-*d*$_6$) δ 23.94, 29.13, 54.12, 59.95, 117.93, 121.67, 123.44, 129.99, 139.84, 140.11, 169.85**.**

***N*-methyl 3-(2-piperidinoacetylamino)-benzenesulfonamide (4b).** 2.0 g (7.6 mmol) of **6**, 0.65 g (7.6 mmol) piperidine, 35 mL acetonitrile and 1.1g (8.0 mmol) potassium carbonate. Crystallization from ethyl acetate yielded 1.97 g of a white solid (83%). 163.0-164.8 °C (m.p); IR (KBr) 3283, 3120, 2930, 1664, 1533, 1323, 1159 cm^{-1}; GC-MS (EI) m/z 311.1 (M^{+}); ^{1}H NMR (CDCl$_3$) δ 1.51-1.53 (m, 2H), 1.65-1.70 (m, 4H), 2.57 (m, 4H), 2.7 (d, *J* = 4.7 Hz, 3H), 3.22 (s, 2H), 7.5 (t, *J* = 8 Hz, 1H), 7.61 (d, *J* = 8 Hz, 1H), 7.95 (d, *J* = 8 Hz, 1H), 7.99 (s, 1H), 9.51 (s, 1H); ^{13}C NMR (CDCl$_3$) δ 23.98, 25.85, 29.14, 54.50, 63.10, 117.85, 121.74, 123.41, 130.03, 139.72, 140.16, 169.64.

***N*-methyl 3-[2-(4-acetlypiperazino)acetylamino]-benzene sulfonamide (4c).** 1 g (3.8 mmol) of **6**, 0.52 g (3.8 mmol) acetylpiperazine, 30 mL acetone and 0.58 g (5.5 mmol) sodium carbonate. Crystallization from dichloromethane-ether yielded 0.90 g of an off-white solid (69%). 84.2-86.0 °C (m.p), IR (KBr) 3229, 3138, 1665, 1624, 1314, 1154 cm^{-1}; GC-MS (EI) m/z 354.2 (M^{+}); ^{1}H NMR (CDCl$_3$) δ 2.13 (s, 3H), 2.60-2.65 (m, 4H), 2.68 (d, *J* = 4.0 Hz, 3H), 3.21 (s, 2H), 3.58 (m, 2H), 3.71 (m, 2H), 5.00 (d, *J* = 4.9 Hz, 1H), 7.51 (t, *J* =8 Hz, 1H), 7.61 (d, *J* = 8 Hz, 1H), 7.95 (d, *J* = 8 Hz, 1H), 8.01 (s, 1H), 9.23 (s, 1H). ^{13}C NMR (CDCl$_3$) δ 21.62, 29.06, 46.01, 52.80, 61.84, 117.96, 121.80, 123.50, 130.07, 139.69, 140.15, 168.67, 169.21.

***N*-methyl 3-[2-(4-hydroxypiperidono)cetylamino]-benzene sulfonamide (4d).** 2.0 g (7.6 mmol) of **6**, 1.62 g (16.0 mmol) 4-hydroxypiperidine, 35 mL acetonitrile and 1.1 g (8.0 mmol) potassium carbonate. Crystallization from ethyl acetate/ether yielded 1.47 g of an off-white solid (60%). 121.3-122.4 °C (m.p); IR (KBr) 3337, 3261, 2933, 1674, 1524, 1332, 1162 cm^{-1}; GC-MS (EI) m/z 328.1 (M^{+}); ^{1}H NMR (DMSO-*d*$_6$) δ 1.50 (m, 2H), 1.72 (m, 2H), 2.23 (m, 2H), 2.41 (s, 3H), 2.73 (m, 2H), 3.1 (s, 2H), 3.46 (m, 1H), 4.58 (bs, 1H), 7.43 (m, 2H), 7.52 (t, *J* = 8 Hz, 1H), 7.83 (d, *J* = 8 Hz, 1H), 8.18 (s, 1H), 10.00 (s, 1H); ^{13}C NMR (DMSO-*d*$_6$) δ 29.13, 34.59, 51.51, 62.37, 66.27, 117.89, 121.75, 123.46, 130.04, 139.72, 140.12, 169.68.

***N*-Methyl-3-(2-morpholinoacetylamino)-benzenesulfonamide (4e).** 2 g (7.6 mmol) of **6**, 1.32 g (15.2 mmol) morpholine, 35 mL acetonitrile and 1.1 g (8.0 mmol) potassium carbonate. Crystallization from ethyl acetate yielded 1.86 g of a white solid (78%). 129.4-131.1°C (m.p); IR (KBr) 3292, 3138, 2847, 1662, 1528, 1326, 1160 cm^{-1}; GC-MS (EI) m/z 313.1 (M^{+}); ^{1}H NMR (CDCl$_3$) δ 2.65 (t, *J* = 4.6 Hz, 4H), 2.70 (d, *J* = 5.2 Hz, 3H), 3.2 1(s, 2H), 3.81 (t, *J* = 4.6 Hz, 4H), 7.51 (t, *J* = 8.0 Hz, 1H), 7.62 (d, *J* = 8.0 Hz, 1H), 7.95 (d, *J* = 8.0 Hz, 1H), 8.01 (s, 1H), 9.28 (s, 1H); ^{13}C NMR (CDCl$_3$) δ 29.05, 53.59, 62.48, 66.51, 117.85, 121.76, 123.39, 130.05, 139.60, 140.15, 169.15.

***N*-Methyl-3-[2-(3,3-dimethylpiperidino)acetylamino]-benzenesulfonamide (4f).** 1 g (3.80 mol) of **6**, 0.43 g (3.8 mmol) 3, 3-dimethylpiperidine, 30 mL acetone and 0.58 g (5.5 mmol) sodium carbonate. Crystallization from dichloromethane/ether yielded 1.12 g of an off-white solid (86%). 148.0-149.9 °C (m.p); IR (KBr) 3316, 3118, 2933, 1667, 1540, 1321, 1158 cm^{-1}; GC-MS (EI) m/z 339.2 (M^{+}); ^{1}H NMR (CDCl$_3$) δ 1.04 (s, 6H), 1.32 (m, 2H), 1.72 (m, 2H), 2.21 (s, 2H), 2.54 (bs, 2H), 2.69 (s, 3H), 3.08 (s, 2H), 7.49 (t, *J* = 8.0 Hz, 1H), 7.61 (d, 8.0 Hz, 1H), 7.79 (d, *J* = 8.0 Hz, 1H), 8.09 (s, 1H), 9.49 (s, 1H); ^{13}C NMR (CDCl$_3$) δ 22.55, 27.47, 29.13, 30.91, 37.01, 54.42, 63.78, 65.97, 117.44, 121.76, 123.04, 130.12, 139.50, 140.28, 168.55.

***N*-Methyl-3-[2-(4-methylpiperazino)acetylamino]-benzenesulfonamide (4g).** 2.0 g (7.6mmol) of **6**, 0.8 g (8.0 mmol) methylpiperazine, 35 mL acetonitrile and 1.1 g (8.0 mmol) potassium carbonate. Crystallization from ethyl acetate yielded 1.64 g of an off-white solid (66%). 189.2-190.5 (m.p); IR (KBr) 3289, 2945, 1692, 1522, 1417, 1327, 1152 cm^{-1}; GC-MS (EI) m/z 326.1 (M^{+}); ^{1}H NMR (CDCl$_3$) δ 2.35 (s, 3H), 2.54 (bs, 3H), 2.79 (m, 7H), 3.18 (s, 2H), 4.81 (bs, 1H), 7.51 (t, *J* = 8.0 Hz, 1H), 7.61 (d, *J* = 8.0 Hz, 1H), 7.95 (d, *J* = 8.0 Hz, 1H), 7.99 (s, 1H), 9.35 (s, 1H); ^{13}C NMR (CDCl$_3$) δ

29.14, 46.19, 53.12, 54.94, 62.25, 117.76, 121.76, 123.31, 130.05, 139.62, 140.16, 169.24.

***N*-Methyl-3-[2-(4-ethylpiperazino)acetylamino]-benzenesulfonamide (4h).** 1 g (3.8 mmol) of **6**, 0.44 g (3.85 mmol) ethylpiperazine, 30 mL acetone and 0.58 g (5.5 mmol) sodium carbonate. Crystallization from dichloromethane/ether yielded 1.00 g of an off-white solid (77.5%). 140.0-141.5 °C (m.p); IR (KBr) 3274, 3080, 2824, 1693, 1518, 1339, 1158 cm^{-1}; GC-MS (EI) m/z 340.3 (M^+); ^1H NMR ($CDCl_3$) δ 1.14 (t, *J* = 7.1 Hz, 3H), 2.49 (q, *J* = 7.1 Hz, 2H), 2.7 (m, 7H), 2.58 (bs, 4H), 3.23 (s, 2H), 7.51 (t, *J* = 8.0 Hz, 1H), 7.61 (d, *J* = 8.0 Hz, 1H), 7.96 (d, *J* = 8.0 Hz, 1H), 7.99 (s, 1H), 9.36 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 12.44, 29.14, 52.04, 52.60, 53.23, 62.30, 117.76, 121.75, 123.41, 130.04, 139.63, 140.16, 169.23.

***N-Methyl*-3-[2-[4-(2-hydroxyethyl)piperazino]acetylamino]-benzenesulfonamide (4i).** 1 g (3.8 mmol) of **6**, 1.03 g (7.91 mmol) 2-hydroxyethylpiperazine, 30 mL acetone and 0.58 g (5.5 mmol) of sodium carbonate. Crystallization from ethanol /ether yielded 1.15g (85%). 108.5-110.5 °C (m.p); IR (KBr) 3400, 3261, 2879, 1667, 1522, 1325, 1149 cm^{-1}; GC-MS (EI) m/z 356.1 (M^+); ^1H NMR (DMSO-d_6) δ 2.37-2.49 (m, 13H), 3.12 (s, 2H), 3.47 (t, *J* = 5.8 Hz, 2H), 4.37 (bs, 1H), 7.43 (m, 2H), 7.52 (t, *J* = 8.0 Hz, 1H), 7.81 (d, *J* = 8.0 Hz, 1H), 8.17 (s, 1H), 10.02 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 29.14, 53.18, 53.40, 58.88, 60.63, 62.28, 117.87, 121.78, 130.06, 139.70, 140.14, 169.34.

***N*-Methyl-3-[2-(4-phenylpiperazine)acetylamino]-benzenesulfonamide (4j).** 2 g (7.6 mmol) of **6**, 1.59 g (9.8 mmol) phenylpiperazine, 30 mL acetonitrile and 1.1 g (8 mmol) potassium carbonate. Crystallization from ethyl acetate yielded 2.30 g of yellow solid (78%). 143.3-144.9 °C (m.p); IR (KBr) 3281, 3073, 2938, 1678, 1598, 1311, 1159 cm^{-1}; GC-MS (EI) m/z 388.1 (M^+); ^1H NMR ($CDCl_3$) δ 2.69 (s, 3H), 2.84 (t, *J* = 4.8 Hz, 4H), 3.26 (s, 2H), 3.30 (t, *J* = 4.8 Hz, 4H), 6.92 (m, 3H), 7.31 (m, 3H), 7.5 (t, 8.0 Hz, 1H), 7.62 (d, *J* = 8.0 Hz, 1H), 7.91 (d, *J* = 8.0 Hz, 1H), 8.04 (s, 1H), 9.36 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 29.13, 48.54, 53.12, 62.10, 115.86, 117.95, 119.27, 121.76, 123.47, 129.39, 130.04, 139.83, 140.16, 151.46, 169.31.

***N*-Methyl-3-[2-(4-benzylpiperazino)acetylamino]-benzenesulfonamide (4k).** 1 g (3.8 mmol) of **6**, 0.71 g (3.8 mmol) benzylpiperazine, 30 mL acetone and 0.58 g (5.5 mmol) sodium carbonate. Crystallization from dichloromethane/ether yielded 1.16 g of a pale yellow solid (75.8%). 124.0-126.0 (m.p); IR (KBr) 3284, 3062, 2822, 1693, 1524, 1331, 1154 cm^{-1}; GC-MS (EI) m/z 402.1 (M^+); ^1H NMR ($CDCl_3$) δ 2.68 (bs, 4H), 2.70 (s, 3H), 2.94 (t, (*J* = 4.8 Hz, 4H), 3.17 (s, 2H), 3.52 (s, 2H), 7.33 (m, 5H), 7.62 (d, *J* = 8.0 Hz, 1H), 7.96 (s, 1H), 7.98 (d, *J* = 8.0 Hz, 1H), 9.38 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 29.12, 45.65, 52.88, 53.23, 53.90, 62.24, 63.19, 117.78, 121.75, 123.30, 127.30, 128.56, 129.27, 130.04, 138.58, 139.66, 140.16, 169.24.

***N*-Methyl-3-[2-(4-piperonylpiperazino)acetylamino)-benzenesulfonamide (4l).** 1 g (3.8 mmol) of **6**, 0.89 g (3.8 mmol), 1-piperonylpiperazine, 30 mL acetone and 0.58 g (5.5 mmol) sodium carbonate. Crystallization from dichloromethane/ether yielded 1.46 g of an off-white solid (85%). 135.7-136.9 (m.p); IR (KBr) 3282, 3067, 2886, 1693, 1595, 1493, 1325, 1130 cm^{-1}; GC-MS (EI) m/z 446.0 (M^+); ^1H NMR ($CDCl_3$) δ 2.67 (m, 11H), 3.24 (s, 2H), 3.51 (s, 2H), 5.97 (s, 2H), 6.77 (s, 2H), 6.87 (s, 1H), 7.51 (t, *J* = 7.6Hz, 1H), 7.62 (d, *J* = 8Hz, 1H), 7.98 (d, *J* = 8Hz, 2H), 9.38 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 29.05, 52.24, 52.70, 62.18, 101.21, 108.27, 109.49, 117.79, 121.76, 122.39, 123.33, 130.06, 132.48, 139.63, 140.07, 146.58, 147.65, 169.24.

***N*-Methyl 3-[2-(1-imidazolyl)acetyl amino)-benzenesulfonamide (4m).** 1.0 g of **6** (3.8 mmol)**,** 0.56 g (4.0 mmol) imidazole, 30 mL acetonitrile and 0.54 g (3.8 mmol) of potassium carbonate. Crystallization from methanol/water yielded 0.64 g of a pale yellow solid (55%). 220-221 (m.p); IR (KBr) 3268, 3118, 1703, 1303, 1151 cm^{-1}; GC-MS (EI) m/z 294.1 (M^+); ^1H NMR (DMSO-d_6) δ 2.40 (d, *J* = 4.8 Hz, 3H), 4.92 (s, 2H), 6.89 (s, 1H), 7.16 (s, 1H), 7.45-7.50 (m, 2H), 7.55 (t, *J* = 8.0 Hz, 1H), 7.63 (s, 1H), 7.74 (d, *J* = 8.4Hz, 1H), 8.13 (s, 1H), 10.71 (s, 1H). ^{13}C NMR (DMSO-d_6) δ 29.02, 49.57, 117.53, 121.22, 121.93, 122.93, 128.77, 130.40, 138.81, 139.56, 140.25, 166.69**.**

Antibacterial Macrodilution Susceptibility Testing

Each bacterial strain was cultured on sterile Muller-Hinton agar 24 hr prior to inoculum preparation. The stock solutions (12800 μg/mL) of the test compunds in DMSO/water cosolvent system were prepared. Five dilutions or more of each stock solution of the compound to be tested were prepared using sterile Muller-Hinton broth. To the 1 mL of the prepared diluted solutions, 1 mL of bacterial inoculum was added resulting in a two-fold dilution to afford final concentrations from 512, 256, 128, 64, 32 and 16 μg/mL. The vials were then incubated at 37°C for 24 hr. In addition, negative and positive controls were used in every run.

Anti-candidal Macrodilution Susceptibility Testing

A clinical isolate of *Candida albicans* was cultured on sterile Sabouraud-Dextrose agar for 24 hr at 35°C prior to inoculum preparation. The stock solutions (12800 μg/mL) of the test compounds in DMSO/water cosolvent system were prepared. Five dilutions or more of each stock solution of the compound to be tested were prepared using sterile Sabouraud-Dextrose broth were prepared taking into consideration that the final concentration of DMSO was always below 10%. To 0.9 mL of fungal inoculum, 0.1 mL from a drug dilution was added resulting in final concentrations ranging from 512, 256, 128, 64, 32 and 16 μg/mL and then they were incubated at 35°C for 48 hr. In addition, negative and positive controls were used in every run.

Brine Shrimp Lethality Test

Brine shrimp eggs (about 100 to 200 mg) and *Artemia salina* Leach cysts, Ocean Star® International (O.S.I.) Inc., U.S.A, were implanted in synthetic ocean water at room temperature for 24 hr to hatch. Samples were prepared by dissolving 20 mg of the compound in 2 mL methanol. Serial dilutions of this stock solution were made to prepare four concentration levels: 1000 ppm, 100 ppm, 10 and 1 ppm. To the prepared dilutions, 5 mL of brine shrimp solution; ocean water, and 10 shrimps was added. The number of living shrimps was counted after 24 hr. Data obtained was processed using Finney PC computer program to estimate LC_{50} values in μg/mL (ppm) with 95% confidence intervals.

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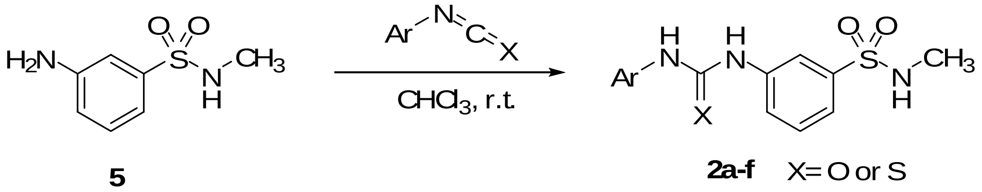
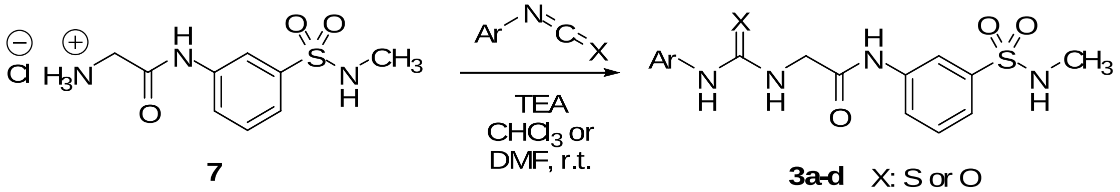
Table 1. Synthetic scheme and yields of compounds (2a-f)



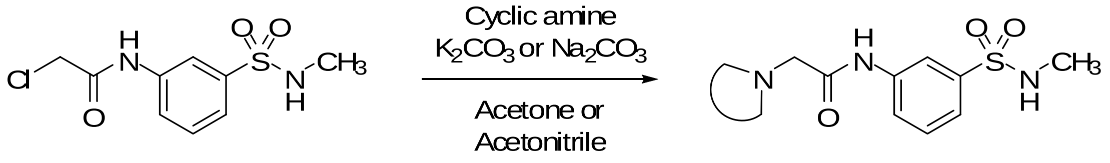
Number	Ar	X	Yield (%)
2a	Phenyl	S	52
2b	Phenyl	O	79
2c	Benzoyl	S	79
2d	3-Tolyl	O	79
2e	4-Tolyl	O	85
2f	Benzyl	S	78

Table 2. Synthetic scheme and yields of compounds (3a-e)



Number	Ar	X	Solvent	Yield (%)
3a	Phenyl	S	$CHCl_3$	58
3b	Phenyl	O	$CHCl_3$	58
3c	3-Tolyl	O	DMF	45
3d	4-Tolyl	O	DMF	31

Table 3. Synthetic scheme and yields of compounds (4a-m)



6 **4a-m**

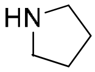
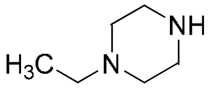
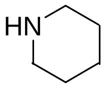
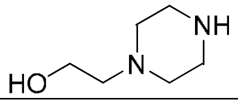
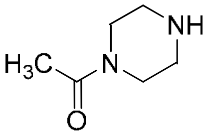
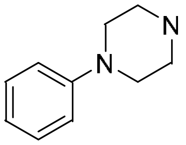
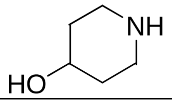
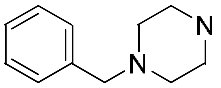
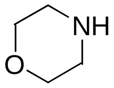
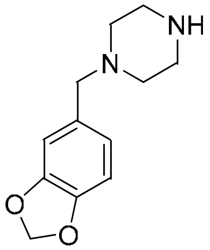
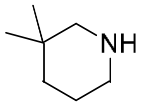
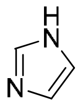
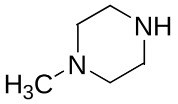
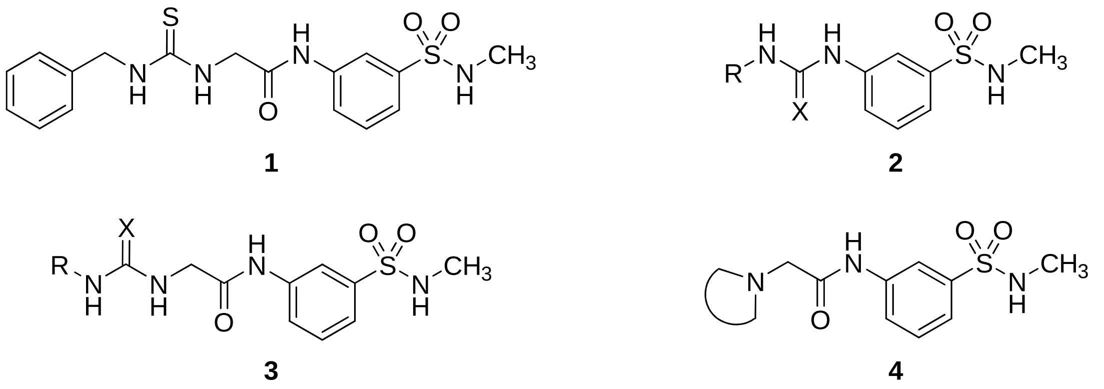
Number	Cyclic amine	Yield (%)	Number	Cyclic amine	Yield (%)
4a		69	4h		78
4b		76	4i		59
4c		86	4j		66
4d		68	4k		78
4e		78	4l		85
4f		83	4m		55
4g		60			

Table 4. Antimicrobial and cytotoxic activities of target compounds

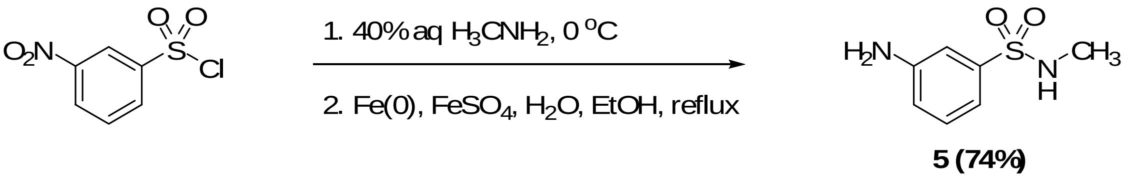
Compound	**MIC (µg/mL)**				**LC_{50} (µg/mL)**
	S. aureus	***E. coli***	***P. aeruginosa***	***C. albicans***	***Brine Shrimp***
1	>512	>512	>512	64	-
2a	>512	>512	>512	64	0.07
2b	>512	256	>512	>512	<0.056
2c	>512	>512	>512	128	0.37
2d	256	256	>512	64	0.42
2e	>512	256	>512	64	0.78
2f	>512	>512	>512	>512	0.91
3a	>512	256	>512	32	0.72
3b	>512	>512	>512	128	0.14
3c	>512	>512	>512	128	5.7
3d	256	256	>512	64	0.23
4a	>512	>512	>512	128	1.02
4b	512	>512	>512	32	-
4c	>512	>512	>512	32	-
4d	>512	>512	>512	32	-
4e	>512	>512	>512	>512	-
4f	>512	>512	>512	>512	-
4g	512	256	256	>512	-
4h	>512	128	256	>512	-
4i	512	>512	>512	>512	-
4j	128	>512	>512	64	-
4k	512	>512	>512	64	-
4l	>512	>512	>512	64	-
4m	>512	>512	>512	16	-
Miconazole	-	-	-	0.5	-
Trimethoprim	4	2	-	-	-
Nalidixic acid	-	32	-	-	-
Ciprofloxacin	1	< 2	0.5	-	-
Colchicine					0.4

Note: DMSO had MIC = 15% v/v on S. aureus (ATCC 29213) and E. coli (ATCC 25922) and MIC = 12.5% v/v on P. Aeruginosa (ATCC 27853) and C. albicans (clinical isolate).

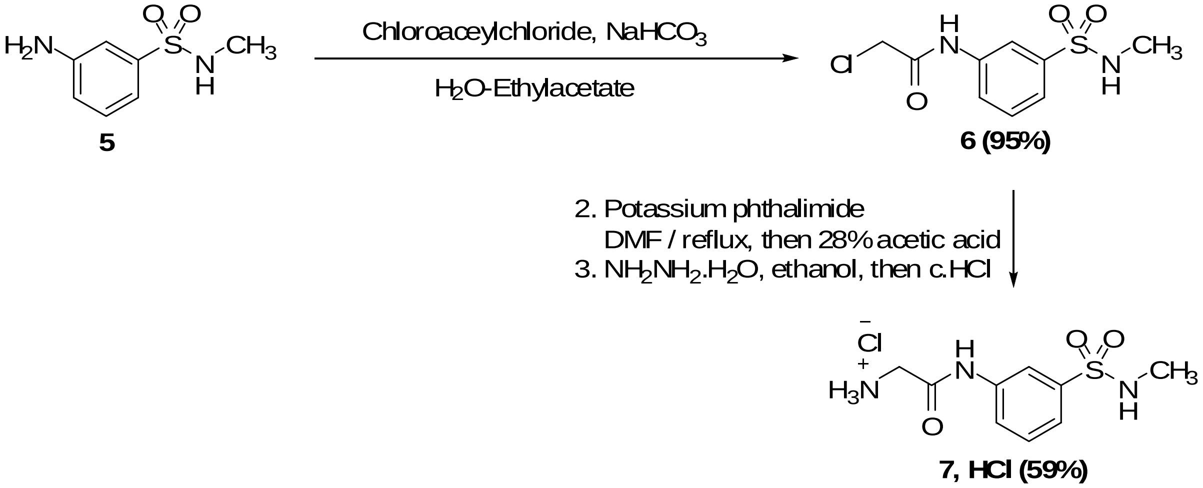


Where, R = aryl, benzyl, or benzoyl. X = O or S.
In structure 4, the nitrogen can be a part of piperidine, piperazine, morpholine or imidazole ring.

Figure 1. Chemical structure of the lead compound (1) and the general chemical structures of series 2, 3 and 4.



Scheme 1. Synthesis of 3-amino-*N*-methyl benzenesulfonamide (5).



Scheme 2. Synthesis of 3-(α-aminoacetylamino)-*N*-methylbenzenesulfonamide (7).

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تصميم وتشييد مشتقات 3-أمينوبنزين سلفون أميد ومسح فعاليتها ضد الميكروبات وسميتها للخلية

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ملخـص

تم تصميم وتشييد مجموعة من مشتقات 3-أمينوبنزين سلفون أميد فيها تشعب على النيتروجين يحتوي على مجموعة اليوريا أو الثيويوريا أو أمين حلقي، ومن ثم فحص فعاليتها ضد البكتيريا وضد الكانديدا ومدى سميتها للخلية. وقد كانت للمركبات المصنعة فعالية ضئيلة ضد البكتيريا، ولكن أظهر كثير منها فعالية جيدة ضد الكانديدا، خاصة المركبات (**2a**, **2d**, **2e**, **3a**, **3d**, **4b**, **4c**, **4d**, **4j**, **4k**, **4l and 4m**) التي كان التركيز الأدنى القاتل لها بين 16 و64 ميكروغرام/ مل، وقد كانت لمشتقات اليوريا والثيويوريا جميعها (المركبات **2a-f** و**3a-d**) سمية عالية ضد يرقات القريدس.

الكلمـات الدالـة: يوريا، ثيويوريا، بنزين سلفون أميد، امين حلقي، مضاد للكانديدا، يرقة القريدس.

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