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Synthesis and Bioassay of Styryl Sulfonylmethyl Oxazolyl Tethered Morpholines and Thiomorpholines

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Abstract. A new class of mono and bis heterocycles- 4-(chloromethyl)-2-((arylethenesulfonyl) methyl)oxazoles and 4-((2-((arylethenesulfonyl)methyl)oxazol-4-yl)methyl)morpholines/ thiomor- pholines were prepared from the synthetic intermediate arylethenesulfonylacetic acid adopting simple and well versed synthetic methodologies and were studied for their respective antimicrobial activity. The compounds **3c** and **6c** having chloro substituent on the aromatic ring showed greater antimicrobial activity than those with electron donating groups. All the entitled compounds were characterized by ^{1}H, ^{13}C NMR, mass spectra.

INTRODUCTION

Oxazole ring containing nitrogen and oxygen atoms is considered as prime scaffold for the drug innovation. oxazole-based compounds display extensively potential applications in medicinal, agricultural, chemical, supramolecular as well as materials sciences. Oxazole containing medicinal drugs have been extensively used in clinic, such as Linezolid, Oxacillin, Sulfisoxazole, Raltegravir, Furazolidone as well as Toloxatone[1]. Substituted oxazoles are found in many natural products and synthetic drugs exhibiting important biological activities. They are also applied as intermediates in organic synthesis[2]. Instead of the morpholine moiety has been used extensively in the pharmaceutical industry for drug design often due to the resulting improvement of the pharmacokinetic properties it can provide. Morpholine is a heterocyclic organic compound, has both features of amine due to the presence of nitrogen atom that it considered as a secondary amine and also ether functional group due to the presence of oxygen atom. Many of morpholine derivatives have very good biological activity in different therapeutic area such as antibacterial[3], antiviral, anticancer, antimicrobial, antidiabetic, anti-inflammatory, antimalarial, antifungal[4] etc. Morpholine used in sensors for selective analysis of Cu^{+2} ion[5], fruit coating[6], generation of enamines[7]. Morpholine and thiomorpholine with an acetamide pendant group are known to be as tridentate chelates. Apart from this thiomorpholine analogs are associated with a variety of pharmacological activities including anti mycobacterial[8], antibacterial[9], analgesic[10] and anti-inflammatory[11]. In continuation of our interest, herein we have planned to synthesis and antimicrobial activity of oxazole linked morpholines and thiomorpholines has been taken up.

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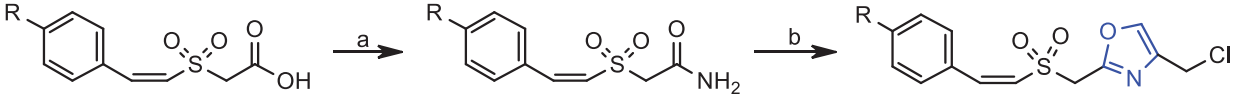
RESULTS AND DISCUSSION

The synthesis of the derivatives of arylethenesulfonylmethyl oxazole ring is outline in scheme **1**. The compound arylethenesulfonylacetic acid (**1**) was prepared as per the literature precedent[12]. The reaction of **1** with $SOCl_2$ presence of CH_2Cl_2 resulted in arylethenesulfonylacetamide (**2**). The ring cyclization of **2** with 1,3-dichloro-acetone in the presence of EtOH and THF produced corresponding 4-(chloromethyl)-2-((arylethenesulfonyl)methyl)- oxazole (**3**). Products morpholino and thiomorpholino substituted arylethenesulfonylmethyl oxazoles were prepared from the reaction of compound **3** with morpholine and thiomorpholine in the presence of 1,4-dioxane (scheme **2**). The structures of all these compounds were further established by ^{1}HNMR, ^{13}C NMR, mass and elemental analyses.

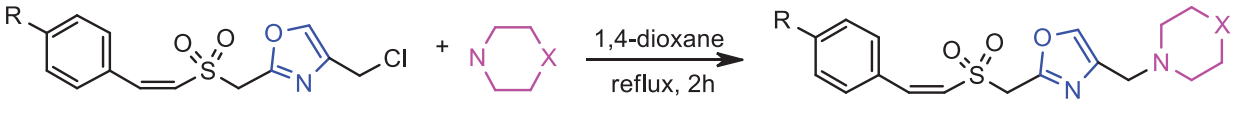


1 **2** **3**

a:1) $SOCl_2$, DCM, reflux, 2) $NH_3.H_2O$, 3h, rt
b: 1,3-dichloroacetone, 130°C, 1h

R = a) H
b) Me
c) Cl

Scheme 1 Synthesis of 4-(chloromethyl)-2-((arylethenesulfonyl)methyl)oxazoles



3 **4** **5/6**

R = a) H
b) Me
c) Cl

X = O / S

Scheme 2 Synthesis of 4-((2-((arylethenesulfonyl)methyl)oxazol-4-yl)methyl)morpholines / thiomorpholines

BIOLOGICAL EVALUATION

ANTIBACTERIAL ACTIVITY

The compounds **3**, **5**, **6** were tested for antimicrobial property. The results of antibacterial activity indicated that Gram-negative bacteria were more susceptible towards the tested compounds than Gram-positive ones. The structure activity relationship of the tested compounds revealed that mono heterocyclic compounds (**3**) displayed slightly higher activity than the respective bis heterocyclic (**5**, **6**) systems. Moreover, thiomorpholine containing oxazoles displayed higher antimicrobial activity than the morpholine containing oxazoles. In fact, the compounds **3c** exhibited excellent antibacterial activity against *Pseudomonas aeruginosa* when compared with the standard drug Chloramphenicol. It was also observed that the compounds **3a**, **5a**, **5c** and **6a**, **6c** exhibited good antimicrobial activity, whereas other compounds displayed less activity.

ANTFUNGAL ACTIVITY

All the tested compounds inhibited the spore germination against tested fungi. In general, most of the compounds showed slightly higher antifungal activity towards *Penicillium chrysogenum* than *Aspergillus niger*. Amongst all the compounds **3c** displayed greater inhibitory activity particularly against *P. chrysogenum* when compared with the standard drug Ketoconazole. Moreover compounds **5c** and **6c** exhibited good activity. In fact compounds having oxazole in combination with thiomorpholine were displayed high inhibitory activity than others.

EXPERIMENTAL

The ^{1}H NMR spectra were recorded in $CDCl_3$ / DMSO-d_6 on a Jeol JNM λ-400 MHz spectrometer. The ^{13}C NMR spectra were recorded in $CDCl_3$ / DMSO-d_6 on a Jeol JNM spectrometer operating at λ-100 MHz. High-resolution mass spectra were recorded on a Micromass Q-TOF micromass spectrometer using electro spray ionization. All chemical shifts were reported in δ (ppm) using TMS as an internal standard. The elemental analyses were determined on a Perkin-Elmer 240C elemental analyzer. The temperature was measured by flexible probe throughout the reaction.

CHEMICAL SYNTHESIS

The target compounds were synthesized as shown in Scheme **1** and most of the intermediates were synthesized immediately for the next step without further purification. The general procedures for the intermediates are as follows:

***General procedure for the synthesis of 2-(arylethenesulfonyl)acetamide* (2)**

A solution of arylethenesulfonylacetic acid (**1**) (10 mmol), thionyl chloride ($SOCl_2$) (20 mmol) and dichloromethane (15 mL) was stirred under reflux for 2 hours, then the reaction mixture was concentrated under reduced pressure, the residue was added to the aqueous ammonia (10 mL) at room temperature or below. Upon reaction completion (as monitored by TLC), the reaction mixture was treated with water, followed by extraction with ethyl acetate (3×10 mL), dried over anhydrous sodium sulphite and then filtered to obtain a crude product and recrystallized to get compound **2**.

***General procedure for the synthesis of 4-(chloromethyl)-2-((arylethenesulfonyl)methyl)oxazoles* (3a-c)**

A mixture of **2** (3 mmol) and 1,3-dichloroacetone (6 mmol) was heated at 130°C for 1 hour. After completion of the reaction the mixture was cooled to room temperature and water (10 mL) was added, then the mixture was extracted with CH_2Cl_2 (3×20 mL). The organic layer was dried over anhydrous sodium sulphite, filtered, and concentrated under reduced pressure, and then the crude product was recrystallized with petroleum ether and ethyl acetate.

General procedure for the synthesis of 4-((2-((arylethenesulfonyl)methyl)oxazol-4-yl)methyl)- morpholine/4-((2-((arylethenesulfonyl)methyl)oxazol-4-yl)methyl)thiomorpholine (5a-c/6a-c)

The compound **3a-c** (1.2 mmol) was suspended in 5 mL of 1,4-dioxane in a 25 mL round-bottomed flask. Morpholine/ thiomorpholine (6 mmol) was added drop-wise while stirring and the reaction mixture was reflux for 2 hours. After completion of the reaction, the mixture was evaporated to dryness in vacuo, washed with diethyl ether before being filtered and recrystallized from a suitable solvent.

4-(chloromethyl)-2-((styrylsulfonyl)methyl)oxazole ***4a****:*

Yield 73%, ^{1}H-NMR (DMSO-d_6, 400 MHz): δ = 4.66 (s, 2H, CH_2Cl), 4.69 (s, 2H, CH_2SO_2), 6.74 (d, 1H, H_B, J = 8.9 Hz), 7.45-7.70 (m, 7H, H_A, C_5-H & Ar-H) ppm. ^{13}C-NMR (DMSO-d_6, 100 MHz): δ = 39.1 (CH_2-Cl), 59.3 (CH_2-SO_2), 124.4 (C-H_B), 126.1 (C-5), 136.2 (C-H_A), 138.4 (C-4), 151.7 (C-2), 129.5, 130.2, 134.4, 134.7 ppm (aromatic carbons). MS (EI) m/z: 297 [M^+]; Anal.calc for $C_{13}H_{12}ClNO_3S$: C, 52.44; H, 4.06; N, 4.70; Found: C, 52.51; H, 4.08; N, 4.95.

4-(chloromethyl)-2-(((4-methylstyryl)sulfonyl)methyl)oxazole ***4b****:*

Yield 69%, ^{1}H-NMR (DMSO-d_6, 400 MHz): δ = 2.38 (s, 3H, CH_3), 4.64 (s, 2H, CH_2Cl), 4.68 (s, 2H, CH_2SO_2), 6.72 (d, 1H, H_B, J = 8.5 Hz), 7.43-7.69 (m, 6H, H_A, C_5-H & Ar-H) ppm. ^{13}C-NMR (DMSO-d_6, 100 MHz): δ = 22.3 (CH_3), 38.9 (CH_2-Cl), 59.2 (CH_2-SO_2), 124.3 (C-H_B), 126.1 (C-5), 136.0 (C-H_A), 138.3 (C-4), 151.5 (C-2), 129.3, 130.1, 134.3, 134.4 ppm (aromatic carbons). MS (EI) m/z: 311 [M^+]; Anal.calc for $C_{14}H_{14}ClNO_3S$: C, 53.93; H, 4.53; N, 4.49; Found: C, 54.04; H, 4.54; N, 4.76.

4-(chloromethyl)-2-(((4-chlorostyryl)sulfonyl)methyl)oxazole ***4c****:*

Yield 76%, ^{1}H-NMR (DMSO-d_6, 400 MHz): δ = 4.68 (s, 2H, CH_2Cl), 4.70 (s, 2H, CH_2SO_2), 6.76 (d, 1H, H_B, J = 9.1 Hz), 7.47-7.72 (m, 6H, H_A, C_5-H & Ar-H) ppm. ^{13}C-NMR (DMSO-d_6, 100 MHz): δ = 39.2 (CH_2-Cl), 59.5 (CH_2-SO_2), 124.6 (C-H_B), 126.3 (C-5), 136.4 (C-H_A), 138.6 (C-4), 151.9 (C-2), 129.7, 130.4, 134.6, 134.9 ppm (aromatic carbons). MS (EI) m/z: 330 [M^+]; Anal.calc for $C_{13}H_{11}Cl_2NO_3S$: C, 47.00; H, 3.34; N, 4.22; Found: C, 47.07; H, 3.36; N, 4.46.

4-((2-((styrylsulfonyl)methyl)oxazol-4-yl)methyl)morpholine ***5a****:*

Yield 75%, ^{1}H-NMR (DMSO-d_6, 400 MHz): δ = 3.72 (s, 2H, CH_2N), 2.62-3.71 (m, 8H, 4xCH_2 of morpholine), 4.73 (s, 2H, CH_2SO_2), 6.79 (d, 1H, H_B, J = 8.9 Hz), 7.35-7.66 (m, 7H, Ar-H & C_5-H) ppm. ^{13}C-NMR (DMSO-d_6,

100 MHz): δ = 56.3 (C-2' & C-6'), 58.9 (CH_2-N), 60.4 (CH_2-SO_2), 67.8 (C-3' & C-5'), 125.4 (C-H_B), 126.7 (C-5), 135.6 (C-H_A), 138.6 (C-4), 151.3 (C-2), 128.4, 128.9, 129.7, 136.5 ppm (aromatic carbons). MS (EI) m/z: 348 [M^+]; Anal.calc for $C_{17}H_{20}N_2O_4S$: C, 58.60; H, 5.79; N, 8.04; Found: C, 58.72; H, 5.81; N, 8.26.

4-((2-(((4-methylstyryl)sulfonyl)methyl)oxazol-4-yl)methyl)morpholine ***5b****:*

Yield 71%, ^{1}H-NMR (DMSO-d_6, 400 MHz): δ = 2.31 (s, 3H, CH_3), 3.70 (s, 2H, CH_2N), 2.60-3.69 (m, 8H, 4xCH_2 of morpholine), 4.71 (s, 2H, CH_2SO_2), 6.77 (d, 1H, H_B, J = 9.3 Hz), 7.33-7.63 (m, 6H, Ar-H & C_5-H) ppm. ^{13}C-NMR (DMSO-d_6, 100 MHz): δ = 22.6 (CH_3), 56.1 (C-2' & C-6'), 58.7 (CH_2-N), 60.2 (CH_2-SO_2), 67.6 (C-3' & C-5'), 125.2 (C-H_B), 126.5 (C-5), 135.4 (C-H_A), 138.4 (C-4), 151.1 (C-2), 128.2, 128.7, 129.5, 136.3 ppm (aromatic carbons). MS (EI) m/z: 362 [M^+]; Anal.calc for $C_{18}H_{22}N_2O_4S$: C, 59.65; H, 6.12; N, 7.73; Found: C, 59.76; H, 6.14; N, 7.96.

4-((2-(((4-chlorostyryl)sulfonyl)methyl)oxazol-4-yl)methyl)morpholine ***5c****:*

Yield 78%, ^{1}H-NMR (DMSO-d_6, 400 MHz): δ = 3.74 (s, 2H, CH_2N), 2.65-3.73 (m, 8H, 4xCH_2 of morpholine), 4.76 (s, 2H, CH_2SO_2), 6.81 (d, 1H, H_B, J = 9.4 Hz), 7.37-7.68 (m, 6H, Ar-H & C_5-H) ppm. ^{13}C-NMR (DMSO-d_6, 100 MHz): δ = 56.5 (C-2' & C-6'), 59.1 (CH_2-N), 60.6 (CH_2-SO_2), 68.1 (C-3' & C-5'), 125.6 (C-H_B), 126.9 (C-5), 135.8 (C-H_A), 138.9 (C-4), 151.5 (C-2), 128.6, 129.1, 129.9, 136.7 ppm (aromatic carbons). MS (EI) m/z: 382 [M^+]; Anal.calc for $C_{17}H_{19}ClN_2O_4S$: C, 53.33; H, 5.00; N, 7.32; Found: C, 53.46; H, 5.03; N, 7.55.

4-((2-((styrylsulfonyl)methyl)oxazol-4-yl)methyl)thiomorpholine ***6a****:*

Yield 77%, ^{1}H-NMR (DMSO-d_6, 400 MHz): δ = 3.76 (s, 2H, CH_2N), 2.66-3.75 (m, 8H, 4xCH_2 of morpholine), 4.77 (s, 2H, CH_2SO_2), 6.83 (d, 1H, H_B, J = 9.4 Hz), 7.39-7.70 (m, 7H, Ar-H & C_5-H) ppm. ^{13}C-NMR (DMSO-d_6, 100 MHz): δ = 56.7 (C-2' & C-6'), 59.3 (CH_2-N), 60.8 (CH_2-SO_2), 68.2 (C-3' & C-5'), 125.8 (C-H_B), 127.1 (C-5), 136.0 (C-H_A), 139.1 (C-4), 151.7 (C-2), 128.8, 129.3, 130.1, 136.9 ppm (aromatic carbons). MS (EI) m/z: 364 [M^+]; Anal.calc for $C_{17}H_{20}N_2O_3S_2$: C, 56.02; H, 5.53; N, 7.69; Found: C, 56.13; H, 5.55; N, 7.94.

4-((2-(((4-methylstyryl)sulfonyl)methyl)oxazol-4-yl)methyl)thiomorpholine ***6b****:*

Yield 73%, ^{1}H-NMR (DMSO-d_6, 400 MHz): δ = 2.33 (s, 3H, CH_3), 3.77 (s, 2H, CH_2N), 2.68-3.77 (m, 8H, 4xCH_2 of morpholine), 4.78 (s, 2H, CH_2SO_2), 6.85 (d, 1H, H_B, J = 9.3 Hz), 7.40-7.72 (m, 6H, Ar-H & C_5-H) ppm. ^{13}C-NMR (DMSO-d_6, 100 MHz): δ = 22.6 (CH_3), 56.8 (C-2' & C-6'), 59.5 (CH_2-N), 60.9 (CH_2-SO_2), 68.4 (C-3' & C-5'), 125.9 (C-H_B), 127.3 (C-5), 136.2 (C-H_A), 139.3 (C-4), 151.8 (C-2), 128.9, 129.5, 130.3, 137.1 ppm (aromatic carbons). MS (EI) m/z: 378 [M^+]; Anal.calc for $C_{18}H_{22}N_2O_3S_2$: C, 57.12; H, 5.86; N, 7.40; Found: C, 57.16; H, 5.88; N, 7.64.

4-((2-(((4-chlorostyryl)sulfonyl)methyl)oxazol-4-yl)methyl)thiomorpholine ***6c****:*

Yield 84%, ^{1}H-NMR (DMSO-d_6, 400 MHz): δ = 3.79 (s, 2H, CH_2N), 2.69-3.78 (m, 8H, 4xCH_2 of morpholine), 4.79 (s, 2H, CH_2SO_2), 6.87 (d, 1H, H_B, J = 9.6 Hz), 7.41-7.73 (m, 6H, Ar-H & C_5-H) ppm. ^{13}C-NMR (DMSO-d_6, 100 MHz): δ = 56.7 (C-2' & C-6'), 59.3 (CH_2-N), 60.8 (CH_2-SO_2), 68.5 (C-3' & C-5'), 125.9 (C-H_B), 127.5 (C-5), 136.3 (C-H_A), 139.6 (C-4), 151.9 (C-2), 129.1, 129.5, 130.4, 137.2 ppm (aromatic carbons). MS (EI) m/z: 398 [M^+]; Anal.calc for $C_{17}H_{19}ClN_2O_3S_2$: C, 51.18; H, 4.80; N, 7.02; Found: C, 51.30; H, 4.83; N, 7.23.

CONCLUSION

A new class of mono and bis heterocycles- 4-(chloromethyl)-2-((arylethenesulfonyl) methyl)oxazoles and 4-((2-((arylethenesulfonyl)methyl)oxazol-4-yl)methyl)morpholines/ thiomor- pholines were prepared from the synthetic intermediate arylethenesulfonylacetic acid adopting simple and well versed synthetic methodologies and were studied for their respective antimicrobial activity. The compounds **3c** and **6c** having chloro substituent on the aromatic ring showed greater antimicrobial activity than those with electron donating groups. All the entitled compounds were characterized by ^{1}H, ^{13}C NMR, mass spectra.

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