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FACILE SYNTHESIS OF SULFONYL AMIDINES BY 1,3-DIPOLAR CYCLOADDITION BETWEEN 1-MORPHOLINOCYCLOALKENES AND SULFONYL AZIDES WITHOUT CATALYST

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Abstract – Three new series of sulfonyl amidines were prepared by 1,3-dipolar cycloaddition reaction between 1-morpholinocycloalkenes and various substituted sulfonyl azides without catalyst at room temperature. This reaction yielded unstable bicyclic Δ^2-1,2,3-triazoline intermediates which rearranged themselves *in situ* into amidines by elimination of a nitrogen molecule. The reactions were performed under mild conditions and with moderate to good yields.

INTRODUCTION

The amidines, nitrogen analogues of carboxylic acids, have fascinating chemical properties due to their structures. They are widely used in the medicinal[1] and synthetic chemistry.[2] Indeed, the amidines featuring very valuable biological properties are found in many bioactive natural products[3] and are identified as important pharmacophores.[4] They are considered as important medical and biochemical agents as anti-inflammatory,[5] antimicrobial,[6] antimalarial,[7] antiparasitic[8] and anti-cancer.[5e,5f,9] They are versatile building blocks for the synthesis of many different nitrogen-containing heterocycles:[10] pyridines,[11] pyrimidines,[12] thiadiazoles,[13] imidazoles, benzimidazoles[14] and triazoles.[15]

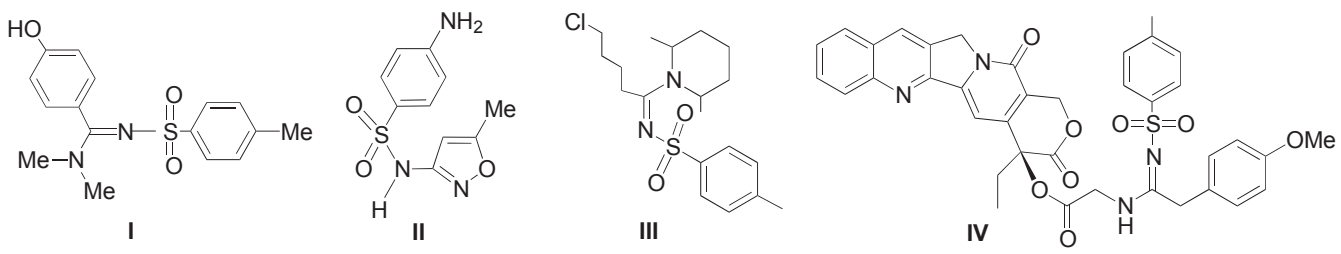


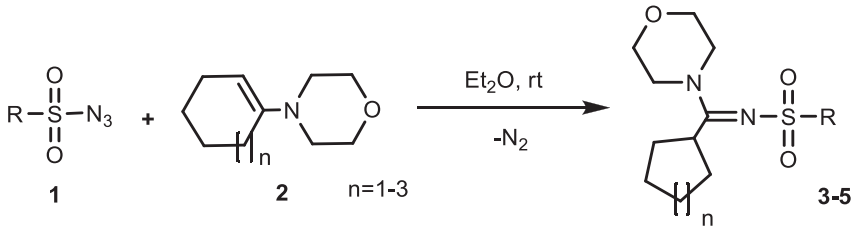
Figure 1. Sulfonyl amidines of biological interest

The sulfonyl amidines, in particular, exhibit various important biological and pharmacological activities such as antifungal I,[16] antibacterial II,[17] anti-resorptive III[18] and antitumor IV[19] (Figure 1).

Therefore, their synthesis has received much attention. Several routes of the amidine synthesis are described in details in the literature. Amidines may be obtained from either amides,[20] nitriles, thioamides,[21] sulfonamides,[22] *N*,*N*-dibromosulfonamides or NBS/sulfonamides.[23] They are also accessible by reduction of amidoximes,[24] imidoylation of amine with imidoyl chlorides.[25] Furthermore, they are prepared using the 1,3-dipolar cycloaddition reaction of imines with nitrile oxides.[26] New protocols for their preparation were recently developed as for example the direct coupling Cu-catalyzed, three component reactions of a terminal alkyne, sulfonyl azide and amine.[27] Moreover, the cycloaddition of tosyl azide with aliphatic enamines using various solvents or in the absence of solvent gives rise to sulfonyl amidines.[28] Also, an easy synthesis of sulfonyl amidines from tertiary amines and various substituted sulfonyl azides in the presence of $FeCl_3$ as catalyst was developed successfully.[29] However, these methods have drawbacks such as long reaction times, low yields and the use of noxious solvents such as benzene, methylene chloride, hexane or 1,4-dioxane.

On the other hand, to our knowledge, there are no previous works on the synthesis of sulfonyl amidines from the cyclic enamines. Therefore, the aim of this study is the synthesis of sulfonyl amidines, potentially bioactive, by 1,3-dipolar cycloaddition reaction between cyclic enamines and various sulfonyl azides.

The sulfonyl amidines **3-5** were obtained by addition of sulfonyl azides on 1-morpholinocycloalkenes in a highly stereoselective manner (Scheme 1).



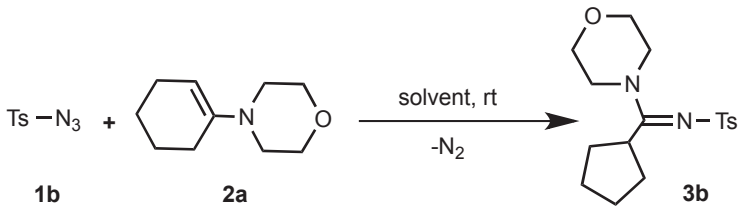
Scheme 1. General synthetic route of sulfonyl amidines

The structures of sulfonyl amidines **3-5** were confirmed by a combination of ^1H and ^{13}C NMR spectroscopy, mass spectroscopy and analysis, which gave good agreement with the proposed structures.

RESULTS AND DISCUSSION

The conditions of this cycloaddition reaction were optimized by varying the solvent. Thus different solvents were used in testing the reaction of 1-morpholinocyclohexene **2a** with tosyl azide **1b**, at room temperature and without the addition of a catalyst. The results of this screening are summarized in Table 1.

Table 1. Optimization of the reaction conditions[a]



1b **2a** **3b**

Entry	Solvent	Time	Yield(%)[b]
1	DMF	20 min	63
2	MeOH	20 min	46
3	H_2O	20 min	77
4	THF	20 min	45
5	**Et_2O**	**20 min**	**86**
6	CH_2Cl_2	20 min	65
7	$CHCl_3$	1 h	61
8	toluene	10 h	44
9	DMSO	20 min	47

[a]Reaction conditions: tosylazide **1b** (1 mmol, 1 equiv.), 1-morpholinocyclohexene **2a** (1 mmol, 1 equiv.), and Et_2O (5 mL). [b]Isolated yield after simple filtration followed by recrystallization in EtOH.

Among the solvents used, DMSO, THF, methanol and toluene gave the desired product in low yields (Table 1, entries 9, 4, 2 and 8) whereas the reaction in diethyl ether induced a good yield (Table 1, entry 5). However, when the reaction was carried out in H_2O, CH_2Cl_2, $CHCl_3$ and DMF, the product was obtained with yields of 77, 65, 61 and 63%, respectively.

Under the optimized reaction conditions, various sulfonyl azides and 1-morpholinocycloalkenes were examined. The enamine **2a** reacted with sulfonyl azides **1** at room temperature and in ether through 1,3-dipolar cycloaddition and produced sulfonyl amidines **3a-n** in moderate to good yields. As can be seen from Table 2, we have utilized sulfonyl azides containing various substituents with the 1-morpholinocyclohexene.

Table 2. Sulfonyl amidines **3** prepared from 1-morpholinocyclohehexene[a]

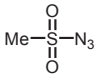
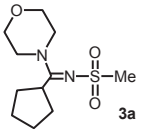
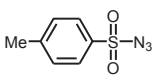
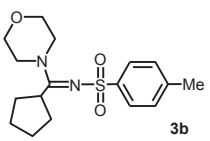
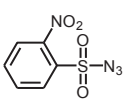
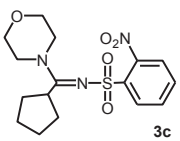
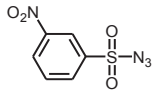
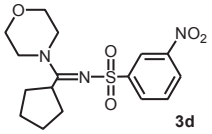
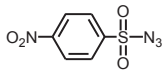
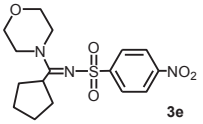
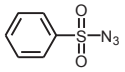
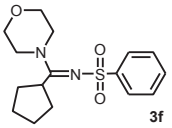
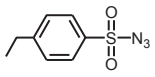
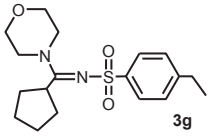
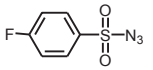
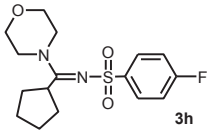
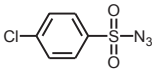
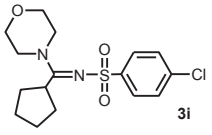
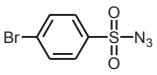
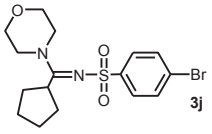
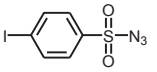
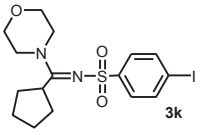
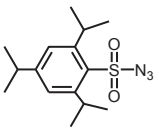
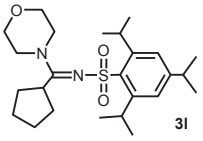
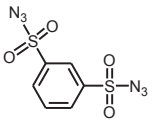
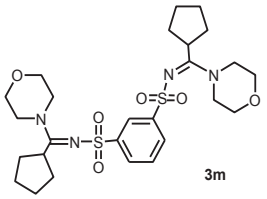
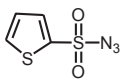
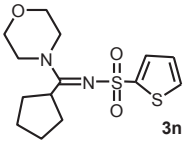
Entry	Azide	Product	Time	Yield (%)[b]
1		 **3a**	20 min	81
2		 **3b**	**20 min**	**86**
3		 **3c**	20 min	71

Table 2. (continued)

4		 **3d**	4 h	60
5		 **3e**	20 min	82
6		 **3f**	1 h	43
7		 **3g**	1 h	43
8		 **3h**	1 h	58
9		 **3i**	20 min	83
10		 **3j**	20 min	76
11		 **3k**	4 h	67
12		 **3l**	24 h	67
13		 **3m**	1 h	35
14		 **3n**	4 h	55

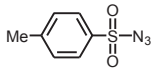
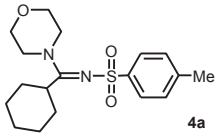
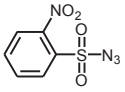
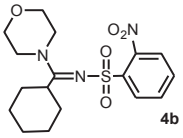
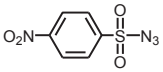
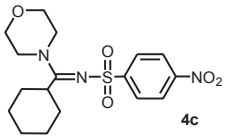
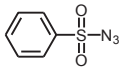
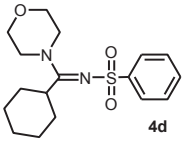
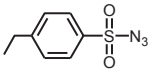
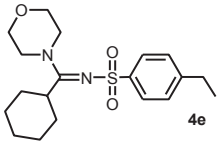
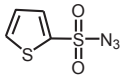
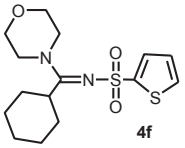
[a]Reaction conditions: sulfonyl azide **1** (1 mmol, 1 equiv.), 1-morpholinocyclohexene **2a** (1 mmol, 1 equiv.), and Et_2O (5 mL). [b]Isolated yield after simple filtration followed by recrystallization in EtOH. [c]Benzene-1,3-disulfonyl azide **1** (1 mmol, 1 equiv.), 1-morpholinocyclohexene **2** (2.0 mmol, 2.0 equiv.).

This reaction carried out with the 1-morpholinocyclohexene **2a** provided access to the sulfonyl amidines **3** which were produced with yields varying from 35 to 86% in a very short reaction time. The best yields were obtained

from the tosyl azide and the sulfonyl azides **1a**, **1e**, **1i**, (Table 2, entries 2, 1, 5 and 9) as 86, 81, 82 and 83%, respectively. The sulfonyl azides with 4-fluoro, 4-bromo or 4-iodo substrate showed good reactivity and generated the corresponding product with 58, 76 and 67% yields (Table 2, entries 8, 10 and 11), respectively. The bulky and strongly electron-donating group of the 2,4,6-tri-isopropylbenzene sulfonyl azide (Table 2, entry 12) gave the desired product in a longer reaction time with a 67% yield. It should be noted that the reaction can be performed not only with electron-donating groups, but also with electron-withdrawing groups (Table 2, entries 3-5). According to the results, the nitro substituents on the aromatic rings of the sulfonyl azides have a strong influence on the formation of sulfonyl amidines. It is observed that the *para* position substituents have a positive influence on the yield. For example, *p*-NO_2 sulfonyl azide leads to sulfonyl amidine **3e** with 82% yield. Similarly, with benzenesufonyl azide and thiophene-2-sulfonyl azide, the formation of **3f** and **3n** is achieved (Table 2, entries 6 and 14), respectively. However, with the 4-ethylbenzensulfonyl azide and benzene-1,3-disulfonyl azide (Table 2, entries 7 and 13), the yields do not exceed 43%.

Then, we investigated the reactivity of 1-morpholinocycloheptene with sulfonyl azides **1**. The results obtained for the synthesis of sulfonyl amidines **4** are given in Table 3.

Table 3. Sulfonyl amidines 4 prepared from 1-morpholinocycloheptene[a]

Entry	Azide	Product	Time	Yield (%)[b]
1		 **4a**	**24**	**71**
2		 **4b**	48	25
3		 **4c**	24	41
4		 **4d**	72	30
5		 **4e**	72	11
6		 **4f**	72	61

[a]Reaction conditions: sulfonyl azide **1** (1 mmol, 1 equiv.), 1-morpholinocycloheptene **2b** (1 mmol, 1 equiv.), and Et_2O (5 mL). [b]Isolated yield after simple filtration followed by recrystallization in EtOH.

Under the same conditions, the sulfonyl azides **1** were added to the 1-morpholinocycloheptene **2b** to provide products **4a-f**. This reaction sequence required a much longer reaction time for the formation of sulfonyl amidines **4**, with yields ranging from 11 to 71%. It was observed that the ethyl electron-donating group in the *para* position on the phenyl ring required a much longer reaction time and resulted in a lower yield than the one associated with the methyl substituent (Table 3, entries 1 and 5). However, NO_2 electron-withdrawing group in the *para* position lead to the corresponding sulfonyl amidines **4c** with 41% yield (Table 3, entry 3). Finally, we examined the reaction of 1-morpholinocyclooctene with sulfonyl azide 1 as shown on Table 4.

Table 4. Sulfonyl amidines **5** prepared from 1-morpholinocyclooctene[a]

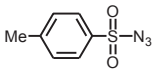
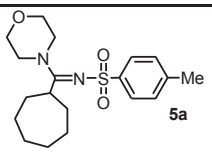
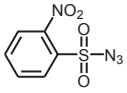
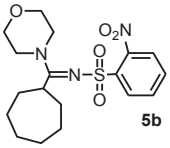
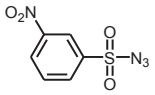
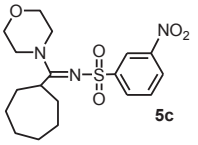
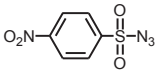
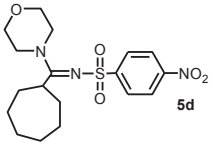
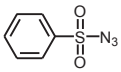
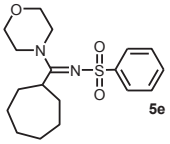
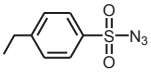
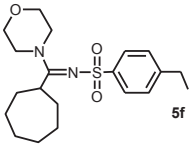
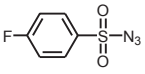
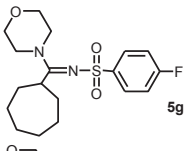
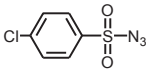
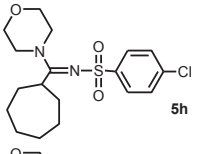
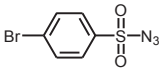
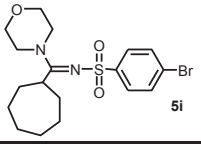
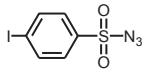
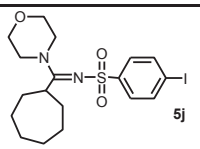
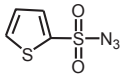
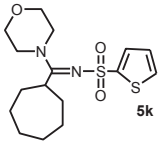
Entry	Azide	Product	Time	Yield (%)[b]
1		 **5a**	20 min	64
2		 **5b**	**20 min**	**98**
3		 **5c**	24 h	71
4		 **5d**	20 min	92
5		 **5e**	20 h	69
6		 **5f**	24 h	85
7		 **5g**	48 h	64
8		 **5h**	1 h	62
9		 **5i**	24 h	62

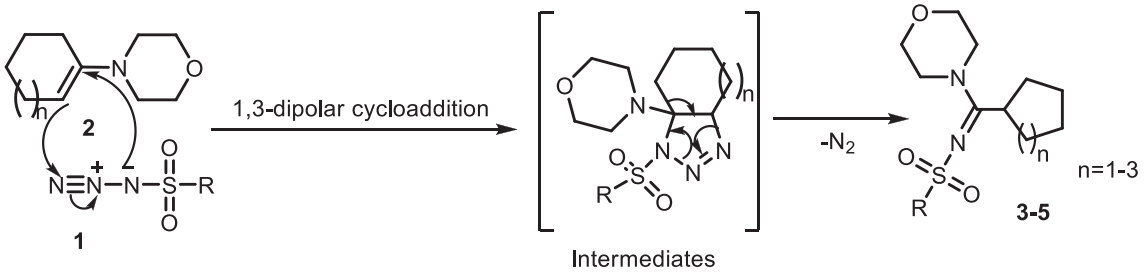
Table 4. (continued)

10		 **5j**	4 h	78
11		 **5k**	48 h	51

[a]Reaction conditions: sulfonyl azide **1** (1 mmol, 1 equiv.), 1-morpholinocyclooctene **2c** (1 mmol, 1 equiv.), and Et_2O (5 mL). [b]Isolated yield after simple filtration followed by recrystallization in EtOH.

The sulfonyl amidines **5a-k** could also be accessed from the 1-morpholinocyclooctene **2c**. This reaction sequence was performed under the same conditions as the previous reactions. The use of the *ortho*-nitrobenzenesulfonyl azide gave a much higher yield (98%) than that of the *para*- and *meta*-nitrobenzenesulfonyl azides (Table 4, entries 2-4). The desired sulfonyl amidines were formed with a high yield when using various sulfonyl azides bearing different electron-donating groups on the phenyl ring. For example, *p*-ethyl sulfonyl azide formed the corresponding sulfonyl amidine **5f** with 85% yield while with *p*-methyl, the yield did not exceed 64% (Table 4, entries 6 and 1). The reaction could also be carried out with halogenated groups as substituent on the phenyl ring to produce the corresponding sulfonyl amidines **5 g-j** with yields ranging from 62 to 78% (Table 4, entries 7-10). However, there is a drastic loss of performance when thiophene-2-sulfonyl azide is used (Table 4, entry 11).

The results, together studies in literature,[30] lead us to propose the following mechanism for the formation of sulfonyl amidines (Scheme 2).



Scheme 2. Proposed Reaction Mechanism

The cyclic enamines **2** react with the sulfonyl azides **1** through a 1,3-dipolar cycloaddition to produce unstable bicyclic Δ^2-1,2,3-triazoline intermediates which by nitrogen loss and ring contraction of the enamines provide the expected sulfonyl amidines **3-5**. It should be noted that the reaction of 1-morpholinocyclohexene led to good yields. The nature of the sulfonyl azide substituents and the enamine ring sizes has a great influence on the yield and time of the reaction.

In conclusion, we have developed a catalyst-free, simple and efficient protocol for the transformation of cyclic enamines and sulfonyl azides into sulfonyl amidines. The reactions performed in diethyl ether at room temperature did not require any special precautions. The products were obtained under mild reaction conditions with moderate to good yields. This approach is economically attractive due to the easy access to several sulfonyl amidines.

EXPERIMENTAL

All reagents and solvents were purchased from commercial suppliers and were used without further purification. Melting points were determined with a Kofler apparatus and they are uncorrected. ^{1}H (300 MHz) and ^{13}C (75 MHz), NMR spectra were recorded using a Bruker AC300 spectrometer using $CDCl_3$ or DMSO. Infrared spectra (IR) were taken on a Nicolet IRFT IR 200 spectrometer, and were obtained as solids in KBr. Peaks are reported in cm^{-1}. High-resolution mass spectra (MS) were obtained at 2.8 kV electrospray voltage, 20 V voltage orifice, and flow of nebulizing gas (nitrogen): 100 L/h. Atmospheric pressure ionization (API) and electrospray (ESI) mass spectra were recorded on a SYNAPT G2 HDMS spectrometer (Waters). Elemental analyses were performed by apparatus CHNS.

General procedure for preparing cyclic enamines and sulfonyl azides: The enamines **2a-c** were prepared by a method reported in the literature.[31] Sulfonyl azides **1** were prepared by the corresponding sulfonyl chlorides according to literature.[32]

General procedure for preparing sulfonyl amidines: To a stirred solution of sulfonyl azide **1** (1 mmol, 1 equiv.) in Et_2O (5 mL) and 1-morpholinocycloalkene **2** (1 mmol, 1 equiv.) was added successively, the mixture was kept at room temperature. The color of the reaction mixture turned light yellow, after that a precipitate was formed. The precipitate was collected by simple filtration followed by recrystallization in EtOH. The products **3-5** together with their physical constants are listed below.

***N*-(Cyclopentyl(morpholino)methylene)methanesulfonamide (3a).** White solid. mp 154-156 °C; Yield 81%; ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 1.65-1.84 (m, 4H), 2.16-2.23 (m, 2H), 2.91-2.94 (m, 2H), 3.00 (s, 3H), 3.61-3.71 (m, 8H), 3.93-4.05 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm: 27.11, 30.76, 43.31, 44.24, 47.40, 66.80, 170.45. Anal. Calcd for $C_{10}H_{20}SO_3N_2$ (%): C 48.36, H 8.12, N 11.28, S 12.91. Found C 48.43, H 7.74, N 10.43, S 12.12.

***N*-(Cyclopentyl(morpholino)methylene)-4-methylbenzenesulfonamide (3b).**[33] White solid. mp 148-150 °C; Yield 86%; IR ν (cm^{-1}): 1535 (C=N), 1351 (SO_2), 1258 (C-N), 1080 (C-O); ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 1.66-1.77 (m, 6H), 2.02-2.10 (m, 2H), 2.37 (s, 3H), 3.61-3.68 (m, 8H), 4.00-4.13 (m, 1H), 7.23 (d, *J*=7.93 Hz, 2H), 7.77 (d, *J*=8.12 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm: 21.35, 26.60, 30.27, 42.39, 47.03, 66.32, 126.05, 129.01, 141.37, 141.74, 170.21.

***N*-(Cyclopentyl(morpholino)methylene)-2-nitrobenzenesulfonamide (3c).** Yellow solid. mp

126-128 °C; Yield 71%; IR ν (cm^{-1}): 1547 (C=N), 1351 (SO_2), 1531 (NO_2), 1224 (C-N), 1032 (C-O); ^1H NMR (300 MHz, $CDCl_3$) δ ppm: 1.68-1.80 (m, 6H), 2.10-2.17 (m, 2H), 3.60-3.71 (m, 8H), 3.88-4.00 (m, 1H), 7.61-7.68 (m, 3H), 8.17-8.20 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm: 26.59, 30.28, 43.18, 47.34, 66.37, 123.88, 128.80, 131.66, 132.20, 136.79, 147.58, 170.36.

***N*-(Cyclopentyl(morpholino)methylene)-3-nitrobenzenesulfonamide (3d).** White solid. mp 118-120 °C; Yield 60%; ^1H NMR (300 MHz, DMSO) δ ppm: 1.59-1.90 (m, 6H), 3.35 (m, 6H), 3.63 (m, 4H), 3.75-3.83 (m, 1H), 7.85 (t, *J*=8.02 Hz, 1H), 8.24 (d, *J*=8.07, Hz, 1H), 8.40-8.45 (m, 2H); ^{13}C NMR (75 MHz, DMSO) δ ppm: 26.54, 30.22, 42.90, 47.93, 66.15, 120.56, 126.64, 131.58, 132.28, 146.46, 148.14, 170.27.

***N*-(Cyclopentyl(morpholino)methylene)-4-nitrobenzenesulfonamide (3e).** Orange solid. mp 150-152 °C; Yield 82%; IR ν (cm^{-1}): 1605 (C=N), 1523 (NO_2), 1348 (SO_2), 1221 (C-N), 1028 (C-O); ^1H NMR (300 MHz, $CDCl_3$) δ ppm: 1.77-1.83 (m, 6H), 2.15-2.22 (m, 2H), 3.65-3.74 (m, 8H), 3.98-4.07 (m, 1H), 8.11 (d, *J*=8.88 Hz, 2H), 8.33 (d, *J*=8.88 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm: 26.67, 30.53, 43.36, 66.33, 123.88, 127.39, 139.32, 141.37, 170.57.

***N*-(Cyclopentyl(morpholino)methylene)benzenesulfonamide (3f).** White solid. mp 140-142 °C; Yield 47%; IR ν (cm^{-1}): 1535 (C=N), 1345 (SO_2), 1224 (C-N), 1033 (C-O); ^1H NMR (300 MHz, $CDCl_3$) δ ppm: 1.63-1.78 (m, 6H), 2.04-2.11 (m, 2H), 3.61-3.70 (m, 8H), 4.01-4.13 (m, 1H), 7.42-7.48 (m, 3H), 7.88-7.92 (dd, *J*=1.93 Hz, *J*=6.05 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm: 26.64, 30.32, 42.57, 47.10, 66.35, 126.07, 128.46, 131.32, 144.16, 170.35.

***N*-(Cyclopentyl(morpholino)methylene)-4-ethylbenzenesulfonamide (3g).** White solid. mp 114-116 °C; Yield 43%; IR ν (cm^{-1}): 1535 (C=N), 1351 (SO_2), 1219 (C-N), 1031 (C-O); ^1H NMR (300 MHz, $CDCl_3$) δ ppm: 1.26 (t, *J*=7.61 Hz, 3H), 1.70-1.80 (m, 6H), 2.09-2.14 (m, 2H), 2.67-2.74 (quadruplet, *J*=7.61 Hz, *J*=7.6 Hz, 2H), 3.63-3.71 (m, 8H), 4.05-4.17 (m, 1H), 7.29 (d, *J*=8.35 Hz, 2H), 7.83 (d, *J*=7.82 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm: 15.29, 26.71, 28.76, 30.37, 42.51, 47.09, 66.42, 126.24, 127.98, 141.59, 148.06, 170.33.

***N*-(Cyclopentyl(morpholino)methylene)-4-fluorobenzenesulfonamide (3h).** White solid. mp 148-150 °C; Yield 58%; IR ν (cm^{-1}): 1538 (C=N), 1344 (SO_2), 1224 (C-N), 1033 (C-O), 1138 (C-F); ^1H NMR (300 MHz, $CDCl_3$) δ ppm: 1.65-1.79 (m, 6H), 2.07-2.15 (m, 2H), 3.61-3.71 (m, 8H), 3.99-4.11 (m, 1H), 7.12 (t, *J*= 8.66 Hz, 2H), 7.89-7.93 (dd, *J*=3.76 Hz, *J*=5.14 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm: 26.66, 30.37, 42.71, 47.18, 66.33, 115.38, 115.67, 128.73, 140.36, 162.56, 170.32.

4-Chloro-*N*-(cyclopentyl(morpholino)methylene)benzenesulfonamide (3i). White solid. mp 134-136 °C; Yield 83%; IR ν (cm^{-1}): 1538 (C=N), 1351 (SO_2), 1219 (C-N), 1034 (C-O), 574 (C-Cl); ^1H NMR (300 MHz, $CDCl_3$) δ ppm: 1.65-1.79 (m, 6H), 2.08-2.16 (m, 2H), 3.61-3.71 (m, 8H), 3.97-4.09 (m, 1H), 7.42 (d, *J*=8.62 Hz, 2H), 7.85 (d, *J*=8.71 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm: 26.65, 30.39, 42.79, 47.20, 66.33, 127.61, 128.70, 137.55, 142.76, 170.33. Anal. Calcd for $C_{16}H_{21}SO_3ClN_2$ (%): C

54.17, H 5.91, N 7.81, S 8.79. Found C 54.19, H 5.92, N 7.78, S 8.68; HRMS (ESI) calcd. for $C_{16}H_{21}SO_3ClN_2$ ($[M+H]^+$) 357.1034. Found 357.1034.

4-Bromo-*N*-(cyclopentyl(morpholino)methylene)benzenesulfonamide (3j). White solid. mp 166-168 °C; Yield 76%; ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 1.65-1.80 (m, 6H), 2.08-2.16 (m, 2H), 3.61-3.71 (m, 8H), 3.97-4.09 (m, 1H), 7.58 (d, *J*=8.62 Hz, 2H), 7.77 (d, *J*=8.62 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm: 26.64, 30.38, 42.79, 47.19, 66.31, 125.97, 127.75, 131.67, 143.25, 170.34.

***N*-(Cyclopentyl(morpholino)methylene)-4-iodobenzenesulfonamide (3k).** White solid. mp 220-222 °C; Yield 67%; IR ν (cm^{-1}): 1529 (C=N), 1346 (SO_2), 1219 (C-N), 1027 (C-O), 579 (C-I); ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 1.65-1.79 (m, 6H), 2.08-2.16 (m, 2H), 3.60-3.70 (m, 8H), 3.96-4.09 (m, 1H), 7.63 (d, *J*=8.44 Hz, 2H), 7.79 (d, *J*=8.44 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm: 26.72, 30.45, 42.86, 47.20, 66.39, 98.32, 127.76, 137.71, 143.97, 170.40.

***N*-(Cyclopentyl(morpholino)methylene)-2,4,6-triisopropylbenzenesulfonamide (3l).** White solid. mp 128-130 °C; Yield 67%; ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 1.13-1.29 (m, 18H), 1.43-1.66 (m, 6H), 2.18-2.37 (m, 2H), 3.39-3.55 (m, 3H), 3.57-3.78 (m, 8H), 4.31-4.40 (m, 1H), 7.10 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm: 23.67, 24.69, 26.51, 29.45, 29.93, 34.09, 41.72, 66.38, 123.20, 137.34, 148.75, 151.46, 169.76.

(*E*)-*N1*,*N3*-Bis(cyclopentyl(morpholino)methylene)benzene-1,3-disulfonamide (3m). White solid. mp 180-182 °C; Yield 35%; IR ν (cm^{-1}): 1529 (C=N), 1353 (SO_2), 1220 (C-N), 1030 (C-O); ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 1.25-1.31 (m, 2H), 1.59-1.81 (m, 10H), 2.06-2.25 (m, 4H), 3.00 (t, *J*=4.61 Hz, 2H), 3.25-3.27 (m, 2H), 3.62-3.70 (m, 12H), 3.93-4.05 (m, 2H), 7.53-7.66 (m, 1H), 8.02-8.11 (dd, *J*=1.74 Hz, *J*=7.79 Hz, 2H), 8.46 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm: 26.73, 30.44, 42.79, 64.65, 66.41, 124.50, 128.86, 129.02, 144.87, 170.52. HRMS (ESI) calcd. for $C_{26}H_{38}N_4O_6S_2$ ($[M+H]^+$) 567.2306. Found 567.2306.

***N*-(Cyclopentyl(morpholino)methylene)thiophene-2-sulfonamide (3n).** White solid. mp 120-122 °C; Yield 55%; IR ν (cm^{-1}): 1539 (C=N), 1343 (SO_2), 1223 (C-N), 1031 (C-O); ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 1.69-1.76 (m, 6H); 2.04-2.11 (m, 2H); 3.65-3.69 (m, 8H), 3.95-4.09 (m, 1H); 7.98 (dd, *J*=1.92 Hz, *J*=3.85 Hz, 1H); 7.44 (dd, *J*=1.28 Hz, *J*=3.76 Hz, 1H), 7.56 (dd, *J*=1.28 Hz, *J*=2.38 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm: 26.71, 30.42, 42.54, 47.37, 66.47, 126.69, 129.57, 130.00, 146.04, 170.40. Anal. Calcd for $C_{14}H_{20}S_2O_3N_2$ (%): C 51.56, H 6.14, N 8.47, S 19.42. Found C 51.55, H 6.12, N 8.45, S 19.30; HRMS (ESI) calcd. for $C_{14}H_{20}S_2O_3N_2$ ($[M+H]^+$) 329.0988. Found 329.0991.

***N*-(Cyclohexyl(morpholino)methylene)-4-methylbenzenesulfonamide (4a).** White solid. mp 110-112 °C; Yield 71%; ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 1.58-1.90 (m, 8H), 2.34-2.42 (m, 2H), 2.43 (s, 3H), 2.91 (m, 2H), 3.69-3.75 (m, 6H), 3.95-3.99 (m, 1H), 7.31 (d, *J*=8.12 Hz, 2H), 7.73 (d, *J*=8.30 Hz, 1H), 7.82 (dd, *J*=2.45 Hz, *J*=8.12 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm: 21.88, 23.94, 26.43, 27.15, 28.69, 33.63, 41.24, 46.71, 51.10, 62.23, 67.03, 126.51, 127.41, 129.47, 130.10, 137.06, 143.95, 209.19.

***N*-(Cyclohexyl(morpholino)methylene)-2-nitrobenzenesulfonamide (4b).** Orange solid. mp

140-142 °C; Yield 25%; ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 1.20-1.84 (m, 10H), 3.44-3.51 (dd, *J*=6.97 Hz, *J*=7.15 Hz, 2H), 3.70-3.84 (m, 6H), 3.85-3.94 (m, 1H), 7.65-7.78 (m, 3H), 8.12-8.26 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm: 15.28, 24.83, 25.04, 26.16, 28.19, 34.87, 54.83, 65.86, 123.94, 125.14, 129.35, 131.82, 133.44, 136.03, 147.73.

***N*-(Cyclohexyl(morpholino)methylene)-4-nitrobenzenesulfonamide (4c).** Yellow solid. mp 134-136 °C; Yield 41%; ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 1.25-1.85 (m, 8H), 2.06-2.19 (m, 2H), 2.35-2.54 (m, 2H), 2.90 (m, 2H), 3.62-3.72 (m, 4H), 4.03-4.07 (m, 1H), 8.01 (d, *J*=8.78 Hz, 2H), 8.33 (t, *J*=8.88 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm: 23.54, 26.72, 28.91, 33.34, 40.86, 62.15, 124.39, 128.23, 143.81, 145.92, 146.79.

***N*-(Cyclohexyl(morpholino)methylene)benzenesulfonamide (4d).** White solid. mp 180-182 °C; Yield 30%; IR ν (cm^{-1}): 1539 (C=N), 1349 (SO_2), 1217 (C-N), 1022 (C-O); ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 1.11-1.37 (m, 2H), 1.51-1.87 (m, 8H), 3.67-3.71 (m, 8H), 3.73-3.75 (m, 1H), 7.41-7.49 (m, 3H), 7.90-7.93 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm: 25.38, 25.96, 28.21, 43.47, 47.66, 66.56, 126.02, 128.44, 131.27, 144.34, 170.14.

***N*-(Cyclohexyl(morpholino)methylene)-4-ethylbenzenesulfonamide (4e).** White solid. mp 168-170 °C; Yield 11%; ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 1.25 (t, *J*=7.56 Hz, 3H), 1.30-1.39 (m, 2H), 1.50-1.89 (m, 8H), 2.67-2.74 (quadruplet, *J*=7.61 Hz, *J*=7.61 Hz, 2H), 3.69-3.74 (m, 8H), 3.74-3.76 (m, 1H), 7.28-7.30 (d, *J*=6.51 Hz, 2H), 7.82-7.85 (d, *J*=8.25 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm: 15.29, 25.55, 26.09, 28.39, 28.76, 43.51, 47.74, 66.68, 126.26, 127.96, 141.88, 148.03, 170.63.

***N*-(Cyclohexyl(morpholino)methylene)thiophene-2-sulfonamide (4f).** White solid. mp 160-162 °C; Yield 61%; IR ν (cm^{-1}): 1537 (C=N), 1348 (SO_2), 1224 (C-N), 1015 (C-O); ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 1.19-1.28 (m, 2H), 1.53-1.80 (m, 6H), 2.41-2.50 (m, 2H), 3.70-3.62 (m, 8H), 4.00-4.04 (m, 1H), 6.92-7.01 (m, 2H), 7.49-7.52 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm: 25.52, 26.09, 28.36, 43.60, 47.96, 66.70, 126.69, 129.60, 129.99, 146.24, 170.20.

***N*-(Cycloheptyl(morpholino)methylene)-4-methylbenzenesulfonamide (5a).** White solid. mp 96-97 °C; Yield 64%; IR ν (cm^{-1}): 2912 (C–H), 1531 (C=N), 1431 (SO_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 1.26-1.36 (m, 2H), 1.49-1.72 (m, 10H), 2.38 (s, 3H), 3.57-3.71 (m, 8H), 4.22-4.30 (m, 1H), 7.23 (d, *J*=8.3 Hz, 2H), 7.69 (d, *J*=8.3 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm: 21.89, 24.71, 26.42, 27.82, 28.37, 28.65, 30.47, 39.37, 51.95, 67.34, 127.40, 129.78, 137.88, 143.52, 146.62.

***N*-(Cycloheptyl(morpholino)methylene)-2-nitrobenzenesulfonamide (5b).** White solid. mp 110-112 °C; Yield 98%; IR ν (cm^{-1}): 1551 (NO_2), 1533 (C=N), 1358 (SO_2), 1260 (C-N), 1067 (C-O); ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 1.48-1.75 (m, 10H), 2.17-2.34 (m, 2H), 3.61-3.75 (m, 8H), 3.77-3.81 (m, 1H), 7.67-7.76 (m, 2H), 7.85-7.90 (m,1H), 8.13-8.17 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm: 22.96, 24.87, 25.74, 26.86, 27.88, 30.12, 31.54, 50.56, 66.80, 125.03, 129.12, 130.78, 133.44, 134.58, 145.99, 147.90.

***N*-(Cycloheptyl(morpholino)methylene)-3-nitrobenzenesulfonamide (5c).** White solid. mp 156-158 °C; Yield 71%; IR ν (cm^{-1}): 1605 (C=N), 1533 (NO_2), 1338 (SO_2), 1219 (C-N), 1027 (C-O); Yield 71%; ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 1.38-1.56 (m, 8H), 2.12-2.17 (m, 2H), 2.38-2.46 (m, 4H), 3.63-3.73 (m, 4H), 3.92-3.99 (m, 1H), 7.73-7.78 (m, 1H), 8.18-8.21 (m, 1H), 8.37-8.43 (m, 1H), 8.63 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm: 22.89, 24.60, 25.83, 26.63, 27.80, 31.40, 50.65, 67.15, 122.14, 127.10, 129.26, 130.45, 132.57, 134.35, 148.22.

***N*-(Cycloheptyl(morpholino)methylene)-4-nitrobenzenesulfonamide (5d).** White solid. mp 156-158 °C; Yield 92%; IR ν (cm^{-1}): 1607 (C=N), 1530 (NO_2), 1339 (SO_2), 1264 (C-N), 1009 (C-O); ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 1.25-1.75 (m, 10H), 1.99-2.17 (m, 2H), 2.36-2.47 (m, 2H), 3.63-3.70 (m, 6H), 4.32-4.38 (m, 1H), 8.00-8.11 (m, 2H), 8.32 (t, *J*=8.92 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm: 24.65, 25.84, 26.62, 27.36, 27.82, 28.31, 30.26, 50.60, 51.67, 66.39, 67.09, 123.89, 124.07, 124.21, 127.44, 128.23, 129.19, 147.22.

***N*-(Cycloheptyl(morpholino)methylene)benzenesulfonamide (5e).** White solid. mp 120-122 °C; Yield 69%; IR ν (cm^{-1}): 1530 (C=N), 1352 (SO_2), 1161 (C-N), 1089 (C-O); ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 1.22-2.04 (m, 12H), 2.21-2.28 (m, 1H), 2.71-2.78 (m, 1H), 3.57-3.71 (m, 6H), 4.24-4.32 (m, 1H), 7.42-7.52 (m, 3H), 7.81-7.83 (dd, *J*=2.02 Hz, *J*=5.96 Hz, 1H), 7.90-7.93 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm: 24.25, 25.99, 27.39, 27.97, 28.19, 30.15, 38.99, 43.51, 51.46, 66.47, 66.93, 126.17, 126.93, 128.52, 128.79, 132.38, 140.34, 146.50.

***N*-(Cycloheptyl(morpholino)methylene)-4-ethylbenzenesulfonamide (5f).** White solid. mp 138-140 °C; Yield 85%; IR ν (cm^{-1}): 1537 (C=N), 1350 (SO_2), 1218 (C-N), 1017 (C-O); ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 1.21-1.27 (t, *J*=7.61 Hz, 3H), 1.34-1.81 (m, 10H), 1.99-2.15 (m, 2H), 2.24-2.30 (m, 2H), 2.66-2.73 (quadruplet, *J*=7.61 Hz, *J*=7.6 Hz, 2H), 3.69-3.72 (m, 6H), 4.25-4.32 (m, 1H), 7.26-7.31 (d, *J*=7.98 Hz, 2H), 7.72-7.75 (d, *J*=8.25 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm: 15.32, 24.30, 26.04, 27.45, 27.99, 28.78, 30.08, 43.40, 50.52, 51.50, 66.52, 66.98, 127.14, 128.37, 137.62, 147.19, 149.36.

***N*-(Cycloheptyl(morpholino)methylene)-4-fluorobenzenesulfonamide (5g).** White solid. mp 146-148 °C; Yield 64%; IR ν (cm^{-1}): 1588 (C=N), 1331 (SO_2), 1227 (C-N), 1152 (C-F), 1023 (C-O); ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 1.20-1.71 (m, 12H), 2.29 (m, 4H), 3.59-3.73 (t, *J*=6.11 Hz, 2H), 4.24-4.31 (m, 1H), 7.10-7.18 (dd, *J*=8.53 Hz, *J*=8.71 Hz, 2H), 7.81-7.87 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm: 22.84, 24.68, 25.91, 26.68, 27.83, 31.50, 39.01, 50.58, 51.57, 67.14, 116.02, 116.32, 129.60, 134.03, 146.00, 163.28.

4-Chloro-*N*-(cycloheptyl(morpholino)methylene)benzenesulfonamide (5h). White solid. mp 136-138 °C; Yield 62%; IR ν (cm^{-1}): 1476 (C=N), 1365 (SO_2), 1237 (C-N), 1024 (C-O), 655 (C-Cl); ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 1.24-1.77 (m, 10H), 1.97-2.16 (m, 2H), 2.26-2.32 (m, 2H), 2.47 (t, *J*= 6.16 Hz, 1H), 2.74-2.81 (m, 1H), 3.58-3.73 (m, 4H), 4.25-4.33 (m, 1H), 7.44 (t, *J*=8.48 Hz, 2H), 7.75-7.78 (dd, *J*=6.51 Hz, *J*=2.11 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm: 24.25, 26.07, 26.66, 27.40, 29.99, 31.47, 39.00, 50.58,

51.56, 66.92, 67.12, 128.42, 129.06, 129.20, 138.83, 139.06, 145.90. Anal. Calcd for $C_{18}H_{25}SO_3ClN_2$ (%): C 56.40, H 6.51, N 7.26, S 8.06. Found 56.62; H, 6.54; N, 7.27; S, 8.18. HRMS (ESI) calcd. for $C_{18}H_{25}SO_3ClN_2$ ($[M+H]^+$) 385.1347. Found 385.1347.

4-Bromo-*N*-(cycloheptyl(morpholino)methylene)benzenesulfonamide (5i). White solid. mp 140-142 °C; Yield 62%; IR ν (cm^{-1}): 1574 (C=N), 1332 (SO_2), 1262 (C-N), 1008 (C-O); 653 (C-Br), ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 1.19-1.82 (m, 10H), 1.96-2.16 (m, 2H), 2.25-2.32 (m, 2H), 2.73-2.79 (m, 2H), 3.56-3.72 (m, 4H), 4.26-4.34 (m, 1H), 7.57-7.60 (d, *J*=8.62 Hz, 2H), 7.67-7.70 (d, *J*=8.62 Hz, 2H);^{13}C NMR (75 MHz, $CDCl_3$) δ ppm: 24.22, 26.06, 27.40, 29.98, 38.96, 50.55, 51.50, 66.86, 113.98, 127.20, 128.50, 131.99, 139.60, 145.83.

***N*-(Cycloheptyl(morpholino)methylene)-4-iodobenzenesulfonamide (5j).** White solid. mp 160-162 °C; Yield 78%; ^{1}H NMR (300 MHz, DMSO) δ ppm: 1.11-2.90 (m, 10H), 2.08-2.12 (m, 2H), 3.37 (s, 8H), 4.43-4.51 (m, 1H), 7.57 (d, *J*=8.53 Hz, 2H), 7.68 (d, *J*=8.53 Hz, 2H), ^{13}C NMR (75 MHz, DMSO) δ ppm: 23.84, 26.34, 27.30, 28.05, 29.00, 30.45, 49.52, 49.52, 50.58, 65.69, 99.62, 128.26, 137.42, 141.44, 145.75.

***N*-(Cycloheptyl(morpholino)methylene)thiophene-2-sulfonamide (5k).** White solid. mp 142-144 °C; Yield 51%; IR ν (cm^{-1}): 1539 (C=N), 1330 (SO_2), 1249 (C-N), 1015 (C-O); ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 1.20-2.13 (m, 12H), 2.29-2.36 (m, 1H), 2.74-2.81 (m, 1H), 3.60-3.71 (m, 6H), 4.31-4.38 (m, 1H), 6.97-7.05 (m, 1H), 7.52-7.57 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm: 24.23, 25.99, 27.85, 28.17, 29.94, 30.11, 43.38, 51.57, 51.84, 66.41, 66.88, 127.11, 129.95, 131.67, 131.67, 141.30, 146.09. Anal. Calcd for $C_{16}H_{24}S_2O_3N_2$ (%): C 54.26, H 6.79, N 7.82, S 17.81. Found C 54.05, H 6.79, N 7.78, S 18.04; HRMS (ESI) calcd. for $C_{16}H_{24}S_2O_3N_2$ ($[M+H]^+$) 357.1301. Found 357.1301.

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