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SYNTHESIS OF SULFONYLAMIDES CONTAINING AN ISOXAZOLE MOIETY

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Abstract*. The authors obtained a number of new sulfonylamides with isoxazole moiety by sulfonyl chlorination of bicyclic systems containing isoxazole heterocycle and interaction of the obtained sulfonyl chlorides with amino compounds. The authors also obtained isoxazole derivatives containing a sulfogroup in the isoxazole ring by sulfonyl chlorination of 3-aryl-5-N-acylaminoisoxazoles.*

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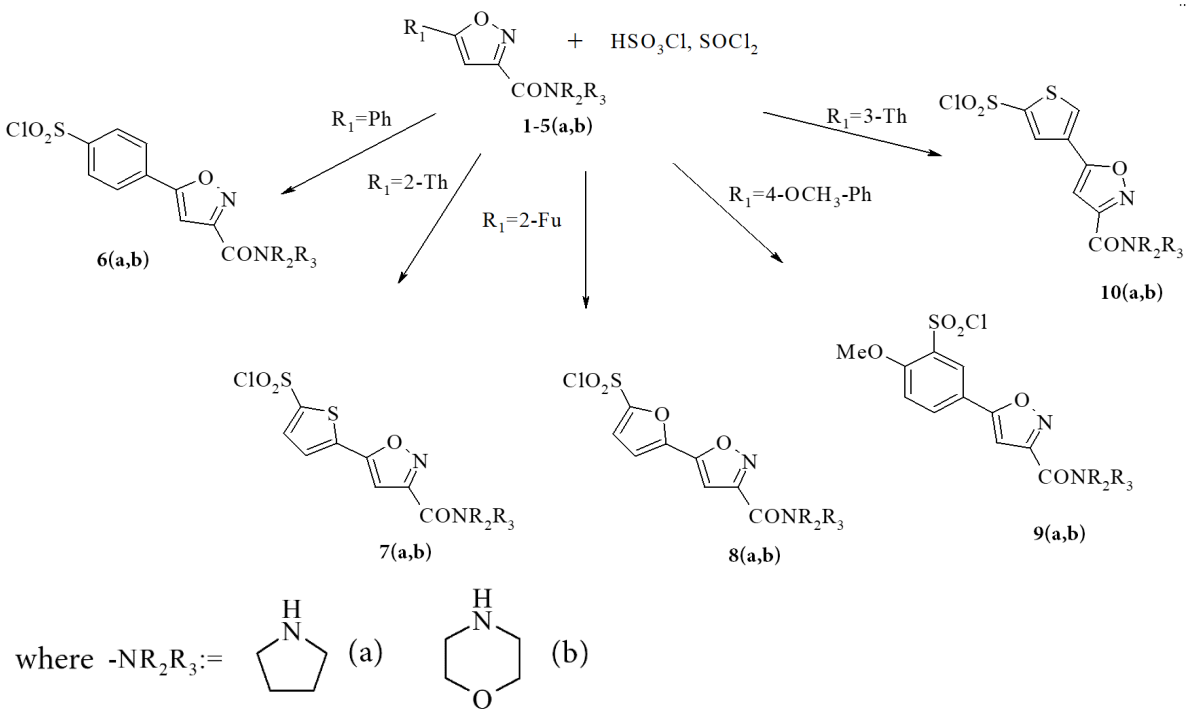
Introduction

Sulfonylamide group is an important functional group in organic compounds. It is widely presented in pharmaceutical preparations in forms of various natural and synthetic compounds. Traditionally, sulfonylamides are considered as antibacterial agents. However, they include compounds with different biological activities: hypoglycaemic [1, 2], antitumour [3], antiviral [4-9], antiepileptic [10], hypotensive [11], antiprotozoal [12], antifungal [13], anticancer [14-16], anti-inflammatory [17], diuretic [18], etc. [19-21]. Also, sulfonylamides are a convenient and efficient source of nitrogen and are used in the construction of C-N bonds [22]. Additionally, an adduct of sulfonylamide and vitamin C improves the optical properties of polyvinyl alcohol, which makes its use in the production of optical devices possible [23].

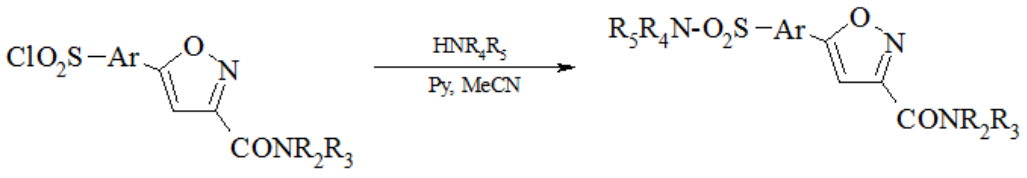
Researchers are focusing on sulfonylamide derivatives of heteroaromatic systems because of their high and specific biological activity. There are few literature data on sulfonylamide derivatives of isoxazoles. However, some of this class compounds have established pharmacological potential [24]. In this regard, the development of methods for the preparation of new sulfonylamides containing the isoxazole fragment is a very urgent task.

The main approach to the synthesis of sulfonylamides is the sulfonyl chlorination of the corresponding substrates [25] and the interaction of the resulting sulfonyl chlorides with ammonia or amino compounds. Carboxamide derivatives of bicyclic systems containing an isoxazole heterocycle, **1-5(a, b)** were sulfonyl chlorinated in the presence of thionyl chloride with excess chlorosulfonic acid. Therefore, we obtained sulfonyl chlorides **6-10(a, b)** regiospecifically.



Nevertheless, the isoxazole radical appears as a *para*-orientant in the benzene ring despite its electron acceptor character. Obviously, it concerns with the stabilisation of the σ-complex in the *para*-position to the isoxazole fragment due to the formation of a resonance structure with the localisation of the positive charge on the oxygen atom.

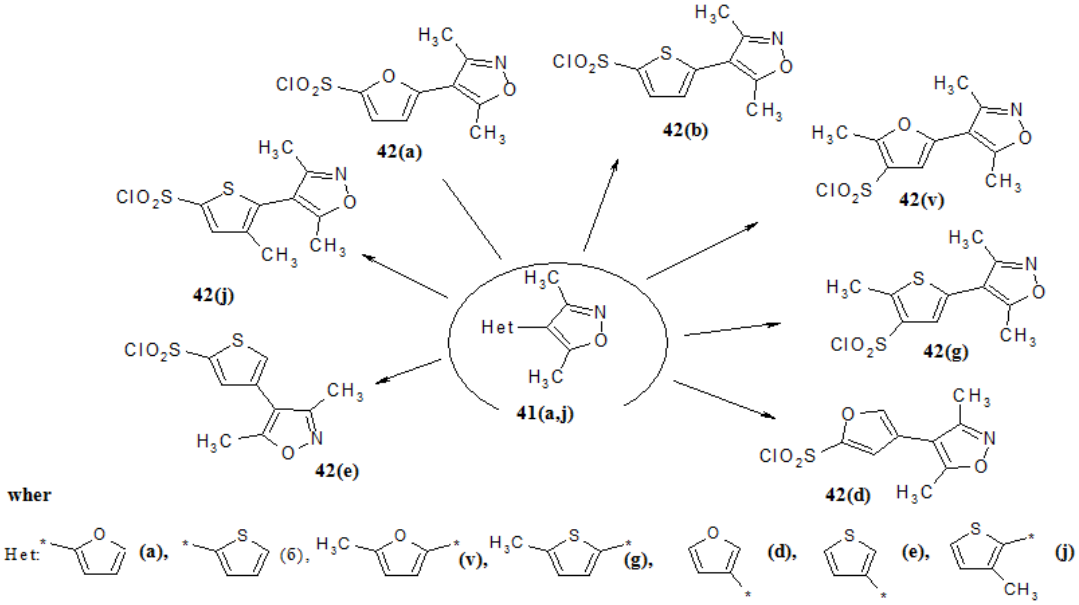
We synthesised a library of sulfonyl chlorides **11-40** containing an isoxazole moiety on the basis of the obtained sulfonyl chlorides **6-10(a, b)** by their interaction with aliphatic and aromatic amines in the presence of pyridine in acetonitrile.



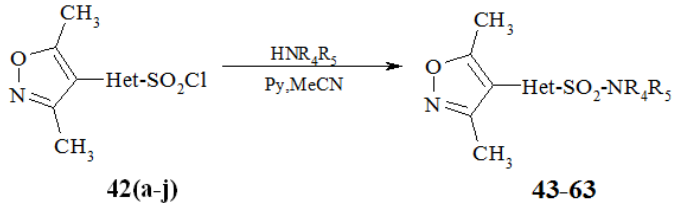
6-10(a,b) **11-40**

where HNR_4R_5 is pyrrolidin, morpholine and 4-methoxyaniline

We obtained the sulfonyl chlorides **42(a-j)** by sulfonyl chlorides of 4-heteryl-substituted-3,5-dimethylisoxazoles **41(a-j)** containing furan or thiophene cycles.

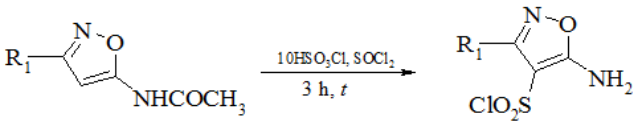


We obtained sulfonamide derivatives of 4-furan- and 4-thiophene-3,5-dimethylisoxazoles from the obtained sulfonyl chlorides.



where HNR_4R_5 is pyrrolidin, morpholine and 4-methoxyaniline

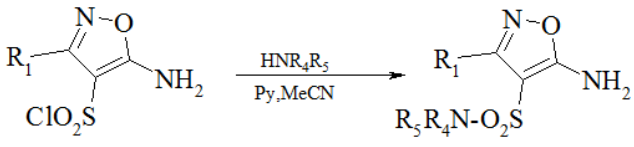
The authors also obtained isoxazole derivatives containing a sulfogroup in the isoxazole ring by sulfonyl chlorination of 3-aryl-5-*N*-acylaminoisoxazoles **64(a,b)**.



where

R_1: = (a), Br (b)

The deacylation reaction of the amino group occurs simultaneously with sulfonyl chlorination. The corresponding sulfonyl chlorides **66-71** were synthesised using sulfonyl chlorides **65(a, b)** in acetonitrile in the presence of pyridine.



where

R_1: (a), Br (b)

where HNR_4R_5 is pyrrolidin, morpholine and 4-methoxyaniline

Thus, we obtained a number of new sulfonylamides with isoxazole fragment. The identification of the synthesized compounds and general methods of their synthesis are presented in the experimental part.

Experimental part

NMR spectra were recorded on a Varian XL-400 instrument for solutions in $CDCl_3$ or DMSO-d_6 at 25 °C. The signal of tetramethylsilane was used as a standard one. We recorded mass spectra on a Perkin Elmer Clarus 680 chromatography-mass spectrometer (GC) + Clarus SQ 8T (MS) using an ELITE-5ms 30m×0.25mm×0.25um capillary column. We performed elemental analysis on a Perkin Elmer 2400. We determined the melting temperature using a Büchi M-560 melting point and boiling point apparatus.

General methodology for sulfonyl chlorides synthesis. We added 0.01 mol of the substrate to a mixture of 0.10 mol of chlorosulfonic acid and 0.01 mol of thionyl chloride cooled in an ice bath under intensive stirring in portions. The mixture was kept under refrigeration until the precipitate was completely dissolved, then heated at 60 °C for 1 h. We poured the mixture into a blend of ice with 50 mL of chloroform. We separated the organic layer, washed with 50 ml of 5% soda solution, dried with sodium sulfate. The flash solution was chromatographed on silica gel, the solvent was evaporated.

General methodology for sulphonylamides synthesis. We added 0.001 mol of the appropriate amine to a mixture of 0.001 mol of sulfonyl chloride and 0.002 mol of pyridine in 5 ml acetonitrile. We have stirred the reaction mixture at 60 °C for 1 h. We added 5 ml of water and filtered off the precipitate. The product was purified by silica gel column chromatography by elution with a 50:50 ethyl acetate-petroleum ether mixture. We obtained crystals of sulfonylamides after evaporation of the solvent.

4-[3-(Pyrrolidin-1-carbonyl)isoxazol-5-yl]-benzenesulfonyl chloride **6(a)**. Yield is 78%, white crystals, *T* melt. 187-189 °C. NMR spectrum ^{1}H ($CDCl_3$, δ, ppm, *J*/Hz): 1.98 (4H, m, $2CH_2$ pyrrolidine); 3.65 (2H, m, CH_2N pyrrolidine); 3.89 (2H, m, CH_2N pyrrolidine); 7.13 (1H, c, H-4 isoxazole); 8.00 (2H, d, *J*=8.5, C_6H_4); 8.14 (2H, d, *J*=8.5, C_6H_4). Mass-spectrum (EI, 70 eV), *m/z* ($I_{rel.}$ %): 340 $[M]^+$ (5), 144 (7), 114 (7), 98 (31), 70 (100), 56 (76). Found, %: C 49.30; H 3.85; N 8.26; S 9.43. $C_{14}H_{13}ClN_2O_4S$. Calculated, %: C 49.34; H 3.85; N 8.22; S 9.41.

4-[3-(Morpholine-1-carbonyl)isoxazol-5-yl]-benzenesulfonyl chloride **6(b)**. Yield is 77%, white crystals, *T* melt. 195-197 °C. NMR spectrum ^{1}H ($CDCl_3$, δ, ppm, *J*/Hz): 3.74 (2H, m, CH_2N morpholine); 3.79 (4H, m, CH_2N, CH_2O morpholine); 3.97 (2H, m, CH_2N morpholine); 7.05 (1H, s, H-4 isoxazole); 8.00 (2H, d, *J*=8.5, C_6H_4), 8.13 (2H, d, *J*=8.5, C_6H_4). Mass-spectrum (EI, 70 eV), *m/z* ($I_{rel.}$ %): 356 $[M]^+$ (7), 326 (13), 270 (15), 115 (15), 114 (29), 86 (55), 56 (100). Found, %: C 47.03; H 3.68; N 7.89; S 9.00. $C_{14}H_{11}ClN_2O_5S$. Calculated, %: C 47.13; H 3.85; N 7.85; S 8.99.

5-[3-(Pyrrolidin-1-carbonyl)isoxazol-5-yl]-thiophene-2-sulfonyl chloride **7(a)**. Yield is 80%, white crystals, *T* melt. 127-129 °C. NMR spectrum ^{1}H ($CDCl_3$, δ, ppm, *J*/Hz): 1.98 (4H, m, $2CH_2$ pyrrolidine); 3.66 (2H, m, CH_2N pyrrolidine); 3.88 (2H, m, CH_2N pyrrolidine); 7.02 (1H, s, H-4 isoxazole); 7.5 (d, *J*=4.3, H-4 thiophene); 7.86 (1H, d, *J*=4.3, H-3 thiophene).

Mass-spectrum (EI, 70 eV), *m/z* ($I_{rel.}$ %): 346 $[M]^+$ (1), 213 (6), 98 (46), 82 (13), 70 (71), 69 (43), 56 (74), 55 (100), 39 (25). Found, %: C 41.49; H 3.20; N 8.12; S 18.53. $C_{12}H_{11}ClN_2O_4S_2$. Calculated, %: C 41.56; H 3.20; N 8.08; S 18.49.

5-[3-(Morpholine-1-carbonyl)isoxazol-5-yl]-thiophene-2-sulfonyl chloride **7(b)**. Yield is 74%, light-brown crystals, *T* melt. 165-167 °C. NMR spectrum ^1H ($CDCl_3$, δ, ppm, *J*/Hz): 1.9 (4H, m, $2CH_2N$ morpholine); 3.72 (2H, m, CH_2O morpholine); 3.93 (2H, m, CH_2O morpholine); 6.94 (1H, s, H-4 isoxazol); 7.51 (1H, d, *J*=1.6, H-4 thiophene); 7.86 (1H, d, *J*=1.6, H-3 thiophene). Mass-spectrum (EI, 70 eV), *m/z* ($I_{rel.}$ %): 362 $[M]^+$ (3), 334 (3), 276 (12), 114 (31), 86 (27), 70 (100), 56 (85). Found, %: C 39.69; H 3.06; N 7.76; S 17.71. $C_{12}H_{11}ClN_2O_5S_2$. Calculated, %: C 39.73; H 3.06; N 7.72; S 17.67.

5-[3-(Pyrrolidin-1-carbonyl)isoxazol-5-yl]-furan-2-sulfonyl chloride **8(a)**. Yield is 81%, white crystals, T melt. 80-83 °C. NMR spectrum ^1H ($CDCl_3$, δ, ppm, *J*/Hz): 1.98 (4H, m, $2CH_2$ pyrrolidine); 3.65 (2H, m, CH_2N pyrrolidine); 3.86 (2H, m, CH_2N pyrrolidine); 7.06 (1H, d, *J*=3.9, H-4 furan); 7.13 (1H, s, H-4 isoxazol); 7.38 (1H, d, *J*=3.9, H-3 furan). Mass-spectrum (EI, 70 eV), *m/z* ($I_{rel.}$ %): 330 $[M]^+$ (2), 295 (1), 98 (54), 70 (59), 56 (100). Found, %: C 43.50; H 3.36; N 8.51; S 9.71. $C_{12}H_{11}ClN_2O_5S$. Calculated, %: C 43.58; H 3.35; N 8.47; S 9.69.

5-[3-(Morpholine-1-carbonyl)isoxazol-5-yl]-furan-2-sulfonyl chloride **8(b)**. Yield is 77%, brown crystals, *T* melt. 110-112 °C. NMR spectrum ^1H ($CDCl_3$, δ, ppm, *J*/Hz): 3.67 (2H, m, CH_2N morpholine); 3.74 (4H, m, CH_2N, CH_2O morpholine); 3.84 (2H, m, CH_2O morpholine); 7.05 (1H, d, *J*=3.9, H-4 furan); 7.24 (1H, s, H-4 isoxazol); 7.37 (1H, d, *J*=3.9, H-3 furan). Mass-spectrum (EI, 70 eV), *m/z* ($I_{rel.}$ %): 346 $[M]^+$ (6), 318 (3), 316 (7), 260 (14), 114 (34), 86 (26), 70 (100), 56 (88). Found, %: C 41.49; H 3.20; N 8.12; S 9.26. $C_{12}H_{11}ClN_2O_6S$. Calculated, %: C 41.57; H 3.20; N 8.08; S 9.25.

2-Methoxy-5-[3-(pyrrolidin-1-carbonyl)isoxazol-5-yl]-benzolsulfonyl chloride **9(a)**. Yield is 77%, white crystals, *T* melt. 80-85 °C. NMR spectrum ^1H ($CDCl_3$, δ, ppm, *J*/Hz): 1.85 (4H, m, $2CH_2$ pyrrolidine); 3.53 (2H, m, CH_2N pyrrolidine); 3.75 (2H, m, CH_2N pyrrolidine); 4.00 (3H, s, OCH_3); 6.81 (1H, s, H-4 isoxazol), 7.15 (1H, d, *J*=8.5, H-3 C_6H_3); 7.97 (1H, dd, J_1= 1.1, J_2=8.5, H-4 C_6H_3); 8.24 (1H, d, *J*=1.1, H-6 C_6H_3). Mass-spectrum (EI, 70 eV), *m/z* ($I_{rel.}$ %): 370 $[M]^+$ (7), 335 (2), 237 (15), 115 (16), 98 (45), 70 (100), 56 (68). Found, %: C 48.50; H 4.08; N 7.59; S 8.66. $C_{15}H_{15}ClN_2O_5S$. Calculated, %: C 48.59; H 4.08; N 7.55; S 8.65.

2-Methoxy-5-[3-(morpholin-1-carbonyl)isoxazol-5-yl]-benzolsulfonyl chloride **9(b)**. Yield is 76%, white crystals, *T* melt. 110-112 °C. NMR spectrum ^1H ($CDCl_3$, δ, ppm, *J*/Гц): 2.58 (2H, м, CH_2N morpholine); 3.61 (4H, m, CH_2N, CH_2O morpholine); 3.74 (2H, m, CH_2O morpholine); 3.95 (3H, s, OCH_3); 6.71 (1H, s, H-4 isoxazol); 7.13 (1H, d, *J*=8.5, H-3 C_6H_3); 7.94 (1H, dd, J_1= 1.1, J_2=8.5, H-4 C_6H_3); 8.17 (2H, d, *J*=1.1, H-6 C_6H_3). Mass-spectrum (EI, 70 eV), *m/z* ($I_{rel.}$ %): 386 $[M]^+$ (2), 351 (1), 237 (6), 115 (24), 114 (40), 86 (38), 56 (100). Calculated, %: C 46.53; H 3.91; N 7.28; S 8.30. $C_{15}H_{15}ClN_2O_6S$. Calculated, %: C 46.58; H 3.91; N 7.24; S 8.29.

4-[3-(Pyrrolidin-1-carbonyl)isoxazol-5-yl]-thiophene-2-sulfonyl chloride **10(a)**. Yield is 76%, white crystals, *T* melt. 175-177 °C. NMR spectrum ^1H ($CDCl_3$, δ, ppm, *J*/Hz): 1.94 (4H, m, $2CH_2$ pyrrolidine); 3.63 (2H, m, CH_2N pyrrolidine); 3.85 (2H, m, CH_2N pyrrolidine); 6.9 (1H, s, H-4 isoxazole); 8.13 (1H, d, *J*=1.6, H-4 thiophene); 8.20 (1H, d, *J*=1.6, H-3 thiophene). Mass-

spectrum (EI, 70 eV), *m/z* ($I_{rel.}$ %): 346 $[M]^+$ (2), 247 (17), 150 (5), 98 (39), 70 (82), 69 (44), 56 (100), 39 (28). Found, %: C 41.49; H 3.20; N 8.12; S 18.53. $C_{12}H_{11}ClN_2O_4S_2$. Calculated, %: C 41.56; H 3.20; N 8.08; S 18.49.

4-[3-(Morpholine-4-carbonyl)isoxazol-5-yl]-thiophene-2-sulfonyl chloride **10(b).** Yield is 78%, light-brown crystals, *T* melt. 170-173 °C. NMR spectrum ^1H ($CDCl_3$, δ, ppm, *J*/Hz): 3.68 (2H, m, CH_2N morpholine); 3.72 (4H, m, CH_2N, CH_2O morpholine); 3.85 (2H, m, CH_2O morpholine); 6.82 (1H, s, H-4 isoxazol); 8.13 (1H, d, *J*=1.6, H-5 thiophene); 8.20 (1H, d, *J*=1.6, H-3 thiophene). Mass-spectrum (EI, 70 eV), *m/z* ($I_{rel.}$ %): 362 $[M]^+$ (2), 276 (10), 233 (20), 114 (23), 86 (30), 70 (83), 56 (95), 42 (100), 39 (11). Found, %: C 39.70; H 3.06; N 7.76; S 17.71. $C_{12}H_{11}ClN_2O_5S_2$. Calculated, %: C 39.73; H 3.06; N 7.72; S 17.67.

{5-[4-(Pyrrolidin-1-sulfonyl)-phenyl]-isoxazol-3-yl}-pyrrolidin-1-yl-methanone **11**. Yield is 74%, white crystals, *T* melt. 190-192 °C. NMR spectrum ^1H (DMSO-d_6, δ, ppm, *J*/Hz): 1.66 (4H, m, $2CH_2$ pyrrolidine); 1.89 (4H, m, $2CH_2$ pyrrolidine); 3.18 (4H, m, CH_2N pyrrolidine); 3.52 (2H, m, CH_2N pyrrolidine); 3.71 (2H, m, $2CH_2N$ pyrrolidine); 7.53 (1H, s, H-4 isoxazol); 7.96 (2H, d, *J*=8.2, H-2, H-6 C_6H_4); 8.18 (2H, d, *J*=8.2, H-3, H-5 C_6H_4). Mass-spectrum (EI, 70 eV), *m/z* ($I_{rel.}$ %): 375 $[M]^+$ (10), 240 (13), 115 (8), 76 (11), 70 (100), 42 (93), 39 (19). Found, %: C 57.49; H 5.64; N 11.25; S 8.56. $C_{18}H_{21}N_3O_4S$. Calculated, %: C 57.59; H 5.64; N 11.19; S 8.54.

{5-[4-(Morphline-4-sulfonyl)-phenyl]-isoxazol-3-yl}-pyrrolidin-1-yl-methanone **12**. Yield is 78%, white crystals, *T* melt. 187-189 °C. NMR spectrum ^1H (DMSO-d_6, δ, ppm, *J*/Hz): 1.90 (4H, m, $2CH_2$ pyrrolidine); 2.92 (4H, m, $2CH_2N$ morpholine); 3.52 (2H, m, CH_2N pyrrolidine); 3.63 (4H, m, CH_2O morphline); 3.72 (2H, m, $2CH_2N$ pyrrolidine); 7.56 (1H, c, H-4 isoxazol); 7.90 (2H, d, *J*=8.5, H-2,6 Ar); 8.22 (2H, d, *J*=8.5, H-3,5 Ar). Mass-spectrum (EI, 70 eV), *m/z* ($I_{rel.}$ %): 391 $[M]^+$ (8), 240 (8), 98 (20), 86 (40), 70 (53), 56 (100), 42 (28). Found, %: C 55.20; H 5.41; N 10.79; S 8.21. $C_{18}H_{21}N_3O_5S$. Calculated, %: C 55.23; H 5.41; N 10.73; S 8.19.

N-(4-methoxy-phenyl)-4-[3-(pyrrolidin-1-carbonyl)-isoxazol-5-yl]-benzene sulphonylamide **13**. Yield is 77%, white crystals, *T* melt. 167-169 °C. NMR spectrum ^1H (DMSO-d_6, δ, ppm, *J*/Hz): 1.88 (4H, m, $2CH_2$ pyrrolidine); 3.51 (2H, m, CH_2N pyrrolidine); 3.66 (3H, s, OCH_3); 3.69 (2H, m, CH_2N pyrrolidine); 6.81 (2H, d, *J*=8.5, H-2,6 Ar^2); 6.98 (2H, d, J=8.5, H-3,5 Ar^2); 7.45 (1H, s, H-4 isoxazol); 7.8 (2H, d, *J*=8.5, 2, H-6 Ar^1); 8.09 (2H, d, J=8.5, H-3,5 Ar^1); 10.04 (1H, s, NH). Mass-spectrum (EI, 70 eV), *m/z* ($I_{rel.}$ %): 427 $[M]^+$ (3), 123 (9), 122 (100), 95 (15), 70 (9), 56 (19), 42 (16). Found, %: C 58.89; H 4.96; N 9.88; S 7.51. $C_{21}H_{21}N_3O_5S$. Calculated, %: C 59.00; H 4.95; N 9.83; S 7.50.

Morpholine-4-yl-{5-[4-(pyrrolidine-1-sulfonyl)-phenyl]-isoxazol-3-yl}-methanone **14**. Yield is 76%, white crystals, *T* melt. 215–217 °C. NMR ^1H (DMSO-d_6, δ, ppm, *J*/Hz): 1.66 (4H, m, $2CH_2$ pyrrolidine); 3.18 (4H, m, $2CH_2N$ pyrrolidine); 3.63 (4H, m, $2CH_2N$ morpholine); 3.68 (4H, m, $2CH_2O$ morpholine); 7.5 (1H, s, H-4 isoxazol); 7.96 (2H, d, *J*=8.5, H-2,6 Ar); 8.17 (2H, d, *J*=8.5, H-3,5 Ar). Mass-spectrum (EI, 70 eV), *m/z* ($I_{rel.}$ %): 391 $[M]^+$ (5), 199 (7), 115 (9), 114 (19), 86 (30), 70 (69), 42 (100), 39(10). Found, %: C 55.19; H 5.41; N 10.79; S 8.21. $C_{18}H_{21}N_3O_5S$. Calculated, %: C 55.23; H 5.41; N 10.73; S 8.19.

{5-[4-(Morphline-4-sulfonyl)-phenyl]-isoxazol-3-yl}-morpholine-4-yl-methanone **15**. Yield is 78%, white crystals, *T* melt. 225-227 °C. NMR ^1H (DMSO-d_6, δ, ppm, *J*/Hz): 2.92 (4H,

m, $2CH_2N$ morpholin); 3.63 (8H, m, $2CH_2N$, $2CH_2O$ morpholin); 7.53 (1H, s, H-4 isoxazol); 7.91 (2H, d, *J*=8.5, H-2 Ar); 8.21 (2H, d, *J*=8.5, H-6 Ar). Mass-spectrum (EI, 70 eV), *m/z* ($I_{rel.}$ %): 407 $[M]^+$ (9), 377 (6), 171 (9), 115 (7), 114 (15), 86 (80), 70 (36), 56 (100), 42 (48). Found, %: C 52.90; H 5.20; N 10.36; S 7.88. $C_{18}H_{21}N_3O_6S$. Calculated, %: C 53.06; H 5.20; N 10.31; S 7.87.

N-(4-methoxy-phenyl)-4-[3-(morpholine-4-carbonyl)-isoxazol-5-yl]-benzene sulphonylamide **16**. Yield is 77%, white crystals, *T* melt. 140-143 °C. NMR ^1H (DMSO-d_6, δ, ppm, *J*/Hz): 3.61 (4H, m, $2CH_2N$ morpholine); 3.66 (4H, m, CH_2N, CH_2O morpholine); 3.67 (3H, s, OCH_3); 6.80 (2H, d, *J*=8.5, H-2,6 Ar^1); 6.97 (2H, d, *J*=8.5, H-3,5 Ar^1); 7.42 (1H, s, H-4 isoxazol); 7.82 (2H, d, *J*=8.0, H-2,6 Ar^2); 8.09 (2H, d, *J*=8.0, H-3,5 Ar^1); 10.04 (1H, s, NH). Mass-spectrum (EI, 70 eV), *m/z* ($I_{rel.}$ %): 443 $[M]^+$ (2), 171 (7), 123 (9), 122 (100), 95 (13), 70 (14), 56 (11). Found, %: C 56.79; H 4.78; N 9.52; S 7.24. $C_{21}H_{11}N_3O_6S$. Calculated, %: C 56.88; H 4.77; N 9.48; S 7.23.

{5-[5-(Pyrrolidin-1-sulfonyl)-thiophen-2-yl]-isoxazol-3-yl}-pyrrolidin-1-yl-methanone **17**. Yield is 75%, white crystals, *T* melt. 195-197 °C. NMR ^1H (DMSO-d_6, δ, ppm, *J*/Hz): 1.71 (4H, m, $2CH_2$ pyrrolidine); 1.89 (4H, m, CH_2 pyrrolidine); 3.25 (8H, m, CH_2 pyrrolidine); 3.51(2H, m, CH_2 pyrrolidine); 3.69 (2H, m, CH_2 pyrrolidine); 7.42 (1H, c, H-4 isoxazol); 7.81 (1H, d, *J*=3.6, H-3 thiophen); 7.8 (1H, d, *J*=3.6, H-2 thiophen). Mass-spectrum (EI, 70 eV), *m/z* ($I_{rel.}$ %): 381 $[M]^+$ (6), 98 (53), 70 (87), 69 (21), 56 (64), 55 (100), 42 (86), 39 (11). Found, %: C 50.29; H 5.03; N 11.07; S 16.84. $C_{16}H_{19}N_3O_4S_2$. Calculated, %: C 50.38; H 5.02; N 11.02; S 16.81.

{5-[5-(Morpholine-4-sulfonyl)-thiophen-2-yl]-isoxazol-3-yl}-pyrrolidin-1-yl-methanone **18**. Yield is 77%, white crystals, *T* melt. 170-173 °C. NMR ^1H (DMSO-d_6, δ, ppm, *J*/Hz): 1.89 (4H, m, $2CH_2$ pyrrolidine); 3.0 (4H, m, CH_2N morpholine); 3.51 (2H, m, CH_2N pyrrolidine); 3.69 (6H, m, $2CH_2O$ morpholine, CH_2 pyrrolidine); 7.43 (1H, s, H-4 isoxazol); 7.78 (1H, d, *J*=3.9, H-3 thiophen); 7.95 (1H, d, *J*=3.9, H-2 thiophen). Mass-spectrum (EI, 70 eV), *m/z* ($I_{rel.}$ %): 397 $[M]^+$ (2), 98 (36), 86 (28), 70 (42), 69 (12), 56 (100), 55 (65). Found, %: C 48.20; H 4.82; N 10.62; S 16.16. $C_{16}H_{19}N_3O_5S_2$. Calculated, %: C 48.35; H 4.82; N 10.57; S 16.13.

5-[3-(Pyrrolidine-1-carbonyl)-isoxazol-5-yl]-thiophene-2-sulphonic acid 4-methoxy-phenylamide **19**. Yield is 78%, white crystals, *T* melt. 215-217 °C. NMR ^1H (DMSO-d_6, δ, ppm, *J*/Hz): 1.88 (4H, m, $2CH_2$ pyrrolidine); 3.49 (2H, m, CH_2N pyrrolidine); 3.65 (2H, m, CH_2N pyrrolidine); 3.69 (3H, s, OCH_3); 6.87 (2H, d, *J*=8.9, CH_2O Ar); 7.05 (2H, d, *J*=8.9, H-4,6 Ar); 7.35 (1H, sc, H-4 isoxazol); 7.52 (d, 1H, *J*=3.9, H-3 thiophen); 7.75 (1H, d, *J*=3.9, H-2 thiophen); 10.3 (1H, s, NH). Mass-spectrum (EI, 70 eV), *m/z* ($I_{rel.}$ %): 433 $[M]^+$ (4), 123 (10), 122 (100), 98 (10), 95 (15), 70 (8), 56 (20), 55 (29), 42 (11). Found, %: C 52.59; H 4.42; N 9.74; S 14.82. $C_{19}H_{19}N_3O_5S_2$. Calculated, %: C 52.64; H 4.42; N 9.69; S 14.79.

Morpholine-4-yl-{5-[5-(pyrrolidin-1-sulfonyl)-thiophen-2-yl]-isoxazol-3-yl}-methanone **20**. Yield is 74%, yellow crystals, *T* melt. 145-147 °C. NMR ^1H (DMSO-d_6, δ, ppm, *J*/Hz): 1.71 (4H, m, $2CH_2$ pyrrolidine); 3.24 (4H, m, $2CH_2N$ pyrrolidine); 3.61 (4H, m, CH_2N morpholine); 3.67 (4H, m, $2CH_2O$ morpholine); 7.38 (1H, s, H-4 isoxazol); 7.82 (1H, d, *J*=3.3, H-3 thiophen); 7.9 (1H, d, *J*=3.3, H-2 thiophen). Mass-spectrum (EI, 70 eV), *m/z* ($I_{rel.}$ %): 397 $[M]^+$ (6), 150 (8), 114 (31), 86 (22), 70 (84), 69 (10), 56 (41), 55 (17), 42 (100). Found, %: C 48.25; H 4.82; N 10.62; S 16.16. $C_{16}H_{19}N_3O_5S_2$. Calculated, %: C 48.35; H 4.82; N 10.57; S 16.13.

{5-[5-(Morpholine-4-sulfonyl)-thiophen-2-yl]-isoxazol-3-yl}-morpholine-4-yl-methanone **21**. Yield is 73%, white crystals, *T* melt. 140-142 °C. NMR ^{1}H (DMSO-d_6, δ, ppm, *J*/Hz): 2.99 (4H, m, 2CH_2N morpholine); 3.61 (4H, m, 2CH_2N morpholine); 3.67 (4H, m, 2CH_2O morpholine); 7.40 (1H, s, H-4 isoxazol); 7.78 (1H, d, *J*=5.3, H-4 thiophen); 7.93 (1H, d, *J*=5.3, H-4 thiophen). Mass-spectrum (EI, 70 eV), *m/z* ($I_{rel.}$ %): 413 $[M]^+$ (6), 114 (23), 86 (50), 70 (49), 56 (100), 42(56). Found, %: C 46.40; H 4.64; N 10.21; S 15.54. $C_{16}H_{19}N_3O_6S_2$. Calculated, %: C 46.48; H 4.63; N 10.16; S 15.51.

5-[3-(Morpholine-4-carbonyl)-isoxazol-5-yl]-thiophene-2-sulphonic acid 4-methoxyphenylamide **22**. Yield is 75%, pink crystals, *T* melt. 130-132 °C. NMR ^{1}H (DMSO-d_6, δ, ppm, *J*/Hz): 3.59 (4H, m, 2CH_2N morpholine); 3.65 (4H, m, 2CH_2N morpholine); 3.69 (3H, s, OCH_3); 6.86 (2H, d, *J*=8.5, H-2 Ar); 7.04 (2H, d, *J*=8.5, H-6 Ar); 7.32 (1H, s, H-4 isoxazol); 7.52 (1H, d, *J*=3.0, H-3 thiophen); 7.73 (1H, d, *J*=3.0, H-2 thiophen); 10.29 (1H, ex.s., NH). Mass-spectrum (EI, 70 eV), *m/z* ($I_{rel.}$ %): 449 $[M]^+$ (2), 122 (100), 114 (5), 70 (22), 56 (16), 42 (27). Found, %: C 50.69; H 4.26; N 9.40; S 14.29. $C_{19}H_{19}N_3O_6S_2$. Calculated, %: C 50.77; H 4.26; N 9.35; S 14.26.

{5-[5-(Pyrrolidin-1-sulfonyl)-furan-2-yl]-isoxazol-3-yl}-pyrrolidin-1-yl-methanone **23**. Yield is 73%, white crystals, *T* melt. 183-185 °C. NMR ^{1}H (DMSO-d_6, δ, ppm, *J*/Hz): 1.75 (4H, m, 2CH_2 pyrrolidine); 1.9 (4H, m, 2CH_2 pyrrolidine); 3.51 (4H,m, 2CH_2N pyrrolidine); 3.68 (4H, m, 2CH_2N pyrrolidine); 7.3 (1H, s, H-4 isoxazol); 7.42 (1H, d, *J*=3.9, H-2 furan); 7.44 (1H, d, *J*=3.9, H-3 furan). Mass-spectrum (EI, 70 eV), *m/z* ($I_{rel.}$ %): 365 $[M]^+$ (3), 135 (6), 98 (61), 70 (82), 69 (18), 55 (100), 42 (74), 39 (24). Found, %: C 52.49; H 5.25; N 11.56; S 8.79. $C_{16}H_{19}N_3O_5S$. Calculated, %: C 52.59; H 5.24; N 11.50; S 8.77.

{5-[5-(Morpholine-4-sulfonyl)-furan-2-yl]-isoxazol-3-yl}-pyrrolidin-1-yl-methanone **24**. Yield is 75%, white crystals, *T* melt. 167-169 °C. NMR ^{1}H (DMSO-d_6, δ, ppm, *J*/Hz): 1.89 (4H, m, 2CH_2 pyrrolidine); 3.13 (4H, m, 2CH_2N pyrrolidine); 3.52 (2H, м, CH_2N morpholine); 3.66 (6H, m, 2CH_2O morpholine, CH_2 pyrrolidine); 7.31 (1H, d, *J*=1.3, H-3 furan); 7.46 (1H, s, H-4 isoxazol); 7.47 (1H, d, *J*=1.3, H-2 furan). Mass-spectrum (EI, 70 eV), *m/z* ($I_{rel.}$ %): 381 $[M]^+$ (2), 98 (47), 70 (42), 69 (12), 56 (100), 42 (33). Found, %: C 50.29; H 5.03; N 11.07; S 8.42. $C_{16}H_{19}N_3O_6S$. Calculated, %: C 50.39; H 5.02; N 11.02; S 8.41.

5-[3-(Pyrrolidine-1-carbonyl)-isoxazol-5-yl]-furan-2-sulphonic acid 4-methoxyphenyl-amide **25**. Yield is 77%, black crystals, *T* melt. 90-92 °C. NMR ^{1}H (DMSO-d_6, δ, ppm, *J*/Hz): 1.89 (4H, m, 2CH_2 pyrrolidine); 3.51 (4H, m, CH_2N pyrrolidine); 6.85 (2H, d, *J*=8.5, CH_2O Ar); 7.05 (2H, d, *J*=8.5, H-2,6 Ar); 7.17 (1H, s, H-4 isoxazol); 7.23 (1H, d, *J*=3.3, H-3 furan); 7.33 (1H, d, *J*=3.3, H-2 furan); 8.0 (1H, s, NH). Mass-spectrum (EI, 70 eV), *m/z* ($I_{rel.}$ %): 417 $[M]^+$ (5), 123 (100), 98 (17), 95(20), 70 (18), 69 (12), 56 (25). Found, %: C 54.54; H 4.59; N 10.12; S 7.70. $C_{19}H_{19}N_3O_6S$. Calculated, %: C 54.67; H 4.59; N 10.07; S 7.68.

Morpholine-4-yl-{5-[5-(pyrrolidin-1-sulfonyl)-furan-2-yl]-isoxazol-3-yl}-methanone **26**. Yield is 74%, orange crystals, *T* melt. 125-127 °C. NMR ^{1}H (DMSO-d_6, δ, ppm, *J*/Hz): 1.74 (4H, m, 2CH_2 pyrrolidine); 3.3 (4H, m, 2CH_2N morpholine); 3.6 (4H, m, 2CH_2N pyrrolidine); 3.67 (4H, m, 2CH_2O morpholine); 7.29 (1H, s, H-4 isoxazol); 7.43 (2H, d, *J*=0.4, H-2,3 furan). Mass-spectrum (EI, 70 eV), *m/z* ($I_{rel.}$ %): 381 $[M]^+$ (5), 114 (37), 86 (22), 70 (100). Found, %: C 50.35; H 5.03; N 11.07; S 8.42. $C_{16}H_{19}N_3O_6S$. Calculated, %: C 50.39; H 5.02; N 11.02; S 8.41.

{5-[5-(Morpholine-4-sulfonyl)-furan-2-yl]-isoxazol-3-yl}-morpholine-4-yl-methanone **27**. Yield is 79%, white crystals, *T* melt. 120-123 °C. NMR ^{1}H (DMSO-d_6, δ, ppm, *J*/Hz): 3.12 (4H, m, 2CH_2N morpholine); 3.6 (4H, m, 2CH_2N morpholine); 3.67 (8H, m, 2CH_2O morpholine); 6.86 (2H, d, *J*=8.5, H-2 Ar); 7.04 (2H, d, *J*=8.5, H-6 Ar); 7.16 (1H, s, H-4 isoxazol); 7.23 (1H, s, NH); 7.32 (2H, d, *J*=2.6, H-2,3 furan). Mass-spectrum (EI, 70 eV), *m/z* ($I_{rel.}$ %): 397 $[M]^+$ (8), 114 (39), 86 (64), 70 (64), 56 (100). Found, %: C 48.21; H 4.82; N 10.63; S 8.08. $C_{16}H_{19}N_3O_7S$. Calculated, %: C 48.36; H 4.82; N 10.57; S 8.07.

5-[3-(Morpholine-4-carbonyl)-isoxazol-5-yl]-furan-2-sulphonic acid 4-methoxy-phenylamide **28**. Yield is 74%, red crystals, *T* melt. 165-167 °C. NMR ^{1}H (DMSO-d_6, δ, ppm, *J*/Hz): 3.6 (3H, s, $COCH_3$); 3.67 (4H, m, 2CH_2N morpholine); 3.68 (4H, m, 2CH_2O morpholine); 6.86 (2H, d, *J*=8.5, H-2 Ar); 7.04 (2H, d, *J*=8.5, H-6 Ar); 7.16 (1H, s, H-4 isoxazol); 7.23 (1H, s, NH); 7.32 (2H, d, *J*=2.6, H2,3 furan). Mass-spectrum (EI, 70 eV), *m/z* ($I_{rel.}$ %): 433 $[M]^+$ (7), 122 (100), 86 (64), 70 (23), 56 (14). Found, %: C 52.59; H 4.42; N 9.74; S 7.41. $C_{19}H_{19}N_3O_7S$. Calculated, %: C 52.65; H 4.42; N 9.69; S 7.40.

{5-[4-Methoxy-3-(pyrrolidin-1-sulfonyl)-phenyl]-isoxazol-3-yl}-pyrrolidin-1-yl-methanone **29**. Yield is 78%, white crystals, *T* melt. 190-195 °C. NMR ^{1}H (DMSO-d_6, δ, ppm, *J*/Hz): 1.76 (4H, m, 2CH_2 pyrrolidine); 1.89 (4H, m, 2CH_2 pyrrolidine); 3.27 (2H, m, CH_2N pyrrolidine); 3.51 (2H, m, CH_2N pyrrolidine); 3.69 (2H, m, CH_2N pyrrolidine); 3.99 (3H, s, OCH_3); 7.32 (1H, s, H-4 isoxazol); 7.45 (1H, d, *J*=7.5, H-6 Ar); 8.2 (1H, d, *J*=7.5, H-5 Ar); 8.22 (1H, s, H-2 Ar). Mass-spectrum (EI, 70 eV), *m/z* ($I_{rel.}$ %): 405 $[M]^+$ (4), 98 (43), 70 (100), 59 (48). Found, %: C 56.19; H 5.72; N 10.42; S 7.92. $C_{19}H_{23}N_3O_5S$. Calculated, %: C 56.28; H 5.72; N 10.36; S 7.91.

{5-[4-Methoxy-3-(morpholine-4-sulfonyl)-phenyl]-isoxazol-3-yl}-pyrrolidin-1-yl-methanone **30**. Yield is 79%, white crystals, *T* melt. 205-208 °C. NMR ^{1}H (DMSO-d_6, δ, ppm, *J*/Hz): 1.89 (4H, m, 2CH_2 pyrrolidine); 3.13 (4H, m, 2CH_2N pyrrolidine), 3.51 (2H, m, CH_2O morpholine); 3.6 (4H, m, CH_2N, CH_2O morpholine); 3.7 (2H, m, 2CH_2N morpholine); 3,99 (3H, s, OCH_3); 7.34 (1H, s, H-4 isoxazol); 7.46 (2H, d, *J*=8.5, H-2 Ar); 8.2 (1H, s, H-6 Ar); 8.23 (1H, d, *J*=8.5, H-5 Ar); 9.03 (1H, s, NH). Mass-spectrum (EI, 70 eV), *m/z* ($I_{rel.}$ %): 421 $[M]^+$ (5), 98 (34), 86 (36), 70 (45), 59 (100). Found, %: C 54.07; H 5.72; N 10.42; S 7.92. $C_{19}H_{23}N_3O_5S$. Calculated, %: C 56.28; H 5.72; N 10.36; S 7.91.

2-Methoxy-N-(4-methoxyphenyl)-5-[3-(pyrrolidine-1-carbonyl)-isoxazol-5-yl]-benzene sulfonamide **31**. Yield is 76%, pink crystals, *T* melt. 125-127 °C. NMR ^{1}H (DMSO-d_6, δ, ppm, *J*/Hz): 1.88 (4H, m, 2CH_2 pyrrolidine); 3.49 (4H, m, 2CH_2N pyrrolidine); 4.38 (6H, s, 2OCH_3); 3.99 (2H, m, CH_2N pyrrolidin); 6.77 (2H, d, *J*=8.9, H-2 Ar^2); 7.00 (2H, d, *J*=8.9, H-4,5 Ar^2); 7.25 (1H, s, H-4 isoxazol); 7.33 (1H, d, *J*=8.5, 6-H Ar^1); 8.10 (1H, s, H-2 Ar^1); 8.14 (1H, d, *J*=8.5, H-5 Ar^1); 9.8 (s, 1H, NH). Mass-spectrum (EI, 70 eV), *m/z* ($I_{rel.}$ %): 457 $[M]^+$ (5), 122 (100), 98 (13), 70 (14), 59 (24). Found, %: C 57.69; H 5.07; N 9.23; S 7.02. $C_{22}H_{23}N_3O_6S$. Calculated, %: C 57.76; H 5.07; N 9.18; S 7.01.

{5-[4-Methoxy-3-(pyrrolidin-1-sulfonyl)-phenyl]-isoxazol-3-yl}-morpholine-4-yl-methanone **32**. Yield is 77%, light-brown crystals, *T* melt. 110-115 °C. NMR ^{1}H (DMSO-d_6, δ, ppm, *J*/Hz): 1.76 (4H, m, 2CH_2 pyrrolidine); 3.26 (4H, m, 2CH_2N pyrrolidine); 3.62 (4H, m, 2CH_2N morpholine); 3.68 (4H, m, 2CH_2O morpholine); 3.99 (3H, s, OCH_3); 7.30 (1H, s, H-4 isoxazol); 7.45 (2H, d, *J*=9.0, H-2,6 Ar); 8.17 (2H, d, *J*=9.0, H-3,5 Ar). Mass-spectrum (EI,

70 eV), *m/z* ($I_{rel.}$ %): 421 $[M]^+$ (8), 114 (28), 86 (29), 70 (100), 59 (9). Found, %: C 54.04; H 4.08; N 7.59; S 8.66. $C_{19}H_{23}N_3O_6S$. Calculated, %: C 54.15; H 5.50; N 9.97; S 7.61.

{5-[4-Methoxy-3-(morpholine-4-sulfonyl)-phenyl]-isoxazol-3-yl}-morpholine-4-yl-methanone **33**. Yield is 80%, light-brown crystals, *T* melt. 145-150 °C. NMR ^{1}H (DMSO-d_6, δ, ppm, *J*/Hz): 3.13 (4H, m, $2CH_2N$ morpholine); 3.62 (8H, m, $2CH_2N$, $2CH_2O$ morpholine); 3.67 (4H, m, $2CH_2O$ morpholine); 3.99 (3H, s, OCH_3); 7.3 (1H, s, H-4 isoxazol); 7.47 (1H, d, *J*=7.5, H-6 Ar); 8.18 (1H, s, H-2 Ar); 8.02 (1H, d, *J*=7.5, H-5 Ar). Mass-spectrum (EI, 70 eV), *m/z* ($I_{rel.}$ %): 437 $[M]^+$ (4), 114 (25), 86 (70), 59 (100). Found, %: C 52.10; H 5.30; N 9.65; S 7.34. $C_{19}H_{23}N_3O_7S$. Calculated, %: C 52.17; H 5.30; N 9.61; S 7.33.

2-Methoxy-N-(4-methoxyphenyl)-5-[3-(morpholine-4-carbonyl)-isoxazol-5-yl]-benzene sulfonamide **34**. Yield is 77%, brown crystals, *T* melt. 110-115 °C. NMR ^{1}H (DMSO-d_6, δ, ppm, *J*/Hz): 3.6 (4H, m, $2CH_2N$ morpholine); 3.62 (3H, s, OCH_3); 3.66 (4H, m, $2CH_2O$ morpholine); 4.00 (s, 3H, OCH_3); 6.77 (2H, d, *J*=8.9, H-2 Ar^2); 7.01 (2H, d, *J*=8.9, H-6 Ar^2); 7.25 (1H, s, H-4 isoxazol); 7.38 (1H, d, *J*=8.5, H-6 Ar^1); 8.09 (1H, s, H-2 Ar^1); 8.12 (1H, d, *J*=8.5, H-5 Ar^1). Mass-spectrum (EI, 70 eV), *m/z* ($I_{rel.}$ %): 473 $[M]^+$ (9), 122 (100), 114 (5), 59 (9). Found, %: C 55.74; H 4.90; N 8.92; S 6.78. $C_{22}H_{23}N_3O_7S$. Calculated, %: C 55.81; H 4.90; N 8.87; S 6.77.

{5-[5-(Pyrrolidin-1-sulfonyl)-thiophen-3-yl]-thiophene-3-yl}-pyrrolidin-1-yl-methanone **35**. Yield is 77%, light-brown crystals, *T* melt. 190-194 °C. NMR ^{1}H (DMSO-d_6, δ, ppm, *J*/Hz): 1.94 (4H, m, $2CH_2N$ pyrrolidine); 3.0 (4H, m, $2CH_2N$ morpholine); 3.54 (2H, m, $2CH_2N$ pyrrolidine); 3.7 (4H, m, $2CH_2O$ morpholine); 3.76 (2H, m, $2CH_2$ pyrrolidine); 7.31 (1H, s, H-4 isoxazol); 8.15 (1H, d, *J*=1.6, H-4 thiophene); 8.61 (1H, d, *J*=1.6, H-2 thiophene). Mass-spectrum (EI, 70 eV), *m/z* ($I_{rel.}$ %): 381 $[M]^+$ (4), 247 (36), 215 (27), 122 (5), 98 (44), 70 (100), 56 (55), 42 (89). Found, %: C 50.29; H 5.03; N 11.07; S 16.84. $C_{16}H_{19}N_3O_4S_2$. Calculated, %: C 50.38; H 5.02; N 11.02; S 16.81.

{5-[5-(Morpholine-4-sulfonyl)-thiophen-3-yl]-isoxazol-3-yl}-pyrrolidin-1-yl-methanone **36**. Yield is 80%, orange crystals, *T* melt. 185-188 °C. NMR ^{1}H (DMSO-d_6, δ, ppm, *J*/Hz): 1.94 (4H, m, $2CH_2N$ pyrrolidine); 3.0 (4H, m, $2CH_2N$ morpholine); 3.54 (2H, m, $2CH_2N$ pyrrolidine); 3.7 (4H, m, $2CH_2O$ morpholine); 3.76 (2H, m, $2CH_2$ pyrrolidine); 7.31 (1H, s, H-4 isoxazol); 8.15 (1H, d, *J*=1.6, H-4 thiophene); 8.61 (1H, d, *J*=1.6, H-2 thiophene). Mass-spectrum (EI, 70 eV), *m/z* ($I_{rel.}$ %): 397 $[M]^+$ (2), 247 (16), 98 (17), 86 (46), 70 (30), 56 (100), 42 (24). Found, %: C 48.29; H 4.82; N 10.62; S 16.16. $C_{16}H_{19}N_3O_5S_2$. Calculated, %: C 48.35; H 4.82; N 10.57; S 16.13.

4-[3-(Pyrrolidine-1-carbonyl)-isoxazol-5-yl]-thiophene-2-sulphonic acid 4-methoxy-phenylamide **37**. Yield is 80%, black crystals, *T* melt. 110-113 °C. NMR ^{1}H (DMSO-d_6, δ, ppm, *J*/Hz): 1.8 (4H, m, $2CH_2N$ pyrrolidine); 3.53 (2H, m, $2CH_2$ pyrrolidine); 3.7 (3H, s, OCH_3); 3.75 (2H, m, $2CH_2$ pyrrolidine); 6.8 (2H, d, *J*=8.5, H-3,5 Ar); 7.05 (2H, d, *J*=8.5, H-2,6 Ar); 7.19 (1H, s, H-4 isoxazol); 7.9 (1H, d, *J*=1.1, H-4 thiophene); 8.41 (1H, d, *J*=1.1, H-2 thiophene); 10.13 (s, 1H, NH). Mass-spectrum (EI, 70 eV), *m/z* ($I_{rel.}$ %): 433 $[M]^+$ (2), 122 (61), 98 (19), 70 (44), 56 (48), 39 (100). Found, %: C 50.59; H 4.42; N 9.74; S 14.82. $C_{19}H_{19}N_3O_5S_2$. Calculated, %: C 52.64; H 4.42; N 9.69; S 14.79.

Morpholine-4-yl-{5-[5-(pyrrolidin-1-sulfonyl)-thiophen-3-yl]-isoxazol-3-yl}-methanone **38**. Yield is 80%, white crystals, *T* melt. 170-172 °C. NMR ^{1}H (DMSO-d_6, δ, ppm, *J*/Hz):

1.75 (4H, m, $2CH_2$ pyrrolidine); 3.64 (8H, m, $2CH_2N$ pyrrolidine, $2CH_2N$ morpholine); 3.69 (4H, m, CH_2 morpholine); 7.26 (1H, s, H-4 isoxazol); 8.17 (1H, d, *J*=1.0, H-4 thiophene); 7.17 (1H, d, *J*= 1.0, H-2 thiophene). Mass-spectrum (EI, 70 eV), *m/z* ($I_{rel.}$ %): 397 $[M]^+$ (2), 114 (19), 86 (31), 70 (81), 56 (40), 42 (100). Found, %: C 48.29; H 4.82; N 10.62; S 16.16. $C_{16}H_{19}N_3O_5S_2$. Calculated, %: C 48.35; H 4.82; N 10.57; S 16.13.

{5-[5-(Morpholine-4-sulfonyl)-thiophen-3-yl]-isoxazol-3-yl}-morpholine-4-yl-methanone **39**. Yield is 83%, white crystals, *T* melt. 140-143 °C. NMR ^1H (DMSO-d_6, δ, ppm, *J*/Hz): 2.99 (4H, m, CH_2N morpholine); 3.65(4H, m, CH_2N morpholine); 3.69 (8H, m, $4CH_2O$ morpholine); 7.27 (1H, s, H-4 isoxazol); 8.1 (1H, d, *J*=1.0, H-1 thiophene); 8.15 (1H, d, *J*=1.0, H-3 thiophene). Mass-spectrum (EI, 70 eV), *m/z* ($I_{rel.}$ %): 413 $[M]^+$ (1), 114 (14), 86 (46), 70 (37), 56 (100), 42 (50). Found, %: C 46.40; H 4.64; N 10.21; S 15.54. $C_{16}H_{19}N_3O_6S_2$. Calculated, %: C 46.48; H 4.63; N 10.16; S 15.51.

4-[3-(Morpholine-4-carbonyl)-isoxazol-5-yl]-thiophene-2-sulphonic acid 4-methoxy-phenylamide **40**. Yield is 81%, brown crystals, *T* melt. 155-157 °C. NMR ^1H (DMSO-d_6, δ, ppm, *J*/Hz): 3.63 (4H, m, $2CH_2N$ morpholine); 3.69 (4H, m, $2CH_2O$ morpholine); 3.7 (3H, s, OCH_3); 6.81 (2H, d, *J*=8.9, H-3,5 Ar); 7.05 (2H, d, *J*=8.9, H-2,6 Ar); 7.18 (1H, s, H-4 isoxazol); 7.89 (1H, d, *J*=1.0, H-4 thiophene); 8.45 (1H, d, *J*=1.0, H-2 thiophene); 10.14 (1H, s, NH). Mass-spectrum (EI, 70 eV), *m/z* ($I_{rel.}$ %): 449 $[M]^+$ (2), 122 (100), 95 (15), 70 (17), 56 (14). Found, %: C 50.69; H 4.26; N 9.40; S 14.29. $C_{19}H_{19}N_3O_6S_2$. Calculated, %: C 50.77; H 4.26; N 9.35; S 14.26.

5-(3,5-Dimethylisoxazol-4-yl)furan-2-sulfonyl chloride **42(a).** Yield is 78%, brown crystals, *T* melt. 61-63 °C. NMR ^1H ($CDCl_3$, δ, ppm, *J*/Hz): 2.44 (3H, s, CH_3); 2.64 (3H, s, CH_3); 6.53 (1H, d, *J*=3.7, CH furan); 7.36 (1H, d, *J*=3.7, CH furan). Mass-spectrum (EI, 70 eV)), *m/z* ($I_{rel.}$ %): 261 $[M]^+$ (16), 178 (9), 136 (15), 134 (27), 121 (62), 90 (22), 79 (100), 76 (18), 65 (15). Found (%): C 41.19; H 3.08; N 5.38; S 12.28. $C_9H_8ClNO_4S$. Calculated (%): C 41.31; H 3.08; N 5.35; S 12.25.

5-(3,5-Dimethylisoxazol-4-yl)thiophene-2-sulfonyl chloride **42(b).** Yield is 82%, brown crystals, *T* melt. 82-84 °C. NMR ^1H ($CDCl_3$, δ, ppm, *J*/Hz): 2.39 (3H, s, CH_3); 2.56 (3H, s, CH_3); 7.04 (1H, d, *J*=3.7, CH thiophene); 7.87 (1H, d, *J*=3.7 CH thiophene). Mass-spectrum (EI, 70 eV), *m/z* ($I_{rel.}$ %): 277 $[M]^+$ (7), 194 (5), 152 (8), 137 (23), 120 (17), 109 (11), 95 (12), 93 (12), 69 (100). Found (%): C 38.85; H 2.91; N 5.07; S 23.13. $C_9H_8ClNO_3S_2$. Calculated (%): C 38.31; H 5.06; N 7.81; S 17.89.

5-(3,5-Dimethylisoxazol-4-yl)-2-methylfuran-3-sulfonyl chloride **42(c).** Yield is 80%, white crystals, *T* melt. 115-117 °C. NMR^1H ($CDCl_3$, δ, ppm, *J*/Hz): 2.39 (3H, s, CH_3); 2.56 (3H, s, CH_3); 2.69 (3H, s, CH_3); 6.63 (1H, s, CH furan). Mass-spectrum (EI, 70 eV), *m/z* ($I_{rel.}$ %): 275 $[M]^+$ (32), 240 (16), 192 (11), 148 (13), 124 (20), 106 (15), 90 (29), 43 (100). Found (%): C 43.55; H 3.66; N 5.11; S 11.65. $C_{10}H_{10}ClNO_4S$. Calculated (%): C 43.56; H 3.66; N 5.08; S 11.63.

5-(3,5-Dimethylisoxazol-4-yl)-2-methylfuran-3-sulfonyl chloride **42(d).** Yield is 76%, dark brown crystals, *T* melt. 78-80 °C. NMR ^1H ($CDCl_3$, δ, ppm, *J*/Hz): 2.26 (3H, s, CH_3); 2.42 (3H, s, CH_3); 2.75 (3H, s, CH_3); 7.18 (1H, s, CH thiophene). Mass-spectrum (EI, 70 eV), *m/z* ($I_{rel.}$ %): 291 $[M]^+$ (6), 256 (3), 148 (6), 123 (7), 69 (9), 63 (7), 43 (100). Found (%): C 41.15; H 3.46; N 4.82; S 22.02. $C_{10}H_{10}ClNO_3S_2$. Calculated (%): C 41.17; H 3.45; N 4.80; S 21.98.

4-(3,5-Dimethylisoxazol-4-yl)furan-2-sulfonyl chloride **42(e).** Yield is 76%, brown crystals, *T* melt. 62-65 °C. NMR^{1}H ($CDCl_3$, δ, ppm, *J*/Hz): 2.22 (3H, s, CH_3); 2.42 (3H, s, CH_3); 7.04 (1H, s, CH furan); 7.35 (1H, s, CH furan). Mass-spectrum (EI, 70 eV), *m/z* ($I_{rel.}$ %): 261 $[M]^+$ (12), 162 (7), 157 (6), 43 (100). Found (%): C 41.19; H 3.08; N 5.38; S 12.28. $C_9H_8ClNO_4S$. Calculated (%): C 41.31; H 3.08; N 5.35; S 12.25.

4-(3,5-Dimethylisoxazol-4-yl)thiophene-2-sulfonyl chloride **42(f)**. Yield is 80%, brown crystals, *T* melt. 103-105 °C. NMR ^{1}H ($CDCl_3$, δ, ppm, *J*/Hz): 2.24 (3H, s, CH_3); 2.41 (3H, s, CH_3); 7.19 (1H, s, CH thiophene); 7.47 (1H, s, CH thiophene). Mass-spectrum (EI, 70 eV), *m/z* ($I_{rel.}$ %): 277 $[M]^+$ (4), 178 (5), 173 (5), 48 (8), 45 (12), 43 (100). Found (%): C 38.85; H 2.91; N 5.07; S 23.13. $C_9H_8ClNO_3S_2$. Calculated (%): C 38.31; H 5.06; N 7.81; S 17.89.

5-(3,5-Dimethylisoxazol-4-yl)4-methylthiophene-2-sulfonyl chloride **42(g)**. Yield is 82%, brown crystals, *T* melt. 102-104 °C. NMR ^{1}H ($CDCl_3$, δ, ppm, *J*/Hz): 2.03 (3H, s, CH_3); 2.10 (3H, s, CH_3); 2.26 (3H, s, CH_3); 7.64 (1H, s, CH thiophene). Mass-spectrum (EI, 70 eV), *m/z* ($I_{rel.}$ %): 291 $[M]^+$ (16), 256 (7), 166 (10), 152 (5), 151 (53), 134 (22), 123 (20), 109 (22), 93 (17), 69 (100). Found (%): C 41.15; H 3.46; N 4.82; S 22.02. $C_{10}H_{10}ClNO_3S_2$. Calculated (%): C 41.17; H 3.45; N 4.80; S 21.98.

3,5-Dimethyl-4-[5-pyrrolidin-1-sulfonyl)-furan-2-yl]-isoxazole **43**. Yield is 73%, white crystals, *T* melt. 103-107 °C. NMR ^{1}H (DMSO-d_6, δ, ppm, *J*/Hz): 2.38 (3H, s, CH_3); 2.60 (3H, s, CH_3); 3.08 (4H, m, $2CH_2$ pyrrolidine); 3.66 (4H, m, $2CH_2N$ pyrrolidine); 6.89 (1H, d, *J*=1.8, 4-H furan); 7.36 (1H, d, *J*=1.8, 3-H furan). Mass-spectrum (EI, 70 eV), *m/z* ($I_{rel.}$ %): 296 $[M]^+$ (14), 178 (7), 163 (66), 136 (10), 134 (12), 122 (15), 121 (25), 79 (30), 76 (14), 51 (100). Found, %: C 52.63; H 5.45; N 9.50; S 10.84. $C_{13}H_{16}N_2O_4S$. Calculated, %: C 52.69; H 5.44; N 9.45; S 10.82.

3,5-Dimethyl-4-[5-morpholine-1-sulfonyl)-furan-2-yl]-isoxazole **44**. Yield is 77%, light-brown crystals, *T* melt. 111-113 °C. NMR ^{1}H (DMSO-d_6, δ, ppm, *J*/Hz): 1.73 (4H, m, $2CH_2N$ morpholine); 2.37 (3H, s, CH_3); 2.59 (3H, s, CH_3); 3.27 (4H, m, $2CH_2O$ morpholine); 6.86 (1H, d, *J*=1.8, 4-H furan); 7.32 (1H, d, *J*=1.8, 3-H furan). Mass-spectrum (EI, 70 eV), *m/z* ($I_{rel.}$ %): 312 $[M]^+$ (54), 178 (8), 136 (10), 121 (18), 90 (10), 86 (22), 79 (25), 56 (100). Found, %: C 49.89; H 5.17; N 9.01; S 10.28. $C_{13}H_{16}N_2O_5S$. Calculated, %: C 49.99; H 5.16; N 8.97; S 10.26.

5-(3,5-Dimethylisoxazol-4-yl)-furan-2-sulphonic acid 4-methoxyphenylamide **45**. Yield is 73%, red crystals, *T* melt. 97-99 °C. NMR ^{1}H (DMSO-d_6, δ, ppm, *J*/Hz): 2.29 (3H, s, CH_3); 2.51 (3H, s, CH_3); 3.68 (3H, s, OCH_3); 6.73 (1H, d, *J*=3.3, 4-H furan); 6.85 (2H, d, *J*=8.5, CH-Ar); 7.05 (2H, d, *J*=8.5, CH-Ar); 7.15 (1H, d, *J*=3.3, 3-H furan); 10.36 (1H, s, NH). Mass-spectrum (EI, 70 eV), *m/z* ($I_{rel.}$ %): 348 $[M]^+$ (3), 122 (100), 95 (21), 80 (9), 79 (20), 65 (11), 52 (16). Found, %: C 55.09; H 4.63; N 8.08; S 9.22. $C_{16}H_{16}N_2O_5S$. Calculated, %: C 55.16; H 4.63; N 8.04; S 9.20.

3,5-Dimethyl-4-[5-pyrrolidin-1-sulfonyl)-thiophene-2-yl]-isoxazole **46**. Yield is 75%, brown crystals, *T* melt. 98-100 °C. NMR ^{1}H (DMSO-d_6, δ, ppm, *J*/Hz): 1.71 (4H, m, $2CH_2$ pyrrolidine); 2.35 (3H, s, CH_3); 2.55 (3H, s, CH_3); 3.23 (4H, m, $2CH_2N$ pyrrolidine); 7.37 (1H, d, *J*=4.0, H-3 -thiophene); 7.73 (1H, d, *J*=4.0, 4-CH thiophene). Mass-spectrum (EI, 70 eV), *m/z* ($I_{rel.}$ %): 312 $[M]^+$ (17), 194 (5), 179 (100), 152 (10), 137 (28), 122 (5), 120 (13), 110 (20), 95 (16), 69 (11). Found, %: C 49.88; H 5.17; N 9.01; S 20.57. $C_{13}H_{16}N_2O_3S_2$. Calculated, %: C 49.98; H 5.16; N 8.97; S 20.52.

3,5-Dimethyl-4-[5-morpholine-1-sulfonyl)-thiophene-2-yl]-isoxazole **47**. Yield is 78%, brown crystals, *T* melt. 103-105 °C. NMR ^{1}H (DMSO-d_6, δ, ppm, *J*/Hz): 2.36 (3H, s, CH_3); 2.56 (3H, s, CH_3); 2.97 (4H, m, $2CH_2N$ morpholine); 3.69 (4H, m, $2CH_2O$ morpholine); 7.41 (1H, d, *J*=4.0, 3-CH thiophene); 7.71 (1H, d, *J*=4.0, 4-CH thiophene). Mass-spectrum (EI, 70 eV), *m/z* ($I_{rel.}$ %): 328 $[M]^+$ (15), 179 (14), 137 (21), 122 (5), 95 (14), 86 (26), 69 (7), 56 (100). Found, %: C 47.45; H 4.92; N 8.57; S 19.56. $C_{13}H_{16}N_2O_4S_2$. Calculated, %: C 47.55; H 4.91; N 8.53; S 19.52.

5-(3,5-Dimethylisoxazol-4-yl)-thiophene-2-sulphonic acid 4-methoxyphenylamide **48**. Yield is 83%, brown crystals, *T* melt. 85-87 °C. NMR ^{1}H (DMSO-d_6, δ, ppm, *J*/Hz): 2.27 (3H, s, CH_3); 2.47 (3H, s, CH_3); 2.69 (3H, s, OCH_3); 6.86 (2H, d, *J*=9.2, 2CH-Ar); 7.05 (2H, d, *J*=9.2, 2CH-Ar); 7.21 (1H, d, *J*=3.7, 3-CH thiophene); (1H, d, *J*=3.7, 4-CH thiophene); 10.12 (1H, s, NH). Mass-spectrum (EI, 70 eV), *m/z* ($I_{rel.}$ %): 364 $[M]^+$ (24), 137 (26), 122 (100), 121 (23), 120 (14), 109 (13), 95 (23), 93 (11), 80 (11). Found, %: C 52.68; H 4.43; N 7.73; S 17.63. $C_{16}H_{16}N_2O_4S_2$. Calculated, %: C 52.73; H 4.43; N 7.69; S 17.59.

3,5-Dimethyl-4-[5-methyl-4-pyrrolidin-1-sulfonyl)-furan-2-yl]-isoxazole **43**. Yield is 71%, white crystals, *T* melt. 145-147 °C. NMR ^{1}H (DMSO-d_6, δ, ppm, *J*/Hz): 1.74 (4H, m, $2CH_2$ pyrrolidine); 2.34 (3H, s, CH_3); 2.5 (3H, s, CH_3); 2.57 (3H, s, CH_3); 3.2 (4H, м, $2CH_2N$ pyrrolidine); 6.82 (1H, d, *J*=1.8, CH furan). Mass-spectrum (EI, 70 eV), *m/z* ($I_{rel.}$ %): 177 $[M]^+$ (9), 176 (10), 175 (9), 148 (9), 124 (24), 106 (9), 70 (90), 42 (100). Found, %: C 54.09; H 5.85; N 9.07; S 10.35. $C_{14}H_{18}N_2O_4S$. Calculated, %: C 54.18; H 5.85; N 9.03; S 10.33.

3,5-Dimethyl-4-[5-methyl-4-(morpholine-1-sulfonyl)-furan-2-yl]-isoxazole **50**. Yield is 79%, white crystals, *T* melt. 143-145 °C. NMR ^{1}H (DMSO-d_6, δ, ppm, *J*/Hz): 2.35 (3H, s, CH_3); 2.57 (3H, s, CH_3); 2.99 (4H, m, $2CH_2N$ morpholine); 3.31 (3H, s, CH_3); 3.67 (4H, m, $2CH_2O$ morpholine); 6.74 (1H, s, CH furan). Mass-spectrum (EI, 70 eV), *m/z* ($I_{rel.}$ %): 326 $[M]^+$ (18), 177 (15), 176 (9), 175 (14), 148 (19), 124 (20), 106 (15), 86 (22), 56 (100). Found, %: C 51.49; H 5.56; N 8.63; S 9.84. $C_{14}H_{18}N_2O_5S$. Calculated, %: C 51.52; H 5.56; N 8.58; S 9.82.

4-[4-(4-Methoxybenzolsulfonyl)-5-methylfuran-2-yl]-3,5-dimethylisoxazole **51**. Yield is 69%, grey crystals, *T* melt. 120-122 °C. NMR ^{1}H (DMSO-d_6, δ, ppm, *J*/Hz): 2.27 (3H, s, CH_3); 2.48 (3H, s, CH_3); 2.5 (3H, s, CH_3); 2.69 (3H, s, OCH_3); 6.55 (1H, s, CH furan); 6.86 (2H, d, *J*=8.9, 2CH-Ar); 7.04 (2H, d, *J*=9.2, 2CH-Ar); 9.79 (1H, s, NH). Mass-spectrum (EI, 70 eV), *m/z* ($I_{rel.}$ %): 347 $[M]^+$ (17), 148 (15), 123 (12), 95 (20), 79 (16), 65 (11), 53 (100). Found, %: C 58.60; H 4.94; N 4.05; S 9.25. $C_{17}H_{17}NO_5S$. Calculated, %: C 58.78; H 4.93; N 4.03; S 9.23.

3,5-Dimethyl-4-[5-methyl-4-(pyrrolidin-1-sulfonyl)-thiophene-2-yl]-isoxazole **52**. Yield is 77%, light-brown crystals, *T* melt. 115-117 °C. NMR ^{1}H (DMSO-d_6, δ, ppm, *J*/Hz): 1.75 (4H, m, $2CH_2$ pyrrolidine); 2.29 (3H, s, CH_3); 2.7 (3H, s, CH_3); 3.22 (4H, m, $2CH_2N$ pyrrolidine); 3.28 (3H, s, CH3); 7.25 (1H, s, 3-CH thiophene). Mass-spectrum (EI, 70 eV), *m/z* ($I_{rel.}$ %): 326 $[M]^+$ (53), 191 (18), 148 (9), 70 (40), 69 (11), 65 (6), 59 (16), 43 (100). Found, %: C 51.48; H 5.56; N 8.62; S 19.68. $C_{14}H_{18}N_2O_3S_2$. Calculated, %: C 51.51; H 5.56; N 8.58; S 19.64.

3,5-Dimethyl-4-[5-methyl-4-(morpholine-1-sulfonyl)-thiophene-2-yl]-isoxazole **53**. Yield is 82%, light-brown crystals, *T* melt. 127-129 °C. NMR ^{1}H (DMSO-d_6, δ, ppm, *J*/Hz): 2.3 (3H, s, CH_3); 2.68 (3H, s, CH_3); 3.0 (4H, m, $2CH_2N$ morpholine); 3.32 (3H, s, CH_3); 3.66 (4H, m, $2CH_2O$ morpholine); 7.20 (1H, s, 3-CH thiophene). Mass-spectrum (EI, 70 eV), *m/z* ($I_{rel.}$ %): 342 $[M]^+$

(13), 193 (15), 192 (20), 191 (25), 148 (17), 106 (7), 86 (28), 69 (7), 56 (100). Found, %: C 48.96; H 5.30; N 8.22; S 18.76. $C_{14}H_{18}N_2O_4S_2$. Calculated, %: C 49.11; H 5.30; N 8.18; S 18.72.

5-(3,5-Dimethylisoxazol-4-yl)-2-methylthiophene-3-sulfonic acid 4-methoxyphenylamide **54**. Yield is 75%, red crystals, *T* melt. 120-122 °C. NMR ^{1}H (DMSO-d_6, δ, ppm, *J*/Hz): 2.20 (3H, s, CH_3); 2.4 (3H, s, CH_3); 2.44 (3H, s, CH_3); 2.68 (3H, s, OCH_3); 6.85 (2H, d, *J*=8.2, CH-Ar); 7.02 (2H, d, *J*=8.2, CH-Ar); 7.06 (1H, s, 3-CH thiophene); 9.86 (1H, s, NH). Mass-spectrum (EI, 70 eV), *m/z* ($I_{rel.}$ %): 378 $[M]^+$ (23), 148 (12), 123 (14), 122 (100), 95 (25), 79 (8), 65 (9). Found, %: C 53.89; H 4.80; N 7.44; S 16.98. $C_{17}H_{18}N_2O_4S_2$. Calculated, %: C 53.95; H 4.79; N 7.40; S 16.94.

3,5-Dimethyl-4-[5-pyrrolidin-1-sulfonyl)-furan-3-yl]-isoxazole **55**. Yield is 73%, white crystals, *T* melt. 104-106 °C. NMR ^{1}H (DMSO-d_6, δ, ppm, *J*/Hz): 1.72 (4H, m, $2CH_2$ pyrrolidine); 2.35 (3H, s, CH_3); 2.57 (3H, s, CH_3); 3.2 (4H, m, $2CH_2N$ pyrrolidine); 6.94 (1H, s, H-3 furan); 7.25 (s, 1 H, H-5 furan). Mass-spectrum (EI, 70 eV), *m/z* ($I_{rel.}$ %): 296 $[M]^+$ (28), 178 (12), 162 (68), 132 (7), 122 (27), 118 (16), 76 (23), 69 (11), 43 (100). Found, %: C 52.63; H 5.45; N 9.50; S 10.84. $C_{13}H_{16}N_2O_4S$. Calculated, %: C 52.69; H 5.44; N 9.45; S 10.82.

3,5-Dimethyl-4-[5-morpholine-1-sulfonyl)-furan-3-yl]-isoxazole **56**. Yield is 76%, light-brown crystals, *T* melt. 146-148 °C. NMR ^{1}H (DMSO-d_6, δ, ppm, *J*/Hz): 2.35 (3H, s, CH_3); 2.57 (3H, s, CH_3); 3.0 (4H, m, $2CH_2N$ morpholine); 3.59 (4H, m, $2CH_2O$ morpholine); 6.96 (1H, s, H-3 furan); 7.28 (s, 1 H, H-5 furan). Mass-spectrum (EI, 70 eV), *m/z* ($I_{rel.}$ %): 312 $[M]^+$ (36), 175 (12), 169 (16), 132 (9), 126 (23), 98 (9), 86 (16), 79 (25), 55 (25), 42 (100). Found, %: C 49.89; H 5.17; N 9.01; S 10.28. $C_{13}H_{16}N_2O_5S$. Calculated, %: C 49.99; H 5.16; N 8.97; S 10.26.

4-[5-(4-Methoxybenzolsulfonyl)-furan-3-yl]-3,5-dimethylisoxazole **57**. Yield is 72%, red crystals, *T* melt. 97-99 °C. NMR ^{1}H (DMSO-d_6, δ, ppm, *J*/Hz): 2.27 (3H, s, CH_3); 2.48 (3H, s, CH_3); 2.69 (3H, s, OCH_3); 6.86 (2H, d, *J*=8.9, 2CH-Ar); 6.96 (1H, s, H-3 furan); 7.03 (2H, d, *J*=9.2, 2CH-Ar); 7.28 (s, 1 H, H-5 furan); 9.76 (1H, s, NH). Mass-spectrum (EI, 70 eV), *m/z* ($I_{rel.}$ %): 348 $[M]^+$ (13), 126 (58), 98 (14), 80 (9), 79 (15), 69 (16), 43 (100). Found, %: C 55.09; H 4.63; N 8.08; S 9.22. $C_{16}H_{16}N_2O_5S$. Calculated, %: C 55.16; H 4.63; N 8.04; S 9.20.

3,5-Dimethyl-4-[5-pyrrolidin-1-sulfonyl)-thiophen-3-yl]-isoxazole **58**. Yield is 79%, light-brown crystals, *T* melt. 90-92 °C. NMR ^{1}H (DMSO-d_6, δ, ppm, *J*/Hz): 1.70 (4H, m, $2CH_2$ pyrrolidin); 2.27 (3H, s, CH_3); 2.45 (3H, s, CH_3); 3.23 (4H, m, $2CH_2N$ pyrrolidin); 7.82 (1H, s, 3-CH thiophen); 8.06 (1H, s, 5-CH thiophen). Mass-spectrum (EI, 70 eV), *m/z* ($I_{rel.}$ %): 312 $[M]^+$ (14), 179 (14), 178 (12), 137 (10), 110 (11), 109 (11), 95 (11), 70 (15), 69 (10), 43 (100). Found, %: C 49.88; H 5.17; N 9.01; S 20.57. $C_{13}H_{16}N_2O_3S_2$. Calculated, %: C 49.98; H 5.16; N 8.97; S 20.52.

3,5-Dimethyl-4-[5-morpholine-1-sulfonyl)-thiophen-3-yl]-isoxazole **59**. Yield is 81%, light-brown crystals, *T* melt. 108-110 °C. NMR ^{1}H (DMSO-d_6, δ, ppm, *J*/Hz): 2.29 (3H, s, CH_3); 2.46 (3H, s, CH_3); 2.96 (4H, m, $2CH_2N$ morpholine); 3.68 (4H, m, $2CH_2O$ morpholine); 7.78 (1H, s, 3-CH thiophen); 8.13 (1H, s, 5-CH thiophen). Mass-spectrum (EI, 70 eV), *m/z* ($I_{rel.}$ %): 328 $[M]^+$ (5), 178 (7), 137 (8), 109 (7), 95 (10), 80 (40), 69 (6), 56 (100). Found, %: C 47.45; H 4.92; N 8.57; S 19.56. $C_{13}H_{16}N_2O_4S_2$. Calculated, %: C 47.55; H 4.91; N 8.53; S 19.52.

4-3,5-Dimethylisoxazol-4-yl)-thiophene-2-sulphonic acid 4-methoxyphenylamide **60**. Yield is 73%, red crystals, *T* melt. 118-120 °C. NMR ^{1}H (DMSO-d_6, δ, ppm, *J*/Hz): 2.16 (3H, s, CH_3); 2.34 (3H, s, OCH_3); 6.87 (2H, d, *J*=9.2, 2CH-Ar); 7.06 (2H, d, *J*=9.2, 2CH-Ar); 7.77 (1H,

s, 3-CH thiophen); 8.13 (1H, s, 5-CH thiophen); 10.12 (1H, s, NH). Mass-spectrum (EI, 70 eV), *m/z* ($I_{rel.}$ %): 364 $[M]^+$ (29), 137 (71), 123 (16), 122 (100), 109 (7), 95 (39), 80 (12), 69 (6), 65 (12), 53 (12). Found, %: C 52.68; H 4.43; N 7.73; S 17.63. $C_{16}H_{16}N_2O_4S_2$. Calculated, %: C 52.73; H 4.43; N 7.69; S 17.59.

3,5-Dimethyl-4-[3-methyl-5-(pyrrolidin-1-sulfonyl)-thiophen-2-yl]-isoxazole **61**. Yield is 73%, light-brown crystals, *T* melt. 116-118 °C. NMR ^{1}H (DMSO-d_6, δ, ppm, *J*/Hz): 1.72 (4H, m, $2CH_2$ pyrrolidin); 2.08 (3H, s, CH_3); 2.13 (3H, s, CH_3); 2.23 (4H, m, $2CH_2N$ pyrrolidin); 2.33 (3H, s, CH_3); 7.63 (1H, s, 3-CH thiophen). Mass-spectrum (EI, 70 eV), *m/z* ($I_{rel.}$ %): 326 $[M]^+$ (21), 193 (29), 166 (7), 151 (43), 134 (11), 124 (17), 109 (16), 70 (100), 69 (11). Found, %: C 51.48; H 5.56; N 8.62; S 19.68. $C_{14}H_{18}N_2O_3S_2$. Calculated, %: C 51.51; H 5.56; N 8.58; S 19.64.

3,5-Dimethyl-4-[3-methyl-5-(morpholine-1-sulfonyl)-thiophen-2-yl]-isoxazole **62**. Yield is 81%, orange crystals, *T* melt. 128-130 °C. NMR ^{1}H (DMSO-d_6, δ, ppm, *J*/Hz): 2.10 (3H, s, CH_3); 2.15 (3H, s, CH_3); 2.34 (3H, s, CH_3); 2.97 (4H, m, $2CH_2N$ morpholine); 3.69 (4H, m, $2CH_2O$ morpholine); 7.61 (1H, s, 3-CH thiophen). Mass-spectrum (EI, 70 eV), *m/z* ($I_{rel.}$ %): 342 $[M]^+$ (30), 256 (5), 193 (16), 151 (30), 123 (6), 109 (15), 86 (39), 57 (12), 56 (100). Found, %: C 48.96; H 5.30; N 8.22; S 18.76. $C_{14}H_{18}N_2O_4S_2$. Calculated, %: C 49.11; H 5.30; N 8.18; S 18.72.

5-(3,5-Dmethylisoxazol-4-yl-)-4-methylthiophene-2-sulphonic acid 4-methoxyphenyl-amide **63**. Yield is 73%, red-brown crystals, *T* melt. 121-123 °C. NMR ^{1}H (DMSO-d_6, δ, ppm, *J*/Hz): 2.00 (3H, s, CH_3); 2.06 (3H, s, CH_3); 2.26 (3H, s, CH_3); 2.61 (3H, s, OCH_3); 3.7 (1H, d, *J*=5.6, 3-CH thiophene); 6.52 (1H, d, *J*=8.9, CH-Ar); 6.65 (1H, d, *J*=9.2, CH-Ar); 6.86 (1H, d, *J*=9.2, CH-Ar); 7.04 (1H, d, *J*=8.9, CH-Ar); 7.39 (1H, s, NH). Mass-spectrum (EI, 70 eV), *m/z* ($I_{rel.}$ %): 378 $[M]^+$ (16), 151 (20), 122 (100), 109 (15), 95 (39), 79 (13), 69 (9), 65 (17). Found, %: C 53.89; H 4.80; N 7.44; S 16.98. $C_{17}H_{18}N_2O_4S_2$. Calculated, %: C 53.95; H 4.79; N 7.40; S 16.94.

4-(5-Acetylaminoisoxazol-3-yl)-benzenesulfonyl chloride **65(a)**. Yield is 78%, light-brown crystals, *T* melt. 107-109 °C. NMR ^{1}H ($CDCl_3$, δ, ppm, *J*/Hz): 6.30 (2H, s, NH_2); 7.49 (3H, t, H-3,4,5 Ar); 7.83 (2H, dd, J_1=4.0, J_2=3.7, H-2,6 Ar). Mass-spectrum (EI, 70 eV), *m/z* ($I_{rel.}$ %): 258 $[M]^+$ (15), 243 (24), 208 (16), 172 (10), 115 (14), 102 (26), 89 (100). Found, %: C 43.86; H 3.02; N 9.36; S 10.68. $C_{11}H_9ClN_2O_4S$. Calculated, %: C 43.93; H 3.02; N 9.32; S 10.66.

5-Amino-3-(4-bromophenyl)isoxazole-4-sulfonyl chloride **65(b)**. Yield is 80%, brown crystals, *T* melt. 73-75 °C. NMR ^{1}H ($CDCl_3$, δ, ppm, *J*/Hz): 6.30 (2H, s, NH_2); 7.67 (4H, m, H-4 Ar). Mass-spectrum (EI, 70 eV), *m/z* ($I_{rel.}$ %): 337 $[M]^+$ (79), 336 (61), 303 (71), 295 (27), 260 (35), 211 (19), 196 (25), 183 (15), 155 (26), 114 (19), 75 (59), 44 (100). Found, %: C 34.70; H 2.13; N 7.42; S 8.46. $C_{11}H_8ClN_2O_4S$. Calculated, %: C 34.80; H 2.12; N 7.38; S 8.45.

N-{3-[4-(pyrrolidin-1-sulfonyl)-phenyl]-isoxazol-5-yl}-acetamide **66**. Yield is 84%, yellow crystals, *T* melt. 95-97 °C. NMR ^{1}H (DMSO-d_6, δ, ppm, *J*/Hz): 1.55 (4H, m, $2CH_2$ pyrrolidine); 2.82 (4H, m, $2CH_2N$ pyrrolidine); 7.49 (3H, m, H-5,4,3 Ar); 7.74 (2H, s, NH_2); 7.85 (2H, m, H-2,6 Ar). Mass-spectrum (EI, 70 eV), *m/z* ($I_{rel.}$ %): 335 $[M]^+$ (12), 323 (25), 190 (14), 189 (24), 132 (9), 70 (100), 69 (23), 42 (39). Found, %: C 53.56; H 5.11; N 12.59; S 9.58. $C_{15}H_{17}N_3O_4S$. Calculated, %: C 53.72; H 5.11; N 12.53; S 9.56.

N-{3-[4-(morpholine-4-sulfonyl)-phenyl]-isoxazol-5-yl}-acetamide **67**. Yield is 75%, white crystals, *T* melt. 138-140 °C. NMR ^{1}H (DMSO-d_6, δ, ppm, *J*/Hz): 2.72 (4H, m, $2CH_2N$ morpholine); 3.37 (4H, m, $2CH_2O$ morpholine); 7.49 (3H, m, H-5,4,3 Ar); 9.87 (2H, s, NH_2);

7.85 (2H, m, H-2,6 Ar). Mass-spectrum (EI, 70 eV), *m/z* ($I_{rel.}$ %): 351 $[M]^+$ (8), 315 (41), 286 (9), 182 (13), 88 (10), 87 (12), 86 (100), 70 (9), 57 (11). Found, %: C 51.12; H 4.88; N 12.02; S 9.14. $C_{15}H_{17}N_3O_5S$. Calculated, %: C 51.27; H 4.88; N 11.96; S 9.12.

N-{3-[4-(4-methoxyphenylsulphamoyl)-phenyl]-isoxazol-5-yl}-acetamide **68**. Yield is 73%, light-brown crystals, *T* melt. 110 -112 °C. NMR ^1H (DMSO-d_6, δ, ppm, *J*/Hz): 3.62 (3H, s, OCH_3); 6.55 (2H, d, *J*=8.9, H-2 Ar_2); 6.75 (2H, d, *J*=8.9, H-2 Ar_2); 7.50 (3H, m, H-5,4,3 Ar); 7.64 (2H, s, NH_2); 7.79 (2H, m, H-2,6 Ar); 9.87 (1H, s, NH). Mass-spectrum (EI, 70 eV), *m/z* ($I_{rel.}$ %): 372 $[M]^+$ (5), 308 (6), 122 (30), 95 (7), 79 (16), 64 (23), 50 (20), 43 (100). Found, %: C 55.64; H 4.43; N 10.90; S 8.29. $C_{18}H_{17}N_3O_5S$. Calculated, %: C 55.81; H 4.42; N 10.85; S 8.28.

3-(4-Bromophenyl)-4-(pyrrolidine-1-sulfonyl)-isoxazole-5-ylamine **69**. Yield is 81%, brown crystals, *T* melt. 62-63 °C. NMR ^1H (DMSO-d_6, δ, ppm, *J*/Hz): 1.60 (4H, m, $2CH_2$ pyrrolidine); 2.67 (4H, m, $2CH_2N$ pyrrolidine); 7.60 (2H, d, *J*=8.5, H-2 Ar); 7.71 (2H, d, *J*=8.5, H-2 Ar); 7.80 (2H, s, NH_2). Mass-spectrum (EI, 70 eV), *m/z* ($I_{rel.}$ %): 372 $[M]^+$ (3), 240 (14), 238 (14), 202 (12), 185 (10), 79 (18), 75 (13), 52 (20), 45 (17), 43 (100). Found, %: C 41.16; H 3.33; N 11.35; S 8.63. $C_{13}H_{14}BrN_3O_3S$. Calculated, %: C 41.95; H 3.79; N 11.29; S 8.61.

3-(4-Bromophenyl)-4-(morpholine-4-sulfonyl)-isoxazole-5-ylamine **70**. Yield is 83%, brown crystals, *T* melt. 129-131 °C. NMR ^1H (DMSO-d_6, δ, ppm, *J*/Hz): 2.76 (4H, m, $2CH_2N$ morpholine); 3.43 (4H, m, $2CH_2O$ morpholine); 7.60 (2H, d, *J*=8.5, H-2 Ar); 7.71 (2H, d, *J*=8.5, H-2 Ar); 7.90 (2H, s, NH_2). Mass-spectrum (EI, 70 eV), *m/z* ($I_{rel.}$ %): 388 $[M]^+$ (6), 387 (37), 240 (56), 238 (56), 211 (16), 209 (18), 155 (15), 86 (88), 75 (18), 56 (100). Found, %: C 40.10; H 3.64; N 10.88; S 8.27. $C_{13}H_{14}BrN_3O_4S$. Calculated, %: C 40.22; H 3.63; N 10.82; S 8.26.

5-Amino-3-(4-bromophenyl)-isoxazole-4-sulphonic acid 4-methoxyphenylamide **71**. Yield is 75%, dark brown crystals, *T* melt. 77-79 °C. NMR ^1H (DMSO-d_6, δ, ppm, *J*/Hz): 3.69 (3H, s, $J=OSN_3$); 6.70 (1H, s, H-4 isoxazole); 6.76 (2H, d, *J*=9.2, H-2 Ar_2); 6.82 (2H, d, *J*=9.2, H-2 Ar_2); 7.40 (2H, d, *J*=8.5, H-2 Ar_1); 7.62 (2H, d, *J*=8.5, H-2 Ar_1); 7.74 (2H, s, NH_2); 9.58 (1H, s, NH). Mass-spectrum (EI, 70 eV), *m/z* ($I_{rel.}$ %): 424 $[M]^+$ (10), 423 (10), 240 (10), 185 (22), 183 (26), 157 (10), 155 (11), 139 (19), 122 (100), 95 (19), 80 (21), 64 (39). Found, %: C 45.16; H 3.33; N 9.95; S 7.57. $C_{16}H_{14}BrN_3O_4S$. Calculated, %: C 45.30; H 3.79; N 9.90; S 7.56.

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