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Stereoselective Synthesis of Isoxazole and Pyrazole Annulated Sultams *Via* Intramolecular 1,3-Dipolar Cycloaddition Reactions

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***Abstract*:** Functionalized isothiazoloisoxazole-4,4-dioxide, pyrazoloisothiazole-1,1-dioxide, [1,2]thiazinoisoxazole-4,4-dioxide and benzo[1,2]thiazinoisoxazole-4,4-dioxide systems have been obtained by intramolecular 1,3-dipolar cycloaddition, starting from substituted α- and β-sulfonamides.

Our continuous interest in the synthesis of biologically active nitrogen heterocycles,[1] obtained by intramolecular rearrangements of suitably substituted isoxazolidines or isoxazolines, led us recently to investigate the synthesis of the complex carbon frameworks occurring in natural and biologically interesting compounds, through the intramolecular version of the 1,3-dipolar cycloaddition process leading to *N,O*-heterocyclic systems.[2] In this context, the effect of different functionalities present in the tether connecting dipole and dipolarophile moieties has been examined. The intramolecular cycloaddition of several differently substituted 5-hexenyl-nitrones with N, S and O at the 3 position has been investigated[3] as a tool for the diastereoselective or enantioselective synthesis of stereochemically defined *cis*-fused heterocycles. Similarly, 6-heptenyl-nitrones (X = N, O) affords *cis*-fused isoxazolidines as exclusive products when the nitrogen or oxygen atoms are part of an amide or ester group, respectively (Figure 1).[4]

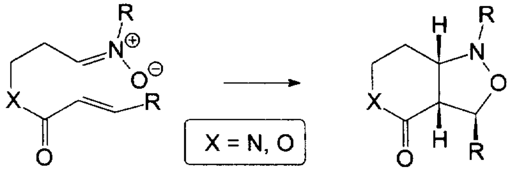


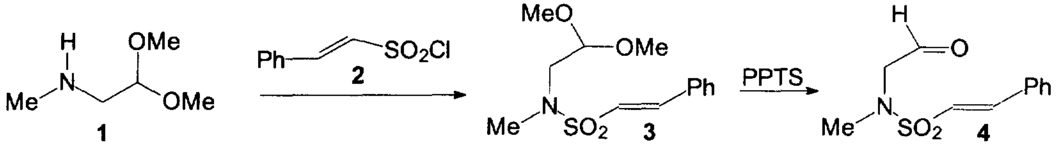
Figure 1

The process has been exploited for the synthesis of pyrrolidine, pyrrolizidine and piperidine systems.[5,6]

In this paper we report the intramolecular 1,3-dipolar cycloaddition of suitably substituted α- and β-sulfonamides which leads to isoxazole and pyrazole annulated γ- and δ-sultams. The obtained isothiazole-1,1-dioxide derivatives belong to a class of heterocycles which exhibit interesting pharmacological properties such as the capacity to act as inhibitors of proteolitic enzymes.[7] Furthermore, the envisaged synthetic pathway assumes particular interest if one considers that sultams have, recently, acquired great importance as chiral auxiliaries in asymmetric synthesis.[8]

RESULTS AND DISCUSSION

The synthetic approach leading to γ-sultams is based on *N*-methylaminoacetaldehyde dimethyl acetal **1** which has been reacted with *trans* β-styrenesulfonyl chloride **2** to give the corresponding sulfonamides **3**. Treatment of derivative **3** with pyridinium *p*-toluensulfonate (PPTS) gave aldehyde **4** (Scheme 1), which has been exploited as starting material for the intramolecular cycloaddition processes investigated (Scheme 2).



Scheme 1

Thus, reaction of **4** with *N*-methylhydroxylamine yielded the not isolated nitrone **5** which readily underwent intramolecular cycloaddition to bicyclo-compound **6** in good yields. Similar treatment of **4** with hydroxylamine *via* oxime **7**, followed by NaOCl oxidation, generated in situ the nitrile oxide intermediate **8** which spontaneously added to the *N*-allyl group to afford **9**.

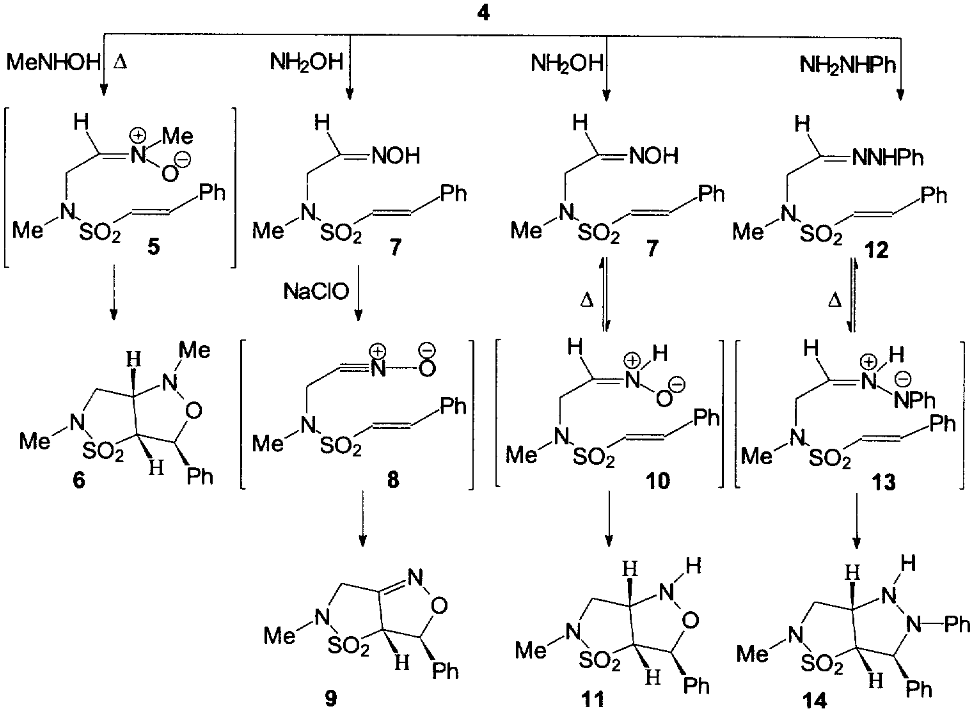
Compounds **11** and **14** result from the thermally induced oxime-nitrone (**7**,**10**) and hydrazone-azomethine imine (**12**,**13**) isomerizations,[9] respectively, followed by the subsequent intramolecular cycloaddition. Noteworthy, the hydrazone-azomethine imine 1,2-prototropic shift takes place under milder conditions than the corresponding oxime-nitrone one.

The structure of the obtained compounds **6**,**9**,**11**,**14** was confirmed by analytical and spectrometric data. High resolution mass spectra showed the correct molecular ions for all the examined compounds. The ^{1}H NMR showed in compounds **6**,**9** and **11** the diagnostic resonance of H_3 proton in the range δ 5.32-6.02, while H_{3a} appear at δ 3.86-4.85. H_{6a} proton, for compounds **6** and **11**, resonate at δ 3.59 and 4.40 respectively. In compound **14**, the resonance of H_6 is at δ 5.37, while H_{3a} and H_{6a} resonate at δ 4.42 and 3.87 respectively. Moreover, in all the obtained compounds, the methylene protons of the thiazole ring showed different chemical shifts with respect to the amidoaldehyde precursor **4**.

The investigated 1,3-dipolar cycloadditions showed high regioselectivity; according to similar intramolecular processes,[10] no bridged adducts have been detected in the crude reaction mixture.

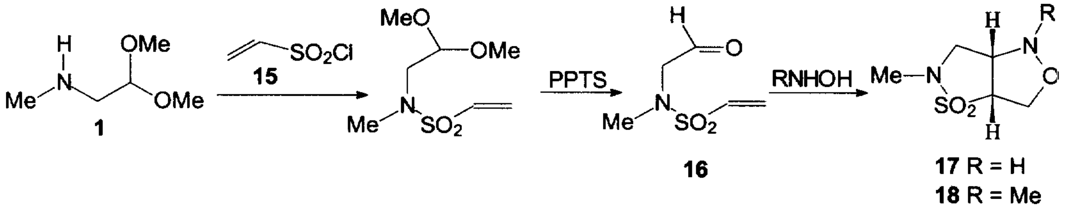
The reaction have been also found to be stereospecific; cycloadducts **6**,**9**,**11**,**14** were obtained stereochemically pure, with no evidence in the NMR spectra or tlc of the crude products of any diastereoisomers. The stereochemical informations present in the dipolarophile moiety are completely retained in the cycloadducts and the relative stereochemistry at C_3 and C_{3a} in the formed isoxazolidine ring is predetermined by the alkene geometry.

Furthermore, the ring junction between the two fused ring in compounds **6**,**11**,**14** is always *cis* as confirmed by coupling constants and NOE measurements. For instance, in compounds **6** the coupling constant for the *cis* ring junction protons ($J_{3a,6a}$) is 9.0 Hz, indicative of a nearly eclipsed dihedral angle between H_{3a} and H_{6a}. When H_{3a} was irradiated, the signals corresponding to H_{6a} proton was enhanced; likewise irradiation of H_{6a} gives rise to a positive NOE effect for H_{3a} and methylene proton at C_6 so indicating a *cis* relationship between these protons.



Scheme 2

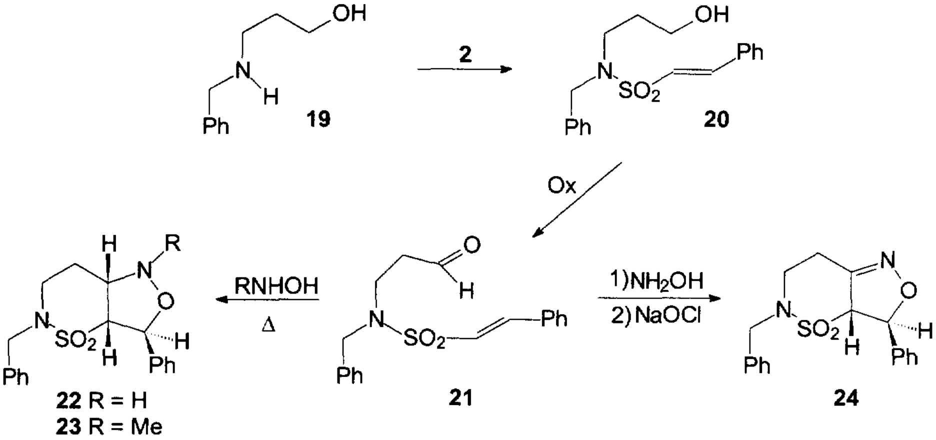
In the attempt to fully establish the scope and limitations of the investigated approach towards bicyclic sultams, we have also examined the synthesis of the unsubstituted isoxazolidino-isothiazolo fused system, starting from the sulfonamidoaldehyde **16**, obtained by reaction of **1** with vinylsulfonyl chloride **15** and subsequent hydrolysis (Scheme 3). Thus the reaction of **16** performed with hydroxylamine gave rise to **17** while with *N*-methyl hydroxylamine lead to **18**.



Scheme 3

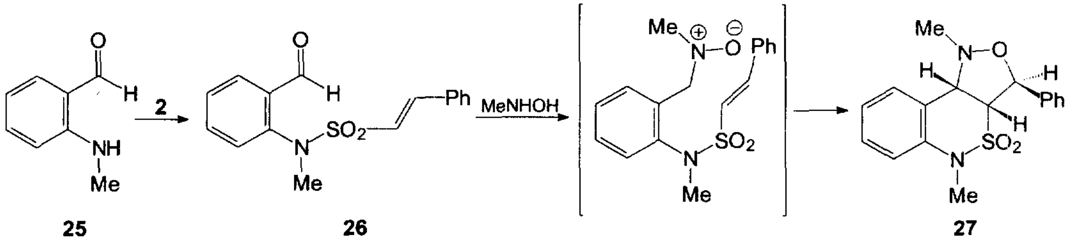
However, the intramolecular nitrile oxide cycloaddition (INOC) of **16** resulted in not identifiable tarry mixtures. The failure of the INOC process, also shown in 1-hydroxyiminoprop-2-yl but-3-enoate[11] can be rationalised on the basis of geometric and steric requirements.[12]

We have also tested the possibility of forming a six-membered cyclic sultams starting from the *trans* β-sulfonamidoaldehyde **21**, obtained from the 3-(*N*-benzylamino)propanol **19** through conversion into the sulfonamido alcohol **20** followed by oxidation with pyridinium chlorochromate (PCC). The synthesis of compounds **22-24** took place in high yields (see experimental) (Scheme 4). ^1H NMR analysis of the crude reaction mixture does not show the presence of diastereomers or bridged adducts, and the relative stereochemistry at C_{3a} and C_{7a} was ascertained as *cis* on the basis of NOE measurements, according to their mutual positive NOE effect.



Scheme 4

The described synthetic approach can represent an interesting route for functionalized polycyclic systems; in this context, the 2-*N*-methylaminobenzaldehyde **25** was reacted with *trans* β-styrenesulfonyl chloride **2** to give the corresponding aldehyde **26**. The subsequent reaction with *N*-methyl hydroxylamine afforded tricyclic compound **27** in 51% yield (Scheme 5).



Scheme 5

Compound **27** was characterised by analytical and spectroscopic data. The magnitude of the vicinal coupling constant, exhibited by H_{3a} and H_{9b} (9.7 Hz) is consistent with a dihedral angle of *ca.* 14° on the basis of the Karplus equation,[13] and hence a *cis* junction between the benzothiazino and isoxazolidine ring. In fact, a *trans* junction for structurally related tricyclic compounds is 12 Hz[14] in accord with a dihedral angle of *ca.* 180°. This hypothesis is supported by NOE experiments: the NOE enhancement observed between H_{9b} and H_{3a} (*ca.* 6%) provide conclusive evidence of their spatial proximity, arising from a *cis* relationship.

In conclusion, besides the possibility of producing unusual annulated heterocycles, promising substrates for further manipulations (*i.e.* the formation of stereochemically defined functionalized sultams through the isoxazolidine ring cleavage), an important aspect of the above reported synthetic schemes which deserves some considerations is the effect of the $-NSO_2-$ group in the intramolecular cycloaddition process; to the best of our knowledge, no reports on systems where the olefinic double bond is linked to the dipole moiety by a tether containing a sulfonamide group are present in literature.

With reference to previously reported INOC processes,[15] the presence of the SO_2 moiety results in a very smooth reaction which proceeds in high yields. The observed behaviour can be explained on the basis of the steric buttressing of the SO_2 group which reduce the available conformational space to the reactants, so optimising their spatial orientation and favouring their mutual approach.

EXPERIMENTAL

Mp were measured on a Kofler apparatus and are uncorrected. Elemental analyses were performed with a Perkin-Elmer elemental analyzer. Infrared spectra were recorded on a Perkin-Elmer 377 instrument. ^1H Nmr spectra were measured on a Bruker WP 200 SY instrument or otherwise specified in $CDCl_3$ as solvent. Chemical shifts are in ppm (δ) from TMS as internal standard. NOE difference spectra were obtained by subtracting alternatively right-off-resonance free induction decays (FIDS) from right-on-resonance-induced FIDS. Merck silica gel 60H was used for preparative short-column chromatography.

Preparation of *trans N*-methyl-*N*-(2-oxoethyl)-2-phenylethene-1-sulfonamide 4.

To a stirred solution containing 1.6 g (13.5 mmol) of *methylaminoacetaldehyde dimethyl acetal* **1**, and 2.0 ml of triethylamine in 15 ml of dry carbon tetrachloride was added dropwise a solution containing 3.0 g (15 mmol) of *trans β-styrenesulfonyl chloride* **2** in 25 ml of dry carbon tetrachloride at 0 °C. The solution was stirred at 25 °C for 6 h and then filtered. The obtained solid was washed with 30 ml of carbon tetrachloride, the combined filtrate washed with 10 ml of water, and dried over sodium sulfate. The solvent was removed and the crude residue was purified by silica-gel chromatography producing 4.2 g (98%) of *trans N-(2,2-dimethoxyethyl)-N-methyl-2-phenylethene-1-sulfonamide* **3** as a colourless oil. Ir (neat) 3060, 3040, 3000, 2940, 2840, 1650, 1620, 1450, 1340, 1100, 1080, 970, 860, 820, 750, 690 cm^{-1}. ^1H Nmr: δ ($CDCl_3$) 2.96 (s, 3H), 3.25 (d, 2H, J = 5.3 Hz), 3.46 (s, 6H), 4.53 (t, 1H, J = 5.3 Hz), 6.72 (d, 1H, J = 15.5 Hz), 7.39-7.51 (m, 6H). ^{13}C Nmr: δ ($CDCl_3$) 36.26, 51.55, 54.62, 103.96, 122.43, 128.10, 129.00, 130.70, 132.63, 141.98. Exact mass calculated for $C_{13}H_{19}NO_4S$: 285.1035. Found: 285.1039.

A stirred solution containing 2.0 g of the above substituted sulfonamido dimethylacetal **3** was converted, by treatment with 1.22 g of PPTS and 7 ml of water in 115 ml of acetone at reflux temperature, into *trans N-methyl-N-(2-oxoethyl)-2-phenylethene-1-sulfonamide* **4** (yellow oil; 2.87 g; 82% yield). Ir (neat) 3060, 3040, 2980, 2920, 2840, 2720, 1730, 1620, 1580, 1500, 1350, 1330, 1130, 970, 880, 860, 820, 750, 690, 660 cm^{-1}. ^1H Nmr: δ ($CDCl_3$) 2.97 (s, 3H), 4.08 (s, 2H), 6.75 (d, 1H, J = 15.3 Hz), 7.41-7.52 (m, 6H), 9.60 (s, 1H). ^{13}C Nmr: δ ($CDCl_3$) 35.89, 49.27, 122.36, 128.28, 129.04, 130.92, 132.40, 142.89, 197.27. Exact mass calculated for

$C_{11}H_{13}NO_3S$: 239.0616. Found: 239.0611.

Preparation of (3SR,3aRS,6aSR)-1,5-dimethyl-3-phenylperhydro-4λ^6-isothiazolo[4,5-c]isoxazole-4,4-dioxide 6.

A mixture containing 1.48 g (6.2 mmol) of compound **4**, 1.0 ml (7.17 mmol) of triethylamine, 599 mg (7.17 mol) of *N*-methylhydroxylamine hydrochloride in 100 ml of absolute ethanol was refluxed for 36 h. At end of this time the solvent was removed and the residue extracted with dichloromethane, washed with water and dried over sodium sulfate. Evaporation of the solvent and silica-gel chromatography (cyclohexane/ethyl acetate 7:3) gave 1.25 g (75%) of *(3SR,3aRS,6aSR)-1,5-dimethyl-3-phenylperhydro-4λ^6-isothiazolo[4,5-c]isoxazole-4,4-dioxide* **6** as a white solid, mp 98-100 °C; ir (KBr): 3070, 3040, 2970, 2860, 1500, 1465, 1450, 1330, 1280, 1230, 1140, 1100, 1000, 960, 800, 770, 750, 700, 680, 640 cm^{-1}. ^{1}H Nmr: δ ($CDCl_3$) 2.77 (s, 3H), 2.86 (s, 3H), 3.11 (d, 1H, $H_{6'}$, J = 10.7 Hz), 3.21 (dd, 1H, $H_{6''}$, J = 4.0 and 10.7 Hz), 3.59 (dd, 1H, H_{6a}, J = 4.0 and 9.0 Hz), 3.86 (dd, 1H, H_{3a}, J = 7.3 and 9.0 Hz), 5.32 (d, 1H, H_3, J = 7.3 Hz), 7.34-7.48 (m, 5H). ^{13}C Nmr: δ ($CDCl_3$) 29.94, 43.28, 50.26, 68.26, 68.89, 81.34, 126.44, 128.76, 128.74, 136.05. Exact mass calculated for $C_{12}H_{16}N_2O_3S$: 268.0882. Found: 268.0880.

Preparation of (3SR,3aRS)-5-methyl-3-phenyl-3,3a,4,5,6-tetrahydro-4λ^6-[1,2]thiazino[4,5-c]isoxazole-4,4-dioxide 9.

A mixture containing 788 mg (3.3 mmol) of compound **4**, 30 ml of 95% aqueous ethanol, 330 mg (4.8 mmol) of hydroxylamine hydrochloride and 390 mg (4.8 mmol) of CH_3CO_2Na was stirred at 0 °C for 6 h. At end of this time the solvent was evaporated at reduced pressure and the residue was extracted with dichloromethane, washed with 10% aqueous $NaHCO_3$ and dried over sodium sulfate. Evaporation of the solvent and silica-gel flash-chromatography (CCl_4/ethyl acetate 7:3) gave 838 mg (100%) as a *syn-anti* mixture (6:4) of *trans N-(2-hydroxyiminoethyl)-N-methyl-2-phenylethene-1-sulfonamide* **7**. White solid. Ir (KBr): 3400-3300 (bs), 3080, 3020, 2940, 2900, 1670, 1620, 1580, 1450, 1330, 1300, 1200, 1140, 1000, 960, 940, 860, 830, 740, 660, 610, 570, 540 cm^{-1}. ^{1}H Nmr: δ ($CDCl_3$) major isomer: 2.80 (s, 3H), 3.88 (d, 1H, J = 5.9 Hz), 6.68 (d, 1H, J = 15.4 Hz), 7.38-7.51 (m, 7H), 7.88 (bs, 1H); minor isomer: 2.86 (s, 3H), 4.08 (d, 1H, J = 4.4 Hz), 6.70 (d, 1H, J = 15.4 Hz), 6.87 (t, 1H, J = 4.4 Hz), 7.42-7.81 (m, 6H), 7.87 (bs, 1H). ^{13}C Nmr: δ ($CDCl_3$) major isomer: 35.00, 48.65, 121.45, 128.10, 128.80, 130.90, 132.30, 142.81, 146.65; minor isomer: 37.05, 45.50, 120.75, 128.10, 128.95, 131.00, 132.30, 143.46, 157.51. Exact mass calculated for $C_{11}H_{14}N_2O_3S$: 254.0725. Found: 254.0731.

To a solution containing 570 mg (2.24 mmol) of sulfonamide oxime **7** in 250 ml of dichloromethane was added dropwise 6 ml of sodium hypochlorite (7% solution) at 0 °C under vigorous stirring. After 3 h the reaction mixture was evaporated and the residue subjected to silica-gel flash-chromatography (CCl_4/ethyl ether 4:6) gave 446 mg (79%) of *(3SR,3aRS)-5-methyl-3-phenyl-3,3a,4,5,6-tetrahydro-4λ^6-[1,2]thiazino[4,5-c]isoxazole-4,4-dioxide* **9**. White solid, mp 106-108 °C. Ir (KBr): 3060, 3040, 2960, 1610, 1480, 1460, 1450, 1330, 1320, 1230, 1200, 1150, 980, 900, 850, 830, 760, 750, 700, 680, 600, 540, 500 cm^{-1}. ^{1}H Nmr: δ ($CDCl_3$): 2.91 (s, 3H), 4.06 (d, 1H, $H_{6'}$, J = 13.6 Hz), 4.19 (d, 1H, $H_{6''}$, J = 13.6 Hz), 4.85 (d, 1H, H_{3a}, J = 11.3 Hz), 6.02 (d, 1H, H_3, J = 11.3 Hz), 7.42-7.56 (m, 5H). ^{13}C Nmr: δ ($CDCl_3$) 30.88, 48.04, 72.93, 84.90, 126.54, 128.47, 129.12, 129.38, 134.83, 144.52, 153.66. Exact mass calculated for $C_{11}H_{12}N_2O_3S$: 252.0569. Found: 252.0572.

Preparation of (3SR,3aRS,6aSR)-5-methyl-3-phenylperhydro-4λ^6-isothiazolo[4,5-c]isoxazole-4,4-dioxide 11.

A solution containing 569 mg (2.24 mmol) of sulfonamide oxime **7** in 100 ml of absolute ethanol was refluxed for 60 h. The reaction mixture subjected to silica-gel flash-chromatography (MeOH/CHCl$_3$ 3:97) gave 427 mg (75%) of *(3SR,3aRS,6aSR)-5-methyl-3-phenylperhydro-4λ^6-isothiazolo[4,5-c]isoxazole-4,4-dioxide* **11**, as a white solid, mp 101-105 °C. Ir (KBr): 3200, 3070, 3040, 3000, 2980, 2900, 1600, 1490, 1460, 1450, 1330, 1320, 1290, 1210, 1180, 1140, 1120, 1100, 1050, 1000, 960, 890, 860, 840, 760, 700, 680, 640, 600, 530, 510, 480 cm^{-1}. ^{1}H Nmr: δ (CDCl$_3$) 2.72 (s, 3H), 3.14 (d, 1H, H$_{6'}$, J = 11.1 Hz), 3.30 (dd, 1H, H$_{6''}$, J = 5.5 and 8.7 Hz), 3.96 (dd, 1H, H$_{3a}$, J = 7.0 and 8.7 Hz), 4.40 (dd, 1H, H$_{6a}$, J = 5.5 and 8.7 Hz), 5.35 (bs, 1H), 5.67 (d, 1H, H$_3$, J = 7.0 Hz), 7.35-7.41 (m, 5H). ^{13}C Nmr: δ (CDCl$_3$) 29.41, 49.50, 61.10, 69.65, 87.05, 126.18, 128.17, 128.92, 135.86. Exact mass calculated for $C_{11}H_{14}N_2O_3S$: 254.0725. Found: 254.0726.

Preparation of (3aRS,6RS,6aSR)-2-methyl-5,6-diphenylperhydro-1λ^6-pyrazolo[3,4-d]isothiazole-1,1-dioxide 14.

A mixture containing 1.48 g (6.2 mmol) of compound 4, 30 ml of 95% aqueous ethanol, 670 mg (6.2 mmol) of phenylhydrazine and 10 mg of *p*-toluensulfonic acid was stirred at 0 °C for 6 h, under nitrogen. At end of this time the solvent was evaporated at reduced pressure and the residue was extracted with dichloromethane, washed with 10% aqueous NaHCO$_3$ and dried over sodium sulfate. Evaporation of the solvent and silica-gel flash-chromatography (CCl$_4$/ethyl acetate 7:3) gave 1.86 g (91%) as a *syn-anti* mixture of *trans N-methyl-N-(2-phenylhydrazino)ethyl-2-phenylethene-1-sulfonamide* **12**. Yellow solid, mp 127-134 °C. Ir (KBr): 3320 (sharp), 3140, 3070, 2980, 2930, 1600, 1540, 1500, 1450, 1340, 1330, 1260, 1140, 980, 960, 920, 860, 820, 750, 690, 610, 540 cm^{-1}. ^{1}H Nmr: δ (CDCl$_3$) 2.87 (s, 3H), 3.99 (d, 2H, J = 4.5 Hz), 6.73 (d, 1H, J = 15.5 Hz), 6.80-7,57 (m, 13H). ^{13}C Nmr: δ (CDCl$_3$) 34.5, 51.16, 112.56, 112.96, 120.22, 122.37, 128.25, 129.04, 129.24, 130.84, 132.54, 136.67, 142.63, 144.38. Exact mass calculated for $C_{17}H_{19}N_3O_2S$: 329.1198. Found: 329.1200.

A solution of **12** 600 mg (1.82 mmol) in 100 ml of ethanol was heated under nitrogen at reflux temperature for 72 h. The solution was cooled off, evaporated and the residue subjected to flash-chromatography gave 462 mg (77 %) of a light yellow solid, mp 47-49 °C, which was identified as *(3aRS,6RS,6aSR)-2-methyl-5,6-diphenylperhydro-1λ^6-pyrazolo[3,4-d]isothiazole-1,1-dioxide* **14**. Ir (KBr): 3300 (sharp), 3060, 2980, 2930, 2870, 1600, 1510, 1490, 1450, 1340, 1300, 1260, 1200, 1130, 1080, 1030, 970, 870, 850, 750, 690, 630, 600 cm^{-1}. ^{1}H Nmr: δ (CDCl$_3$) 2.51 (s, 3H), 3.05 (dd, 1H, H$_{3''}$, J = 6.9 and 10.4 Hz), 3.87 (dd, 1H, H$_{6a}$, J = 4.0 and 6.7 Hz), 4.42 (ddd, 1H, H$_{3a}$, J = 3.3, 6.7 and 6.9 Hz), 4.97 (bs, 1H), 5.37 (d, 1H, H$_6$, J = 4.0 Hz), 6.78-7.47 (m, 10H). ^{13}C Nmr: δ (CDCl$_3$) 29.35, 53.60, 69.30, 71.00, 113.65, 119.51, 125.81, 127.90, 128.78, 129.20, 139.75, 149.15. Exact mass calculated for $C_{17}H_{19}N_3O_2S$: 329.1198. Found: 329.1198.

Preparation of *N*-methyl-*N*-(2-oxoethyl)-1-ethylenesulfonamide 16.

To a stirred solution containing 2.98 g (25 mmol) of *N-methylaminoacetaldehyde dimethyl acetal* **1**, and 3.22 g (30 mmol) of lutidine in 30 ml of dry carbon tetrachloride was added dropwise a solution containing 3.8 g (30 mmol) of *vinylsulfonyl chloride* **15**[16] in 30 ml of dry carbon tetrachloride at 0 °C. The solution was stirred at 25 °C for 6 h and then filtered. The obtained solid was washed with 30 ml of carbon tetrachloride, the combined filtrate washed with 10 ml of water, and dried over sodium sulfate. The solvent was removed and the crude residue was purified by silica-gel chromatography producing 2.87 g (55%) of *N-(2,2-dimethoxyethyl)-N-methylethene-1-sulfonamide* as a colourless oil. Ir (neat) 2950, 2840, 1460, 1450, 1390, 1340, 1150, 1130, 1080, 960, 780,710, 650 cm^{-1}. ^{1}H Nmr: δ (CDCl$_3$) 2.89 (s, 3H), 3.19 (d, 2H, J = 5.3 Hz), 3.43 (s, 6H), 4.49 (t, 1H, J = 5.3 Hz), 5.98 (d, 1H, J = 9.7 Hz), 6.22 (d, 1H, J = 16.5 Hz), 6.47 (dd, 1H, J = 9.7 and 16.5 Hz). ^{13}C Nmr: δ (CDCl$_3$) 36.25, 51.46, 54.71, 104.05, 127.27, 133.23. Exact mass calculated for $C_7H_{15}NO_4S$: 209.0722.

Found: 209.0718.

A stirred solution containing 2.0 g of the above *N-(2,2-dimethoxyethyl)-N-methylethene-1-sulfonamide* was converted, by treatment with 600 mg of PPTS and 7 ml of water in 115 ml of acetone at reflux temperature, into *N-methyl-N-(2-oxoethyl)-1-ethylenesulfonamide* ***16***. Colourless oil, 825 mg (53%). Ir (neat): 2960, 2930, 2860, 2740, 1740, 1460, 1380, 1340, 1150, 970, 880, 760, 740 cm^{-1}. ^{1}H Nmr: δ ($CDCl_3$) 2.90 (s, 3H), 4.06 (s, 2H), 6.05 (d, 1H, J = 16.5 Hz), 6.54 (dd, 1H, J = 9.7 and 16.5 Hz), 9.62 (m, 1H). ^{13}C Nmr: δ ($CDCl_3$) 35.70, 59.11, 128.10, 133.40, 197.00. Exact mass calculated for $C_5H_9NO_3S$: 163.0303. Found: 163.0309.

Preparation of (3aRS,6aSR)-5-methylperhydro-4λ^6-isothiazolo[4,5-c]isoxazole-4,4-dioxide 17.

To a solution of 161 mg of hydroxylamine hydrochloride (2.46 mmol) in 5 ml of H_2O were added at room temperature, under stirring, 200 mg of NaOH (2.46 mmol). The organic layer was separated, and the aqueous phase was extracted with 6 × 5 ml of $CHCl_3$. The combined extracts were dried with anhydrous sodium sulfate, added to a 10 ml solution of 207 mg (1.27 mmol) of *N-methyl-N-(2-oxoethyl)-1-ethylenesulfonamide* ***16*** containing 10 mg of anhydrous sodium sulfate and heated at 60 °C for 16 h. At the end of this time the solution was filtered, and the filtrate was evaporated to give after flash-chromatography (MeOH/$CHCl_3$ 1:9) 90 mg (40%) of a colourless oil which was identified as *(3aRS,6aSR)-5-methylperhydro-4λ^6-isothia-zolo[4,5-c]isoxazole-4,4-dioxide 17*. ^{1}H Nmr: δ ($CDCl_3$) 2.71 (s, 3H), 3.12-3.18 (m, 3H, NH, $H_{6'}$ and $H_{6''}$), 3.94 (dd, 1H, H_{6a}, J = 5.7, and 7.5 Hz), 4.11 (dd, 1H, H_{3a}, J = 4.5 and 7.5 Hz), 4.29 (d, 1H, $H_{4'}$, J = 8.1 Hz), 4.37 (dd, 1H, $H_{4''}$, J = 4.5 and 8.1 Hz). ^{13}C Nmr: δ ($CDCl_3$) 29.75, 49.10, 57.44, 65.97, 66.12. Exact mass calculated for $C_5H_{10}N_2O_3S$: 178.0412. Found: 178.0409.

Preparation of (3aRS,6aSR)-1,5-dimethylperhydro-4λ^6-isothiazolo[4,5-c]isoxazole-4,4-dioxide 18.

To a solution of 400 mg of *N*-methylhydroxylamine hydrochloride (2.46 mmol) in 5 ml of H_2O were added at room temperature, under stirring, 200 mg of NaOH (2.46 mmol). The organic layer was separated, and the aqueous phase was extracted with 6 × 5 ml of $CHCl_3$. The combined extracts were dried with anhydrous sodium sulfate, added to a 10 ml solution of 207 mg (1.27 mmol) of *N-methyl-N-(2-oxoethyl)-1-ethylenesulfonamide* ***16*** containing 10 mg of anhydrous sodium sulfate and heated at 60 °C for 16 h. At the end of this time the solution was filtered, and the filtrate was evaporated to give after flash-chromatography (ethyl aceta-te/cyclohexane 7:3) 158 mg (65%) of a colourless oil which was identified as *(3aRS,6aSR)-1,5-dimethylperhydro-4λ^6-isothia-zolo[4,5-c]isoxazole-4,4-dioxide* ***18***. ^{1}H Nmr: δ ($CDCl_3$) 2.69 (s, 3H), 2.71 (s, 3H), 3.14 (dd, 1H, $H_{6'}$, J = 2.8 and 10.4 Hz), 3.31 (dd, 1H, $H_{6''}$, J = 6.4 and 10.4 Hz), 3.80 (ddd, 1H, H_{6a}, J = 2.8, 6.4 and 7.9 Hz), 4.08 (ddd, 1H, H_{3a}, J = 5.2, 6.2 and 7.9 Hz), 4.28 (dd, 1H, $H_{3'}$, J = 5.2 and 9.4 Hz), 4.35 (dd, 1H, $H_{3''}$, J = 6.2 and 9.4 Hz). ^{13}C Nmr: δ ($CDCl_3$) 29.81, 43.10, 52.61, 62.04, 66.42, 66.67. Exact mass calculated for $C_6H_{12}N_2O_3S$: 192.0569. Found: 192.0564.

Preparation of (3SR,3aRS,7aSR)-5-benzyl-3-phenylperhydro-4λ^6-[1,2]thiazino[5,6-c]isoxazole-4,4-dioxide 22.

To a stirred solution containing 1.9 g (11.5 mmol) of *3-(benzylamino)-1-propanol* ***19***, and 1.75 ml of triethylamine in 15 ml of dry dichloromethane was added dropwise a solution containing 2.5 g (12.6 mmol) of *trans β-styrenesulfonyl chloride* **2** in 25 ml of dry dichloromethane at room temperature. The solution was stirred for 7 h and then filtered. The obtained solid was washed with 30 ml of carbon tetrachloride, the combined filtrate washed with 10 ml of water, and dried over sodium sulfate. The solvent was removed and the crude residue was purified by silica-gel chromatography producing 2.84 g (70%) of *trans (3-hydroxypropyl)-N-*

benzyl-2-phenylethene-1-sulfonamide ***20***. Light yellow oil. Ir (neat): 3600-3350, 3080, 3040, 2980, 2940, 1640, 1615, 1580, 1500, 1450, 1250, 1140, 940, 860, 820 cm^{-1}. ^{1}H Nmr: δ ($CDCl_3$) 1.55 (tt, 2H, J = 5.6 and 6.5 Hz), 2.15 (bs, 1H, OH), 3.27 (t, 2H, J = 6.5 Hz), 3.57 (t, 2H, J = 5.6 Hz), 4.35 (s, 3H, N-CH_2), 6.57 (d, 1H, J = 15.6 Hz), 7.27-7.36 (m, 10H), 7.41 (d, 1H, J = 15.6 Hz). ^{13}C Nmr: δ ($CDCl_3$) 30.74, 44.39, 51.79, 58.85, 123.78, 127.90, 128.08, 128.48, 128.56, 128.92, 130.65, 132.47, 136.18, 141.45. Exact mass calculated for $C_{18}H_{21}NO_3S$: 331.1242. Found: 331.1248.

To a stirred suspension containing 155 mg (7.2 mmol) of pyridinium chlorochromate in 10 ml of anhydrous dichloromethane was added 160 mg (4.8 mmol) of compound **21** and the mixture was allowed to stir for 1.5 h. Anhydrous ether was added to the solution, the mixture was extracted, the organic phase decanted, and the residue was extracted with ether. The combined extracts were filtered through a pad of florosil. The solvent was removed under reduced pressure and the residue was chromatographed on a silica gel column to give 130 mg (83%) of a white sticky solid which was identified as *(3-oxopropyl)-N-benzyl-2-phenylethene-1-sulfonamide 21*. Ir (nujol): 3370, 3330, 2920, 2850, 2730, 1730, 1615, 1500, 1450, 1240, 1150, 1020, 860, 750, 700 cm^{-1}. ^{1}H Nmr: δ ($CDCl_3$) 2.67 (t, 2H, J = 7.0 Hz), 3.48 (t, 2H, J = 7.0 Hz), 4.38 (s, 3H, N-CH_2), 6.64 (d, 1H, J = 15.4 Hz), 7.36-7.46 (m, 10H), 7.47 (d, 1H, J = 15.4 Hz), 9.62 (s, 1H, CHO). ^{13}C Nmr: δ ($CDCl_3$) 41.51, 43.78, 52.55, 123.47, 128.17, 128.46, 128.78, 129.03, 130.85, 132.46, 136.02, 142.01, 200.14. Exact mass calculated for $C_{18}H_{19}NO_3S$: 329.1086. Found: 329.1092.

A mixture containing 500 mg (1.5 mmol) of compound **21**, 30 ml of butanol, 150 mg (2.2 mmol) of hydroxylamine hydrochloride and 0.3 ml (2.2 mmol) of Et_3N was refluxed for 72 h. At the end of this time the solvent was evaporated at reduced pressure and the residue was subjected to silica-gel flash-chromatography (cyclohexane/ethyl Acetate 7:3) gave 314 mg of a white solid, mp 132-136 °C (60%), which was identified as *(3SR,3aRS,7aSR)-5-benzyl-3-phenylperhydro-4λ^6-[1,2]thiazino[5,6-c]isoxazole-4,4-dioxide* ***22***. Ir (KBr): 3240, 3080, 3040, 2980, 2940, 1605, 1500, 1455, 1290, 1140, 1030, 1010, 890, 750, 690 cm^{-1}. ^{1}H Nmr: δ (DMSO-d_6) 1.90 (m, 2H, H_7), 3.28 (m, 2H, H_6), 3.45, (bs, 1H, NH), 4.10 (m, 2H, H_{3a} and H_{7a}), 4.45 (d, 1H, $H_{5'a}$, J = 15 Hz), 4.56 (d, 1H, $H_{5'b}$, J = 15 Hz), 5.17 (d, 1H, H_3, J = 6.3 Hz), 7.32-7.53 (m, 10H); ^{13}C Nmr: δ ($CDCl_3$) 18.65, 43.80, 50.70, 60.87, 68.65, 80.24, 125.88, 128.20, 128.39, 128.44, 128.83, 128.86, 135.38, 135.41. Exact mass calculated for $C_{18}H_{20}N_2O_3S$: 344.1195. Found: 344.1198.

Preparation of (3SR,3aRS,7aSR)-5-benzyl-1-methyl-3-phenylperhydro-4λ^6-[1,2]thiazino[5,6-c]isoxazole-4,4-dioxide 23.

A mixture containing 480 mg (1.45 mmol) of compound **21**, 0.4 ml (2.9 mmol) of triethylamine, 240 mg (2.9 mmol) of methyl hydroxylamine hydrochloride in 50 ml of absolute ethanol was refluxed for 36 h. At end of this time the solvent was removed and the residue extracted with dichloromethane, washed with water and dried over sodium sulfate. Evaporation of the solvent and silica-gel chromatography (cyclohexane/ethyl acetate 7:3) gave 425 mg (82%) of *(3SR,3aRS,7aSR)-5-benzyl-1-methyl-3-phenylperhydro-4λ^6-[1,2]thiazino[5,6-c]isoxazole-4,4-dioxide* ***23***. White solid mp 85-87 °C; ir (KBr): 3050, 3030, 2980, 2960, 1600, 1500, 1330, 1310, 1200, 1140, 1030, 920, 900, 750, 700, 610 cm^{-1}. ^{1}H Nmr: δ ($CDCl_3$): 1.77 (m, 1H, $H_{7'}$, J = 14.9 Hz), 2.33 (m, 1H, $H_{7''}$), 2.74, (s, 3H), 3.13 (m, 1H, H_7), 3.38 (m, 2H, $H_{6'}$ + $H_{6''}$), 3.92 (dd, 1H, H_{3a}, J = 6.7 and 7.8 Hz), 4.50 (d, 1H, $H_{5'a}$, J = 14.8 Hz), 4.64 (d, 1H, $H_{5'b}$, J = 14.8 Hz), 5.30 (d, 1H, H_3, J = 6.7 Hz), 7.29-7.51 (m, 10H). ^{13}C Nmr: δ ($CDCl_3$) 21.87, 44.20, 45.20, 52.98, 67.53, 71.59, 80.72, 124.35, 125.70, 126.70, 127.20, 128.03, 133.14, 135.14, 138.50. Exact mass calculated for $C_{19}H_{22}N_2O_3S$: 358.1351. Found: 358.1346.

Preparation of (3SR,3aRS,)-5-benzyl--3-phenyl-3,3a,4,5,6,7-hexahydro-4λ^6-[1,2]thiazino[5,6-c]isoxazole-4,4-dioxide 24.

A mixture containing 500 mg (1.52 mmol) of compound **21**, 30 ml of 95% aqueous ethanol, 150 mg (2.2 mmol) of hydroxylamine hydrochloride and 180 mg (2.2 mmol) of CH_3CO_2Na was stirred at 0 °C for 6 h. At the end of this time the solvent was evaporated at reduced pressure and the residue was extracted with dichloromethane, washed with 10% aqueous $NaHCO_3$ and dried over sodium sulfate. Evaporation of the solvent and silica-gel flash-chromatography (cyclohexane/ethyl acetate 7:3) gave 490 mg (98%) as a *syn-anti* mixture (6:4) of *trans N-(3-hydroxyiminopropyl)-N-benzyl-2-phenylethene-1-sulfonamide*. White solid. Ir (KBr): 3450-3350 3080, 3040, 2980, 2920, 1620, 1500, 1450, 1330, 1130, 980, 890, 820, 750 680 cm^{-1}. ^{1}H Nmr: δ ($CDCl_3$) (major isomer) 2.59 (dt, 2H, J = 6.4 and 7.3 Hz), 3.37 (t, 2H, J = 7.3 Hz), 4.42 (s, 2H, N-CH_2), 6.64 (d, 1H, J = 15.5 Hz), 6.72 (t, 1H, J = 6.4 Hz), 7.05 (bs, 1H, OH), 7.30-7.45 (m, 10H), 7.48 (d, 1H, J = 15.5 Hz). ^{13}C Nmr: δ ($CDCl_3$) (major isomer) 29.14, 43.58, 51.58, 124.27, 128.20, 128.46, 128.55, 128.79, 129.06, 130.81, 132.61, 135.88, 141.74, 149.10. Exact mass calculated for $C_{18}H_{20}N2O_3S$: 344.1195. Found: 344.1195.

To a solution containing 450 mg (1.3 mmol) of above 3-hydroxyiminopropyl substituted sulfonamide in 150 ml of dichloromethane was added dropwise 6 ml of sodium hypochloride (7% solution) at 0 °C under vigorous stirring. After 3 h the reaction mixture was evaporated and the residue subjected to silica-gel flash-chromatography (CCl_4/ethyl ether 4:6) gave 353 mg (79%) of a white sticky solid, identified as *(3SR,3aRS,)-5-benzyl-3-phenyl-3,3a,4,5,6,7-hexahydro-4λ^6-[1,2]thiazino[5,6-c]isoxazole-4,4-dioxide* **24**. Ir (KBr): 3080, 3060, 2960, 1650, 1600, 1330, 1150, 850, 760 cm^{-1}. ^{1}H Nmr: δ ($CDCl_3$): 2.45 (ddd, 1H, H_{7a}, J = 5.7, 5.8 and 14.2 Hz), 2.77 (ddd, 1H, H_{7b}, J = 1.4, 3.3 and 14.2 Hz), 3.30 (ddd, 1H, H_{6a}, J = 1.4, 5.8 and 14.0 Hz), 3.54 (ddd, 1H, H_{6b}, J = 3.3, 5.7 and 14.0 Hz), 4.31 (d, 1H, $H_{5'a}$, J = 14.4 Hz), 4.43 (d, 1H, H_{3a}, J = 8.7 Hz), 4.56 (d, 1H, $H_{5'b}$, J= 14.4 Hz), 6.02 (d, 1H, J = 8.7 Hz), 7.35-7.45 (m, 10H). ^{13}C Nmr: δ ($CDCl_3$) 22.34, 44.77, 51.12, 75.59, 81.46, 125.69, 128.36, 128.49, 128.84, 129.01, 135.07, 137.70, 150.58. Exact mass calculated for $C_{18}H_{18}N_2O_3S$: 342.1038. Found: 342.1042.

Preparation of (3SR,3aRS,9bSR)-1,5-dimethyl-3-phenyl-1,3,3a,4,5,9b-hexahydro-4λ^6-benzo[3,4] [1,2]-thiazino[5,6-c]isoxazole-4,4-dioxide 27.

To a stirred solution containing 530 mg (3.87 mmol) of *2-N-methylaminobenzaldehyde 25*, and 0.7 ml of triethylamine in 5 ml of dry dichloromethane was added dropwise a solution containing 940 mg (4.64 mmol) of *trans β-styrenesulfonyl chloride* **2** in 10 ml of dry dichloromethane at room temperature. The solution was stirred for 7 h and then filtered. The obtained solid was washed with 20 ml of carbon tetrachloride, the combined filtrate washed with 10 ml of water, and dried over sodium sulfate. The solvent was removed and the crude residue was purified by silica-gel chromatography producing 466 mg (40%) of *trans N-(2-formylphenyl)-N-methyl-2-phenylethene-1-sulfonamide* **26**. Yellow oil. Ir (neat) 3060, 2960, 2920, 2840, 1740, 1680, 1600, 1490, 1450, 1330, 1140, 860, 770, 740 cm^{-1}. ^{1}H Nmr: δ ($CDCl_3$) 3.55 (s, 3H), 6.73 (d, 1H, J = 15.4 Hz), 7.29-8.02 (m, 11H). ^{13}C Nmr: δ ($CDCl_3$) 38.84, 126.69, 127.10, 128.38, 128.53, 128.82, 129.20, 130.19, 130.80, 131.28, 134.42, 134.83, 144.46, 189.85. Exact mass calculated for $C_{16}H_{15}NO_3S$: 301.0773. Found: 301.0769.

A mixture containing 150 mg (0.5 mmol) of compound **26**, 0.1 ml (0.74 mmol) of triethylamine, 62 mg (0.74 mmol) of *N*-methylhydroxylamine hydrochloride in 40 ml of absolute ethanol was refluxed for 36 h. At the end of this time the solvent was removed and the residue extracted with dichloromethane, washed with water and dried over sodium sulfate. Evaporation of the solvent and silica-gel chromatography (cyclohexane/ethyl acetate 6:4) gave 90 mg, (51), of a clear oil identified as *(3SR,3aRS,9bSR)-1,5-dimethyl-3-*

phenyl-1,3,3a,4,5,9b-hexahydro-4λ⁶-benzo[3,4][1,2]-thiazino[5,6-c]isoxazole-4,4-dioxide 27. Ir (neat): 3060, 3040, 2960, 2920, 1600, 1500, 1450, 1340, 1140, 1060, 1040, 900, 7800, 750, 700, cm^{-1}. ^{1}H Nmr: δ ($CDCl_3$) 2.72 (s, 3H), 3.43 (s, 3H), 3.96 (d, 1H, H_{9b}, J = 9.7 Hz), 4.28 (dd, 1H, H_{3a}, J = 7.0 and 9.7 Hz) 5.58 (d, 1H, H_3, J = 7.0 Hz), 7.16-7.55 (m, 9H). ^{13}C Nmr: δ ($CDCl_3$) 33.18, 42.16, 73.06, 73.60, 81.09, 120.52, 124.37, 125.47, 127.00, 128.80, 130.58, 130.82, 130.85, 136.62, 142.66. Exact mass calculated for $C_{17}H_{18}N_2O_3S$: 330.1038. Found: 330.1042.

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