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Synthesis and Characterization of Some new Organotellurium Compounds Derived from Sulphamethoxazole.

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ABSTRACT

A new series of mercurated and tellurated sulphamethoxazole were synthesized by a convenient direct method. Reaction of 4-amino-*N*-(5-methylisoxazol-3-yl) benzene sulfonamide (sulphamethoxazole)with mercuric acetate in presence of sodium chloride gave (2-amino-(*N*-(5-methylisoxazol-3-yl)sulfamoyl)mercuric(II) chloride**1** in a good yield**.** On the other hand, a new organotellurium compound **2** was obtained when mercurated sulphamethoxazole and tellurium tetrabromide brought together in a 1:1 mole ratio. Reduction of **2** by hydrazine hydrate gave a new diorganylditelluride **3** in a good yield. All compounds were characterized by elemental analysis, IR, ^{1}H,^{13}C-NMR, and HSQC-NMR. Molecular modeling study was performed by docking of compound **1** which showed one hydrogen bonding and three hydrophobic interactions.

Keywords: Sulphamethoxazole, HMBC,NMR ,HSQC-NMR, Organotellurium, Amino group, Molecular modeling study.

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INTRODUCTION

There are few examples in the literature dealing with aromatic tellurides bearing amino groups. Such compounds were prepared either by direct [1-3] or indirect methods [4,5]. In recent years, there has been a considerable interest in the preparation and characterization of organic tellurium compounds carrying an amino residue [6-8] in an *ortho* position to a tellurium atom. Engman and Persson[2]were found that *N*-and *ortho*-substituted anilines afforded 2:1 complexes of organic tellurium compounds, which on reduction afforded mixtures of 4-amino-substituted diphenyl tellurides and diphenyl ditellurides. Such complexes were readily converted to 4-amino-substituted diphenyltellurides by Cu – or Pd – induced detelluration of the ditelluride component [3]. Al-Rubaie *etal.*[1] prepared a series of novel organotellurium compounds containing an amino group in an *ortho* position to a tellurium atom by a convenient new route involving reaction of the 2-amino aryl mercury chloride with tellurium tetrabromide in glacial acetic acid. Such compounds have been used as precursors in preparation of new polymers containing tellurium [9].

To the best of our knowledge, there is no method to prepare organotellurium compounds derived from sulpha drugs. The present work describes the synthesis of some new organomercury and organotellurium compounds derived from sulphamethoxazole drug, aiming to study the biological activity of these new compounds.

EXPERIMENTAL

Physical measurements

The IR spectra were recorded in the range 4000-200 cm^{-1} on a Pye-Unicam SP3-300 spectrometer using KBr discs.^{1}H,^{13}C, HSQC NMR spectra were measured on a Brucker at 600 MHz with TMS as internal reference at Universitaet Konstanz, Germany. Elemental analysis were determined on MT-3 elemental analyzer within ±5% of the theoretical values. Melting points were measured by a Philip Harris melting point apparatus and are uncorrected.

SYNTHESIS

Mercurated of sulphamethoxazole

***(2-Amino-(N-(5-methylisoxazol-3-yl)sulfamoyl)mercuric(II) chloride*(1)**. This compound was prepared according to a literature method [10]. A mixture of 4-amino-*N*-(5-methylisoxazol-3-yl)benzene sulfonamide (5.06 g, 20 mmol) and mercuric acetate (7.6 g, 24 mmol) in ethanol (80 ml) was heated under reflux for 14 h. Sodium chloride (1.4 g, 24 mmol) in boiling methanol was added to the above cooled reaction mixture with vigorous stirring for 1h. The precipitate was washed with water, then ethanol and dried over $CaCl_2$ to give white crystals of **1.** Yield: 82%, M.P. = 222-225^{o}C. Anal. Calcd. For $C_{10}H_{10}N_3O_3SHgCl$;C,24.60; H, 2.06; N, 8.61% ; Found: C, 24.47; H, 2.02, N, 8.69%. FT-IR (KBr,ν, cm^{-1}): 3350 (NH),2980, 3018 (CH),1600-1550 (C=C, C=N), 1375 (SO, SO_2).^{1}H NMR (600 MHz, DMSO-d_6, δ, ppm): 7.64 (m, 1H, $H_{arom.}$-5), 7.60 (m, 1H, $H_{arom.}$-3), 6.60 (d, 1H, J = 8.0 Hz, $H_{arom.}$-2), 6.58 (s, 1H, $H_{isoxazol}$-4'), 6.01(s, 1H,NH-SO_2), 5.96 (s, 2H, NH_2), 3.62 (s, 3H, CH_3).^{13}C NMR (600 MHz, DMSO-d_6, δ, ppm): 165.2 ($C_{isoxazol}$-3'), 153.2($C_{arom.}$-4 +$C_{arom.}$-1), 129.9, 125.5 ($C_{arom.}$-3 + $C_{arom.}$-4 + $C_{arom.}$-5), 113.0 ($C_{arom.}$-2 + $C_{arom.}$-6), 96.0 ($C_{isoxazol}$-4'), 12.8 (CH_3).

Tellurated of sulphamethoxazole

***(2-Amino-(N-(5-methylisooxazol-3-yl)sulfamoyl)tellurium tribromide*(2)**. A mixture of tellurium tetra bromide (4.00 mmol, 1.78 g) and aryl mercuric chloride **1** (1.95 g, 4.00 mmol) in dry chloroform (50 ml) was heated under reflux with stirring for 4 h under argon atmosphere. The resulting solution was cooled and the precipitate filtered off. Recrystallization from a mixture of ethanol and hexane (7:3) gave a pale yellow solid of **2**. Yield: 76%, M.P.= 272-274 ^{o}C. Anal. Calcd. For $C_{10}H_{10}N_3O_3STeBr_3$: C, 19.39; H, 1.63; N, 6.78%. Found: C, 19.23; H, 1.48; N, 6.83%. FT-IR (KBr,ν,cm^{-1}): 3345 (NH),2983,3016 (CH),1605-1560 (C=C, C=N), 1380 (SO, SO_2). ^{1}H NMR (600 MHz, DMSO-d_6, δ, ppm): 3.43 (s, 3H, CH_3), 6.63-7.67 (m, 3H, Ar-H), 6.21(s, 1H, -NH-SO_2), 5.75 (s, 2H, NH_2).^{13}C NMR (600 MHz, DMSO-d_6, δ, ppm): 164.3 ($C_{isoxazol}$-3'), 155.4($C_{arom.}$-4), 155.1 ($C_{arom.}$-1), 129.0, 127.5 ($C_{arom.}$-3 + $C_{arom.}$-4 + $C_{arom.}$-5), 117.0 ($C_{arom.}$-6), 113.2 ($C_{arom.}$-2), 96.8 ($C_{isoxazol}$-4'), 12.5 (CH_3).

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Diarylditullride (Ar_2Te_2)

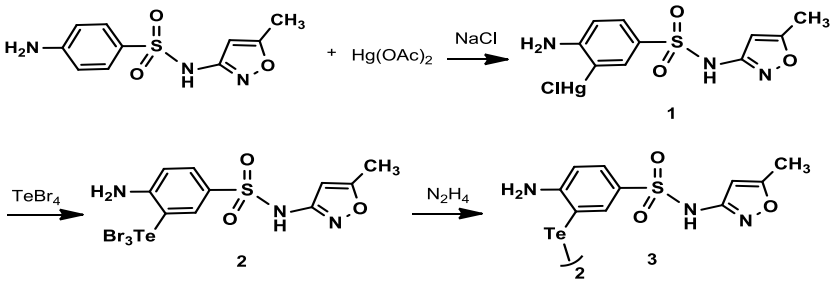
***Bis-(2-amino-(N-(5-methylisooxazol-3-yl)sulfamoyl)ditelluride*(3)**.

Aryltelluriumtribromide **2** (1.86 g, 3.00 mmol) was refluxed in ethanol (25 ml). An ethanolic solution of hydrazine hydrate was added drop wise to the refluxing solution until the evaluation of nitrogen was ceased. The resulting solution was cooled to room temperature and the precipitate was filtered off. Recrystallization of the product by hot ethanol gave a brown solid of **3**. Yield: 74%, M.P. = 197-199 ^{o}C. Anal. Calcd. For $C_{20}H_{20}N_6O_6S_6Te_2$: C, 31.62; H, 2.65; N, 11.06%. Found: C, 31.50; H, 2.58; N, 11.23%. FT-IR (KBr, ν, cm^{-1}): 3340 (NH),2990,3022 (CH),1600-1565 (C=C, C=N), 1385 (SO, SO_2).^{1}H NMR (600 MHz, DMSO-d_6, δ, ppm): 2.39 (s, 3H, CH_3), 6.61-7.47 (m, 3H, $H_{arom.}$), 6.08 (s, 1H,NH-SO_2), 5.48(s, 2H, NH_2).^{13}C NMR (600 MHz, DMSO-d_6, δ, ppm): 164.0 ($C_{isoxazol}$-3'), 155.2($C_{arom.}$-4), 155.0 ($C_{arom.}$-1), 127.5, 126.0 ($C_{arom.}$-3 + $C_{arom.}$-4 + $C_{arom.}$-5), 117.3 ($C_{arom.}$-6), 113.3 ($C_{arom.}$-2), 96.9 ($C_{isoxazol}$-4'), 12.6 (CH_3).

RESULTS AND DISCUSSION

The Present work describes the synthesis of new mercurated and tellurated of 4-amino-*N*-(5-methylisoxazol-3-yl)benzene sulfonamide (sulphamethoxazole drug) by a convenient method, thus, the reaction of sulphamethoxazole with mercuric acetate in presence of sodium chloride gave a new organomercurated of sulphamethoxazole **1** in a good yield. The preparation of **2** based on *trans*-telluration of (2-Amino-(N-(5-methylisoxazol-3-yl)sulfamoyl)mercuric(II) chloride **1** with tellurium tetra bromidein a 1:1mole ratio using dry chloroform as a solvent to affordthe required tellurium containing material ($ArTeBr_3$, **2**). Reduction of **2** by ethanolic solution of hydrazine hydrate gave diorganoditelluride **3** in 74% yield (Scheme 1).

The structures of the new synthesized derivatives were assigned from their IR, ^{1}H and ^{13}C NMR spectra, which showed a common spectral pattern. Thus, IR spectra of compounds**1**-**3** displayed common features in certain regions and characteristic bands in the fingerprint and other regions. The spectra showed broad strong bands in the rang 3400-3500 cm^{-1} due to ν(N-H). In addition, the IR spectra confirmed the presence of the sulphoxide groups (SO_2) stretching with a sharp region around 1375-1380 cm^{-1}.The ^{1}H NMR spectra of **1-3** were recorded in DMSO-d_6 as a solvent and exhibited the expected protons with proper integrated and intensity ratio. The aromatic protons appeared as multiplet signals at the regions δ =7.67-6.58 ppm, whereas the resonances at δ = 3.62, 3.43 and 2.39 ppm, were attributed to the methyl protons, respectively [11].The singlet signals at δ = 5.96, 5.75 and 5.48 ppm were assigned to the amino protons, respectively [12], while the singlet signals at δ = 6.01, 6.21 and 6.08 ppm were belonged to the amino protons of NH-SO_2 groups, respectively. In the ^{13}C NMR spectra of **1-3**, δ= 165.2, 164.3 and 164.0 ppm were assigned to C-3' of the isoxazole ring, whereas, the resonances at δ=153.2, 155.4 and 155.2 ppm were attributed to C-4' of the same ring, respectively. The resonances at δ= 153.1, 155.1 and 155.0 ppm were assigned to C-1 of the aromatic ring, while the signals at the regions δ= 129.2- 125.5 ppm were belonged to the aromatic carbon atoms 3-5. C-2 and C-6 of the aromatic ring of analogue **1** was oriented together at δ= 113.0 ppm, whereas C-2 of the analogues **2, 3** were appeared at δ= 113.2 and 113.3 ppm. In addition, C-6 appeared at δ=117.3 and 117.3 ppm, respectively. Carbon atom 4' of the isoxazole scaffold of the analogues **1-3** were appeared at δ= 96.0, 96.8 and 96.9 ppm, respectively, meanwhile the methyl carbon atom at C-3' of the isoxazole ring were resonated at δ= 12.8, 12.5 and 12.6 ppm, respectively.The variation in the chemical shifts of carbon atoms bearing tellurium in compounds **2** and **3**might be explained in term of the polarity of Te-C bond [13].



Scheme 1. Synthesis of some organomercury and organotellurium compounds (**1-3**) derived from sulphamethazole

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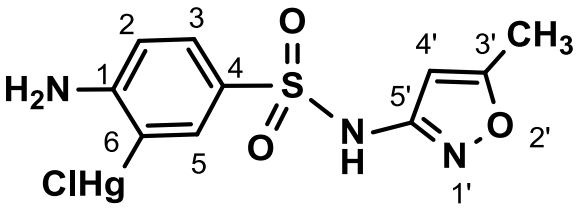
The ^{1}H, ^{13}C HSQC NMR spectrum [14] of compound **1** showed a cross peak at δ_H/δ_C = 2.25/12.8 ppm, belonged to methyl group (CH_3). Thus, the correlation of protons and carbon atoms such as δ_H/δ_C = 6.01/96.3, 6.6/113 and 7.7/130 ppm can be assigned to the protons and carbon atoms of the aromatic rings [15] (Table 1, Fig. 1).

Table 1.^{1}H, ^{13}C HSQC NMR spectrum of (2-amino-(*N*-(5-methylisooxazol-3-yl) sulfamoyl) mercuric (II)chloride (1)

Compound Structure	δ_H(ppm)	δ_C(ppm)	Position
	2.25	12.8	CH_3
	6.01	96.0	C,H(4')
	6.60	113	C,H(2)
	7.64	125.5	C,H(5)
	7.60	129.0	C,H(3)

Compound **1** was selected for further NMR experiment. The gradient HMBC [15] NMR spectrum of**1**showed five $^{2}J_{C,H}$ couplings: two of themwere characterized between H-4' of the isoxazole moiety at δ= 6.01 ppm and C-3' at δ= 165.2 ppm as well as C-5' at δ=153.2 ppm of the same ring. The other three $^{2}J_{C,H}$ couplings were observed between C-4 at δ= 129.7 ppm and H-3 and H-5 at δ= 7.64 and7.60 ppm, respectively, in addition to the coupling between H-2 at δ= 6.60 ppm and C-1 at δ= 156.1 ppm of the aromatic ring. Additionally, a $^{3}J_{C,H}$ coupling between H-2 at δ= 6.60 ppm and C-6 (C-Hg) at δ = 117.3 ppm of the aromatic ring was observed (Fig. 1).

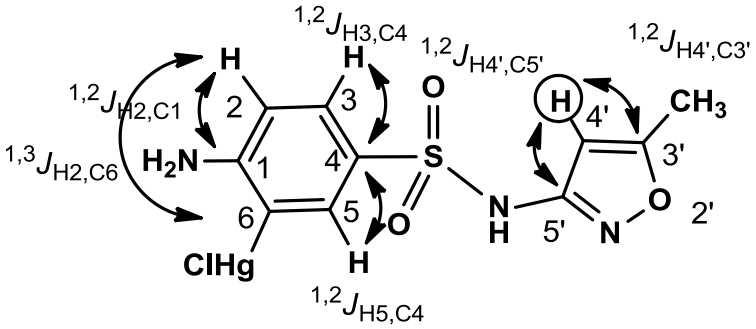


Figure 1. $J_{C,H}$ correlations in the HMBC NMR spectrum of compound **1**.

MOLECULAR DOCKING STUDY

The molecular docking was performed using SYBYL-X 1.1 and the docking results were shown by PyMOL [16]. Our molecular docking analysis of the new analogues based on the modeling study which was performed to understand the binding mode of these analogues with the HIV-RT binding pocket (NNIBP) (PDB code: 3DLG, [17]).

Compound **1** has been selected for the docking modeling study, since its binding energy score -8.2, indicating a selectivity of murcuratedsulfamethoxazole**1** compound in binding mode alterations, and showing its binding to the enzyme pocket (Figure 2). As shown in figure 2, the aromatic ring of **1** fitted into an aromatic rich sub pocket surrounded by the aromatic side chains of Tyr181 and Tyr186. The isoxazole backbone was located in the middle of the binding pocket, anchoring the SO_2NH group in a favourable position for hydrogen bonding with the NH_2 group of Lys103 and other three hydrophobic interactions of the phenyl ring with Tyr181, Tyr186 and Trp227of the RT enzyme. Theoretically, the combination of hydrophobic interaction and δ-stacking appears to govern the binding of **1** with HIV RT. For this reason, we have selected the analogue **1** for further biological study.

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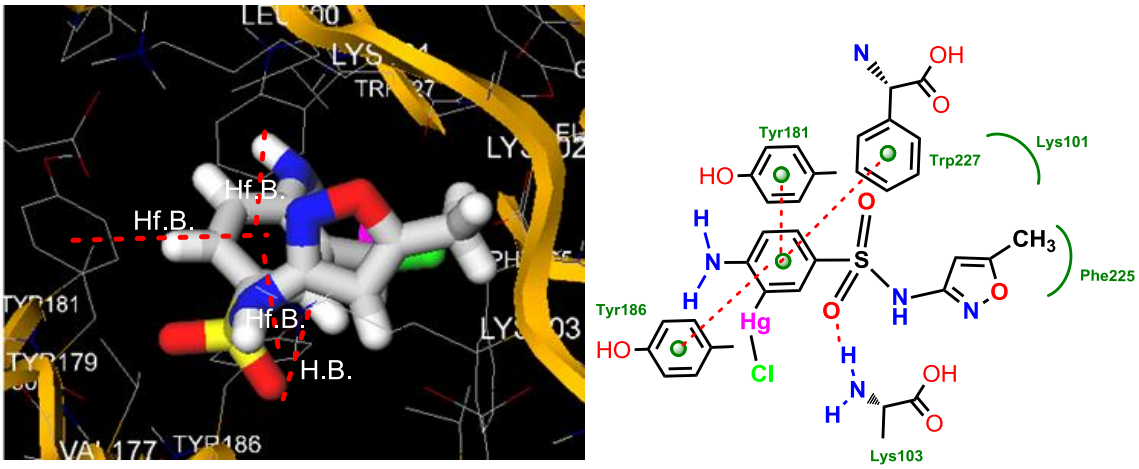

Figure 2: Docked conformation of 1 showing one hydrogen bonding: Lys103 with oxygen atom of SO_2 group as well as exhibited three hydrophobic interactions: between phenyl moiety of compound 1andTyr181, Tyr186 and Trp227 of reverse transcriptase (RT) enzyme residues.

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REFERENCES

[1] AZ Al-Rubaie, NI Al-Salim and SAN Al-Jaddan. J Organomet Chem 1993;67:443.
[2] L Engman and J Person. J Organomet Chem 1993;12:1068.
[3] L Engman, D Stern, IA Cotgreave, CM Andersson. J Am Chem Soc 1992;114:9737.
[4] E Cobbledick, FWB Einstein, WR Mc Whinnie, FH Musa. J Chem Soc (S) 1979;145:1901.
[5] MAK Ahmed, WR McWhinnie, TA Hamor. J Organomet Chem 1985;281:205.
[6] AZ Al-Rubaie, WA Al-Masoudi, S AN Al-Jadaan, AF Jalbout, AJ Hameed. Hetroatom Chem 2008;19:307.
[7] AZ Al-Rubaie, WA Al-Masoudi, S AN Al-Jadaanand, EA Ahmad. Int J Sci Res 2002;18.
[8] RH Al-Asadi, TA Fahad, BA Saeed, WA Al-Masoudi. J Adv Chem 2014;8:1464.
[9] AZ Al-Rubaie, SAN Al-Jadaan. App Orgmetallic Chem 1998;12:79.
[10] Makarova, Nesmeyanov. Meth Elemen Org Chem 1976;4:94.
[11] RM Silverstein, GC Bassler, TC Morrill. 'Spectrometric Identification of Organic Compounds' 5th.Ed., John Wiley (1991).
[12] L Mosula, B Zimenkovsky, D Havrylyuk, A Missir, IC Chirita, R Lesyk. Farmacia 2009;3:321.
[13] AZ Al-Rubaie, AK Al-Derawi. Heteroatom Chem 2007;18:93.
[14] AL Davis, J Keeler, ED Laue, D Moskau. J Magn Reson 1992;98:207.
[15] AZ Al-Rubaie, WA Al-Masoudi, SAN Al-Jadaan, ET Ahmed. Int J Sci Res 2009;18:11.
[16] S Seeliger, BL de Groot. J Computer-Aided Mol Design 2010;24:417.
[17] P Zhan, X Liu, Z Li, Z Fang, C Pannecouque, E De Clercq. Chem Biodivers 2010;7:1717.