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ARTICLE *in* BIOORGANIC & MEDICINAL CHEMISTRY LETTERS · MARCH 2003

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Synthesis, Spectral Studies and Screening for Amoebicidal Activity of New Palladium(II) Complexes Derived from Thiophene-2-carboxaldehyde Thiosemicarbazones

Shailendra, Neelam Bharti,[†] Fehmida Naqvi and Amir Azam*

Department of Chemistry, Jamia Millia Islamia, Jamia Nagar, New Delhi 110025, India

Received 19 September 2002; accepted 11 November 2002

Abstract—In view of the antiamoebic properties observed for many thiophene-2-carboxaldehyde thiosemicarbazones, a series of N^4-substituted thiosemicarbazones metal complexes derived from thiophene-2-carboxaldehyde was prepared for evaluation against *Entamoeba histolytica*. Reaction of thiophene-2-carboxaldehyde with cycloalkylaminothiocarbonylhydrazines having different amines gave the corresponding thiosemicarbazones. Reaction of latter with $[Pd(DMSO)_2Cl_2]$ gave requisite palladium thiosemicarbazone complexes of the type $[Pd(TSC)Cl_2]$ (where TSC = thiosemicarbazones). Screening of antiamoebic activity of these compounds was assayed in vitro against (*HM-1:1MSS*) strain of *E. histolytica*. Enhancement of antiamoebic resulted from introducing palladium metal in the thiosemicarbazone moiety. Among the studied compounds, [Pd(2-TCA-1,2,3,4-THQTSC)Cl_2] (**2a**) showed better activity.

Introduction

Entamoeba histolytica is a protozoan parasite causing amoebic dysentery and liver abscess. It is therefore responsible for significant morbidity and mortality in a number of countries. Infection occurs worldwide, resulting in 36–50 million cases of invasive disease and up to 110,000 deaths per year.[1] The first-line drugs of amoebiasis chemotherapy are nitroimidazoles, with their prototype metronidazole [1-(2-hydroxyethyl)-2-methyl-5-nitroimidazole] being the drug of choice.[2,3] It is effective and the most widely used medicament for treating amoebiasis. However, resistance against metronidazole is common in bacteria and other protozoan organisms, and in vitro trophozoites of *E. histolytica* are able to adapt to therapeutically relevant levels of the drug.[4,5] Because cross-resistance exists among the nitroimidazoles,[6] there is no equally effective and tolerated class of drug available in case of rising resistance to metronidazole.

Thiosemicarbazones usually react as chelating ligands with transition metal ions by bonding through the sulphur and hydrazinic nitrogen atoms. Thiosemicarbazones not only have wide inhibitory activity against tuberculosis,[7] protozoa,[8] malaria,[9] viral[10] and several kinds of tumors[11,12] but also can be used as pesticides[13] and fungicides.[14] The success of *cis*-$[PtCl_2(NH_3)_2]$ as an anticancer drugs has stimulated a renewed interest in metal-based chemotherapies.[15–17] The transition metal complexes of thiosemicarbazones derived from 2-acetylpyridine are widely studied because of their potential for therapeutic uses.[18] However, thiosemicarbazone metal complexes with non-pyridine heterocyclic rings have not been exhaustively studied.[19–21] These findings have led to increasing interest in the complexes of thiosemicarbazones with transition metals. If derivatives of thiosemicarbazone and the transition metal elements are used together to synthesize a new drug, it might have good biological activity due to the cooperative effectiveness.

In our earlier studies, some thiophene-2-carboxaldehyde thiosemicarbazones and their Ru(II) complexes showed promising results against *E. histolytica*.[22] We now report the synthesis and characterization of new thiophene-2-carboxaldehyde thiosemicarbazones having aliphatic and aromatic substituent, respectively, together with their palladium(II) complexes. The antiamoebic screening of these compounds indicating that they possessed strong inhibitory action against *E. histolytica*.

*Corresponding author. Tel.: +91-11-683-1717x338; fax: +91-11-682-1232 or +91-11-684-0229; e-mail: amir_sumbul@yahoo.co.in
[†]Present address: Department of Medicinal Chemistry, University of Florida, Gainesville, FL 32610, USA.

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PII: S0960-894X(02)01005-3

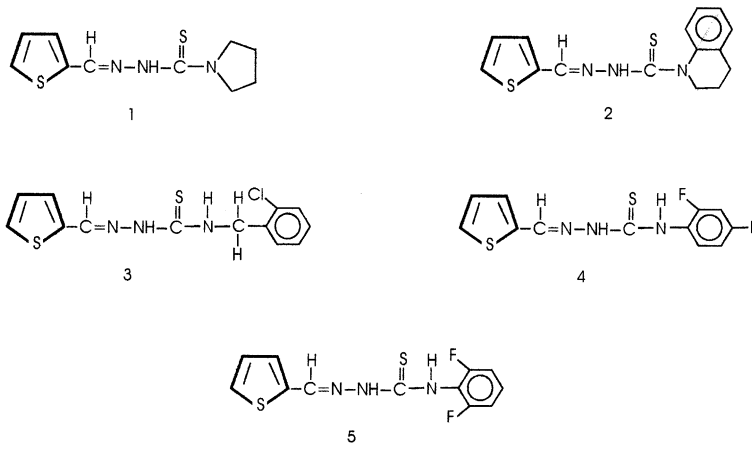

Figure 1. 1. 2-TCA-PYRTSC, thiophene-2-carboxaldehyde-pyrrolidine thiosemicarbazone; 2. 2-TCA-1,2,3,4-THQTSC, thiophene-2-carboxaldehyde-1,2,3,4-tetrahydroquinoline thiosemicarbazone; 3. 2-TCA-2-CBTSC, thiophene-2-carboxaldehyde-2-chlorobenzyl thiosemicarbazone; 4. 2-TCA-2,4-DFATSC, thiophene-2-carboxaldehyde-2,4-difluoroaniline thiosemicarbazone; 5. 2-TCA-2,6-DFATSC, thiophene-2-carboxaldehyde-2,6-difluoroaniline thiosemicarbazone.

Chemistry

O'Sullivan reported di-methyl, di-ethyl, di-*n*-propyl, di-*n*-butyl, and methylphenyl thiocarbamylthioglycolic acid.[23] All the thioglycolic acids were prepared by the same method. Cycloalkylaminothiocarbonylhydrazines were prepared by refluxing the alkaline solution of thioglycolic acid with hydrazine hydrate and their thiosemicarbazones were synthesized by stirring the solution of Cycloalkylaminothiocarbonylhydrazines (0.003 mol) in water (10 mL) and the solution of thiophene-2-carboxaldehyde (0.003 mol) in ethanol (10 mL) at 25 °C for 3 h. After cooling the crystals were filtered and recrystallized from appropriate solvent. The precursor used for the synthesis of Pd(II) complexes $[Pd(DMSO)_2Cl_2]$ was synthesized by the literature procedure.[24] Melting point determination was carried out to check the purity of the compounds. Structures were confirmed by IR, ^1H NMR and electronic spectral studies. All Pd(II) complexes were prepared by mixing the equimolar ratio of ligand and $[Pd(DMSO)_2Cl_2]$ in refluxing methanol. The solution was kept at 0 °C overnight, the product was separated by filtration and finally, washed with methanol. Recrystallization was effected in methanol: DMF (8:2).

$$[Pd(DMSO)_2Cl_2] + TSC \xrightarrow[5h,\ reflux]{CH_3OH} [Pd(TSC)Cl_2] + 2\,DMSO$$

where TSC = thiosemicarbazones **1–5**.

All Pd(II) complexes are soluble in DMF and DMSO, sparingly soluble in methanol, ethanol and insoluble in water. Analytical and spectral data (IR, electronic and ^1H NMR spectra)[25] are in good agreement with the composition of thiosemicarbazones **1–5** (Fig. 1) and their Pd (II) complexes **1a–5a** (Fig. 2). Analytical and other physicochemical data of the compounds are presented in Table 1. In the IR spectra, the band due to ν (C–S–C) (ring) of thiophene moiety remains unaltered in **1a–5a** whereas the disappearance of the band due to NH–C=S upon complexation and the appearance of a new band of azine nitrogen and the thio sulphur of the ligand along with the negative shift of (15–41 cm^{-1}) of C=N band observed in the complexes. It indicates the involvement of azomethine nitrogen in complexation.[26] This was supported by the shift of N–N band of ligand to a higher frequency upon coordination. The broad band observed in region 3250 cm^{-1} may be due to ν(N–H) stretch is slightly shifted in complex. A strong band at 1045–1069 cm^{-1} ascribed to ν(C=S) of ligands is shifted to lower frequency (16–34 cm^{-1}) indicating the bonding of metal through thionic sulphur. The electronic spectra of the ligands exhibit three bands in the region 29,154–29,412, 37,453–38,343 and 48,309–48,780 cm^{-1}. The probable assignment for these bands are due to the $n\rightarrow\pi^*$, $\pi\rightarrow\pi^*$ and $\varphi\rightarrow\varphi^*$ transitions, respectively. In the spectra of complexes, these bands appeared at ca. 25,000, 36,000 and 49,000 cm^{-1}, respectively, with little change in the energy of these bands. In the ^1H NMR spectra, the –NH proton signal of the ligands **1–5**, which resonate at 8.98–11.39 ppm, usually shifts to up field and it appeared at 3.29–3.75 ppm for their respective complexes. This information suggests the adjustment of electronic current upon coordination of >C=S group to the metal ion. The preferential coordination of thionic sulphur over sulphur of thiophene is due to more nucleophilic character of the former. Other protons, namely CH_2 protons and aryl carbons in complexes **1a–5a** resonate nearly at the same region as that of free ligands.

In vitro antiamoebic activity

The thiosemicarbazones (**1–5**) and their Pd(II) complexes (**1a–5a**) were tested for amoebiasis in vitro

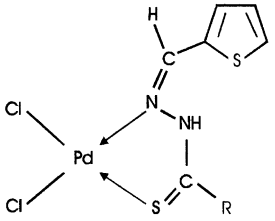

Figure 2. Structure of Palladium(II) complexes (**1a**. R = $-NC_4H_8$, **2a**. R = $-NC_9H_{10}$, **3a**. R = $-NHC_7H_6Cl$, **4a**. R = $-NHC_6H_3F_2$, **5a**. R = –NH $C_6H_3F_2$).

Table 1. Analytical and physicochemical data of thiosemicarbazones and their Pd(II) complexes

S. no.	Compd/stiochiometry[a]	Color	Yield (%)	M.pt./Dec.temp. (°C)	Found (calcd)			
					C	H	N	Cl
1	2-TCA-PYRTSC $C_{10}H_{13}N_3S_2$	Light yellow	51	165	50.07 (50.21)	5.41 (5.44)	17.64 (17.47)	
1a	[Pd(2-TCA-PYRTSC)Cl_2] $C_{10}H_{13}N_3S_2Cl_2Pd$	Orange	64	300	28.84 (28.81)	3.05 (3.12)	10.21 (10.08)	16.92 (17.05)
2	2-TCA-1,2,3,4-THQTSC $C_{15}H_{15}N_3S_2$	Light yellow	60	177	59.85 (59.80)	4.75 (4.98)	14.07 (13.95)	
2a	[Pd(2-TCA-1,2,3,4-THQTSC)Cl_2] $C_{15}H_{15}N_3S_2Cl_2Pd$	Brick red	69	291	37.81 (37.62)	2.97 (3.13)	8.76 (8.78)	14.73 (14.84)
3	2-TCA-2-CBTSC $C_{13}H_{12}N_3S_2Cl$	White	49	197	50.64 (50.40)	3.79 (3.88)	13.44 (13.57)	
3a	[Pd(2-TCA-2-CBTSC)Cl_2] $C_{13}H_{12}N_3S_2Cl_3Pd$	Orange	54	276	31.95 (32.04)	2.31 (2.46)	8.70 (8.63)	21.96 (21.87)
4	2-TCA-2,4-DFATSC $C_{12}H_9N_3S_2F_2$	Light yellow	53	186	48.59 (48.48)	2.96 (3.03)	14.09 (14.14)	
4a	[Pd(2-TCA-2,4-DFATSC)Cl_2] $C_{12}H_9N_3S_2F_2Cl_2Pd$	Orange	62	261	29.81 (29.73)	3.76 (3.72)	8.63 (8.67)	14.70 (14.66)
5	2-TCA-2,6-DFATSC $C_{12}H_9N_3S_2F_2$	White	55	190	48.65 (48.48)	2.94 (3.03)	14.11 (14.14)	
5a	[Pd(2-TCA-2,6-DFATSC)Cl_2] $C_{12}H_9N_3S_2F_2Cl_2Pd$	Orange	63	278	29.70 (29.73)	3.83 (3.72)	8.72 (8.67)	14.54 (14.66)

[a]For abbreviation, see Figure 1.

against (*HM-1:1MSS*) strain of *E. histolytica* by microdilution method.[27] Metronidazole was used as reference amoebicidal drug. The biological test was carried out using DMSO as the solvent in which the compounds are stable. The in vitro antiamoebic activity of thiosemicarbazones and their palladium(II) complexes are listed in Table 2. Metronidazole had a 50% inhibitory concentration (IC_{50}) against (*HM1:1MSS*) strain of *E. histolytica* ranging from 1.05 to 2.16 μM.[28] It has been observed that the presence of certain bulky groups at position N^4 of the thiosemicarbazone moiety greatly enhances the activity.[29] As shown in Table 2, Pd(II) complexes cause a marked inhibition as compared to their respective ligands. Most of the palladium(II) complexes showed significant antiamoebic activity. The highest level of activity was exhibited by **2a**. The incorporation of metal ion enhanced the activity of the basic molecule. It was noted that antiparasitic activity was limited to those compounds in which the alkylidene group is attached to the 2-position, rather than 3- or 4-position of the heterocyclic ring and also to those in which a thiocarbonyl, rather than a carbonyl group, is present.[30] The IC_{50} value of Pd-complex precursor [Pd$(DMSO)_2Cl_2$] was also determined establishing that it has no activity against *E. histolytica*.

Table 2. In vitro antiamoebic activities of thiosemicarbazones and their Pd(II) complexes against (*HM-1:1MSS*) strain of *E. histolytica*

S. no.	Compd	IC_{50} (μM)	SD[a]
1	2-TCA-PYRTSC	3.29	0.63
1a	[Pd(2-TCA-PYRTSC)Cl_2]	1.65	0.32
2	TCA-1,2,3,4-THQTSC	2.78	0.58
2a	[Pd(2-TCA-1,2,3,4-THQTSC)Cl_2]	1.15	0.34
3	2-TCA-2-CBTSC	5.74	1.39
3a	[Pd(2-TCA-2-CBTSC)Cl_2]	3.06	0.72
4	2-TCA-2,4-DFATSC	6.18	1.24
4a	[Pd(2-TCA-2,4-DFATSC)Cl_2]	2.65	0.36
5	2-TCA-2,6-DFATSC	5.73	0.97
5a	[Pd(2-TCA-2,6-DFATSC)Cl_2]	2.41	0.32
	[Pd$(DMSO)_2Cl_2$]	8.24	1.67
	Metronidazole	2.03	0.35

[a]Standard deviation.

Acknowledgements

This work was supported from Council of Scientific and Industrial Research [Grant no. 27(0117)/02/EMR-ll], New Delhi, India. Shailendra acknowledges the senior research fellowship from CSIR, New Delhi, India. The authors are thankful to Prof. Alok Bhattacharya and Dr. Sudha Bhattacharya, School of Life Sciences and School of Environmental Sciences, Jawaharlal Nehru University, New Delhi, respectively for providing Laboratory facilities for biological activities.

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25. **1** ^{1}H NMR ($CDCl_3$) δ 8.98 (1H, s, –NH), 7.82 (1H, s, –CH=N), 7.02–7.62 (3H, m, aryl), 3.94 (8H, m, CH_2); IR ν (cm^{-1}) 3302 (NH), 1639 (C=N), 1597 (C=C), 1045 (C=S), 915 (N–N); λ_{max} (cm^{-1}) 29,154, 37,453, 48,490. **2** ^{1}H NMR ($CDCl_3$) δ 9.36 (1H, s, –NH), 8.84 (1H, s, –CH=N), 7.07–7.78 (7H, m, aryl), 4.07 (6H, m, CH_2); IR ν (cm^{-1}) 3254 (NH), 1653 (C=N), 1588 (C=C), 1055 (C=S), 924 (N–N); λ_{max} (cm^{-1}) 29,239, 37,593, 48,780. **3** ^{1}H NMR ($CDCl_3$) δ 11.18 (1H, s, –NH), 8.10 (1H, s, –CH=N), 6.92–7.39 (7H, m, aryl), 4.92 (2H, d, CH_2); IR ν (cm^{-1}) 3289 (NH), 1635 (C=N), 1592 (C=C), 1051 (C=S), 928 (N–N); λ_{max} (cm^{-1}) 29,412, 37,984, 48,544. **4** ^{1}H NMR ($CDCl_3$) δ 10.21 (1H, s, –NH), 9.03 (1H, s, –CH=N), 6.81–7.45 (6H, m, aryl); IR ν (cm^{-1}) 3264 (NH), 1615 (C=N), 1548 (C=C), 1054 (C=S), 921 (N–N); λ_{max} (cm^{-1}) 29,239, 38,343, 48,309. **5** ^{1}H NMR ($CDCl_3$) δ 11.39 (1H, s, –NH), 9.37 (1H, s, –CH = N), 7.07–7.63 (6H, m, aryl); IR ν (cm^{-1}) 3269 (NH), 1596 (C=N), 1550 (C=C), 1069 (C=S), 923 (N–N); λ_{max} (cm^{-1}) 29,326, 37,736, 48,754. **1a** ^{1}H NMR (DMSO-d_6) δ 3.48 (1H, s, –NH), 7.31 (1H, s, –CH=N), 4.05 (8H, m, CH_2), 7.14–7.80 (3H, m, aryl); IR ν (cm^{-1}) 3175 (NH), 1666 (C=N), 1589 (C=C), 1029 (C=S), 939 (N–N), 504, 457 (Pd–N, Pd–S); λ_{max} (cm^{-1}) 25,413, 36,987, 49,423. **2a** ^{1}H NMR (DMSO-d_6) δ 3.29 (1H, s, –NH), 8.25 (1H, s, –CH=N) 4.17 (6H, m, CH_2), 6.95–7.54 (7H, m, aryl); IR ν (cm^{-1}) 3173 (NH), 1668 (C=N), 1585 (C=C), 1030 (C=S), 943 (N–N), 514, 459 (Pd–N, Pd–S); λ_{max} (cm^{-1}) 25,315, 36,112, 49,513. **3a** ^{1}H NMR (DMSO-d_6) δ 3.68 (1H, s, –NH), 7.58 (1H, s, –CH=N) 4.87 (2H, d, CH_2), 7.02–7.59 (7H, m, aryl); IR ν (cm^{-1}) 3163 (NH), 1676 (C=N), 1597 (C=C), 1028 (C=S), 957 (N–N), 524, 478, 449 (Pd–N, Pd–S); λ_{max} (cm^{-1}) 24,975, 35,423, 49,419. **4a** ^{1}H NMR (DMSO-d_6) δ 3.75 (1H, s,–NH), 8.49 (1H, s, –CH=N), 6.95–7.61 (6H, m, aryl); IR ν (cm^{-1}) 3151 (NH), 1646 (C=N), 1552 (C=C), 1020 (C=S), 937 (N–N), 497, 439 (Pd–N, Pd–S); λ_{max} (cm^{-1}) 24453, 36410, 48914. **5a** ^{1}H NMR (DMSO-d_6) δ 3.51 (1H, s, –NH), 8.67 (1H, s, –CH=N), 7.12–7.75 (6H, m, aryl); IR ν (cm^{-1}) 3157 (NH), 1627 (C=N), 1556 (C=C), 1047 (C=S), 958 (N–N), 517, 475, 423 (Pd–N, Pd–S); λ_{max} (cm^{-1}) 25,517, 35,998, 49,607.
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