Synthesis, characterization and biological studies of some new organometallic compounds containing mercury, selenium and tellurium based on p-aminobenzoic acid

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Abstract. Ten chalcogen and mercury bearing compounds based on 4-aminobenzoic acid (i.e., (2-amino-5-(ethoxycarbonyl)phenyl)mercury(II) chloride (1), (2-amino-5-(ethoxycarbonyl)phenyl) phenyl selenide (2), (2-amino-5-(ethoxycarbonyl)phenyl) phenyl telluride (3), (4-carboxyphenyl)mercury(II) chloride (4), 4-selenocyanatobenzoic acid (5), 4-tellurocyanatobenzoic acid (6), bis(4-carboxyphenyl) diselenide (7) bis(4-carboxyphenyl) ditelluride (8), bis(4-carboxyphenyl) selenide (9) bis(4-carboxyphenyl) telluride (10) were prepared and characterized by various spectroscopic techniques. All compounds were screened for antibacterial activity against Gram-positive bacterial strains of Staphylococcus aureus and the Gram-negative bacteria Escherichia coli by using the disk diffusion technique. The antibacterial activity of these compounds was dependent on the molecular structure of the compounds, and the bacterial strain under consideration.

1. Introduction

p-Aminobenzoic acid (PABA) and its derivatives showed interesting pharmacological properties [1,2]. PABA is a chemical found in the folic acid vitamin and also in several foods including grains, eggs, milk, and meat. Furthermore, this compound is a water soluble, non-poisonous drug and is easily absorbed by intestinal treatment. Some of its derivatives are used as acetyl cholinesterase inhibitors for the treatment of Alzheimer’s disease [3]. p-Aminobenzoic acid analogs such as procaine and lidocaine are anesthetics [4]. p-Aminobenzoic acid is also a member of the B vitamins and is part of the folic acid molecule which showed antioxidant properties [5]. It is well known that PABA is important to skin, hair pigment, and intestinal health. It is used as a sunscreen; it also can protect against the development of sunburn and skin cancer from excess ultraviolet light exposure [6]. On the other hand, the interest in the field of synthesis and reactivity of organoselenium and organotellurium compounds has increased; particularly, because of the observations that they can exhibit important biological activities [7-9].

The present work describes the synthesis of several compounds based on p-aminobenzoic acid-containing mercury, selenium, and tellurium and investigates their biological activity.

2. Experimental

2.1. Physical measurements

All melting points were determined on a Gallenkamp melting point apparatus and are uncorrected. FT-IR spectra were recorded on FT-IR spectrophotometer -8400s Shimadza as KBr disc. The 1H and
13C NMR spectra were measured on a Bruker spectrometer at 300 (1H NMR) MHz and 75 (13C NMR) MHz or 200/50 MHz on an AC-200 NMR spectrometer. Spectra were recorded in CDCl3 solutions. Chemical shifts are reported in ppm, referenced to the solvent peak of CDCl3 or tetramethylsilane (TMS) as the external reference. Elemental analyses were determined on an MT-3 elemental analyzer within ±5 % of the theoretical values. Mass spectra were recorded on a HP-598 8A MS instrument at 70 eV.

2.2. Synthesis
All reactions were carried out under nitrogen or argon atmosphere and monitored by the conventional TLC method. All organic solvents were dried prior to use according to standard methods. Ethyl 4-aminobenzoate (Benzocaine) was prepared by the reaction of p-aminobenzoic acid with absolute ethanol in presence of conc. H2SO4 [10]. Phenylselenium trichloride and phenyltellurium tribromide were prepared according to literature methods [11, 12].

2.1.1. (2-Amino-5-(ethoxycarbonyl)phenyl)mercury(II) chloride (1)
Ethyl 4-aminobenzoate (5.0 g; 30 mmol) was treated with mercuric acetate by a similar method used for the preparation of 2-aminio-5-methylphenyl mercury chloride [13].

2.1.2. (2-Amino-5-(ethoxycarbonyl)phenyl) phenyl selenide (2)
(2-Amino-5-(ethoxycarbonyl)phenyl)mercury(II) chloride (4.83 g, 12.5 mmol) and phenylselenium trichloride (3.28 g, 12.5 mmol) in dry dioxane (100 cm3) was refluxed for 12 h. The hot solution was filtered hot. The filtrate was cooled to room temperature. The HgClBr.2diox complex was removed by filtration as white plates. The filtrate was evaporated to dryness on a rotary evaporator at 40°C. A dark brown precipitate was obtained. The product was dissolved in CH2Cl2 (100 cm3) and shaken vigorously in a separating funnel for 30 min with an aqueous solution (50 cm3) of Na2S2O3 (1.73 g; 9 mmol). The yellow organic phase was separated, washed with water, and dried over calcium chloride. Evaporation and recrystallization from petroleum ether (60-80°C) gave a brown-yellow precipitate.

2.1.3. (2-Amino-5-(ethoxycarbonyl)phenyl) phenyl telluride (3)
This compound was prepared by the same above method by reaction of phenyltellurium tribromide (3.55 g; 8 mmol) with (2-Amino-5-(ethoxy-carbonyl)phenyl)mercury(II) chloride (3.10 g, 8 mmol). A brown precipitate was obtained.

2.1.4. (4-Carboxyphenyl)mercury(II) chloride (4)
Compound (4-carboxyphenyl) mercury (II) chloride was prepared according to a literature method [14] by heating the double salt of p-toluenediazonium chloride and mercuric chloride in acetone with copper powder, followed by oxidation of p-tolylmercuric chloride by KMnO4 [14], m.p. 287°C (dec.).

2.1.5. 4-Selenocyanatobenzoic acid (5)
A stirred solution containing p-aminobenzoic acid (4.7 g, 34.91 mmol), 20 cm3 of conc. hydrochloric acid and 20 cm3 of water in an ice bath (0 - 5°C), was added dropwise to sodium nitrite (9.0 g, 134.31 mmol) in 25 cm3 of water. A solution of p-carboxybenzodiazonium chloride was formed. The resulting solution was added dropwise to a stirred solution of potassium selenocyanate (5.0 g; 34.91 mmol) in ethanol (25 cm3) while a brisk stream of dry nitrogen was passed into the system. The mixture was stirred at room temperature for an additional 2 h. The mixture was diluted with CH2Cl2 (250 cm3), filtered from the dark insoluble material and washed several times with H2O. The solution was dried (CaCl2) and evaporated, giving a solid, which was dissolved in CH2Cl2 and filtered through a short SiO2 column.

2.1.6. 4-Tellurocyanatobenzoic acid (6)
Finely ground tellurium powder (1.6 g, 12.5 mmol) and KCN (0.82 g, 12.5 mmol) in dry DMSO (20 cm3) were heated at 100°C, for 1 h under dry nitrogen. After all the tellurium dissolved, the mixture was cooled in an ice bath until most of the solvent has solidified. The p-carboxybenzodiazonium chloride
(12.5 mmol) was added rapidly while a brisk stream of nitrogen is passed into the system. When the initial violent gas evolution has ceased, the ice bath was removed and stirring was continued at room temperature for 6 h. The mixture was diluted with CH$_2$Cl$_2$ (200 cm$^3$), filtered from the dark insoluble material and washed several times with H$_2$O. The solution was dried over anhydrous calcium chloride. Evaporation of solvent gave a yellow solid which was dissolved in dichloromethane and filtered through a short SiO$_2$ column. A yellow solid was obtained in 58% yield.

2.1.7. Bis(4-carboxyphenyl) diselenide (7)
This compound was prepared by two methods and as follow:
a) Compound 5 (2.26g; 10 mmol) was acidified with aqueous HCl (10%, 25 cm$^3$), gently heated with mixing and left at room temperature overnight. The solid was filtered off, washed with hot water several times, and air-dried. The crude product was recrystallized from hot dioxane to give compound 7 as a pale brick powder. Yield: 37%; m.p. 321–323°C.
b) NaBH$_4$ (0.22g, 6 mmol) was added in small portions with caution to a solution of 4-selenocyanatobenzoic acid (1.36g; 6 mmol) in absolute ethanol (40 cm$^3$). The mixture was stirred at room temperature for 2 h. The solvents were removed under vacuum by a rotary evaporator and the residue was treated with water. The mixture was extracted with dichloromethane. The organic phase was washed with water and dried with anhydrous Na$_2$SO$_4$. The dichloromethane was removed under vacuum and the residue product was recrystallized from hot dioxane to give compound 7 in 26% yield.

2.1.8. Bis(4-carboxyphenyl) ditelluride (8)
Compound 6 (2.75 g; 10 mmol) was treated with aqueous hydrochloric acid (10%, 25 cm$^3$) in a similar above method (method b) described for compound 7. A yellow precipitate was obtained in 41% yield; m.p. 288–290°C.

2.1.9. Bis(4-carboxyphenyl) selenide (9)
This compound was prepared by using previously reported method [15] with a slight modification. A solution of bis(4-carboxyphenyl) diselenide (7) (2 g; 5 mmol) in dioxane (50 cm$^3$) was refluxed in presence of copper powder (0.70g; 11 mmol) for 12 h. The hot solution was filtered and the filtrate was evaporated to give compound 9 in almost quantitative yield, m.p. 198-199°C.

2.1.10. Bis(4-carboxyphenyl) telluride (10)
Compound 8 was converted into bis(4-carboxyphenyl) telluride (10) by treatment with copper powder in refluxing dioxane by the same above method. Compound 10 was obtained in 87% yield, m.p. 135-137°C.

2.2. Antibacterial Activity
Compounds 1-10 were tested for their antibacterial activity by using cup plate agar diffusion method [16] and the inhibition zones were measured in millimetre (mm). The nutrient agar broth prepared by the usual method, was inoculated aseptically with 0.5 cm$^3$ of 24 h old subculture of S. aureus and E. coli in separate conical flasks at 40-50°C and mixed well by gentle shaking. About 25 cm$^3$ of the contents of the flask were poured and evenly spread in petridish (90 mm in diameter) and allowed to set for 2h. The cups (10 mm in diameter) were formed by the help of borer in agar medium and filled with 0.02 cm$^3$ (20 µg/ cm$^3$) and 0.04 cm$^3$ (40 µg/ cm$^3$) solution of sample in DMSO. The plates were incubated at 37°C for 24 h and the control was also maintained with 0.04 cm$^3$ of DMSO similarly and the zones of inhibition of the bacterial growth were measured in millimetre and recorded in Table 3.

3. Results and Discussion
3.1. Synthesis
Organoselenium and organotellurium compounds are fast gaining contemporary interest due to their indispensable applications in the electronic industry [17], as organic conductors [18] and precursors for
semiconducting materials [19], in biology [20], and medical imaging. They also finding renewed interest as synthetic reagents in organic synthesis [21, 22]. Thus, in the present work, a new series of new organometallic compounds containing mercury, selenium, and tellurium based on p-aminobenzoic acid were prepared.

Compound (2-Amino-5-(ethoxycarbonyl)phenyl)mercury(II) chloride (1) can be easily prepared from the reaction of ethyl 4-aminobenzoate with mercuric acetate followed by addition of lithium chloride, Scheme 1. Compound 1 was reacted with phenylselenium trichloride and phenylltellurium tribromide followed by reduction by Na$_2$S$_2$O$_5$ to give compounds 2 and 3, respectively in good yield, Scheme 1, Table 1. It is worth noting that direct mercuration of p-aminobenzoic acid gave an unidentified product although a previous work [23] reported the formation of (2-amino-5-carboxyphenyl) mercury (II) chloride by direct mercuration of p-aminobenzoic acid.

Scheme 1. Preparative methods for compounds 1, 2 and 3.

Compound 4 (4-carboxyphenyl)mercury(II) chloride ) was prepared by heating the double salt of p-toluenediazonium chloride and mercuric chloride in acetone with copper powder, followed by oxidation of p-tolylmercuric chloride by KMnO$_4$[14], Scheme 2. Compounds 5 and 6 were prepared by reaction of p-carboxybenzodiazonium chloride with KSeCN and KTeCN, respectively, Scheme 2. Acid hydrolysis of compounds 5 and 6 gave bis(4-carboxyphenyl) diselenide (7) and bis(4-carboxyphenyl) ditelluride (8), respectively. Compound 7 was also prepared in low yield by reaction of 4-carboxybenzodiazonium chloride with NaBH$_4$, Scheme 2. The subsequent reaction of Compounds 7 and 8 with copper powder in refluxing dioxane afforded bis(4-carboxyphenyl) selenide (9) and Bis(4-carboxyphenyl) telluride (10), Scheme 2.
Scheme 2. Preparative methods for compounds 4 – 10

All compounds are brown to white solids and mostly soluble in DMF and DMSO. Isolated yields, melting points, colours, and analytical data for compounds 1-10 are shown in Table 1.

Table 1. Isolated yield, analytical and IR data for compounds 1-10

| Compd. | Yield (%) | M. p. (°C) | Found (calc.) (%) | IR (cm⁻¹, KBr) |
|--------|-----------|------------|-------------------|----------------|
| 1      | 86        | 234        | 26.76 (27.01)     | 3560(OH), 3340, 3285(NH), 3047 (C-H str.), 2931 (C-H str.), 1699 (C=O stretch), 1600(NH), 1581 (C=C), 1365 (CH₃), 1045 (CO str.), 775 (C-H). |
| 2      | 74        | 204-206    | 55.84 (56.26)     | 3562(OH), 3328, 3265(NH), 3034 (C-H str.), 2925 (C-H str.), 1706 (C=O), 1602(NH), 1585 (C=C), 1313 (CH₃), 1024 (C-O str.), 815 (C-H). |
| 3      | 68        | 175-177    | 48.47 (48.84)     | 3556(OH), 3315, 3257(NH), 3032 (C-H str.), 2943 (C-H str.), 1705 (C=O), 1608 (NH), 1578(C=C), 1280 (CH₃), 1103 (C-O str.), 871 (C-H). |
| 4      | 59        | 282-284 (dec.) | 23.22 (23.54) | 3532(OH), 3012(CH), 1686(CO). |
| 5      | 75        | 193        | 41.83 (42.50)     | 3455(OH), 3105(CH), 2065(νCN), 1686(CO), 690(νC-Se), 430(δ(NCS)), |
| 6      | 58        | 104        | 34.77 (34.98)     | 3502 (OH), 3095(CH), 2172(νCN), 1692(CO), 540(νC=Te), 415(δ(NCTe)), |
| 7      | 37        | 278-280    | 41.76 (42.02)     | 3478 (OH), 3078(C-H), 1678(CO). |
| 8      | 41        | 188-190    | 34.21 (33.80)     | 3490 (OH), 3011(C-H), 1674(CO). |
| 9      | 95        | 198-199    | 52.41 (52.35)     | 3504(OH), 3060(C-H), 1664(CO). |
| 10     | 87        | 135-137    | 44.87 (45.47)     | 3493(OH), 3088(C-H), 1667(CO). |

* Lit. 287°C[14]
The IR spectra of compounds 1-3 the compounds showed medium bands due to N-H asymmetric and symmetric stretching ($\nu_{as}$ and $\nu_s$) between 3560 and 3315 cm$^{-1}$, respectively. The spectra showed strong bands at 1600 cm$^{-1}$ due to the internal deformation mode of N-H. A comparison of the $\nu$(N-H) bands in compounds 1-3 with ethyl 4-aminobenzoate indicates that the NH$_2$ frequencies in the new compounds are shifted to a lower position. This may indicate that the NH$_2$ group coordinates to the mercury, selenium, or tellurium atom by donation of the lone pair of nitrogen, as was observed for bis(2-aminophenyl) ditelluride [24]. Furthermore, a band around 1700 cm$^{-1}$ may be attributed to carbonyl group. The IR spectra of compounds 4 and 5 show strong bands at 2078, and 2160 cm$^{-1}$, which are attributed to $\nu$(Se-CN) and $\nu$(Te-CN), respectively [25, 26] together with a strong band at 1695 and cm$^{-1}$, respectively are due to carbonyl group.

Table 2. NMR spectroscopic data for compounds 1-10

| Compound | $^1$H NMR (δ, 300 MHz, CDCl$_3$); TMS= 0 ppm | $^{13}$C NMR |
|----------|---------------------------------------------|-------------|
| 1        | 8.03 (d, $J = 1.5$ Hz, 1H), 7.73 (dd, $J = 7.4$, 1.5 Hz, 1H), 6.71 (d, $J = 7.5$ Hz, 1H), 4.65 (s, br, 2H), 4.34 (q, $J = 8.0$ Hz, 2H), 1.39 (t, $J = 8.0$ Hz, 3H). | 166.2, 153.0, 138.1, 135.1, 129.8, 121.8, 116.3, 60.9, 14.4. |
| 2        | 7.68 (d, $J = 2.0$ Hz, 1H), 7.60 (dd, $J = 7.46$, 2.0 Hz, 1H), 7.29 (s, 5H), 6.72 (d, $J = 7.5$ Hz, 1H), 4.48 (s, 2H), 4.32(q, 4H), 1.34 (t, $J = 8.0$ Hz, 3H). | 166.2, 150.4, 138.5, 133.7 ,132.8, 131.7, 129.3, 129.0, 127.2, 122.8, 117.5, 61.3, 14.42. |
| 3        | 7.80 (d, $J = 2.0$ Hz, 1H), 7.46 (ddd, $J = 9.8$, 7.6, 2.0 Hz, 3H), 7.38 –7.24 (m, 2H), 6.58 (d, $J = 7.5$ Hz, 1H), 4.38 –4.24 (m, 4H), 1.34 (t, $J = 8.0$ Hz, 3H). | 165.4, 149.2, 136.1, 135.2, 130.8, 129.15, 127.7, 127.5, 126.3, 117.3, 116.3, 60.8, 14.3. |
| 4        | 12.54 (s, 1H, OH), 8.15 (d, $J = 7.8$ Hz, 2H), 7.52 (d, $J = 7.8$ Hz, 2H). | 170.0, 155.6, 136.7, 128.4, 131.1 |
| 5        | 8.12 – 8.02 (m, 1H), 7.55 – 7.45 (m, 1H). | 172.2, 132.9, 128.5, 127.1, 124.1, 103.0. |
| 6        | 11.8 (s, 1H, OH), 7.73 (d, $J = 8.1$ Hz, 2H), 6.80 (d, $J = 7.9$ Hz, 2H). | 169.6, 136.5, 129.4, 127.4, 115.6, 103.3. |
| 7        | 12.0 (s, 1H, OH), 8.12 (d, $J = 7.9$ Hz, 2H), 7.55 – 7.45 (m, 2H). | 168.8, 138.7, 130.4, 129.1, 124.7. |
| 8        | 11.7 (s, 2H, OH), 7.9 (d, 4H), 7.6 (d, $J = 8.4$ Hz, 4H). | 167.5, 135.1, 130.0, 127.2, 113.2. |
| 9        | 11.9(s, 2H, OH), 8.08(d, $J = 7.5$ Hz, 4H), 7.44(d, $J = 8.0$ Hz, 4H). | 172.3, 133.8, 128.4, 127.3, 101.9 |
| 10       | 11.5(s, 2H, OH), 8.27(d, $J = 8.5$ Hz, 4H), 7.64(d, $J = 8.2$ Hz, 4H). | 169.8, 134.3, 126.4, 125.3, 108.8. |

Compounds 4-10 showed one or two broad strong bands in the range 3495 -3220 cm$^{-1}$ due to $\nu$(OH). All protons in compounds 1-10 were identified, and the total number of protons calculated from the integration curve was tallied with the expected molecular formula in the $^1$H NMR spectra, Table 2. Thus, the methylene protons (COCH$_2$-CH$_3$) appeared as a quartet at around 4.40 ppm for 1, 2 and 3,
while for \( CH_3 \) proton appeared as triplets, Table 2. \(^{13}\)C-NMR spectra of compounds 1, 2, and 3 revealed the presence of CO at around 170.0 ppm.

Treatment of compounds 5 and 6 with aqueous hydrochloric acid (10%) is the most obvious way to prepare the diselenide (7) and ditelluride (8) respectively, Scheme 1. Compounds 7 and 8 were obtained as red solids. These new compounds were obtained in good yields and quite stable to handle at room temperature (Scheme 1). IR and NMR data together with elemental analyses support the formation of these new compounds. IR spectra of 7 and 8 indicate the presence of νCO at 1678 and 1674 cm\(^{-1}\), respectively as a strong band. \(^{13}\)C-NMR spectra of 7 and 8 showed the presence of CO signal at 168.8 and 167.5 ppm, respectively, Tables 1 and 2.

Refluxing compounds 7 and 8 in dry dioxane in presence of a threefold molar excess of activated copper gave compounds 9 and 10, respectively as yellow solids in good yields, Table 1, Scheme 1. The structure of the obtained compounds was assessed according to IR, \(^1\)H NMR, \(^{13}\)C NMR spectroscopic data and their element analysis, Tables 1 and 2.

### 3.2. Antibacterial Activity

The in vitro antimicrobial activity of compounds 1-10 were screened against Gram-positive bacterial strains (\( S. \) \textit{aureus} ) and Gram-negative bacterial strains (\( E. \) \textit{coli} ). Inhibition zones demonstrated that compounds 1 and 4 showed significant high activity which may be due to the presence of mercury and N in the form of the amine group. Compounds 2 and 3 showed high activity. The presence of the cyano group in compounds 5 and 6, is probably responsible for the high activity against bacterial strains than compounds 2 and 3, Table 3. This may be due to an increase in lipophilicity and easier penetration of the compounds into the outer cell wall of the microorganisms, which causes death due to cell membrane rupture. Compounds 7–10 were also effective against both bacterial strains, Table 3.

| Compound | Diameter of inhibition zone (mm)* |
|----------|-----------------------------------|
|          | \( S. \) \textit{aureus} \n20 \( \mu \)g/ml | \( 40 \) \( \mu \)g/ml | \( E. \) \textit{coli} \n20 \( \mu \)g/ml | \( 40 \) \( \mu \)g/ml |
| 1        | 30                  | 43                  | 38                  | 44                  |
| 2        | 24                  | 28                  | 20                  | 28                  |
| 3        | 26                  | 30                  | 25                  | 32                  |
| 4        | 24                  | 39                  | 35                  | 39                  |
| 5        | 18                  | 22                  | 15                  | 19                  |
| 6        | 15                  | 18                  | 13                  | 15                  |
| 7        | 22                  | 25                  | 17                  | 22                  |
| 8        | 18                  | 21                  | 15                  | 19                  |
| 9        | 25                  | 28                  | 24                  | 30                  |
| 10       | 23                  | 27                  | 17                  | 22                  |
| Ampicillin | 25                  | 30                  | 24                  | 29                  |

* the diameter (mm) of the inhibition zone, produced around each disc, are average of three separate experiments; DMSO was used as a control and ampicillin as standard drug.

In general, the presence of NH\(_2\) and COOH groups, as well as Hg, Se or Te in the studied compounds, leads to higher activity.

The results presented in Table 3 indicate that compounds 9 and 10 are higher activity against both bacterial strains compared to compounds 7 and 8. This may be attributed to the structures of diselenide (9) and ditelluride (10). This agrees with the previous work [27-30] described that diorganyl dichalcogenides have higher biological activities in comparison with other types of organoselenium and organotellurium compounds [27-30].
4. CONCLUSION
In this study, several new compounds were prepared and characterized by various spectroscopic techniques and elemental analysis. All prepared compounds (1-10) exhibited high antimicrobial activity against *Staphylococcus aureus* and *Escherchia coli*. The combination of an organochalcogen group with nitrogen and/or oxygen in the same molecule increases the antibacterial capabilities of these compounds.

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