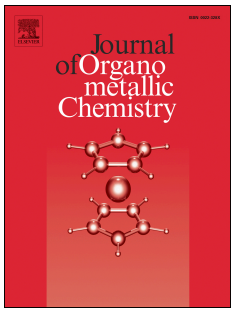

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Bioactive Heteroleptic Bismuth(V) Carboxylates: Synthetic Stratagem, Characterization and Binding Pattern Validation

Mehwish Mehmood[a], Imtiaz-ud-Din[a*], Sumaira Abbas[a], Syed Sikander Azam[b], Ihsan-ul-Haq[c] Muhammad Nawaz Tahir[d], Nousheen Parvaiz[b], Asim Tameez-Ud Din[e]

[a] Department of Chemistry, Quaid-i-Azam University, Islamabad 45320, Pakistan.
[b] Computational Biology Lab, National Center for Bioinformatics, Quaid-i-Azam University, Islamabad 45320, Pakistan
[c] Department of Pharmacy, Faculty of Biological Sciences, Quaid-i-Azam University, Islamabad 45320, Pakistan.
[d] Department of Physics, University of Sargodha, Sargodha 40100, Pakistan.
e. Rawalpindi Medical University, Rawalpindi, Pakistan

Corresponding Author: drimtiazuddin@yahoo.com

Abstract

A series of heteroleptic triorganobismuth(V) carboxylates **(1-8)** of general formula $Ar_3Bi(COOR)_2$**;** where Ar = C_6H_5 **(1-4)**, p-$CH_3C_6H_4$ **(5-8)** and R = $C_{10}H_7$ **(1, 5)**, 2-$CH_3C_6H_4$ **(2, 6)**, 3, 4- $(OCH_2CH_3)C_6H_3$ **(3, 7)**, 2-ClC_6H_4 **(4, 8);** were synthesized by a stoichiometric reaction between the precursor, Ar_3BiBr_2 and the respective carboxylic acid, using triethylamine as a base in dry toluene. They were characterized by FT-IR, NMR spectroscopy and X-ray diffraction technique to get unequivocal evidence for their structural motifs. The single crystal XRD data for **(2** & **5)** revealed the existence of five coordinated bismuth centre having distorted trigonal bipyramidal molecular geometry, whereas **(6)** described weakly hexacoordinated bismuth including a unique anisobidentate interaction of one carboxyl group with the resultant distorted octahedral molecular geometry. The molecular docking studies demonstrate that compounds **(1, 2** and **7)** give significant GOLD fitness scores of 60.09, 62.65 and 56.30 against EGFR tyrosine kinase, human pancreatic alpha amylase and H. pylori urease respectively. The synthesized compounds were also preliminary screened for their antimicrobial, α-amylase inhibition and protein kinase inhibition activities to determine their biological efficacy. The antibacterial activity profile for **(2)** looks good with MIC value 6.25 µg/mL against *E.coli* whereas, **(1**, **2** and **5)** show significant antifungal activity against *A.flavus* having MIC value of 6.25 µg/mL and the values are comparable to the reference drug(s). Compound **(6)** displays significant % alpha amylase inhibition of 34.80, whereas **(2)** exhibit 30 mm bald inhibition zone for protein kinase

inhibition study, thus, proving their worth as moderate enzyme inhibitors. The molecular docking studies for **(1-8)** demonstrate strong interactions between the receptor and the molecule and a firm protein-ligand complex formation described their effective role in enzymes' inhibition .The bioactivity data obtained from both in silico analysis and in vitro studies are quite promising ones and the synthesized compounds may find a leading role in future drug discovery programs.

Keywords: Bismuth carboxylates, X-ray Structure, H. pylori, Enzyme inhibition, Molecular docking.

1. INTRODUCTION

Bismuth is considered to be the least toxic heavy metal which is stable and possesses medicinal importance since 1900 especially when a mixture of bismuth nitrate (or chloride) with common hydroxyl carboxylic acid began to be used in wide range of medicinal capacities [1, 2]. Being a green element and having lowest toxicity level, most of its' compounds are used in some commercially available medicines [3, 4]. The important derivatives of bismuth, being currently used as medicinal products, are colloidal bismuth subcitrate (CBS) with the trade name of De-Nol® and bismuth subsalicylate (BSS) trade named as Pepto-Bismol® [5-10]. These medicines are used worldwide to control dyspepsia, diarrhea, duodenal and peptic ulcers caused by bacterial strain named *Helicobacter pylori*. The organometallic complexes of bismuth are of extraordinary interest due to their chemically well-defined structure and possibility of tuning their both activity & toxicity [11, 12]. Over the past few years, bismuth derivatives of carboxylates, thiocarboxylates, amides, sulfamates and sulfonates have also been explored for their possible *in vitro* activity against H. pylori and found promising results [13-17].

Urea amino-hydrolase, commonly known as urease, is a nickel containing enzyme which is responsible for the synthesis of urea into carbamic acid and ammonia. The carbamic acid further hydrolyses under the action of urease to form carbonic acid and a molecule of ammonia. Ammonia, being strong base, is responsible for elevation of pH and consequently it creates feasible scenario for the survival of *H. pylori* in stomach that have harsh acidic conditions. Moreover additional production of ammonia also leads to the formation of certain cytotoxins like monochloramine which is responsible for causing peptic ulcer and gastric carcinoma [18, 19]. The epidermal growth factor receptor (EGFR) tyrosine kinases are considered to be responsible

for cell growth and its irregular behavior may lead to the development of tumors in body organs like lungs, breast, ovary and colon. It has been reported that blocking of EGFR tyrosine kinases may serve as a tool to prevent the growth of cancerous cells [20]. The human pancreatic alpha amylase is responsible for cleaving bulky starch molecules into glucose so as to enable them to cross the blood brain barrier; however, an excessive conversion of starch into glucose may cause hyperglycemia or diabetes mellitus which is an endocrine disorder [21].

In continuation to our previous work [22-24], we report here the synthesis, structural characterization and biological applications of triarylbismuth(V) derivatives **(1-8)**. The synthesized compounds were preliminary assayed for their possible agentive role as antimicrobial, alpha amylase and protein kinase inhibitors besides checking their level of toxicity using brine shrimp lethality assay. One of the methods of computer-aided drug design (CADD), known as molecular docking, was also carried out to validate the binding pattern of H. pylori urease, EGFR tyrosine kinase and human pancreatic alpha amylase with the synthesized compounds. In recent times, the application of *in silico* tools provide an additional support to the experimental data for the development and discovery of new drugs [25, 26]. The molecular docking approach has been used to model the interactions between the selected drug receptors and the synthesized bismuth(IV) compounds to unravel their behavior in active sites of the target protein(s).

2. Experimental Section

2.1 Materials and methods

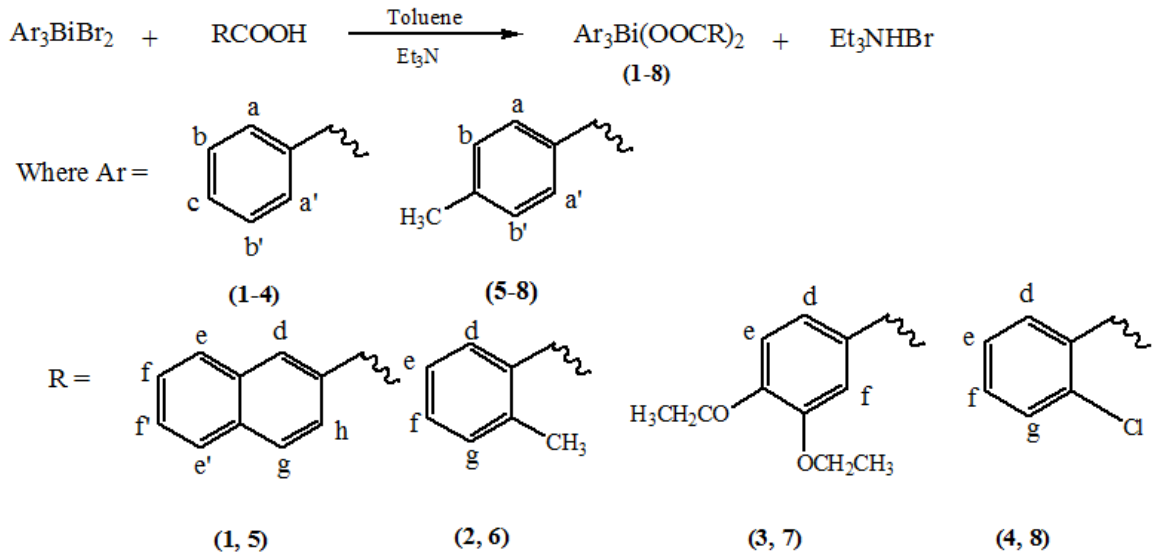
The commercially available chemicals were purchased from Sigma Aldrich (USA). Some of which are; 2-napthoic acid, o-toluic acid, 3,4-diethoxybenzoic acid and 2-chlorobenzoic acid and were used as received. Tri-phenylbismuth(V) / tri-p-tolylbismuth(V) dibromide were prepared by a reported methodology [27]. All the solvents used were of analytical grade and dried before use [28]. The melting point of the compounds were determined by using electro thermal melting point apparatus (model MP-D Mitamura Riken Kogyo Japan). The IR spectra were recorded with Bio-Rad Excalibur (model FTS 3000 MX), as KBr discs. The multinuclear (^{1}H, ^{13}C) NMR spectra were recorded on Bruker Advance Digital 300 MHz FT-NMR spectrometer (Switzerland) in deuterated chloroform as solvent relative to Me_4Si as internal reference. The single crystal X-ray diffraction analysis was performed on Bruker Kappa APEXII CCD

diffractometer equipped with a four-circle goniometer. The X-ray structures were solved with the ShelXT structure solution program using Direct Methods and refined with the ShelXL-1997 refinement package using Least squares minimization.

2.2 Synthesis

The compounds **(1-8)** were synthesized using the procedure as reported earlier with slight modification [17, 29, 30]. Firstly triarylbismuth(III) species,symbolized as $Ar_3Bi(III)$ (where, Ar = C_6H_5-, CH_3-C_6H_4), were synthesized by reacting the respective Grignard's reagent with $BiCl_3$ in dry THF under argon at 0^oC, and the reaction mixture was stirred for 8-10 hours followed by extraction in chloroform. The oxidative addition of the respective $Ar_3Bi(III)$ species was accomplished by drop wise addition of liquid bromine into the solution to achieve the precursor as $Ar_3Bi(V)$ Br_2 [31].

The second step involves the preparation of target compounds **(1-8)** by using stoichiometric amounts of the respective carboxylic acid (1 mmole), Ar_3BiBr_2 (0.5 mmole) and triethylamine (1 mmole) as base in 20 mL toluene. The reaction mixture was refluxed for 3-4 hours at room temperature under argon gas. The triethylammonium bromide salt, thus formed, was filtered off and the clear filtrate was allowed to evaporate at room temperature for solidification which was subsequently recrystallized in a mixture of chloroform and pet-ether (3:1) to get the pure compound(s) as illustrated in Scheme-**1**.



Scheme-1: Synthetic Stratagem for **1-8**

The physico-analytical and spectroscopic data pertaining to the synthesized compounds are summarized as follows:

Bis(2-napthoato)triphenylbismuth(V) (1)

Quantities used; 2-napthoic acid (0.17 g, 1 mmole), triphenylbismuth dibromide (0.3 g, 0.5 mmole), triethylamine (0.14 mL, 1 mmole), crystalline product, yield: 75%, m.p: 159 ^{o}C, Anal. Calcd. for $C_{40}H_{29}BiO_4$ (782.64g/mole), C, 61.39, H, 3.73%, Found, C, 61.36, H, 3.74%; FT-IR data (ν, cm^{-1}, KBr) C-$H_{aromatic}$ (3052), COO_{asym} (1555), COO_{sym} (1323), Δν (232), Bi-C (469), Bi-O (444); ^{1}H NMR data (300 MHz, $CDCl_3$, ppm) δ 8.56 (s, 2H, Ar-H_d), 8.42-8.40 (d, 2H, *J*=7.2Hz, Ar-H_h), 8.08-8.05 (d, 2H, *J*=7.5Hz, Ar-H_g), 7.93-7.91 (d, 4H, *J*=7.5Hz, Ar-$H_{e = e'}$), 7.85-7.79 (t, 4H, *J*=7.8Hz, Ar-$H_{f = f'}$), 7.66 -7.61 (t, 9H, *J*=7.5Hz, Ar- $H_{b = b' = c}$), 7.55-7.53 (d, 6H, *J*=6.9Hz, Ar-$H_{a = a'}$); ^{13}C NMR data (75MHz, $CDCl_3$, ppm) δ 160.7 (COO),134.1 (Bi-C_{ipso}), 131.3 (o-$CH_{aromatic}$), 130.8 (m-$CH_{aromatic}$), 129.1 (C-COO), 127.6 (p-$CH_{aromatic}$).

Bis(2-methylbenzoato)triphenylbismuth(V) (2)

Quantities used; 2-methylbenzoic acid (0.14 g, 1 mmole), triphenylbismuth dibromide (0.3 g, 0.5 mmole), triethylamine (0.14 mL, 1 mmole), crystalline product, yield: 81%, m.p: 128^{o}C, Anal. Calcd. for $C_{34}H_{29}BiO_4$ (710.57g/mole), C, 57.47, H, 4.11%, Found, C, 57.48, H, 4.12%; FT-IR data (ν, cm^{-1}, KBr) C-$H_{aromatic}$ (3052), C-$H_{aliphatic}$ (2962), COO_{asym} (1547), COO_{sym} (1336), Δν (211), Bi-C (488), Bi-O (444); ^{1}H NMR data (300 MHz, $CDCl_3$, ppm) δ 8.37-8.35 (d, 6H, *J*=7.2Hz, Ar- $H_{a = a'}$), 7.74-7.72 (d, 2H, *J*=7.5 Hz, Ar-H_d), 7.64-7.59 (t, 6H, *J*=7.5Hz, Ar-$H_{b = b'}$), 7.51-7.46 (t, 3H, *J*=7.2Hz, Ar-H_c), 7.28 -7.24 (t, 2H, *J*=7.5Hz, Ar- H_e), 7.17-7.11 (t, 4H, *J*=7.5Hz, Ar- $H_{f, g}$), 2.41 (s, 6H, -CH_3); ^{13}C NMR data (75 MHz, $CDCl_3$, ppm) δ 174.8 (COO), 161.5 (Bi-C_{ipso}), 138.6 (C-CH_3), 133.3 (C-COO), 134.1 (o-$CH_{aromatic}$), 131.0 (m,p-$CH_{aromatic}$), 21.4 (-CH_3).

Bis(3,4-diethoxybenzoato)triphenylbismuth(V) (3)

Quantities used; 3,4-diethoxybenzoic acid (0.21 g, 1 mmole), triphenylbismuth dibromide (0.3 g, 0.5 mmole), triethylamine (0.14 mL, 1 mmole), crystalline product, yield: 82%, m.p: 170 ^{o}C, Anal. Calcd. for $C_{40}H_{41}BiO_8$ (858.73 g/mole), C, 55.95, H, 4.81%, Found, C, 55.93, H, 4.80%;

FT-IR data (ν, cm^{-1}, KBr) C-$H_{aromatic}$ (3051), C-$H_{aliphatic}$ (2982), COO_{asym} (1558), COO_{sym} (1327), Δν (231), Bi-C (510), Bi-O (443); ^{1}H NMR data (300 MHz, $CDCl_3$, ppm) δ 8.32-8.30 (d, 6H, *J*=7.5 Hz, Ar-$H_{a = a'}$), 7.63-7.61 (t, 6H, *J*=4.8 Hz, Ar-$H_{b = b'}$), 7.59 (s, 2H, Ar-H_f), 7.57-7.48 (t, 3H, *J*=13.2 Hz, Ar- H_c), 7.45-7.43 (d, 2H, *J*=7.2 Hz, Ar- H_d), 6.83 -6.81 (d, 2H, *J*=8.4 Hz, Ar-H_e), 4.15-4.08 (q, 8H, *J*=6.6Hz, -CH_2), 1.47-1.43 (t, 12H, *J*=6.6 Hz, -CH_3); ^{13}C NMR data (75 MHz, $CDCl_3$, ppm) δ 172.4 (COO),161.1 (Bi-C_{ipso}), 151.7 (C_3-OEt), 147.7 (C_4-OEt), 133.9 (o-$CH_{aromatic}$), 131.2 (m-$CH_{aromatic}$), 130.6(p-$CH_{aromatic}$), 64.5 (-CH_2), 14.8 (-CH_3).

Bis(2-chlorobenzoato)triphenylbismuth(V) (4)

Quantities used; 2-chlorobenzoic acid (0.16 g, 1 mmole), triphenylbismuth dibromide (0.3 g, 0.5 mmole), triethylamine (0.14 mL, 1 mmole), crystalline product, yield: 75%, m.p: 138^{o}C, Anal. Calcd. for $C_{32}H_{23}BiCl_2O_4$ (750.41g/mole), C, 51.15, H, 3.09%, Found, C, 51.17, H, 3.06%; FT-IR data (ν, cm^{-1}, KBr) C-$H_{aromatic}$ (3062), COO_{asym} (1587), COO_{sym} (1347), Δν (240), Bi-C (464), Bi-O (405); ^{1}H NMR data (300 MHz, $CDCl_3$, ppm) δ 8.40-8.37 (d, 6H, *J*=7.2 Hz, Ar- $H_{a = a'}$), 7.69-6.70 (d, 6H, *J*=6.9Hz, Ar-$H_{b = b'}$), 7.65-7.62 (d, 2H, *J*=6.9Hz, Ar- H_d), 7.53-7.50 (m, 6H, Ar-$H_{e, f, g}$), 7.31-7.26 (t, 3H, *J*=8.7Hz, Ar-H_c); ^{13}C NMR data (75 MHz, $CDCl_3$, ppm) δ 172.2 (COO), 159.7 (Bi-C_{ipso}), 134.3 (o-$CH_{aromatic}$), 133.9 (C-Cl), 131.7 (C-COO), 131.4 (m,p-$CH_{aromatic}$).

Bis(2-napthoato)tri(p-tolyl)bismuth(V) (5)

Quantities used were 2-napthoic acid (0.17 g, 1 mmole), p-tritolylbismuth dibromide (0.31 g, 0.5 mmole), triethylamine (0.14 mL, 1 mmole), crystalline product, yield: 78%, m.p: 232 ^{o}C, Anal. Calcd. for $C_{43}H_{35}BiO_4$ (824.72g/mole), C, 62.62, H, 4.28%, Found, C, 62.62, H, 4.27%; FT-IR Data (ν, cm^{-1}, KBr) C-$H_{aromatic}$ (3055), C-$H_{aliphatic}$ (2961), COO_{asym} (1562), COO_{sym} (1326), Δν (236), Bi-C (470), Bi-O (415); ^{1}H NMR Data (300 MHz, $CDCl_3$, ppm) δ 8.56 (s, 2H, Ar-H_d), 8.29-8.27 (d, 2H, *J*=8.1Hz, Ar-H_h), 8.08-8.06 (d, 2H, *J*=7.8 Hz, Ar-H_g), 7.93-7.91 (d, 4H, *J*=6.3Hz, Ar-$H_{e = e'}$), 7.85-7.79 (t, 4H, *J*=7.8 Hz, Ar- $H_{f = f'}$), 7.52-7.49 (d, 6H, *J*=8.1 Hz, Ar-$H_{a = a'}$), 7.44-7.41 (d, 6H, *J*=8.1Hz, Ar-$H_{b = b'}$), 2.41(s, 9H, -CH_3); ^{13}C NMR Data (75 MHz, $CDCl_3$, ppm) δ 157.1 (COO), 1401.0 (Bi-C_{ipso}), 133.9 (o-$CH_{aromatic}$), 131.8 (m-$CH_{aromatic}$), 130.8 (CCOO), 127.4 (p-$CH_{aromatic}$), 21.4 (-CH_3).

Bis(2-methylbenzoato)tri(p-tolyl)bismuth(V) (6)

Quantities used; 2-methylbenzoic acid (0.14 g, 1 mmole), p-tritolylbismuth dibromide (0.31 g, 0.5 mmole), triethylamine (0.14 mL, 1mmole), crystalline product, yield: 75%, m.p: 151^{o}C, Anal. Calcd. for $C_{37}H_{35}BiO_4$ (752.65 g/mole), C, 59.04, H, 4.69%, Found, C, 59.02, H, 4.71%; FT-IR data (ν, cm^{-1}, KBr) C-$H_{aromatic}$ (3053), C-$H_{aliphatic}$ (2964), COO_{asym} (1588), COO_{sym} (1338), Δν (250), Bi-C (474), Bi-O (434); ^{1}H NMR data (300 MHz, $CDCl_3$, ppm) δ 8.24-8.22 (d, 6H, *J*=8.4Hz, Ar- $H_{a = a'}$), 7.75-7.31 (d, 2H, *J*=6 Hz, Ar-H_d), 7.46-7.39 (t, 6H, *J*=8.1Hz, Ar-$H_{b = b'}$), 7.42-7.39 (d, 2H, *J*=8.1Hz, Ar- H_g), 7.28-7.12 (t, 4H, *J*=9Hz, Ar- $H_{e,f}$), 2.41 (s, 15H, -CH_3); ^{13}C NMR data (75 MHz, $CDCl_3$, ppm) δ174.5 (COO), 170.4 (Bi-C_{ipso}), 158.0 (C-CH_3), 141.5 (p-CH_3), 140.8 (C-COO), 133.9 (o-$CH_{aromatic}$), 131.0 (m-$CH_{aromatic}$), 22.0 (CH_3-$CH_{aromatic}$), 21.4 (CH_3-p-$CH_{aromatic}$).

Bis(3,4-diethoxybenzoato)tri(p-tolyl)bismuth(V) (7)

Quantities used; 3,4-Diethoxybenzoic acid (0.21 g, 1 mmole), p-tritolylbismuth dibromide (0.31 g, 0.5 mmole), triethylamine (0.14 mL, 1 mmole), crystalline product, yield: 75%, m.p: 201 ^{o}C, Anal. Calcd. for $C_{43}H_{47}BiO_8$ (900.81 g/mole), C, 57.33, H, 5.26%, Found, C, 57.34, H, 45.26%; FT-IR data (ν, cm^{-1}, KBr) C-$H_{aromatic}$ (2984), C-$H_{aliphatic}$ (2922), COO_{asym} (1549), COO_{sym} (1351), Δν (198), Bi-C (474), Bi-O (434); ^{1}H NMR data (300 MHz, $CDCl_3$, ppm) δ 8.19-8.16 (d, 6H, *J*=8.1Hz, Ar-$H_{a = a'}$), 7.62-7.59 (t, 2H, *J*=4.8 Hz, Ar-H_d), 7.52 (s, 2H, Ar-H_f), 7.40-7.37 (d, 6H, *J*=8.1Hz, Ar-$H_{b = b'}$), 6.82-6.80 (d, 2H, *J*=8.1 Hz, Ar- H_e), 4.15-4.08 (q, 8H, *J*=6.6 Hz, -CH_2), 2.37(s, 9H, p-CH_3), 1.47-1.43 (t, 12H, *J*=6.9Hz, -CH_3); ^{13}C NMR data (75 MHz, $CDCl_3$, ppm) δ 172.1 (COO), 154.4 (C_3-OEt), 151.5 (C_4-OEt), 140.8 (p-$CH_{aromatic}$), 133.8 (o-$CH_{aromatic}$), 132.1 (m-$CH_{aromatic}$), 64.5 (-CH_2), 21.4 (p-$CH_{3aromatic}$), 14.6 (-CH_3).

Bis(2-chlorobenzoato)tri(p-tolyl)bismuth(V) (8)

Quantities used; 2-chlorobenzoic acid (0.16 g, 1 mmole), p-tritolylbismuth dibromide (0.31 g, 0.5 mmole), triethylamine (0.14 mL, 1 mmole), crystalline product, yield: 75%, m.p: 110^{o}C, Anal. Calcd. for $C_{35}H_{29}BiCl_2O_4$ (793.49 g/mole), C, 52.98, H, 3.68%, Found, C, 52.95, H, 3.70%; FT-IR data (ν, cm^{-1}, KBr) C-$H_{aromatic}$ (3068), C-$H_{aliphatic}$ (2917), COO_{asym} (1585), COO_{sym} (1353), Δν (232), Bi-C (472), Bi-O (426); ^{1}H NMR data (300 MHz, $CDCl_3$, ppm) δ 8.26-8.24 (d, 6H, *J*=8.1Hz, Ar- $H_{a = a'}$), 7.52-7.42 (m, 8H, Ar- $H_{d, e, f, g}$), 7.27-7.24 (d, 6H, *J*=8.1Hz, Ar- $H_{b=b'}$), 2.41 (s, 9H, -CH_3); ^{13}C NMR data (75 MHz, $CDCl_3$, ppm) δ 156.2 (COO), 154.1 (Bi-C_{ipso}), 141.7

(C-Cl), 141.2 (p-$CH_{aromatic}$), 138.2 (CCOO), 134.1 (o-$CH_{aromatic}$), 132.1 (m-$CH_{aromatic}$), 21.4 (-CH_3).

2.3 X-ray Crystallography

Single crystal XRD analyses for **2**, **5** and **6** were performed by mounting a suitable size crystal on a thin glass fiber and kept at 296(2) K. All the reflections were collected on Kappa APEXII CCD (Bruker) diffractometer equipped by graphite monochromatic radiation MoKα (λ= 0.71073A^o) [32]. For structural refinement, SHELXL 2014/7 (Sheldrick, 2014) program was used. All the crystallographic details and structural refinement parameters are given in Tables **1** and **2**.

2.4 Biological Activities

2.4.1 Antibacterial activity

To evaluate the antibacterial activity for **(1-8)**, the refreshed bacterial cultures of *Staphylococcus aureus* (ATCC-6538), *Bacillus subtilis* (ATCC-6633), *Escherichia coli* (ATCC-25922) and *Klebsiella pneumoniae* (ATCC-1705) were employed in order to determine their minimum inhibitory concentration (MIC) by using Broth dilution technique and the detailed procedure has been given as supplementary files [33].

2.4.2 Antifungal activity

The antifungal activity of the synthesized compounds was explored by using agar disc diffusion technique. The spores of four fungal strains, namely *Aspergillus fumigatus* (FCBP-66), *A. niger* (FCBP-0198), *Mucor* species (FCBP-0300) and *Aspergillus flavus* (FCBP-0064) were used in order to determine MIC and for details see supplementary files [34].

2.4.3 Alpha amylase inhibition assay

The alpha amylase inhibition assay was performed to evaluate the antidiabetic potential of synthesized complexes as well as the precursors by using a reported method [35]. Acarbose (250 µM) and DMSO was used as positive and negative control respectively. Absorbance was measured at 540 nm and percentage inhibition of alpha amylase enzyme was calculated, and for detailed procedure sees supplementary files.

2.4.4 Protein kinase inhibition assay

Protein kinase inhibition assay was executed by utilizing Streptomyces 85E bacterial strain and surfactin and DMSO were used as positive and negative controls respectively. The protocol details for the assay have been given as supplementary files [36].

2.4.5 Brine shrimp lethality assay

Brine shrimp lethality assay was performed according to the standard protocol with little modifications [34]. The doxorubicin (4 mg/ml DMSO) and DMSO were used as positive and negative standards respectively. The degree of lethality induced by each compound was quantified after 24 hours. The median lethal doses (LD_{50}) of the compounds with $\geq$ 50% mortality was calculated using table curve 2D vs. 5.01 software and for procedural details see supplementary files.

2.4.6 Computational Studies

Molecular docking studies were performed using Genetic Optimization for Ligand Docking (GOLD) program to explore the antibacterial, antidiabetic and anticancer potential of the synthesized compounds [37, 38]. The GOLD implements a genetic algorithm for docking flexible lead compounds into the active pocket of the selected receptor. The crystal structures of Helicobacter Pylori urease (PDB ID: 1E9Y), Human Pancreatic Alpha Amylase (PDB ID: 5U3A), and Epidermal Growth Factor Receptor tyrosine kinase (PDB ID: 1M17) were retrieved from RCSB Protein Data Bank (PDB) for molecular docking studies. It is crucial to identify the active pocket of the protein for targeted inhibition. The binding site of the selected target proteins was taken from the literature studies [39-41] and for more details see elsewhere [42]. Gold fitness function was selected to rank active compounds according to their binding affinity with the active site residues of the selected receptors. Compounds exhibiting greater Gold fitness score will be considered as having better binding affinity with the receptor [43].

3. Results and discussion

3.1 Chemistry

The salt metathesis method was employed to prepare the pure products from the reaction mixture. The triarylbismuth(V) carboxylates **(1-8)** were synthesized by a stoichiometric reaction between the substituted benzoic acid and appropriate triarylbismuth(V) dibromide in dry toluene, using triethylamine as a base (Scheme 1). They are stable in moist air and for their stability tests see elsewhere [27] and were characterized by FT-IR, NMR spectroscopy and single crystal XRD technique. The data have already been mentioned in the experimental section.

3.2 Spectroscopic Studies

3.2.1 FTIR Data

The IR absorption band for hydroxyl stretching frequency, $\nu_{OH,}$ appeared around 3400 cm^{-1} in the free carboxylic acid (ligand), whereas it disappeared in complexes **(1-8)** which clearly indicate deprotonation of acid and successful coordination to the organobismuth moiety through its oxygen(s). The stretching frequencies for carboxyl group appeared in range 1547-1588 & 1323-1353 cm^{-1} for ν_{asym} (COO) and ν_{sym} (COO) respectively. The $\Delta\nu$ [= ν_{asym} (COO) – ν_{sym} (COO)] for carboxyl group(s) has been determined to be greater than 200 cm^{-1} for all the synthesized complexes [44, 45] which depict its monodentate and/or anisobidentate mode of coordination with the metal centre which was further authenticated by single crystal XRD data for **(2**, **5** and **6)**. Another indication for the deprotonation of the carboxylic acid(s) came from lowering of values of symmetric and asymmetric stretching frequency by 30-40 cm^{-1} in the complexes than in free acids. The presence of two new stretching bands in range 462-510 and 405-444 cm^{-1} demonstrate the bismuth linkages to carbon ((Bi-C) and oxygen (Bi-O) respectively in the synthesized compounds when compared with the spectra of the free ligands [27]. The other characteristic vibrational bands attributable to certain organic groups, present in the compounds, are; 2984-3068 cm^{-1} for ν (C-$H_{aromatic}$) and 2917-2982 cm^{-1} for ν (C-$H_{aliphatic}$).

The IR absorption bands appeared for **(6)** are, ν C-$H_{aromatic}$ (3053), ν C-$H_{aliphatic}$ (2964), ν_{asym} COO (1588), ν_{sym} COO (1338), ν Bi-C (474), ν Bi-O (434). The characteristic $\Delta\nu$ value for this particular carboxyl group is 250 cm^{-1}, which qualified the ligand for anisobidentate mode of chelation with the organobismuth moiety [27]. Thus IR data fully support the proposed structural motifs for the synthesized compounds and are in accordance to the earlier reports [27, 46].

3.2.2 NMR Data

The chemical structures assigned to **(1-8**) were further ascertained by their multinuclear (^{1}H and ^{13}C) NMR spectral data which were recorded in $CDCl_3$ as solvent. The data explicitly determine magnetically non-equivalent protons present in the synthesized organobismuth dervatives along with their coupling constant values. The ^{1}H NMR data for these compounds revealed the successful coordination of the appropriate carboxylic acid to the metal centre by its deprotonation as indicated by absence of resonance around 11 ppm which was present in the free acids. The resonances for all the aromatic protons were observed in range 8.30-7.30 ppm as reported earlier [22, 23]. The ethoxy protons of **(3**, **7)** show quartet and triplet signals for -CH_2- and -CH_3 groups that resonate in range 4.15-4.08 and 1.47-1.43 ppm respectively [27].

The ^{13}C NMR data for **(1-8)** clearly manifested the presence of all the unique carbons in their structural motifs. The characteristic resonance peak pertaining to C=O functionality appears in range 174.8-156.2 ppm for the compounds. The methyl carbon of p-tolyl group resonate around 21 ppm as for (**5-8**) which further confirmed attachment of the respective arylbismuth moiety to the substituted carboxylic acid. The aromatic carbons appear in their usual region such as; C_{ipso}-Bi (161.5-134.1), o-$CH_{aromatic}$ (131.3-134.3), o-$CH_{aromatic}$ (130.8-132.1), p-$CH_{aromatic}$ (141.2-127.4), C_3-OEt (151.7-154.4), C_4-OEt (147.7-151.5) [30]. The -CH_2 and -CH_3 carbons of ethoxy group present in compounds **(3**, **7)** appear at 64.5 and 14.8 ppm respectively [30]. The coupling constants provide useful structural information as well as about precise location of the substituent on the aromatic ring.

3.3 X-ray Crystallography

Three synthesized compounds; [$BiPh_3(O_2CC_6H_4(2\text{-}CH_3))_2$] **(2)**, [$Bi(p\text{-}tol)_3(O_2CC_{10}H_7)_2$] **(5)** and [$Bi(p\text{-}tol)_3(O_2CC_6H_4(2\text{-}CH_3))_2$] **(6),** were also analyzed by single crystal XRD technique and their ORTEP diagrams are shown in Figures 1-3 whereas the selected bond lengths and bond angles are presented in Tables 1 and 2. The XRD data for **(2** & **5)** revealed the existence of five coordinated bismuth centre having distorted trigonal bipyramidal molecular geometry whereas compound **(6)** described hexacoordination for bismuth atom including a unique anisobidentate interaction of one carboxyl group that rendered the molecular geometry as distorted octahedral. It is worth mentioning here that the lability of Bi-O interaction is sensitive to the basicity of the donor species and the reactions, involving multifunctional ligands, are very dependent on

reaction conditions. Moreover, flexibility of the ligand backbone may result in structural variability in terms of chelation and bridging.

As mentioned earlier the compounds **(2** & **5)** are isostructural with each other having slight changes in bond lengths and bond angles. They emerging out five coordinated metal centre occupies carboxylates at axial positions and phenyl or p-tolyl moiety fits in equatorial positions [12, 29]. The Bi-C bond lengths for phenyl and p-tolyl groups appear in range 2.206(4) - 2.223(5) and 2.185(4) - 2.209(5) with average bond length of 2.247 and 2.197 A^o respectively and the data are compatible with the reported ones [29, 30, 47]. The bond lengths for Bi1-O1 and Bi1-O3 appear at 2.276(4) and 2.292(4) A^o for **(2)**, whereas these values fall at 2.288(3) and 2.293(3) A^o respectively for **(5)**. The XRD data for two compounds are in accordance to IR findings that described monodentate binding behavior for the two carboxylates with the metal centre. However the Bi-C bond lengths for phenyl and p-tolyl groups are found in range 2.185(4) -2.288(4) with the average bond length of 2.236 A^o for compound **(6)**. The bond lengths for Bi1-O1 and Bi1-O3 in the complex are determined as 2.294(3) and 2.286(3) A^o respectively, whereas the bond length for (Bi1-O2) is determined to be 2.729(3) A^o indicating lengthening of the bond that compel the carboxyl group to coordinate with the bismuth centre via anisobidentate manner and the molecule assumed overall distorted octahedral geometry [27].

Table-1: Crystallographic data and refinement details for **2**, **5** and **6**

Identification Codes	**2**	**5**	**6**
Empirical formula	$C_{34}H_{29}O_4Bi$	$C_{43}H_{35}BiO_4$	$C_{37}H_{35}O_4Bi$
Formula weight	710.55	824.69	752.63
Temperature/K	296(2)	296(2)	296(2)
Crystal system	Triclinic	Monoclinic	Monoclinic
Space group	P-1	$P2_1/n$	$P2_1/c$
a/Å	8.7736(16)	12.9031(9)	14.412(3)
b/Å	10.672(2)	12.2299(9)	10.6492(19)
c/Å	16.635(3)	22.6797(18)	22.286(3)
α/°	99.948(4)	90	90
β/°	103.612(4)	100.520(3)	105.089(9)
γ/°	102.951(5)	90	90
Volume/Å^3	1432.9(4)	3518.8(5)	3302.5(11)
Z	2	4	4
μ/mm^{-1}	6.189	5.052	5.375
F(000)	696.0	1632.0	1488.0
Crystal size/mm^3	0.400 × 0.320 × 0.160	0.420×0.230×0.180	0.380 × 0.260 × 0.220
Radiation	MoKα (λ = 0.71073)	MoKα (λ = 0.71073)	MoKα (λ = 0.71073)
2θ range for data collection/°	5.29 - 56.344	4.9°- 53.9°	4.816 - 55.92
Index ranges	$-11 \le h \le 11$, $-14 \le k \le 14$, $-16 \le l \le 21$	$-16 \le h \le 15$, $-14 \le k \le 15$, $-28 \le l \le 26$	$-18 \le h \le 18$, $-14 \le k \le 12$, $-29 \le l \le 27$
Reflections collected	18133	23550	22673
Independent reflections	6711	7671	7879
R_{int}	6.189	0.0571	0.0528
Goodness of Fit	1.022	0.968	1.014
Final R indexes[I>=2σ (I)]	$R_1 = 0.0365$, $wR_2 = 0.0878$	$R_1 = 0.0354$, $wR_2 = 0.0685$	$R_1 = 0.0349$, $wR_2 = 0.0708$
Final R indexes [all data]	$R_1 = 0.0476$, $wR_2 = 0.0931$	$R_1 = 0.0643$, $wR_2 = 0.0787$	$R_1 = 0.0628$, $wR_2 = 0.0807$

Table-2 : Selected bond lengths (Å) and bond angles (°) for **2**, **5** and **6**

2	
Bi1—C29 2.206 (4)	C23—Bi1—O1 91.84° (16)
Bi1—C23 2.210 (4)	C17—Bi1—O1 84.88° (16)
Bi1—C17 2.223 (5)	C29—Bi1—O3 93.01° (16)
Bi1—O1 2.276 (4)	C23—Bi1—O3 89.36° (17)
Bi1—O3 2.292 (4)	C17—Bi1—O3 84.27° (17)
C29—Bi1—C23 147.3° (2)	O1—Bi1—O3 168.91° (13)
C29—Bi1—C17 104.41° (17)	C1—O1—Bi1 105.7° (3)
C23—Bi1—C17 108.23° (18)	C9—O3—Bi1 108.0° (3)
C29—Bi1—O1 91.92° (15)	
5	
Bi1—C37 2.185 (4)	C23—Bi1—O3 89.41 (14)
Bi1—C23 2.202 (4)	C30—Bi1—O3 85.70 (15)
Bi1—C30 2.209 (5)	C37—Bi1—O1 92.42 (14)
Bi1—O1 2.293 (3)	C23—Bi1—O1 92.51 (14)
Bi1—O3 2.288 (3)	C30—Bi1—O1 86.19 (15)
C37—Bi1—C23 142.77 (19)	O3—Bi1—O1 171.87 (12)
C37—Bi1—C30 109.47 (18)	C1—O1—Bi1 107.6 (3)
C23—Bi1—C30 107.67 (17)	C12—O3—Bi1 109.5 (3)
C37—Bi1—O3 90.82 (14)	
6	
Bi1—C17 2.198 (4)	C17—Bi1—O3 88.50° (14)
Bi1—C31 2.202 (4)	C31—Bi1—O3 90.69° (14)
Bi1—C24 2.218 (4)	C24—Bi1—O3 87.08° (14)
Bi1—O1 2.294 (3)	C17—Bi1—O1 89.49 ° (14)
Bi1—O2 2.729 (3)	C31—Bi1—O1 93.90° (14)
Bi1—O3 2.286 (3)	C24—Bi1—O1 87.95° (14)
C17—Bi1—C31 150.27° (16)	O3—Bi1—O1 173.92° (10)
C17—Bi1—C24 105.76° (16)	C1—O1—Bi1 103.7° (3)
C31—Bi1—C24 103.88° (15)	C1—O1—Bi1 103.7° (3)

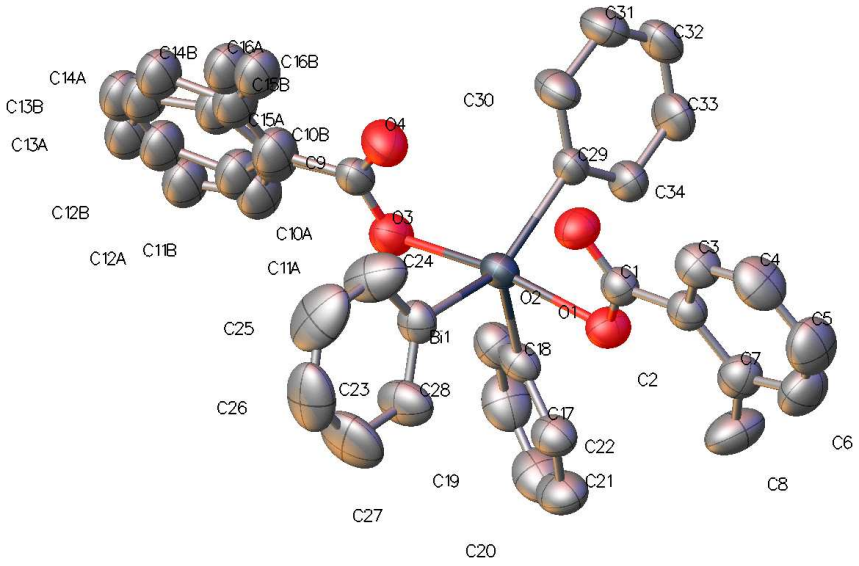


Fig.1 ORTEP view showing 50 % probability ellipsoids for **2,** with atom numbering scheme

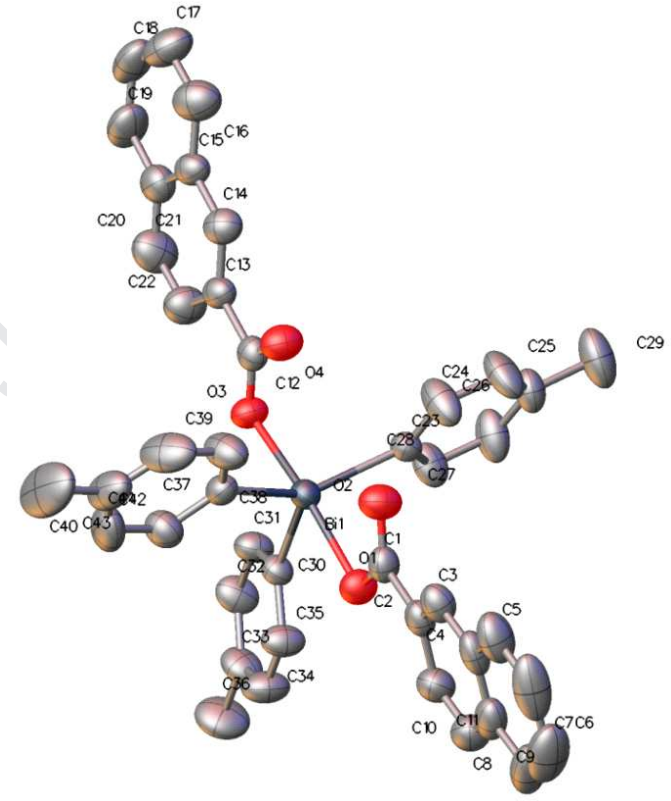


Fig.2 ORTEP diagram for **5,** showing 50 % probability ellipsoids with atom numbering scheme

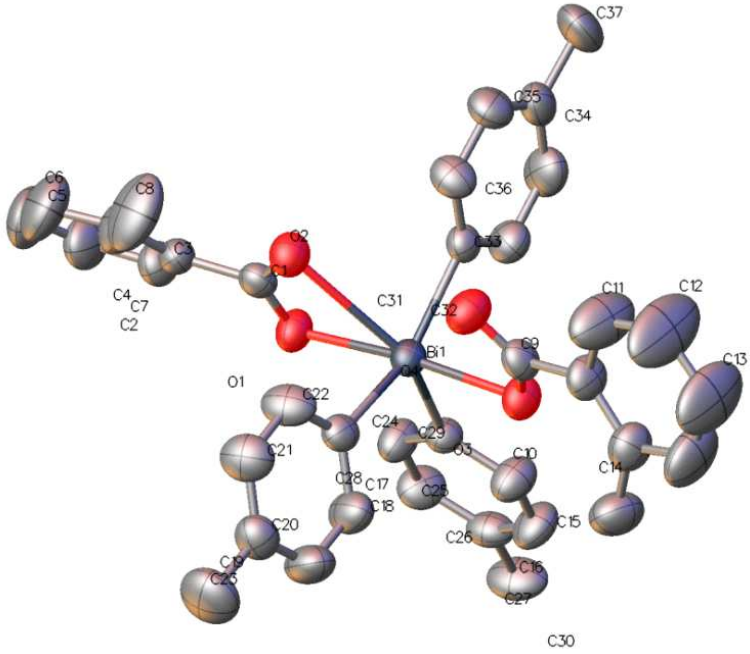


Fig.3 ORTEP view for **6,** showing 50 % probability ellipsoids with atom numbering scheme

3.4 Biological Studies

Organobismuth(V) compounds have been considered to be potentially bioactive species owing to their biocidal properties and low toxicity [3, 4]. They were preliminary screened for their antimicrobial, alpha amylase and protein kinase inhibition activity so as to find out their biological significance in medicinal chemistry.

3.4.1 Antimicrobial assay

Compounds **(1-8)** were screened *in vitro* to determine their antimicrobial potential against four bacterial as well as four fungal strains using the standard drugs cefixime or roxithromycin and clotrimazole as the case may be and the data are given in Table-3. The compound **2**, has shown significant antibacterial activity against *E.coli*, having MIC value of 6.25 µg/mL, whereas **1**, **5** and **8**, with MIC value 12.5 µg/mL for each also exhibit good activity against the two bacterial strains, namely *B.subtilus* and *E.coli*. The antifungal activity profile for **1**, **2** and **5** described their significant activity against *A.flavus* with MIC value of 6.25 µg/mL. The results are encouraging when compare with relevant standard drug and data demonstrate that antimicrobial activity of the target compounds became enhanced when appropriate carboxylic acids were complexed with respective triarylbismuth moiety as evinced by their least MIC values (lesser the MIC value for the compound, more it will be effective).

The increased antimicrobial activity of the compounds may be attributed to the effect of pentavalent bismuth metal ion and the current data can be interpreted in light of Tweedy's theory of chelation [48]. The polarity of metal ion becomes generally reduced due to chelation because of the partial sharing of positive charge of bismuth with the donor carboxylate moiety. The delocalization of π electrons on the aromatic ring may also contribute in enhancing the antimicrobial potential of the compounds when compared with the reported data [49]. The presented work demonstrate that compounds **1**, **2** and **5** showed significant MIC value of 6.25µg/mL which have naphthalene and methyl substituents (electron donating group) in their structural motifs that seem to facilitate the delocalization of π electrons within the system. The delocalization further increase lipophilic character of the synthesized complexes that aids in gaining entry into the lipid bilayer of bacterial and fungal cell membrane with ultimate increase in their antimicrobial properties [50, 51].

Table.3 Antimicrobial activity data for **(1-8)**

Number of compounds	MIC(µg/mL)							
	Antibacterial Strains				Antifungal Strains			
	Bacillus Subtilis	***Staphylococcus Aureus***	***Klebsiella Pneumoniae***	***Escherichia coli***	***Aspergillus Flavus***	***Aspergillus Niger***	***Aspergillus Fumigatus***	***Mucor***
1	**12.5**	50	25	25	**6.25**	25	12.5	50
2	25	12.5	50	**6.25**	**6.25**	12.5	12.5	>50
3	50	50	50	50	25	25	12.5	>50
4	25	50	25	25	12.5	50	12.5	>50
5	**12.5**	25	25	50	**6.25**	50	25	>50
6	25	25	50	25	25	25	12.5	50
7	50	50	50	25	25	50	25	>50
8	25	25	25	**12.5**	25	50	50	>50
Ph_3BiBr_2	50	25	25	25	12.5	12.5	12.5	12.5
$(p\text{-tolyl})_3BiBr_2$	25	25	12.5	12.5	12.5	12.5	12.5	12.5
Cefixime*	1.11	0.334	0.334	1.11	-	-	-	-
Roxithromycin*	0.334	0.334	0.334	0.334	-	-	-	-
Clotrimazole*	-	-	-	-	10	5	5	2.5
DMSO	-	-	-	-	-	-	-	-

* Standard drug

- No activity

3.4.2 Alpha amylase inhibition

The compounds **(1-8)** were bioassayed for their chromogenic alpha amylase inhibition activity. The reported percentage inhibition of alpha amylase has been observed at 100µg/mL, using acarbose as a positive control and DMSO as a negative control and the data are presented in Table 4. The data shows that **(2)** and **(6)** exhibit highest percentage inhibition of 31.49 and 34.80 % respectively, as both compounds contain an electron donating group ($-CH_3$) in their structures. The activity of the complexes were also compared with the precursors, [Ph_3BiBr_2 and $(p\text{-tolyl})_3BiBr_2$] and found the least % age inhibition of -33.54 and -33.70 % respectively for them, but on derivatization with substituted carboxylic acids, the percent inhibition became enhanced about 15 to 35 % for the metal complexes [27]. Hence greater the percentage inhibition value for alpha amylase enzyme, more it will be effective against hyperglycemia or diabetes mellites. The

data are presented with the prospects that the reported compounds may prove themselves as potent candidates in future drug development and delivery processes.

3.4.3 Protein kinase inhibition assay

To evaluate the protein kinase inhibitory potential for **(1-8)** surfactin and DMSO were used as positive and negative control and data are presented in Table 4. The non-toxic effect of DMSO was verified by the absence of growth inhibition zone. A significant inhibition zone of 30 mm bald phenotype corresponds to **(2)** which is equivalent to the standard drug (surfactin; 100 µg /disc) whereas **(7)** and **(8)** show bald zone at 20 mm for each. The zones of inhibition greater than 20 mm bald and clear (zones) are attributable to significant activity and cytotoxic nature respectively for the under trialed compounds. The electron donating group ($-CH_3$) attached to the carboxylic moiety in compound **(2)** is responsible for this exceptional percentage inhibition of protein kinase enzyme at 100 µg disc loading. The assay involves *Streptomyces* 85E strain to envisage the protein kinase inhibition, as it resembles with the eukaryotic cells that readily provides evidence about anticancer and cytotoxic nature of the synthesized products. The protein kinases are involved in phosphorylation of various eukaryotic cells, whereas the protein kinase inhibitors are specifically involved in blocking them in order to stop the proliferation of cancerous cells. The kinase inhibition data for some of the organobismuth compounds are encouraging and may prove suitable agents in futuristic drug discovery projects [27].

3.4.4 Brine shrimp lethality assay

The brine shrimp lethality assay is a simple, robust and least expensive technique for assessing the cytotoxic nature of the synthesized organobismuth(V) complexes , so as to develop a toxicity appraisal for them in comparison to the reference drug (doxorubicin). The results were documented in term of LD_{50} value, which refer to the dose required to kill half of the tested population in specific time duration (Table 4). The percentage mortality of *Artemia salina* was tested in serial dilutions as 200, 100, 50 and 25 µg/mL. The least LD_{50} value for **1**, **4** and **7** were found to be 18.61, 5.25 and 19.05 µg/mL respectively, describing their toxic nature whereas **5** show the least toxic nature having the value of 114.39 µg/mL,. The data suggest that the synthesized compounds are moderately toxic and can be further optimized for future drug discovery processes by altering their structural motifs [24].

Table.4 Alpha amylase and Protein kinase inhibition activity data for **(1-8)** with LD_{50} values

Number of compounds	Alpha amylase inhibition assay	Protein kinase inhibition assay		Brine shrimp lethality assay				
		Zones (mm) at 100µg/disc		% age Mortality				
	% age inhibition 100 (µg/mL)	Clear zone (mm)	Bald zone (mm)	200 (µg/mL)	100 (µg/mL)	50 (µg/mL)	25 (µg/mL)	LD_{50} (µg/mL)
1	18.58	25	-	100	80	70	60	18.61
2	31.49	-	30	100	60	50	40	44.45
3	11.65	22	18	100	60	50	20	56.95
4	27.40	30	-	100	90	80	80	5.25
5	21.10	-	-	100	10	0	0	114.39
6	34.80	-	15	100	90	80	50	24.77
7	14.64	-	20	100	90	80	60	19.05
8	23.50	25	20	100	70	60	30	42.54
Ph_3BiBr_2	-33.54	-	20	100	100	90	30	30.31
$(p\text{-}tolyl)_3BiBr_2$	-33.70	24	-	100	100	90	50	25.01
Acarbose*	69.29							
Surfactin*		-	30					
Doxorubicin*				90	80	60	30	5.93
DMSO	-	-	-	-	-	-	-	-

* Standard drug

- No activity

3.5 Computational Studies

Molecular docking studies of the synthesized compounds against various enzymes were carried out to find out their biological potential as the CADD tools are diagnostic in this regards.

3.5.1 *H. pylori* Urease

The molecular docking data for **(1-8**), presented in Table 5, suggest that compound **(7)** exhibit the highest GOLD fitness score of 56 and could serve as a lead compound in the present study. The active site residues of protein that interact directly with (**7)** include Asp403, Ala407, His459, Cys559, His560, Arg576, Val558, Met555, Asp554, Glu551, Arg606, Gly605, Gln602, Ile376,

Ser601, Val607, and Thr408 (Fig.4). The binding pattern analysis of the docked complex depicts strong hydrogen bonding between oxygen atoms of the ligand with the Arg606 and Cys559 residues of the receptor. The amide-pi stacking interactions play an important role towards improved binding affinity in receptor-ligand complexes [52]. Moreover the binding orientation analysis demonstrates that multiple aromatic interactions such as amide-pi and alkyl-pi, in docked complexes, are playing a crucial role in anchoring the ligand within the binding pocket of the protein (Fig.**5**). For instance, protein residues Arg606, Val558, Cys559, and Asn406 are stabilizing the complex by forming aromatic interactions with the benzene ring of the ligand. The results of the docking studies suggest that reported compounds are potentially active against *H. pylori* urease that could find place for themselves as potent inhibitors in future drug discovery and development projects.

Table-5 : GOLD fitness score against various enzymes* for **(1-8)**

Compound	**GOLD Fitness Score**		
	H. pylori* Urease	**Tyrosine kinase***	**Human pancreatic alpha amylase***
1	40.49	**64.09**	55.69
2	29.38	46.28	**62.65**
3	55.99	40.51	57.15
4	41.10	40.72	**57.19**
5	44.25	41.82	**60.91**
6	28.45	41.91	58.64
7	**56.30**	58.85	**62.1**
8	42.2	17.44	45.79

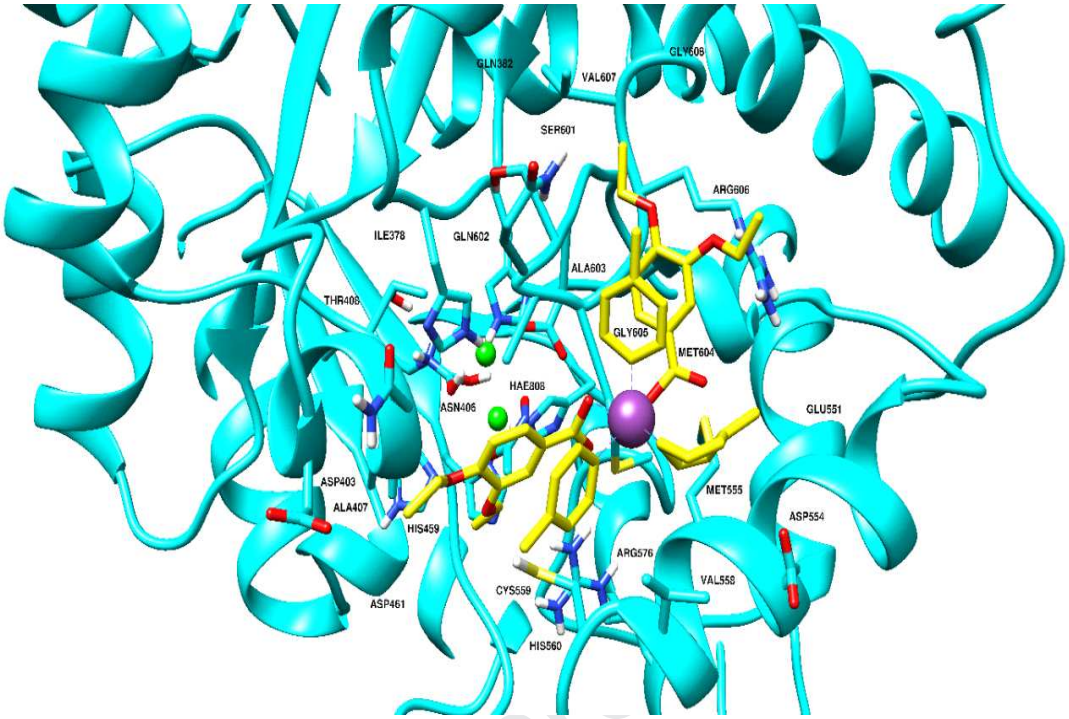


Fig.-4 Preferred binding mode for **(7)** in the active site of *H. pylori* urease

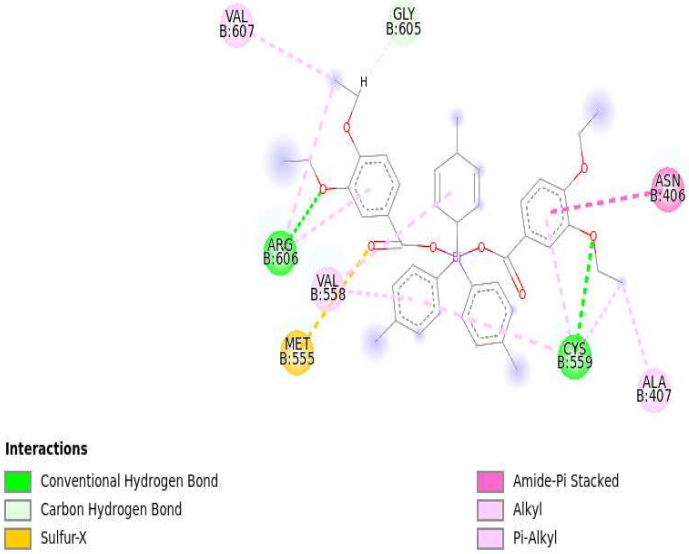


Fig.-5 Two-dimensional depiction of docked lead compound within the binding pocket of urease protein through DS Visualizer.

3.5.2 Tyrosine kinase

The molecular docking studies for **(1-8)** against the receptor tyrosine kinase were accomplished as the studies widely suggests that kinases play an important role in the onset of cancer by increasing cell proliferation [53, 54]. The data show that compound **(1)** with the GOLD fitness score of 64.09 has the higher binding potential to kinase, whereas rest of the compounds also demonstrates substantial binding affinity with the enzyme structure (Table 5). The active site residues of protein that involved in binding with the ligand include; Ala27, Lys180, Pro182, Gly26, Asp160, Asp105, Leu149, Leu104, Asn147, Arg146, Thr159, and Phe28 (Fig.**14**^{S}). The strong hydrogen bondings have been observed between protein residues (Asp160, Asn147, and Arg146) and the oxygen atoms of the ligand (Fig.**15**^{S}). It is worth to be mentioned here, that compound **(7)** in addition to **(1)** may prove as a potential candidate for "lead compound" against receptor tyrosine kinase in future studies as it's *in silico* binding interactions with the enzyme are also significant.

3.5.3 Human Pancreatic Alpha Amylase

Molecular docking studies were performed to analyze the amylase inhibitory potential of the synthesized compounds and the data are given in Table 5. The highest GOLD fitness score of 62.65 was determined for **(2)** which suggest its firm binding affinity in the protein active site and may be regarded as lead compound in the present study. The GOLD fitness scores for other compounds are also impressive and may be considered for their possible role as amylase inhibitors in future drug discovery processes. The active site residues involved in receptor-ligand interactions include Trp59, Gln63, Thr163, Leu162, Leu165, His201, Ala198, Glu233, Asp300, and Ile235 as illustrated in Fig.6. A strong hydrogen bond interaction has been observed between Thr163 and oxygen atom of the ligand. The major role of anchoring and stabilizing the ligand within the binding pocket has been played by several pi-pi and pi-alkyl interactions of benzene ring of the ligand with the protein residues (Fig.**7**).

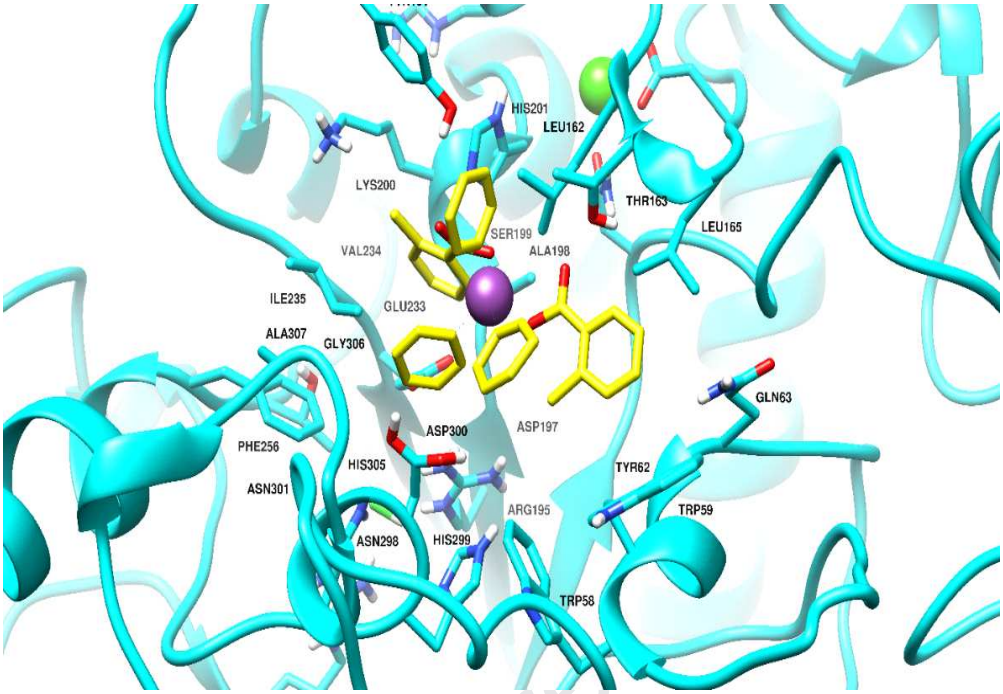


Fig 6 Preferred binding modes for **(2)** in active sites of human pancreatic alpha amylase

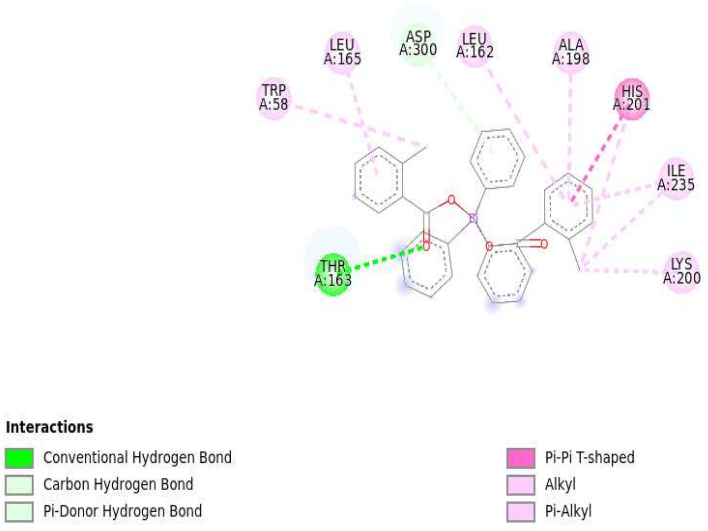


Fig.7. 2-D depiction for **(2)** showing interactions within the binding pocket of alpha amylase protein (through DS Visualizer).

Conclusions

Eight new triarylbismuth(V) carboxylates **(1-8)** were successfully synthesized and were well characterized by FTIR, NMR spectroscopy and single crystal X-ray diffraction techniques. The X-ray structure for **(6)** described anisobidentate nature of one (of the two) carboxyl group that ultimately leads to hexa-coordination for bismuth with distorted octahedral molecular geometry, while for **(2), and (5)** the bismuth center is five coordinated with having distorted trigonal bipyramidal molecular geometry. They were preliminary assayed to check their biocidal properties like anti-microbial, antidiabetic, protein kinase inhibition and brine shrimp lethality assay in order to develop a limited structure to activity relationship (SAR). *In silico* molecular docking studies of these compounds were also conducted against three enzyme systems namely; H. pylori urease, EGFR tyrosine kinase and human pancreatic alpha amylase; to investigate their binding potential in the active sites of target protein receptors. The Gold fitness scores for **1**, **2** and **7** against EGFR tyrosine kinase, human pancreatic alpha amylase and H. pylori urease are 60.09, 62.65 and 56.30 respectively which placed them lead compounds in their respective biological study domains. The hydrogen bonding and aromatic interactions (such as pi-pi stacked, pi-sigma, and pi-alkyl) have played a crucial role in anchoring the ligands within the binding pockets of the receptor. The outcomes of the docking studies demonstrate the inhibitory potential of the compounds against the selected drug targets that may provide a basic scaffold for discovering new therapeutic agents in future drug discovery processes. Furthermore the docking data manifest that tolyl group of tritolylbismuth derivatives provide the best fit for the binding pockets of the receptor proteins that may rendered them as potent enzyme inhibitors whereas triphenylbismuth compounds show strong antimicrobial character in particular to those having carboxylate moiety with aromatic ring bear electron donating groups. The results obtained from experimental and computational studies suggest that the organobismuth carboxylates, particularly **1**, **2**, **5** and **8** have promising biocidal activity profiles that could provide a clue to the development of even more potent antimicrobial agents besides improving their anti-diabetic, anti-cancer and gastrointestinal properties by altering/modifying their chemical structures.

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Appendix - Supplementary data

The CCDC numbers for the reported compounds are 1969180, 1969182 and 1969184. The data can be downloaded from CCDC data base which can be obtained free of charge via http://www.ccdc.cam.ac.uk/conts/retrieving.html, or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223-336-033; or e-mail: deposit@ccdc.cam.ac.uk.

Abbreviations

LD_{50} : Lethal dose 50%, **BSLA :** Brine shrimp lethality assay, **EGFR :** Epidermal growth factor receptor, **NMR :** Nuclear magnetic resonance, **THF :** Tetrahydrofuran, **XRD :** X-ray diffraction. **SAR :** Structure to activity relationship, **GOLD :** Genetic Optimization for Ligand Docking, **CADD :** Computer-aided drug design, **ATCC :** American type culture collection, **FCBP :** Fungal Culture Bank of Pakistan.

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Highlights

- Bismuth(V) carboxylates of type $Ar_3Bi(OOCR)_2$ were synthesized and characterized
- The X-ray structure for **(6)** revealed a rare anisobidentate behavior of one carboxyl group with the emergence of hexacoordinated bismuth centre.
- They are quite stable both in solid and solution phase to exert a powerful bioactive role.
- The compound **(2)**, **(5) (7)** and **(8)** show substantial inhibition activity against alpha amylase as well as kinases when compared with the respective standard drug.
- Molecular docking data disclosed that some compounds are potentially active against *H. pylori* urease especially **(7)** with the highest GOLD fitness score.

Declaration of interest statements

The authors whose names are listed below certify that they have no affiliation with any organization with any financial interest. The corresponding author declared on the title page is Imtiaz-ud-Din.

1. **Mehwish Mehmood**
   Research work carried out by the scholar and prepared first draft of the manuscript.

2. **Dr. Imtiaz-ud-Din (Corresponding author)**
   Research supervisor and main motivator for the reported research work. The article was prepared in a presentable form so as to be submitted in the journal.

3. **Sumaira Abbas**
   She helped the scholar in interpretation of the spectra of the synthesized compounds.

4. **Dr. Syed Sikander Azam**
   He carried out the molecular docking studies.

5. **Dr. Ihsan-ul Haq**
   He assisted in gathering the biological activities data

6. **Dr. Muhammad N. Tahir**
   (X-ray Crystallographer) He helped in collecting the single crystal data for the compounds.

7. **Nousheen Parvaiz**
   Helped the scholar in interpretation the results of molecular docking studies.