SYNTHESIS, CHARACTERIZATION AND ANTIBACTERIAL ACTIVITY OF LAUROYLTHIOAMIDE AMINO ACID DERIVATIVES AND THEIR METAL COMPLEXES

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The study on thiourea derivatives has become a subject of interest due to their potential application in biological area as antibacterial and anticancer agents. In this study, four new thiourea derivatives have been successfully synthesized from the combination of three bioactive molecules such as lauroyl, thiourea and amino acids. The respective compounds namely 3-(3-dodecanoyl-thioureido)-propionic acid **(R1)**, 2-(3-dodecanoyl-thioureido)-3-methyl-butyric acid **(R2)**, (3-dodecanoyl-thioureido)-acetic acid **(R3)** and 2-(3-dodecanoyl-thioureido)-3-phenyl-propionic acid **(R4)** were prepared from reactions between β-alanine, DL-valine, L-glycine and L-phenylalanine with lauroyl isothiocyanate. In order to investigate the potential of metal complexes as antibacterial agents, compounds **R2** and **R4** which are two most potential ligands during antibacterial screening were reacted with zinc(II) chloride and copper(II) chloride to give [Zn(**R2-H**)Cl_2] (**M1**), [Zn(**R4-H**)Cl_2] (**M2**) and [Cu(**R4-H**)Cl_2] (**M3**). Compounds **R1-R4** and their metal complexes (**M1-M3**) were characterized using spectroscopic techniques such as Fourier Transform Infrared (FTIR), ^1H and ^{13}C Nuclear Magnetic Resonance (NMR), Ultraviolet spectroscopy (UV) and Gas Chromatography-Mass Spectrometry (GC-MS). The chemical formula

of all compounds were confirmed by elemental analysis. For compounds **R1-R4**, five significant peaks were assigned to ν((N-H + ν(O-H)), ν(C=O) carboxylic acid, ν(C=O) amide, ν(C-N) and ν(C=S) at 3214-3332 cm^{-1}, 1695-1712 cm^{-1}, 1634-1692cm^{-1}, 1233-1249 cm^{-1} and 698-723 cm^{-1}, respectively in the FTIR spectra. In the ^{1}H NMR spectra, the presence of N-H and O-H protons were detected at range of δ_H 6.13-10.97 ppm and δ_H 9.65-11.28 ppm, respectively. While in ^{13}C NMR spectra, the thione carbons (C=S) appeared at δ_C174-179 ppm. The absorption bands for C=S, C=O and p-band aryl were indicated in the UV spectra as n-π^* and π-π^* electronic transitions. In the FTIR spectra of the complexes, a significant loss of ν(C=O) carboxylic acid peak at range 1710-1712 cm^{-1} and appearance of asymmetric and symmetric stretching of carboxylate at range 1589-1596 cm^{-1} and 1406-1435 cm^{-1} were indicated comparing to the ligands. In addition to this, the appearance of new peak, Zn-O and Cu-O were detected at range 422-456 cm^{-1} suggesting the formation of metal complexes through oxygen chelating donors. The structure of the complexes were also confirmed by Gas Chromatography-Mass Spectrometry (GC-MS) analysis where the peaks of the metal complexes in the form of ion [**M1** + $CH_3OH]^+$, [**M2** + $CH_3O]^-$, [**M3** + $CH_3OH]^+$ were found in low abundance at m/z 528, 571 and 575, respectively. The compounds obtained were further investigated for antibacterial activities. They were tested against Gram-positive and Gram-negative strains using agar-well diffusion method. **R4** has the highest bacteriostatic activity towards two respective Gram-negative bacteria, *Escherichia coli* and *Salmonella typhimurium*. However, complexes **M1-M3** showed weak inhibition towards the Gram-negative bacteria reflecting the effect of metal ions in decreasing the antibacterial activity of the ligands. Nevertheless, complex **M3** showed good antibacterial activity towards *S. epidermidis* with inhibition zone measured at

approximately 17 mm. Thus, two potential antibacterial agents namely **R4** and **M3** were obtained with specific antibacterial activity towards Gram-negative (*E. coli* and *S. typhimurium*) and Gram-positive (*S. epidermidis*) bacteria, respectively.

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SINTESIS, PENCIRIAN DAN AKTIVITI ANTIBAKTERIA TERBITAN AMINO ASID LAUROILTIOAMIDA DAN KOMPLEKS LOGAMNYA

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Kajian ke atas terbitan tiourea telah menjadi subjek yang menarik kerana potensi aplikasinya dalam bidang biologi sebagai agen antibakteria dan antikanser. Dalam kajian ini, empat terbitan baru tiourea telah berjaya disintesis daripada gabungan tiga molekul bioaktif seperti lauroil, tiourea dan amino asid. Sebatian-sebatian tersebut adalah 3-(3-dodekanoil-tioureido)-propionik asid **(R1)**, 2-(3-dodekanoil-tioureido)-3-metil-butirik asid **(R2)**, (3-dodekanoil-tioureido)-asetik asid **(R3)** dan 2-(3-dodekanoil-tioureido)-3-fenil-propionik asid **(R4)** yang disediakan daripada tindak balas antara β-alanin, DL-valin, L-glisin dan L-fenilalanin dengan lauroil isotiosianat. Untuk mengkaji potensi kompleks logam sebagai agen antibakteria, sebatian **R2** dan **R4** telah ditindakbalaskan dengan zink(II) klorida dan kuprum(II) klorida untuk menghasilkan [Zn(**R2**-H)Cl_2] (**M1**), [Zn(**R4**-H)Cl_2] (**M2**) dan [Cu(**R4**-H)Cl_2] (**M3**). Sebatian **R1-R4** dan kompleks logamnya (**M1-M3**) telah dicirikan menggunakan teknik spektroskopi seperti Inframerah Penukaran Fourier (FTIR), ^{1}H dan ^{13}C Resonans Magnet Nukleus (RMN), specktroskopi Ultra-Lembayung (UV) dan Gas Kromatografi Spektrometer Jisim (GC-MS). Formula kimia bagi semua sebatian telah ditentukan melalui analisis unsur. Bagi sebatian **R1-R4**, lima puncak

penting yang merujuk kepada ν((N-H + ν(O-H)), ν(C=O) asid karboksilik, ν(C=O) amida, ν(C-N) dan ν(C=S) telah diperhatikan masing-masing pada julat 3314-3332 cm^{-1}, 1695-1712 cm^{-1}, 1634-1692 cm^{-1}, 1233-1249 cm^{-1} dan 698-723 cm^{-1} dalam spektra FTIR. Dalam spektra ^{1}H NMR bagi ligan, kehadiran proton N-H dan O-H dikesan masing-masing pada julat δ_H 6.13-10.97 ppm dan δ_H 9.65-11.28 ppm. Manakala dalam ^{13}C RMN, karbon tion (C=S) muncul pada δ_C174-179 ppm. Puncak serapan bagi C=S , C=O dan puncak-p aril juga telah dicerap dalam spektra Ultra-Lembayung sebagai peralihan elektronik n-π^* dan π-π^*. Dalam spektra FTIR bagi kompleks, kehilangan puncak penting ν(C=O) asid karboksilik pada julat 1710-1712 cm^{-1} telah diperhatikan dan kemunculan regangan asimetrik dan simetrik bagi karboksilat pada julat 1589-1596 cm^{-1} dan 1406-1435 cm^{-1} dibandingkan dengan spektra ligan. Tambahan lagi, kemunculan puncak baru, Zn-O dan Cu-O telah dikesan pada julat 422-456 cm^{-1} yang mencadangkan pembentukan kompleks logam melalui pengkelatan penderma oksigen. Struktur kompleks disahkan melalui analisis Gas Kromatografi Spektrometer Jisim (GCMS) di mana puncak untuk kompleks dalam bentuk ion [**M1** + $CH_3OH]^+$, [**M2** + $CH_3O]^-$, [**M3** + $CH_3OH]^+$ dicerap pada kelimpahan yang rendah masing-masing pada m/z 528, 571 dan 575. Sebatian yang diperolehi telah dilanjutkan kajian untuk aktiviti antibakterianya. Kesemua sebatian tersebut telah diuji terhadap strain Gram-positif dan Gram-negatif menggunakan kaedah penyerapan 'agar-well'. **R4** mempunyai aktiviti bakteriostatik paling tinggi terhadap dua bakteria Gram-negatif, *Escherichia coli* dan *Salmonella typhimurium*. Namun, kompleks **M1-M3** menunjukkan perencatan yang lemah terhadap bakteria Gram-negatif menunjukkan kesan ion logam dalam pengurangan aktiviti antibakteria bagi ligan. Walaubagaimanapun, kompleks **M3** menunjukkan aktiviti antibakteria yang baik terhadap *S. epidermidis* dengan ukuran zon perencatan lebih kurang 17

mm. Oleh itu, daripada kajian ini, dua sebatian yang berpotensi untuk dibangunkan sebagai agen antibakteria ialah **R4** dan **M3** dengan aktiviti antibakteria masing-masing terhadap bakteria Gram-negatif (*E. coli* dan *S. typhimurium*) dan Gram-positif (*S. epidermidis*).