

SYNTHESIS, CHARACTERIZATION AND ANTICANCER
ACTIVITIES OF METHYLBENZOYLTHIOUREA AND ITS COPPER (II)
COMPLEXES

RABIA'TUN HIDAYAH BINTI JUSOH

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Hidayah Jusoh.

PERPUSTAKAAN SULTANAH NURZAHIRAH
UNIVERSITI MALAYSIA TERENGGANU (UMT)
21000 KUALA TERENGGANU

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COPPER(II) COMPLEXES**

RABIA'TUN HIDAYAH BINTI JUSOH

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Chairperson : Wan Mohd Khairul Wan Mohamed Zin, Ph.D.

Member : Mohd Sukeri Mohd Yusof, Ph.D.

Faculty : Science and Technology

Thiourea derivatives are potentially versatile ligand and various substituted thioureas have attracted interest in recent years because of their coordination ability to the transition metals and widely used in numerous applications. In this present study, copper(II) complexes featuring methylbenzoylthiourea derivatives are tested for its chemical and physical characteristics and in turn, screened for their anticancer activity. Twenty-eight novel series of 2, 3 and 4-methylbenzoylthiourea derivatives ligands with general formula $R_1PhC(O)NHC(S)NHR_2$ (**L1-L28**), with different substituted groups and two designated complexes (**D1-D2**) have been successfully synthesised and characterised. It was found that the synthesised compounds' yield were in low to good yields (24-85%). The synthesised title compounds were then characterised by usual spectroscopic and analytical methods namely Fourier Transform Infrared (FTIR), UV-Visible analysis, 1H and ^{13}C Multi-nuclear Magnetic Resonance (NMR), CHNS elemental analysis and melting point analysis. Whilst, only twelve molecular structures of the compounds synthesised were confirmed by using single crystal X-ray diffraction method. The IR spectra show the compounds functional groups of interests namely $\nu(N-H)$, $\nu(C=O)$, $\nu(C-N)$ and $\nu(C=S)$ absorbed at $3155-3422\text{ cm}^{-1}$, $1645-1683\text{ cm}^{-1}$, $1241-1384\text{ cm}^{-1}$, $666-799\text{ cm}^{-1}$, respectively. In addition, the $\nu(OH)$ and $\nu(C=O)$ stretching vibration in carboxylic acid for **L3** and **L22** are observed as medium intensity bands in the region $3318-3342\text{ cm}^{-1}$ and $1712-1716\text{ cm}^{-1}$. Infrared spectra of new complexes showed the changes on the frequency absorptions, the $\nu(C=O)$ is shifted from 1662 cm^{-1} to 1591 cm^{-1} and $\nu(C=S)$ from 730 to 770 cm^{-1} in (**D1**). In the case of (**D2**), the frequency of $\nu(C=O)$ has shifted from 1666 cm^{-1} to 1586 cm^{-1} and for $\nu(C-N)$, from 1339 cm^{-1} to 1327 cm^{-1} which indicate the ligand acts as bidentate chelating agents. Infrared spectrum of the (**D1**) shows medium absorption band at 420 cm^{-1} and 597 cm^{-1} which could be assigned to the $\nu(Cu-O)$ and $\nu(Cu-S)$ stretching, whereas the bands at 480 cm^{-1} and 536 cm^{-1} are attributed to $\nu(Cu-O)$ and $\nu(Cu-N)$ stretching for (**D2**). The UV-Vis transitions characteristic for (**L1-L28**) were observed between λ_{max} 201-338

nm which can be assigned as mixture of $n \rightarrow \pi^*$ and $\pi \rightarrow \pi^*$ transitions. The UV-Vis absorption bands for (**D1-D2**) were assigned as $\pi \rightarrow \pi^*$ transition of the rings in the 220-228 nm ($\epsilon = 48700, 60100 \text{ M}^{-1} \text{ cm}^{-1}$) range. These complexes also showed absorption bands assigned as mixture of $n \rightarrow \pi^*$ and $\pi \rightarrow \pi^*$ transitions of conjugated C=O, C=N and C=S chromophores. The absorption bands for complexes in the 400-459 nm ($\epsilon = 476, 747 \text{ M}^{-1} \text{ cm}^{-1}$) range are identified as overlapped between charge transfers (CT) transition and d-d bands in the UV-Vis spectra. In the ^1H NMR spectra, the signal of $\delta_{\text{H}}(\text{N1})$ and $\delta_{\text{H}}(\text{N2})$ presence at around $\delta_{\text{H}}10-13$ ppm. Whilst in ^{13}C NMR spectra, the signal for carbonyl and thione atoms were observed at around $\delta_{\text{C}} 169-182$ ppm and $\delta_{\text{C}} 153-174$ ppm. The molecular structures of the title compounds of (**L1-L2, L4-L7, L12, L14, L18 and L25**) adopt *trans-cis* configuration with respect to the positions of the methylbenzoyl and amine substituent groups relative to the thiono S atom across their C-N bonds, respectively. However, only (**L13**) does not show any configuration. The molecules are stabilised by intra and inter-molecular hydrogen bonds, whereas no inter-molecular hydrogen formed in the case of **L13**. An X-ray investigation for (**D2**) shows that the ligands are chelated to the central Cu atom in bidentate manner in four coordination square-planar geometry via nitrogen and oxygen atoms. From the cytotoxic assay study, the several compounds were evaluated for *in vitro* cytotoxicity against human leukemic (HL60) and human breast cancer (MCF-7) cell lines. Compounds **L15** and **L17-L19** were found to be the most active from these series which have shown inhibition against HL60 cells in the range at 2.5-6.0 $\mu\text{g/ml}$, respectively. Moreover, copper(II) complexes (**D1-D2**) exhibited moderate cytotoxic potency against MCF-7 cancer cells tested at the 13-14 $\mu\text{g/ml}$ concentration.

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SINTESIS, PENCIRIAN DAN AKTIVITI ANTIKANSER METILBENZOILTIOUREA DAN KOMPLEKS KUPRUM(II)

RABIA'TUN HIDAYAH BINTI JUSOH

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Pengerusi : Wan Mohd Khairul Wan Mohamed Zin, Ph.D.

Ahli : Mohd Sukeri Mohd Yusof, Ph.D.

Fakulti : Sains dan Teknologi

Terbitan tiourea berpotensi sebagai ligan serba boleh dan dengan pelbagai kumpulan pengganti telah mendapat perhatian sejak kebelakangan ini disebabkan kebolehnya berkoordinat dengan logam-logam peralihan dan digunakan di dalam pelbagai aplikasi. Dalam kajian ini, kompleks kuprum(II) menampilkan terbitan-terbitan metilbenzoiltiourea telah dikaji untuk ciri-ciri fizika, kimia dan kemudiannya diuji di dalam aktiviti antikanser. Sebanyak 28 siri terbitan baru 2, 3 dan 4-metilbenzoiltiourea mempunyai formula am $R_1PhC(O)NHC(S)NHR_2$ (**L1-L28**), dengan pelbagai kumpulan pengganti telah berjaya disintesis and dicirikan. Didapati peratus hasil sebatian-sebatian yang disintesis adalah (24-85%) dalam lingkungan rendah hingga baik. Kesemua sebatian yang disintesis seterusnya dicirikan dengan menggunakan analisis spektroskopi iaitu spektroskopi Infra Merah (IR), Ultralembayung Sinar Nampak (UV-Vis), 1H dan ^{13}C Resonans Magnetik Nukleus (NMR), analisis unsur CHNS dan juga penentuan takat lebur. Sementara itu, sebanyak 12 struktur hablur yang terbentuk dikaji secara kristalografi hablur sinar-X tunggal. Spektra IR menunjukkan empat kumpulan berfungsi iaitu $\nu(N-H)$, $\nu(C=O)$, $\nu(C-N)$ dan $\nu(C=S)$ pada julat masing-masing $3155-3422\text{ cm}^{-1}$, $1645-1683\text{ cm}^{-1}$, $1241-1384\text{ cm}^{-1}$ dan $666-799\text{ cm}^{-1}$. Sebagai tambahannya, regangan $\nu(OH)$ dan $\nu(C=O)$ di dalam asid karboksilik untuk **L3** and **L22** diperhatikan sebagai puncak medium pada sekitar $3318-3342\text{ cm}^{-1}$ dan $1712-1716\text{ cm}^{-1}$. Spektra inframerah bagi kedua-dua kompleks baru menunjukkan perubahan penyerapan frekuensi, puncak $\nu(C=O)$ teranjak dari 1662 cm^{-1} kepada 1591 cm^{-1} dan $\nu(C=S)$ dari 730 kepada 770 cm^{-1} untuk (**D1**). Dalam kes (**D2**), frekuensi $\nu(C=O)$ telah teranjak dari 1666 cm^{-1} kepada 1586 cm^{-1} dan $\nu(C-N)$ dari 1339 cm^{-1} kepada 1327 cm^{-1} di mana menunjukkan ligan bertindak sebagai agen pengkelat bidentat. Spektrum inframerah (**D1**) menunjukkan puncak penyerapan medium pada 420 cm^{-1} and 597 cm^{-1} yang merujuk kepada regangan $\nu(Cu-O)$ dan $\nu(Cu-S)$, manakala pada puncak 480 cm^{-1} dan 536 cm^{-1} adalah merujuk kepada regangan $\nu(Cu-O)$ dan $\nu(Cu-N)$ untuk (**D2**). Ciri-ciri Ultralembayung Sinar Nampak (UV-Vis) bagi (**L1-L28**) telah dikenalpasti pada panjang gelombang $201-338\text{ nm}$ sebagai pencampuran peralihan elektronik $n \rightarrow \pi^*$ dan $\pi \rightarrow \pi^*$. Jalur-jalur penyerapan Ultralembayung Sinar Nampak (UV-Vis) bagi (**D1-D2**) pada sekitar $220-$

228 nm ($\epsilon = 48700, 60100 \text{ M}^{-1} \text{ cm}^{-1}$) dikenalpasti sebagai peralihan $\pi \rightarrow \pi^*$ adalah bagi gelang fenil. Kompleks-kompleks ini juga menunjukkan jalur-jalur penyerapan sebagai pencampuran peralihan elektronik $n \rightarrow \pi^*$ dan $\pi \rightarrow \pi^*$ adalah merujuk kepada kromofor C=O, C=N and C=S yang terkonjugat. Jalur-jalur penyerapan bagi kompleks pada sekitar 400-459 nm ($\epsilon = 476, 747 \text{ M}^{-1} \text{ cm}^{-1}$) adalah dikenalpasti sebagai pertindihan di antara peralihan cas (CT) dan d-d di dalam spektra ultralembayung. Dalam spektra ^1H NMR, kehadiran isyarat bagi $\delta_{\text{H}}(\text{C}(\text{O})\text{NH})$ dan $\delta_{\text{H}}(\text{Ph-NH})$ pada sekitar $\delta_{\text{H}}10-13$ ppm. Manakala spektra ^{13}C NMR pula, isyarat bagi karbon karbonil dan tion dapat diperhatikan pada sekitar $\delta_{\text{C}} 169-182$ ppm dan $\delta_{\text{C}} 153-174$ ppm. Struktur hablur bagi (**L1-L2**, **L4-L7**, **L12**, **L14**, **L18** dan **L25**) yang disintesis menunjukkan konfigurasi *trans-cis* bagi kedudukan kumpulan metilbenzoil dan amina terhadap kumpulan tion C=S pada ikatan C-N masing-masing. Walaubagaimanapun, hanya molekul (**L13**) tidak memberikan konfigurasi. Molekul-molekul ini distabilkan oleh ikatan hidrogen intra dan inter-molekul, manakala molekul **L13** tidak mempunyai ikatan hidrogen inter-molekul. Kajian sinar-X untuk (**D2**) menunjukkan ligan terkelat kepada atom Cu secara bidentat yang berkoordinasi di dalam segi empat planar. Daripada kajian sitotoksik *in vitro*, beberapa sebatian yang disintesis diuji terhadap sel leukemia manusia (HL60) dan sel kanser payu dara (MCF-7). Didapati sebatian **L15** dan **L17-L19** dalam siri ini, menunjukkan perencatan aktif terhadap (HL60) pada sekitar 2.5-6.0 $\mu\text{g/ml}$, masing-masing. Di samping itu, kompleks kuprum(II) (**D1-D2**) menunjukkan sitotoksik yang sederhana terhadap MCF-7 pada kepekatan 13-14 $\mu\text{g/ml}$.