SYNTHESIS, CHARACTERIZATION, ANTIMICROBIAL AND MOLECULAR DOCKING STUDIES OF 1,3-THIAZOLE DERIVATIVES

BY

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ABSTRACT

There is growing urge to develop treatment systems to cure the diseases and one of the main options is drug development. Heterocyclic thiazole emerges as one of the most frequently reported in those fields. Since thiazole derivatives have been recognized in various biologically active agents, two series of thiazole derivatives which were 5-acetyl-4-methyl-1,3-thiazole (Series **A**; **T1A**-**T17A**) and 4,5-dimethyl-1,3-thiazole (Series **B**; **T1B**-**T17B**) were synthesized and characterized *via* ^{1}H and ^{13}C NMR, FTIR, UV-Vis and EI-MS. In IR analysis, all synthesized compounds exhibited important absorption bands. The data of UV analysis confirmed the presence of several chromophores which contributed in formation of electronic transition of $\pi \rightarrow \pi^*$ and $n \rightarrow \pi^*$ in the molecules. All resonances can be observed at expected regions in ^{1}H and ^{13}C NMR analysis. Mass spectra of all compounds showed acceptable m/z values which is in accordance with their theoretical molecular mass. In order to investigate the potential of compounds as antimicrobial agents, screening and *in-vitro* assays were applied. In disc diffusion test, all compounds in Series **A** inhibited the tested microbial strains with inhibition zone of 7.0 – 18.5 mm. In Series **B**, maximum inhibition zone is 16.3 mm. Based on this preliminary screening, ten newly synthesized compounds from Series **A** which contain substituted phenyl ring at position 2 of thiazole ring which are **T3A**, **T4A**, **T5A**, **T7A**, **T8A**, **T10A**, **T11A**, **T12A**, **T15A** and **T16A** were selected for further *in-vitro* assays. The MIC values revealed that all the selected compounds showing remarkable antimicrobial activity against both bacterial strains and fungus with **T3A**, **T4A**, **T5A** and **T7A** exhibited highest MIC value of 1.25 mg/mL towards *B. cereus*. The MBC assay indicated that all compounds demonstrating highest mortality properties towards *K. pneumoniae* with concentration of 10.0 mg/mL. The result of all combinations from synergistic effect between antibiotic and compound showed major antagonism and indifferent effects but a synergistic effect was observed in **T4A**, **T7A**, **T10A**, **T11A**, **T12A** and **T16A** compounds in combination with Tetracycline with FICI values of 0.2-0.3 against *E. coli*. Compound **T4A** was the most active compound with significant killing ability towards all tested microbes by showing the lowest number of colonies survived after 30 minutes at range of 13×10^2 - 43×10^2 CFU/mL followed by **T7A** and **T5A** at range of 17×10^2 - 48×10^2 and 13×10^2 - 51×10^2 CFU/mL respectively. **T4A** showed highest percentage of CV uptake towards *E. coli* and *S. flexneri* with percentage of 77.7% and 83.1%, respectively. Leakage determination of nucleic acids (UV_{260}) and protein (UV_{280}) absorbing materials showed **T4A** and **T7A** showed promising results with highest absorbance values of OD_{260} were recorded at 1.07 and 0.98 against *E. coli* while, OD_{280} were recorded at 1.00 and 0.98 towards *B. subtilis* at concentration of 4×MIC. All synthesized compounds of both series were subjected to *in silico* molecular docking screenings towards GlcN-6-P synthase as the target enzyme. The results revealed the significant binding energy values of **T4A**, **T7A** and **T5A** which are in agreement with antimicrobial results with -7.73, -7.32 and -7.31 kcal/mol respectively.

خلاصة البحث

دوافع متزايدة لتطوير أنظمة علاجية لعلاج الأمراض، وأحد الخيارات الرئيسية هو تطوير الأدوية. يعتبر الثيازول الحلقي غير المتجانس من أكثر المركبات التي تم الإبلاغ عنها في هذه المجالات. منذ بداية التعرف على مشتقات الثيازول في العديد من المواد النشطة بيولوجيا تم توليف سلسلتين من مشتقات الثيازول، وهي: 5-أسيتيل-4-ميثيل-1،3-ثيازول (السلسلة **A**: **T17A–T1A**) و 4،5-ثنائي ميثيل -1،3-ثيازول (السلسلة **B**: **T17B–T1B**) وتمييزها من خلال الرنين المغناطيسي النووي لـ H^1 و C^{13} (NMR)، وتحويل فورييه للطيف بالأشعة تحت الحمراء (FTIR)، ومطيافية الأشعة المرئية وفوق البنفسجية (UV-Vis)، و EI-MS. في تحليل الأشعة تحت الحمراء أظهرت جميع المركبات التي تم توليفها نطاقات امتصاص مهمة. أكدت بيانات تحليل UV- وجود العديد من الكروموفورات التي ساهمت في تشكيل الانتقال الإلكتروني لـ $\pi \rightarrow \pi^*$ و $n \rightarrow \pi^*$ في الجزيئات، وبالإمكان ملاحظة جميع الرنات في المناطق المتوقعة في تحليل الرنين المغناطيسي النووي لـ H^1 و C^{13}. أظهرت أطياف الكتلة لجميع المركبات قيم m/z مقبولة والتي توافقت مع كتلها الجزيئية النظرية. من أجل التحقيق في إمكانيات المركبات كمواد مضادة للميكروبات، تم تطبيق فحوصات مسحية وفحوصات مخبرية خارج الجسم الحي تجاه سلالات. في اختبار انتشار الأقراص، ثبطت جميع المركبات في السلسلة **A** السلالات البكتيرية المختبرة بمنطقة تثبيط بلغت 7.0 – 18.5 مم. في السلسلة **B**، بلغ الحد الأقصى لمنطقة التثبيط 16.3 مم. استنادًا إلى هذا الفحص الأولي، تم اختيار عشرة مركبات من السلسلة A المولفة حديثًا والمحتوية على حلقة فينيل مستبدلة في الموضع 2 من حلقة الثيازول، وهي **T3A**، **T4A**، **T5A**، **T7A**، **T8A**، **T10A**، **T11A**، **T12A**، **T15A** و **T16A** لمزيد من الاختبارات خارج الجسم الحي. أظهرت قيم التركيز الأدنى للتثبيط (MIC) أن جميع المركبات المختارة امتلكت نشاطًا ملحوظا مضادًا للميكروبات ضد كل من السلالات البكتيرية والفطريات، حيث أظهرت **T3A** و**A4T** و **T5A** و **T7A** أعلى قيم MIC حيث بلغت 1.25 مجم/مل تجاه العصويات الشمعية. أشارت اختبارات التركيز الأدنى المضاد للبكتيريا إلى أن جميع المركبات قد أظهرت أعلى خاصية للإبادة تجاه الكَلِبْسية الرئوية بتركيز 10.0 مجم/مل. أظهرت نتائج جميع التوليفات بين المضادات الحيوية والمركبات المولفة تأثيرا تناقضيا كبيرا وتأثيرات حيادية، ولكن لوحظت تأثيرات تآزرية في المركبات **T4A** و **T7A** و **T10A** و **T11A** و **T12A** و **T16A** المدمجة مع التتراسيكلين مع قيم FICI بلغت 0.2 إلى 0.3 ضد الإشريكية القولونية.. كان المركب **T4A** المركب الأكثر نشاطًا مع قدرة إبادة كبيرة تجاه جميع الميكروبات المختبرة لإنتاجه أقل عدد من المستزرعات الناجية بعد 30 دقيقة وذلك في مجال 13×10^2-43×10^2 CFU/مل، يليه المركبين **T7A** و **T5A** في نطاق 17×10^2-48×10^2 و 13×10^2-51×10^2 CFU/مل لكل منهما. أظهر **T4A** أعلى نسبة امتصاص لـ CV ضد الإشريكية القولونية والشيغيلة الفلكسنرية وذلك بنسبة 77.7٪ و 83.1٪ على التوالي. أشار تحديد تسرب الأحماض النووية (UV_{260}) والمواد الممتصة للبروتين (UV_{280}) إلى أن **T4A** و **T7A** قد أظهرا نتائج واعدة بأعلى قيم امتصاص لـ OD_{260} عند 1.07 و 0.98 ضد الإشريكية القولونية، بينما تم تسجيل OD_{280} عند 1.00 و 0.98 ضد العصوية الرقيقة بتركيز 4×MIC. تم إخضاع جميع المركبات التي تم توليفها من كلا السلسلتين لاختبارات الإرساء الجزيئي الحاسوبية ضد GlcN-6-P باعتباره الإنزيم المستهدف، وأوضحت النتائج قيم هامة لطاقات الربط لكل من **T4A** و **T7A** و **T5A** والتي توافقت مع نتائج النشاط المضاد للميكروبات بنسب -7.73 و -7.32 و -7.31 كيلو كالوري/مول على التوالي.

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APPROVAL PAGE

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DECLARATION

I hereby declare that this thesis is the result of my own investigations, except where otherwise stated. I also declare that it has not been previously or concurrently submitted as a whole for any other degrees at IIUM or other institutions.

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To Yummy,

Without your constant love and support, none of this would have been possible. Thank you so much.

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LIST OF SYMBOLS

α	Alpha
δ	Chemical shift
ν	Frequency
°C	Degree Celcius
°	Degree
eV	Electronvolt
ε	Extinction Coefficient
%	Percent
π	pi
λ	Wavelength
Å	angstrom
ca.	circa
cm	centimeter
cm^{-1}	Wavenumbers (reciprocal centimeters)
g	gram
Hz	Hertz
J_{HH}	Proton Coupling Constant
kcal/mol	Kilocalories per mole
kJ/mol	KiloJoules per mole
K*i*	Inhibition constant
Log P	Partition Coefficient
m	Medium

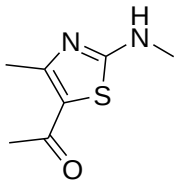
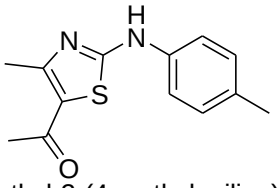
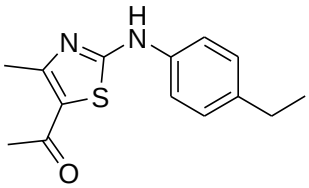
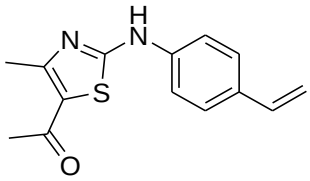
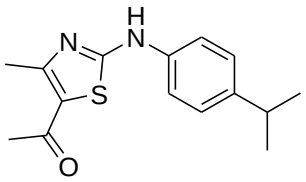
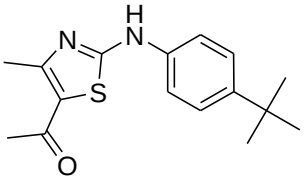
m	Multiplet
mm	Milimeter
m/z	Mass
M	Molarity
MHz	Mega Hertz
$M^{-1}cm^{-1}$	Molar absorptivity
mg	Milligram
min	Minute
mmol	Milimole
mL	Mililiter
nm	Nanometre
µg	Microgram
µL	Microliter
µM	Micrometre

LIST OF ABBREVIATIONS

Abs	Absorbance	KBr	Potassium bromide
$CDCl_3$	Deuterated Chloroform	LUMO	Lowest Unoccupied Molecular Orbital
CFU	Colony-forming unit	ppm	Part per million
DMSO-d_6	Deuterated Dimethyl sulfoxide	NMR	Nuclear Magnetic Resonance
d	Doublet	pseudo-d	Pseudo doublet
EDTA	Ethylenediamine tetraacetic acid	s	Singlet
et al	and others (in Latin)	s	Strong
FTIR	Fourier Transform Infrared	sp	Species
HCl	Hydrochloric acid	t	Triplet
HOMO	Highest Occupied Molecular Orbital	TMS	Tetramethylsilane
IC_{50}	Half maximal inhibitory concentration	UV-vis	Ultraviolet-visible
IR	Infrared	w	weak

COMPOUNDS NUMBERING SCHEME OF SYNTHESIZED THIAZOLE DERIVATIVES

SERIES A (5-ACETYL-4-METHYL-1,3-THIAZOLE)

NO.	MOLECULAR STRUCTURE	MOLECULAR FORMULA	NOVELTY
T1A	 5-acetyl-4-methyl-2-methylamine-1,3-thiazole	$C_7H_{10}N_2OS$	X
T2A	 5-acetyl-4-methyl-2-(4-methylaniline)-1,3-thiazole	$C_{13}H_{14}N_2OS$	X
T3A	 5-acetyl-4-methyl-2-(4-ethylaniline)-1,3-thiazole	$C_{14}H_{16}N_2OS$	/
T4A	 5-acetyl-4-methyl-2-(4-vinylaniline)-1,3-thiazole	$C_{14}H_{14}N_2OS$	/
T5A	 5-acetyl-4-methyl-2-(4-isopropylaniline)-1,3-thiazole	$C_{15}H_{18}N_2OS$	/
T6A	 5-acetyl-4-methyl-2-(4-tertbutylaniline)-1,3-thiazole	$C_{16}H_{20}N_2OS$	X