SYNTHESIS, MOLECULAR DOCKING AND BIOCHEMICAL ANALYSIS OF AMINOALKYLATED NAPHTHALENE-BASED CHALCONES AS ACETYLCHOLINESTERASE INHIBITORS

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ABSTRACT

In this study, an efficient microwave-assisted one-step synthetic route towards Mannich base reactions was developed from 4-hydroxyacetophenone and different secondary amines in quantitative yields. The reaction was non-catalysed, reproducible on a gram scale and accomplished in a short time. Three derivatives of 2-alkyloxynaphthaldehydes were obtained from 2-hydroxynaphthaldehyde using the sonication method over a short time. All the precursors were characterised using infrared spectroscopy (IR), one-dimensional nuclear magnetic resonance spectroscopy (1D-NMR) and electron impact mass spectrometry (EIMS). Twelve novel chalcones were synthesised using thionyl chloride via Claisen-Schmidt condensation reaction between 2-alkyloxynaphthaldehydes and Mannich bases of 4-hydroxyacetophenone. The synthesised chalcones were characterised using IR, 1D- and 2D-NMR and high resolution mass spectrometry (HRMS). The selected chalcone **(68)** was used for crystallography analysis. X-ray single-crystal structural analysis revealed that chalcone **(68)** comprises three planar aromatic ring groups and a chair-shaped piperidine ring with intramolecular and intermolecular interactions. The synthesised chalcones were evaluated for their metal chelating properties using *in situ* ultraviolet (UV) and NMR titration studies. The presence of Mannich bases on the chalcone skeleton promotes the chelation capacity of the chalcone. The SwissADME web tool was used to assess the *in silico* drug-likeness properties, toxicity and pharmacokinetics of the novel chalcones. The Molinspiration server was used for target prediction, which showed the likelihood of the general scaffold of chalcone to be 93% enzyme inhibitor while the chalcones bearing the Mannich base could be a ChE inhibitor. Comparative docking analysis was carried out on all chalcone derivatives to screen their binding affinity towards the AChE enzyme (PDB 1EVE) using AutoDock4.2 and the results were visualised using BIOVIA Discovery Studio Visualizer. All the synthesised chalcones showed lower binding energy (-13.06 to -10.43 kcal/mol) against AChE, better than donepezil (-10.52 kcal/mol). All the chalcones were found active as antioxidants against 2,2-diphenyl-1-picrylhydrazyl with IC_{50} values that ranged between 12.57 and 55.52 µg/mL. The *in vitro* assessment of the chalcones inhibition activity against AChE and BuChE was carried out using the spectrophotometric method. All chalcones were potent inhibitors towards AChE, with IC_{50} values ranging between 0.11 and 5.34 nM more than donepezil (IC_{50} 33.4 nM) and selectivity indexes (0.66–23.83), despite the fact that chalcones **(71)** and **(74)** were inactive. A correlation between the structure and inhibitory activity towards AChE of the synthesised chalcones was established. In short, introducing diethylamine in ring A of the chalcone skeleton and the propargyl moiety at ring B was affirmed to be a prospective drug against AChE. The multifunctional properties of chalcone **(76)** involving the potent AChE inhibitory activity (IC_{50} 0.11 nM, SI 23.83) as well as its good antioxidant activity (IC_{50} 40.58 µg/mL), low log P 3.87, and ability to permeate through the blood-brain barrier were all advantages that demonstrate it as an excellent candidate for the development of an effective drug against AChE.

ABSTRAK

Dalam kajian ini, suatu laluan sintetik satu langkah berbantukan gelombang mikro ke arah tindak balas bes Mannich yang cekap telah dibangunkan menggunakan 4-hidroksiasetofenon dan amina sekunder berlainan dalam hasil kuantitatif. Tindak balas telah dijalankan tanpa mangkin dengan kebolehulangan pada skala gram dan berjaya dalam masa yang singkat. Tiga terbitan 2-alkoksinaftaldehid telah diperoleh daripada 2-hidroksinaftaldehid menggunakan kaedah sonikasi dalam masa yang singkat. Semua bahan pendahulu telah dicirikan menggunakan spektroskopi inframerah (IR), spektroskopi resonans magnet nukleus satu dimensi (1D-NMR) dan spektrometri jisim hentaman elektron (EIMS). Dua belas kalkon baharu telah disintesis menggunakan tionil klorida melalui tindak balas kondensasi Claisen-Schmidt antara 2-alkoksinaftaldehid dan bes Mannich 4-hidroksiasetofenon. Kalkon yang disintesis telah dicirikan menggunakan IR, 1D- dan 2D-NMR dan spektroskopi jisim resolusi tinggi (HRMS). Kalkon terpilih **(68)** telah digunakan untuk analisis kristalografi. Analisis sinar-X struktur kristal tunggal mendedahkan bahawa kalkon **(68)** terdiri daripada tiga kumpulan gelang aromatik planar dan gelang piperidina konformasi kerusi dengan interaksi intramolekul dan antara molekul. Kalkon yang disintesis telah dinilai sifat pengkelatan logamnya menggunakan kajian *in situ* pentitratan ultralembayung (UV) dan NMR. Kehadiran bes Mannich pada rangka kalkon meningkatkan kapasiti pengkelatan kalkon itu. Aplikasi SwissADME telah digunakan untuk menilai secara *in siliko* ciri-ciri keserupaan dadah, ketoksikan dan farmakokinetik. Pelayan Molinspirasi yang diguna meramalkan kemungkinan 93% kerangka asas kalkon merupakan perencat enzim manakala kalkon yang mengandungi bes Mannich berpotensi sebagai perencat ChE. Analisis kemasukan perbandingan telah dijalankan terhadap semua terbitan untuk menyaring tenaga pengikatannya terhadap enzim AChE (PDB 1EVE) menggunakan AutoDock4.2 dan hasilnya telah digambarkan menggunakan BIOVIA Discovery Studio Visualizer. Kesemua kalkon yang disintesis menunjukkan tenaga pengikatan yang lebih rendah (-13.06 hingga -10.43 kcal/mol) terhadap AChE, lebih baik daripada donepezil (-10.52 kcal/mol). Kesemua kalkon tersebut didapati aktif sebagai antioksidan terhadap 2,2-difenil-1-pikrilhidrazil dengan nilai IC_{50} antara 12.57 dan 55.52 µg/mL. Penilaian aktiviti penghambatan kalkon secara *in vitro* terhadap AChE dan BuChE telah dilakukan menggunakan kaedah spektrofotometri. Kesemua kalkon itu adalah perencat yang kuat terhadap AChE, dengan nilai IC_{50} antara 0.11 dan 5.34 nM mengatasi keupayaan donepezil (IC_{50} 33.4 nM) dan indeks kepilihan (0.66-23.83), walaupun kalkon **(71)** dan **(74)** tidak aktif. Korelasi antara struktur dan aktiviti perencatan kalkon yang disintesis terhadap AChE telah dibentuk. Secara ringkasnya, kehadiran dietilamina pada gelang A kerangka kalkon dan bahagian propargil pada gelang B telah dikenalpasti sebagai ubat yang berpotensi menghambat aktiviti AChE. Sifat multifungsi kalkon **(76)** yang melibatkan aktiviti penghambatan AChE yang kuat (IC_{50} 0.11 nM, SI 23.83) serta aktiviti antioksidan yang baik (IC_{50} 40.58 µg/mL), nilai log P 3.87 yang rendah, dan keupayaan untuk telap melalui sempadan darah-otak kesemuanya adalah kelebihan yang menunjukkan sebatian ini boleh dibangunkan sebagai perencat aktiviti AChE yang berkesan.

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)))		Sonication
°C	-	Degree Celsius
%	-	Percentage
μg	-	Microgram
μL	-	Microliter
Aβ	-	Amyloid β-peptide
Abs	-	Absorbance
ACh	-	Acetylcholine
AChE	-	Acetylcholinesterase
AD	-	Alzheimer's disease
ADT	-	AutoDockTools
ADMET	-	Absorption, distribution, metabolism, excretion and toxicity
$AlCl_3$	-	Aluminium trichloride
AS	-	Anionic subsite
ATCI	-	Acetylthiocholine iodide
BBB	-	Blood-brain barrier
br	-	Broad
BTCH	-	Butyrylthiocholine
BuChE	-	Butyrylcholinesterase
^{13}C	-	Carbon-13
CAS	-	Catalytic anionic site
CC	-	Column Chromatography
$CDCl_3$	-	Deuterated chloroform
CD_3OD	-	Deuterated methanol
COSY	-	Correlation Spectroscopy
$CHCl_3$	-	Chloroform
CH_2Cl_2	-	Dichloromethane
ChE	-	Cholinesterase
ChEIs	-	Cholinesterase inhibitors
CNS	-	Central nervous system

CYPs	-	Cytochromes P450
d	-	Doublet
dd	-	Doublet of doublets
DEPT	-	Distortionless Enhancement by Polarization Transfer
DMF	-	N, N-dimethylformamide
DMSO	-	Dimethyl sulfoxide
D_2O	-	Deuterated water
DPPH	-	2,2-diphenyl-1-picrylhydrazyl
DTNB	-	5,5'-dithiobis-2-nitrobenzoic acid
EIMS	-	Electron Impact Mass Spectrometry
ES	-	esteratic site
EtOAc	-	Ethyl Acetate
FDA	-	Food and Drug Administration
FRAP	-	Ferric reducing antioxidant power
GA	-	Genetic algorithm
G*P*	-	*Guanine nucleotide-binding protein*
GPCR	-	*Guanine nucleotide-binding protein-coupled receptor*
^1H	-	Proton
HBA	-	Hydrogen bond acceptors
HBD	-	Hydrogen bond donors
HMBC	-	Heteronuclear Multiple Bond Correlation
HMQC	-	Heteronuclear Multiple Quantum Coherence
HRMS	-	High-Resolution Mass Spectrometry
Hz	-	Hertz
HCl	-	Hydrochloric acid
H_2SO_4	-	Sulphuric acid
IC_{50}	-	Inhibition Concentration at 50%
IR	-	Infrared
J	-	Coupling constant
kg	-	Kilogram
LBDD	-	ligand-based drug designing
LD_{50}	-	median lethal dose
LGA	-	Lamarckian Genetic Algorithm
log*P*	-	logarithm of partition coefficient

M	-	Molar
m	-	multiplet
mM	-	millimolar
MCRs	-	multicomponent reactions
mg	-	milligram
MeOH	-	methanol
MTDLs	-	Multi-target directed ligands
MHz	-	Megahertz
min	-	Minute
mL	-	Millilitre
MS	-	Mass Spectrometry
mp	-	Melting point
MW	-	Microwave
m/z	-	Mass to charge ion
ND	-	not detected
NaCl	-	Sodium chloride
NaOH	-	Sodium hydroxide
NaOAc	-	Sodium acetate
NMR	-	Nuclear Magnetic Resonance
PAS	-	peripheral anionic site
PDB	-	Protein Data Bank
P-gp	-	permeability glycoprotein
ppm	-	parts per million
q	-	Quartet
Rf	-	Retention factor
ROS	-	Reactive oxygen species
s	-	Singlet
SAR	-	Structure-activity relationship
SBDD	-	Structure-based drug designing
SD	-	Standard Deviation
SI	-	Selectivity index
SiO2	-	Silicon dioxide
$SOCl_2$	-	Thionyl chloride
t	-	Triplet

TLC	-	Thin Layer Chromatography
UV	-	Ultraviolet
VLC	-	Vacuum Liquid Chromatography
W	-	Watt

LIST OF APPENDICES

CHAPTER 1

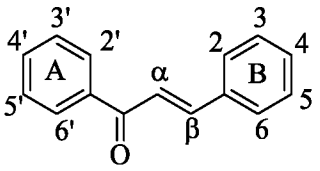
INTRODUCTION

1.1 Research Background

Chalcone **(1)** based derivatives have gained attention due to its simple structures with diverse pharmacological actions (Berar, 2013). The presence of a reactive α, β-unsaturated keto function in chalcones, is found to be responsible for their bioactivities. In the past years, a variety of chalcones have been reviewed to highlight the recent evidence of chalcone as a privileged scaffold in medicinal chemistry (Matos *et al.*, 2015; Chavan *et al.*, 2016; Zhuang *et al.*, 2017). Chalcones bearing Mannich bases **(2)** were reported as potential antitumor agents (Mete *et al.*, 2007; Reddy *et al.*, 2008; Bui *et al.*, 2012). The bioactivity of the Mannich bases is attributed to the deamination of the Mannich base group into the corresponding cyclohexadienones, which created a higher number of molecular sites for nucleophilic attack by cellular constituents. Fascinatingly, it has been reported that molecules bearing phenolic Mannich base moieties may exhibit good antioxidant and metal chelation properties (Yang *et al.*, 2017).

Alzheimer's disease (AD) is a progressing neurodegenerative disease and the most common cause of dementia among older people (Cavalli *et al.*, 2008). The decline of acetylcholine (ACh) **(3)** levels due to its hydrolysis via cholinesterase enzymes significantly causes impairment in cognitive function. One of the approaches to prolong the availability of ACh **(3)** levels is by inhibiting the acetylcholinesterase enzyme (Soreq, 2001). A report on the acetylcholinesterase (AChE) inhibition of nitrogen-containing chalcone derivatives found that compound **(4)** has a potential AChE inhibitory activity (Liu *et al.*, 2016). A previous preliminary study by Ibrahim and Ahmad (2014) on the synthesis of chalcones and their AChE activity found that 4'-hydroxy-2,6-dichlorochalcone **(5)** and 2'-hydroxy-4-(dimethyl) aminochalcone **(6)** showed promising activity against AChE.

Studies have shown that AChE also promoted the aggregation of toxic amyloid β-peptide (Aβ) (Inestrosa *et al.*, 1996; Soreq, 2001). Metal chelators and reactive oxygen species scavengers (ROS) have demonstrated promise in the treatment of AD due to the increased level of metal ions in plaque that can accelerate Aβ aggregation (Bush and Tanzi, 2008).



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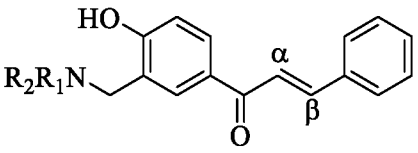
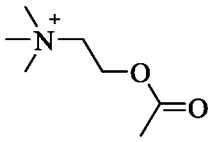


NR_1R_2: secondary amines

(2)



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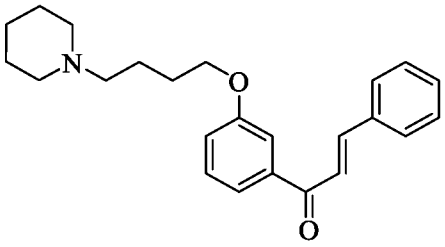

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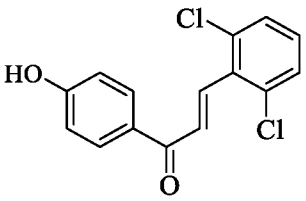

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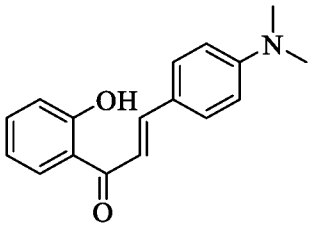


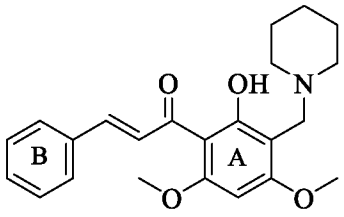
(6)

1.2 Problem Statement

Acetylcholinesterase (AChE) is associated with the cognitive symptoms of Alzheimer's disease (AD) (Dvir *et al.*, 2010). According to the classic cholinergic hypothesis, it terminates the neurotransmission at the cholinergic synapse by hydrolysing the neurotransmitter, ACh, thus causing cognitive impairment in AD patients. The Food and Drug Administration (FDA) has approved forms of treatment for AD that belong to a category of acetylcholinesterase inhibitors (AChEIs), but most

of the recent medications were observed to be associated with adverse side effects (Dhanjal *et al.*, 2015). Hence, the search for novel AChEIs is still of great interest.

Recently, there has been a trend in using natural products, such as chalcones, to discover cholinesterase inhibitors, due to their minor side-effects (Liu *et al.*, 2015). In relation to the structure of AChEIs, tertiary amine groups were the possible key pharmacophores for the inhibitors. Consequently, Liu *et al.* (2014b) have modified the chalcone skeleton **(1)**, at ring A by introducing alkyl amine through the Mannich base reaction. Interestingly they concluded that 4',6'-dimethoxy-3'-(piperidinyl)-N-methyl-2'-hydroxy chalcone **(7)** demonstrated potent AChEI at a rate of two times more than the commercial inhibitor, rivastigmine **(8)**. Thus, modification in the chalcone skeleton using the Mannich base needs to be explored. Recent evidence indicates that the presence of a different ring or fused ring system such as naphthalene, making the drug structure more rigid (Young, 2009). This rigidity increases the probability of binding to the active site in the correct conformation. Thus, the introduction of an active site in ring B, using a fused ring and alkoxy groups, was selected to promote the reactivity of the desired chalcones against AChE.



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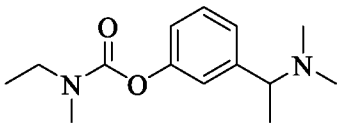
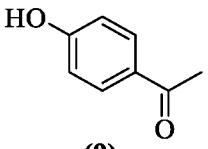


(8)

A classic Mannich base reaction is carried out under aqueous acidic conditions (Tramontini, 1973), which could limit the number of substrates suitable for this chemical transformation. Moreover, the prolonged reaction times, high temperatures, low yields and side reactions are unfavourable issues associated with this reaction (Nagrik *et al.*, 2010). To further explore the Mannich reaction, a new synthetic method to obtain Mannich bases using microwave irradiation (MW) is of interests. So far, Mannich bases being derivatised from 4-hydroxyacetophenone **(9)** have only been reported under harsh conventional conditions (Reddy *et al.*, 2008). As a result, MW

irradiation, without any catalyst, was chosen as a potential new pathway to synthesise phenolic Mannich base precursors.



(9)

Considerable effort was devoted to achieve selectivity with regards to AChE as a target, and these days many ligands that are endowed with outstanding *in vitro* selectivity are indeed available (Cavalli *et al.*, 2008). Nevertheless, it should be noted that a highly selective ligand for a given target does not always result in a clinically efficient drug. This inadequacy may be due to the ligand not reaching the site of action, it not recognising the target *in vivo*, or it could be because the interaction with the respective target does not have enough impact on the diseased system to restore it effectively. Medicinal chemists often encounter these frustrating aspects of drug research. Experimental biological investigation of such ligands is not only significantly intricate but also expensive. Computational methods, including docking, are commonly used to simulate the ligand interactions with the target to highlight their affinity. Furthermore, pharmacokinetic issues can be predicted using software tools. Hence, this research is conducted to synthesise aminoalkylated naphthalene chalcones firstly as these targets are novel chalcones. Then computational methods (virtual screening) like docking and drug-likeness, absorption, distribution, metabolism, excretion and toxicity (ADME/Tox) prediction tools are utilised to evaluate the efficacy of the synthesised chalcones before the *in vitro* analysis.

1.3 Research Objectives

The objectives of this research are:

1. To develop a microwave-assisted procedure to synthesise 4-hydroxyacetophenone Mannich base derivatives.
2. To synthesise chalcone derivatives using Claisen-Schmidt reaction between the synthesised Mannich bases and 2-alkoxynaphthaldehydes and characterize. the derivatives.

3. To simulate the physicochemical properties, drug-likeness, pharmacokinetic and the inhibition activity of the synthesised chalcones towards acetylcholinesterase.
4. To evaluate the metal chelation ability, antioxidant and cholinesterase inhibitory activity of the synthesised chalcones.
5. To disclose the structure-activity relationships (SAR) of the newly synthesised chalcones as acetylcholinesterase inhibitors.

1.4 Research Significance

This project focuses on the structure-based drug design of acetylcholinesterase inhibitors. The technique used does not employ a single tool, but rather it incorporates both experimental and computational methods. Accordingly, in this research, a hybrid molecule represents the incorporation of two pharmacophores that were proposed to synthesise aminoalkylated naphthalene-based chalcones. Aminoalkylation of aromatic substrates by the Mannich reaction has considerable importance for the synthesis and modification of biologically active compounds. As a consequence, the synthetic methodology used to obtain a Mannich base, with the assistance of microwaves, can be offered as an efficient protocol to synthesise similar compounds in a short time with high yield under the described conditions.

In silico study is a valuable tool in the establishment of the viability of any biochemical reaction, as it is carried out before the experimental part of any investigation. Molecular docking can predict the capability of the synthetic chalcones to inhibit the acetylcholinesterase as a target enzyme before they move on to the wet lab experiment for validation. Moreover, it is an essential tool in combination with the practical results to determine the SAR of the novel chalcones as AChEIs. For a compound that has the potential to treat AD, the ability to penetrate the blood-brain barrier (BBB) is vital to reach the target enzyme AChE. The prediction software for the pharmacokinetics and lipophilicity of the novel chalcones, therefore becomes a determining factor.

1.5 Scope of the Study

This research aims to develop a new synthetic method using microwave irradiation to obtain Mannich bases of 4-hydroxyacetophenone, and by utilising aliphatic and secondary cyclic amines. Moreover, the secondary area of scope is to exploit Mannich bases to synthesise the novel chalcones of 2-alkoxynaphthayldehyde via the Claisen-Schmidt reaction. Structure elucidation of the pure compounds was carried out using several spectroscopic methods, including IR, 1D NMR (^{1}H, ^{13}C, DEPT), 2D NMR (COSY, HMBC and HMQC) and HRMS.

The metal chelation ability of the target chalcones was studied using a UV-visible spectrophotometer and an NMR titration technique to highlight the chelation site in the novel chalcones. What is more, *in silico* predictions relating to drug-likeness and the pharmacokinetic properties of aminoalkylated naphthalene-based chalcones were predicted using the SwissADME web tool. A Molinspiration server was used to predict the bioactivity of the synthesised chalcones. Meanwhile, before embarking on *in vitro* study, molecular docking was carried out using the AutoDock 4.2 package, and the results were visualised with the Discovery studio 2017 software package to evaluate the probability of binding modes of the synthesised chalcones being used against the acetylcholinesterase enzyme, AChE (1EVE). Bioactivity evaluations were carried out on target chalcones, including antioxidant property and cholinesterase (ChE) inhibitory activity. The screening of ChE inhibitory and selectivity assay was conducted using Ellman's microplate assay. This was accomplished using AChE from an *electric eel* and BuChE from *equine serum* to validate the computational pre-evaluations. An extensive structure-relationship study was performed based on the simulation and experimental results of the aminoalkylated naphthalene-based chalcones as AChEIs.

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LIST OF PUBLICATIONS

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1. Aljohani, G., Lentz, D., Said, M.A., Alraqa, S.Y., Ali, A.A., Basar, N., (2019a). Crystal Structure of 2-(prop-2-yn-1-yloxy)-1-naphthaldehyde, $C_{14}H_{10}O_2$. Zeitschrift für Krist. - New Cryst. Struct. 234, 977–978. https://doi.org/10.1515/ncrs-2019-0195. **(Q4, IF: 0.29)**

2. Aljohani, G., Said, M.A., Lentz, D., Basar, N., Albar, A., Alraqa, S.Y., Al-Sheikh Ali, A., (2019b). Microwave-Assisted Synthesis of Mono- and Disubstituted 4-hydroxyacetophenone Derivatives via Mannich Reaction: Synthesis, XRD and HS-Analysis. Molecules 24, 590. https://doi.org/10.3390/molecules24030590. **(Q2, IF: 3.06)**

3. Aljohani, G., Ali, A. A.-S., Said, M. A., Hughes, D. L., Alraqa, S. Y., Amran, S., Ahmad, F. and Basar, N. (2020) '2-Benzyloxynaphthalene aminoalkylated chalcone designed as acetylcholinesterase inhibitor: Structural characterisation, in vitro biological activity and molecular docking studies', Journal of Molecular Structure, 1222, 128898. https://doi.org/10.1016/j.molstruc.2020.128898. **(Q3, IF: 2.46)**