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Design, Synthesis and Characterization of Novel Coumarin Derivatives

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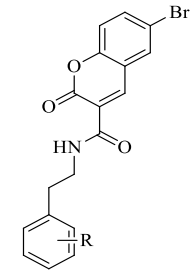
GRAPHICAL ABSTRACT



R=H, 2-OCH_3, 3-OCH_3, 4-OCH_3,2-F. 3-F, 4-F

ABSTRACT

Currently, the cholinesterase inhibitors (ChEIs) and an *N*-methyl-*D*-aspartate (NMDA) receptor antagonist are the only approved therapies for Alzheimer's Disease (AD). Coumarins are the phytochemicals with vast biological activities including AChE inhibition. In this study, several structural change of coumarin derivatives were introduced by varying the substitution pattern of electron withdrawing (fluorine) and electron donating group (methoxy) to explore the role of specific positions with respect to biological activity. Among them, compound **2c** shows the highest binding energy value (-10.30 kcal/mol) while **2g** show the lowest binding energy (-9.68 kcal/mol) when being compared to the reference drug, Donepezil (-11.29 kcal/mol) by using molecular docking analysis. Both compounds were in para position. The starting material was successfully synthesized via Knoevenagel condensation using piperidium acetate as catalyst with yield of 73.95%. Then, two methods were used for the second reaction. 60.35% yield of compound **2a** was obtained for the first method by carbodiimides coupling to active carboxylic acid to amide formation in mild reaction condition reaction while the second method gave yield of 31.02% for compound **2b** by using $SOCl_2$ as the activating agent. The targeted compounds were obtained with impurities. Structural characterization using ATR-FTIR, ^{1}H NMR and ^{13}C NMR were utilized to confirm the compounds.

Keywords: Ccoumarin, cholinesterase inhibitor, Knoevenagel condensation, hionyl chloride, molecular docking

1. INTRODUCTION

Coumarin is a heterocyclic compound since its molecule comprises of a ring of atoms of more than one element with molecular formula of $C_9H_6O_2$. The structure is made up of lactone ring having 1-benzopyran-2-one cyclic framework and it exists as a colourless crystalline substance in its standard state. This sweet-scented natural chemical compound can be found in numerous plant kingdom and fruits. Coumarin also located in flavonoid class in plant secondary metabolite and it exhibits many biological activities, such as acetylcholinesterase inhibitor, anticoagulant [1], anti-inflammatory [2], antimicrobial, antifungal, anti-HIV analogous with low toxicity and have gained great attentiveness due to their good potential affecting human health [3]

Alzheimer's Disease (AD) is the most widely recognized single reason for dementia in our maturing society [4]. Generally thought of as an untreatable degenerative condition, recent propels in medication treatment have tested this view. The number of aged people with this malady worldwide is estimated to increase at twofold every 20 years. With its fast growth and morbidity, AD ranks second on the burden of illness in Asia Pacific region. Cholinesterase inhibitors and memantine are the main presently accessible symptomatic drugs for discernment and worldwide working in patients with dementia. AChE is the chemical that catalyses the breakdown of acetylcholine (ACh): a synapse vital in cognitive work, which is exhausted in AD patients. AChEIs increment accessible ACh inside the neural connections of remaining cholinergic neurons by restraining its debasement. They have demonstrated a modest enhancement for perception and worldwide works however have little effect on the inevitable movement of the infection. The efficacy of the drugs available to cure AD on the market is at an alarming rate due to drug effect and side effects. Besides, there is no effective cure available against AD, only delay its progression. Hence, development of new cure for AD is urgently needed.

Molecular docking is used in this study and it is a method that demonstrates bio-information which includes the interaction of at least two molecules to form a stable complex. Based on the binding properties of ligand and target, molecular docking can foresee the three-dimensional structure of any adduct. The relationship between biomolecules, for example, proteins, peptides, nucleic acids, starches, and lipids play a vital part in signal transduction. Moreover, the orientation between two interacting molecules may influence the signal created. Thusly, docking is valuable for foreseeing both the quality and kind of signal generated. Molecular docking is the most used method in structure-based drug design since it is capable to foresee the binding affinity of ligands to the targeted site. Properties of the binding affinity play a critical job in elucidating fundamental biochemical processes as well as in drug design [5]

We will use molecular docking analysis to determine the highest and lowest inhibition constant and binding energy of potential coumarin derivatives using Autodock 4.2. This study also will focus on the synthesis of the interested compound

and the characterization of the compound synthesized using spectroscopic techniques such as IR, and NMR. The objectives of this study are to study the molecular docking analysis of the potential coumarin derivatives for acetylcholinesterase study and to synthesise and characterize the target coumarin by using spectroscopic methods

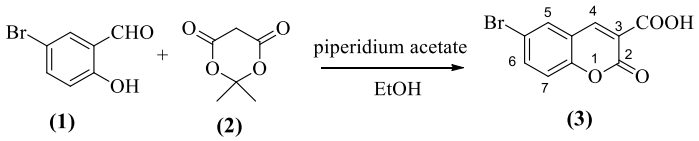
2. EXPERIMENTAL

2.1. Molecular Docking

The docking study was performed using AutoDock 4.2. The designed coumarin derivatives were docked into the active site of the selected enzymes to explore, predict and understand the protein/enzyme interactions. The reference standards employed were drawn and subjected to the docking protocol along with the designed series of coumarins, in order to visualize the binding affinity and strength, and to ascertain the docking process and validate it.

2.2. Synthesis of 6-bromo-2-oxo-2*H*-chromene-3-carboxylic acid **(3)**

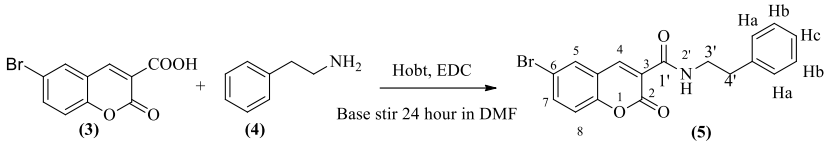
Bromosalicylaldehydes **(1)** (10 mmol), meldrum acid **(2)** (10 mmol), piperidinium acetate (29 mg, 0.4 mmol) and ethanol (10 mL) were added in the round bottomed flask. The mixture was stirred for 20 min at room temperature and then refluxed for 2 hours to complete the reaction. Next, the reaction mixture was cooled down to room temperature, followed by 1 hour chilling in an ice bath. The product was filtered, washed with ethanol and dried in the oven. The coumarin was obtained as white solid (1.99 g, 73.95% yield), m.p 194-196 ºC; IR (KBr) (Figure 1), *v* max (cm^{-1}):3347 (O-H), 3045 (sp^2 CH), 1726 (C=O ester), 1680 (C=O carboxylic acid), 1596 & 1478 (C=C aromatic), 1220 (C-O) and 663 (C-Br). ^{1}H NMR **(**Figure 1) δ (300 MHz, DMSO): 8.64 (s, 1H, H-4), 8.14 (1H, d, *J*=2.4 Hz, H-5), 7.84 (1H, dd, *J*=2.4 Hz, 8.7 Hz, H-7), 7.39 (1H, d, *J*=8.7 Hz, H-8). ^{13}C-NMR (Figure 1**)**, δ (75 MHz, $CDCl_3$) ppm: 116.5 (C-10), 118.8 (C-8), 118.9 (C-3), 119.8 (C-6), 132.3 (C-5), 138.3(C-7), 149.8 (C-4), 153.3(C-9), 162.3 (C-2), 163.1 (C-1').



Scheme 1. Synthesis of 6-bromo-2-oxo-2*H*-chromene-3-carboxylic acid

2.3 Synthesis of 6-bromo-2-oxo-*N*-phenethyl-2*H*-chromene-3-carboxamide **(5)**

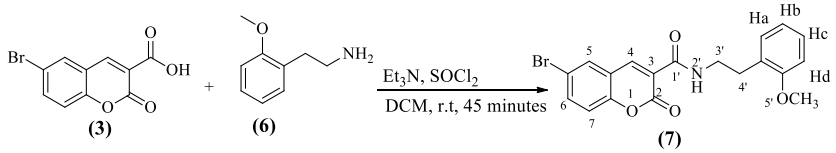
6-Bromocoumarin-3-carboxylic acid **(3)** (1.50 mmol) was added into dimethylformamide (DMF) solution (10 mL) at 0°C. After reaching at 0°C, hydroxybenzotriazole (HOBt) (153.3 g/mol, 1.77 mmol) was added to the mixture. Then, 10 min later the phenylethylamine **(2**) (121.2 g/mol, 1.50 mmol) was added to mixture, continued with 10 min later with base 4-dimethylaminopyridine (DMAP) (122.2 g/mol, 3.14 mmol) and lastly after 15 minutes *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimidehydrochloride (EDC) (191.7g/mol, 1.77 mmol) also was added. The mixture was stirred at room temperature for 24 hours. After the reaction was completed the mixture was transferred into separatory funnel for extractive workup with excess ethyl acetate as a solvent and washed up with saturated brine 5 mL (2 times), followed by 1.5 N HCl (5 mL) and distilled water (5 mL x2) to remove all the dimethylformamide (DMF) solvent and the base. The organic layer was obtained and removed under pressure to give the desired product Compound **2a (3)** was obtained as yellow solid (0.34 g, 60.35%), m.p 195-198ºC; ATR, *v* max (cm^{-1}): 3298 (N-H), 3052 (sp^2 CH), 2929 (sp^3 CH), 1728 (C=O ester), 1707 (C=O amide), 1648 (C=C conjugated), 1601 & 1472 (C=C aromatic), 1240 (C-O), 1205 (C-N), 663 (C-Br). ^{1}H NMR δ (300 MHz, $CDCl_3$): 8.83 (1H, H-4), 7.83 (1H, d, *J*=2.4 Hz, H-5), 7.77 (1H, dd, *J*=2.4, 8.7 Hz, H-7), 7.37 (1H, s, H-2'), 7.29 (4H, m, Ha, Hb, Hc, H-8), 3.74 (2H, t, *J*=7.2 Hz, H-3'), 2.95 (2H, t, *J* =7.2 Hz, H-4').



Scheme 2. Synthesis of 6-bromo-2-oxo-*N*-phenethyl-2*H*-chromene-3-carboxamide

2.4 Synthesis of 6-bromo-*N*(2-methoxyphenethyl)-2-oxo-2*H*-chromene3-carboxamide **(7)**

6-Bromocoumarin-3-carboxylic acid **(3)** (1.5 mmol) is added to 2-methoxyphenethylamine **(4)** (151.209 g/mo, 1.5mmol) and triethylamine (Et_3N) (101.19 g/mol, 4.5mmol) in 10 mL dichloromethane, then $SOCl_2$ (118.97 g/mol, 1.5 mmol) is added at room temperature. The mixture is stirred for 45 minutes at room temperature. The recovery of the reaction product is performed by evaporating the solvent under reduced pressure. The resulting residue is taken up in dichloromethane and washed 2 times with 1 N HCl and distilled water. The organic phase was dried using $MgSO_4$, and evaporated to dryness to afford the corresponding carboxylic amide. Compound **2b (5)** obtained as yellow solid (0.19 g, 31.02%), m.p 194-197ºC ATR *v* max (cm^{-1}): 3341 (N-H), 3048 (sp^2 CH), 2934 (sp^3 CH), 1739 (C=O ester), 1713 (C=O amide), 1650 (C=C conjugated), 1603 & 1477 (C=C aromatic), 1050 (C-O), 1100 (C-N), 664 (C-Br). ^{1}H NMR δ (300 MHz, $CDCl_3$): 8.81 (1H, s, H-4), 7.82 (1H, d, *J*=2.4 Hz, H-5), 7.74(1H, dd, *J*=2.4, 8.7 H-7), 7.30 (1H, s, H-2'), 6.80 (5H, m, Ha, Hb, Hc, Hd, H-8), 3.78 (3H, s, H-5'), 2.88 (2H, t, *J*=7.4 Hz, H-3'), 2.63 (2H, t, *J*=7.4 Hz, H-4').



Scheme 3. Synthesis of of 6-bromo-*N*(2-methoxyphenethyl)-2-oxo-2*H*-chromene3-carboxamide

3. RESULTS AND DISCUSSION

3.1. Docking Studies Chemistry

The validation of the docking process is indicated by the root mean square deviation (RMSD) value, respectively. The RSMD values are affirmative that the overall docking study showed RMSD value for all coumarin derivatives proposed is less than 1. Hence, the docking results are acceptable and indicative that the docking protocol is validated. From Table 1, all the coumarin derivatives did not have the same value of inhibition constant and binding energy with the Donepezil. This is due to the fact that the structure of the coumarin derivatives themselves is different from the Donepezil thus leading to different kind and number of interaction as well as different AChE residues involved in the interaction as compared to Donepezil. Compound **2c** possessed the highest binding energy (-10.30 kcal/mol) among the coumarin derivatives. The lowest binding energy by compound **2g** (-9.68 kcal/mol) can be observed from the table. Based on the above analysis, it can be confirmed that the coumarin derivatives will have same binding energy with Donepezil if their structures entirely overlapped with Donepezil structure. Protein-Ligand Interaction Profiler (PLIP) was used to analyze the interaction between the coumarin derivatives, donepezil and AChE residues. In **Table 2** Donepezil structure has 8 hydrophobic interaction with Trp286, Tyr337, Phe338 and Tyr341 residues, 1 hydrogen bond interaction with Phe295 residue and 2 π-stacking interaction with Trp86 and Tyr341 residues. All the data obtained for the coumarin derivatives are not exactly the same with the Donepezil structure. These differences are accounted for the difference in binding energy and inhibition constant value as comparable with Donepezil.For example, compound **2a** has 9 hydrophobic interaction with Tyr72, Trp286, Phe297, Tyr337, Phe338, Tyr341 residues while Donepezil has only 8 hydrophobic interaction. **2a** also could formed 3 hydrogen bonds interactions with Phe295, Arg296 residue while Donepezil can only form 1 hydrogen bonding. For compound **2c** which has the highest binding energy among these coumarin derivatives, the difference in binding energy and inhibition constant with Donepezil is due to its ability to form salt bridge with His447. Besides, **2c** also did not have any π-stacking interaction with AChE residues unlike Donepezil. Compound **2g** with the lowest binding

energy has many differences in its interaction with AChE as comparable with Donepezil. Albeit **2g** has 8 hydrophobic interaction with the residues just like Donepezil, some residues participated in this interaction are different. Trp86 and Tyr341 residue are involved in the hydrophobic interaction between **2g** and AChE residues but not for Donepezil. Besides, **2g** can form halogen bond with Ser293 residue in AChE while Donepezil cannot form any halogen bond with any of the residue. Compound that has intermediate binding energy among the coumarin derivatives, **2e** has 3 hydrogen bonds with Phe295 and Arg296 residue. Donepezil can only form 1 hydrogen bond with one of the AChE residue. Another difference that contribute to the value obtained in **2g** binding energy and inhibition constant is its ability to form π-stacking interaction with Trp286. Based on the analysis, it can be concluded that the deviation of binding energy and inhibition constant values obtained for the coumarin derivatives from the reference (Donepezil) values is due to the binding interaction differences of the respective structures such as the number of interaction, the type of interaction and the type of the AChE residue participated in the interaction.

Table 1. Results obtained for inhibition constant and binding energy with respect to each coumarin derivatives

Compound	-R	Inhibition constant (Ki)	Binding Energy
2a	H	51.00 nM	-9.95 kcal/mol
2b	2-OCH_3	36.26 nM	-10.15 kcal/mol
2c	3-OCH_3	28.21 nM	-10.30 kcal/mol
2d	4-OCH_3	33.06 nM	-10.21 kcal/mol
2e	2-F	57.01 nM	-9.88 kcal/mol
2f	4-F	51.41 nM	-9.94 kcal/mol
2g	3-F	79.63 nM	-9.68 kcal/mol
Donepezil	-	5.30 nM	-11.29 kcal/mol

Table 2. Hydrophobic interaction between all the compound and interacting residue

Interacting residues	Hydrophobic Interaction							
	2a	**2b**	**2c**	**2d**	**2e**	**2f**	**2g**	**Donepezil**
Tyr72	1	1	-	-	1	1	-	-
Trp286	2	1	2	1	1	2	2	1
Phe297	1	1	1	1	1	-	-	-
Tyr337	1	-	1	1	-	2	1	1
Phe338	1	1	1	1	2	1	1	2
Tyr341	3	3	2	2	2	3	2	4
Trp86	-	-	1	-	-	-	1	-
Tyr124	-	-	1	-	1	-	1	-
Val294	-	-	-	1	-	-	-	-
Asp74	-	-	-	-	-	1	-	-

Table 3. Hydrogen bond interaction between coumarin derivatives and AChE residues

Interacting residues	Hydrogen Bond Interaction							
	2a	**2b**	**2c**	**2d**	**2e**	**2f**	**2g**	**Donepezil**
Phe295	1	1	-	-	1	1	-	1
Arg296	1	2	1	1	2	1	-	-
Asp74	-	-	-	1	-	-	-	-
Tyr124	-	-	-	1	-	-	-	-

Table 4. π-stacking interaction between all the compound and interacting residue

Interacting residues	π-Stacking Interaction							
	2a	**2b**	**2c**	**2d**	**2e**	**2f**	**2g**	**Donepezil**
Trp286	-	1	-	-	2	-	-	-
Trp86	-	-	-	3	-	-	-	1
Tyr341	-	-	-	-	-	-	-	1

Table 5. Salt bridge interaction between the all the compound and interacting residue

Interacting residues	Salt Bridge Interaction							
	2a	**2b**	**2c**	**2d**	**2e**	**2f**	**2g**	**Donepezil**
His447	-	-	1	-	-	-	-	-

Table 6. Halogen bond interaction between the involved compound and residue

Interacting residues	Halogen Bond Interaction							
	2a	**2b**	**2c**	**2d**	**2e**	**2f**	**2g**	**Donepezil**
Ser293	-	-	-	-	-	-	1	-

3.2. Chemistry

The target compounds **(3), (5)** and **(7)** were synthesized as depicted in **Scheme 1**,**2** and **3**. Substituted coumarin **(3)** was obtained as white powder with 73.95% yield. The obtained melting point range for this coumarin **(3)** is 194-196 °C. While, its FTIR (Figure 1**)** spectrum using KBr pellet showed a broad band at 3347 cm^{-1} indicating the presence of carboxylic acid. The peak at 3045 cm^{-1} was assigned to sp^2 CH. Carbonyl functional group peak (for ester) can be seen at 1726 cm^{-1} while for the carboxylic acid (1680 cm^{-1}). C=C for aromatic can be proven at 1478 cm^{-1} and 1596 cm^{-1}. An intense C-Br peak was also observed at 663 cm^{-1} while a C-O peak at 1220 cm^{-1}. The ^{1}H NMR spectrum of compound **(3)** in Figure 2 accounts for four protons. H-4 gave a singlet peak at δ 8.64 while H-5 peak with its coupling constant, *J*=2.5 Hz is a doublet at δ 8.14 because it is splitted with hydrogen at its meta position while H-7 with its coupling constant, *J*=8.3 is responsible for the doublet of doublet peak at δ 7.84 since H-7 with J value of 8.7 Hz and 2.4 Hz. Doublet splitting at δ 7.39 was the peak for H-8 with coupling constant, *J*=8.7Hz. The broad peak for H-1' at δ 11-13 specifically for COOH group is not noticeable since the solvent have high water content from the big peak at δ 3.4, usually corresponds to water

showing the product **(3)** was too wet. From the spectrum, it showed total no of exhibit 12 distinct peaks with peak integration giving a total of 4 hydrogen atoms concurrent to the expected hydrogens in the coumarin **(3)**. The 10 carbon atoms expected from the targeted molecular structure were observed from ^{13}C NMR spectrum as shown in Figure 2. The carbon of carbonyl C1' for COOH group was present at δ 163.0 and the peak at δ 162.3 represent carbonyl group for ester group, C2. Both carbonyl group appeared at low field due to the electronegative atom, oxygen. The rest of the carbons; C9, C4, C7, C5, C6, C3, C8 and C10 can be seen at δ 153.3, δ 149.8, δ 138.3, δ 132.3, δ 119.8, δ 118.9, δ 118.8, δ 116.5 respectively. This one-pot procedure is convenient since no recrystallization is needed. The product were obtained in excellent yield and purity. Therefore, from all the data obtained proved that the product obtained was indeed the desired 6-bromocoumarin-3-carboxylic acid **(3)**.

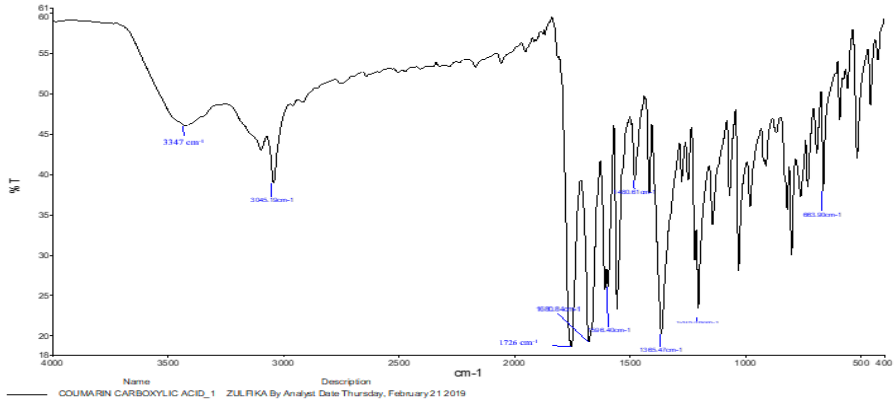


Figure 1. IR Spectrum of compound **(3)**

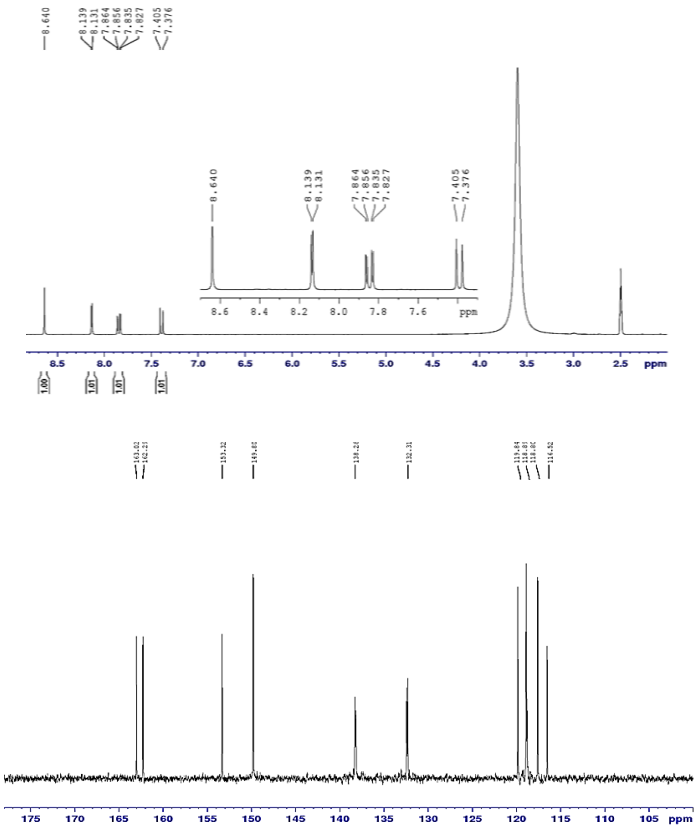


Figure 2. ^{1}H NMR and^{13}C NMR of 6-bromo-2-oxo-2*H*-chromene-3-carboxylic acid **(3)**

The first model coumarin derivative of 3-[phenylethylcarboxamide]-6-bromo-chromen-2-one **(5)** was obtained as yellow solid with yield of 60.35% and its melting point range is 195-198 ºC using phenylethylamine **(4)**. The ATR-FTIR spectrum (Figure 3**)** of coumarin showed the presence of NH spike at 3298 cm^{-1}, sp^2 CH at 3052 cm^{-1} and sp^3 CH at 2929 cm^{-1} .The carbonyl C=O (1728 cm^{-1}) in the coumarin moiety has higher absorption than for C=O amide (1707 cm^{-1}) Peak at 1648 cm^{-1} was responsible for conjugated C=C while aromatic C=C was observed at 1601 cm^{-1} and 1472 cm^{-1} respectively. Peak at 1240 cm^{-1} can be observed which represented C-O absorption band meantime C-N bond can be found at 1205 cm^{-1}. Lastly, C-Br bond can be seen from the peak at 663 cm^{-1}. The 1H NMR spectrum (Figure 3) showed the presence of the new peak by condensation with phenylethylamine **(4)**. The triplet at δ 2.95 with coupling constant, *J*=7.2 Hz represented H-4' while triplet at δ 3.74 with *J*=7.2 Hz represented H-5'. H-5 appeared as a doublet at δ7.83 with 2.4 Hz as its J value. H7 as a doublet of doublet with the coupling constant, *J*= 2.4 Hz and *J*=8.7 Hz respectively. The spectrum also showed the singlet peak responsible for the N-H group was found at δ 7.37 as a singlet. Multiplet at δ 7.29 is assigned to Ha, Hb, Hc and H8. From the IR and 1H NMR spectrum we can see that the targeted product was obtained but unfortunately there are impurities affecting the result causing the IR band is not smooth and the integral is not perfectly accurate though the splitting is quite acceptable.

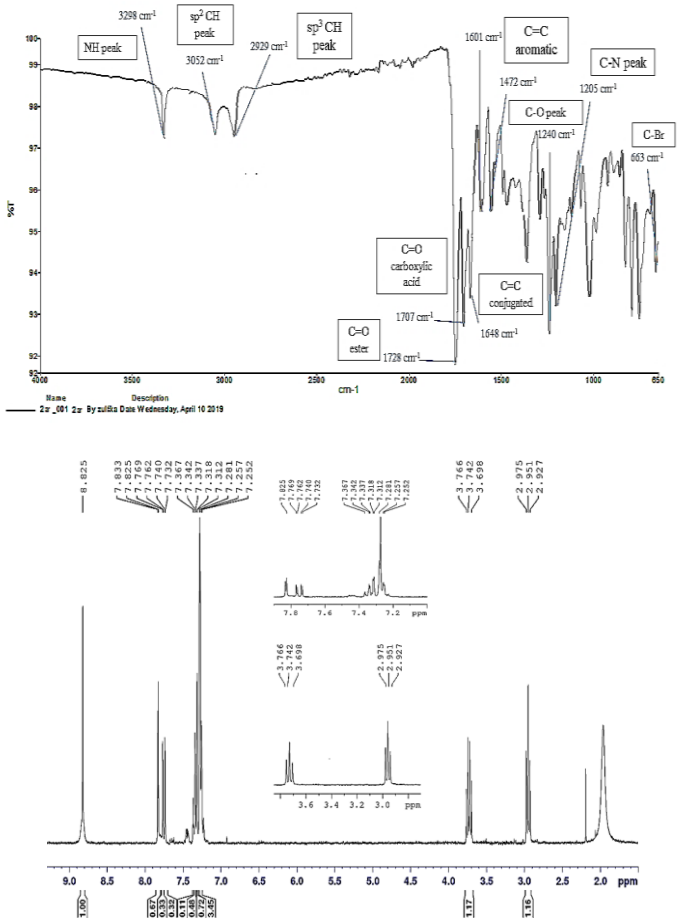


Figure 3. [1]H NMR and[13]C NMR of of 6-bromo-2-oxo-*N*-phenethyl-2*H*-chromene-3-carboxamide

Since the product obtained in the first method is not pure and take longer time to get the product, we decided to use alternative method by using $SOCl_2$ as the activating agent. The second coumarin derivatives used in this research are electron-donating group of amines as a reagent. The second derivative was obtained as yellow light solid with a yield 31.02% and melting point in range of 195-197ºC. The ATR-FTIR spectra **(**Figure 4) were done to confirm the presence of targeted functional groups. NH spike was observed at 3341 cm^{-1}, while sp^2 and sp^3 CH group presence are proven at 3048 and 2934 cm^{-1} .C=O functional group for amide can be seen at 1713 cm^{-1} and for ester at 1739 cm^{-1}. The band absorption observed at 1603 cm^{-1} and 1477 cm^{-1} were responsible for aromatic C=C while peak at 1650 cm^{-1} appeared due to the

presence of conjugated C=C. The presence of C-O group can be proven at 1050 cm^{-1} while for C-N group at 1100 cm^{-1}.C-Br bond also appeared at 664 cm^{-1}. The ^{1}H NMR spectrum (Figure 4) exhibit 11 distinct peaks for molecular structure of ortho coumarin derivatives. H-4 singlet peak that came from the coumarin moiety can be observed at δ 8.81. Meantime, H-5 which at meta position from H-7 has 2.4 Hz as its coupling constant appeared as a doublet at δ 7.82. H-7 appeared as a doublet of doublet with *J*=2.4 and 8.7 Hz at δ 7.74. H-2' proton at δ 7.30 represented N-H group appeared as a singlet. Muliplet at δ 6.80 was assigned for Ha, Hb, Hc, Hd and H-8. Singlet peak appeared at δ 3.78 representing H-5' from OCH_3. Meantime the triplets that appeared at δ 2.86 and δ 2.63 were for H-3' and H-4' as both are being coupled to each other with 7.35 Hz as their *J* value respectively. Based on the results, IR showed unsmooth spectrum and the ^{1}H NMR spectrum showed extra splitting and inaccurate integral, the targeted compound was obtained but with the impurities presence. Based on the results, IR showed unsmooth spectrum and the ^{1}H NMR spectrum showed extra splitting and inaccurate integral, the targeted compound was obtained but with the impurities presence.

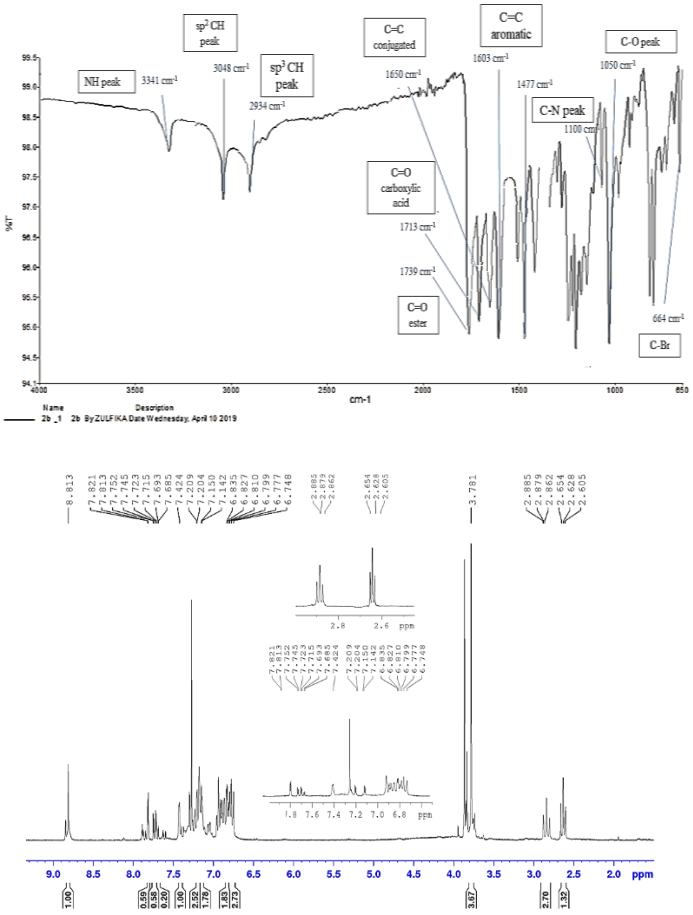


Figure 4. ^{1}H NMR and^{13}C NMR of of 6-bromo-*N*(2-methoxyphenethyl)-2-oxo-*2H*-chromene3-carboxamide **(7)**

4. CONCLUSION

Molecular docking was successfully done for compound **2a**, **2b**, **2c**, **2d**, **2e**, **2f** and **2g** using Autodock 4.2. Among all the coumarin derivatives proposed, compound **2c** possessing electron donating group (methoxy) shows the highest binding energy value (-10.30 kcal/mol) while **2g** possessing electron accepting group (fluorine) show the lowest binding energy (-9.68 kcal/mol) when being compared to the reference drug, Donepezil (-11.29 kcal/mol) by using molecular docking analysis. Both **2c** and **2g** have the substituents at para position showing that substituent at para position played a crucial rule in explaining the binding behaviour between the protein (4ey7) and the ligands (coumarin derivatives) used. The analysis also showed that the greater the binding energy, the lower the inhibition constant value. The starting material was successfully synthesized via Knoevenagel condensation using piperidium acetate as catalyst with yield of 73.95%.

Then, two method were used for the second reaction. 60.35% yield of compound **2a** was obtained for the first method by carbodiimides coupling to active carboxylic acid to amide formation in mild reaction condition reaction while the second method gave yield of 31.02% for compound **2b** by using $SOCl_2$ as the activating agent. The final targeted compounds were obtained with impurities. Structural characterization using ATR-FTIR, ^{1}H NMR and ^{13}C NMR were utilized to confirm the products. The new seven coumarin derivatives should be evaluated for their biological activity and their toxicity in the form of inhibition of AChE assays. It would be very beneficial to the mankind if one or more of these compounds are found to be biologically active and equally or more effective in the fight against Alzheimer Disease than the AChE inhibitor currently available. Besides that, the new proposed compound; **2a**, **2b**, **2c**, **2d**, **2e**, **2f** and **2g** should also evaluated another wide spectrum of biological activities spanning from anticoagulant [1], anti-inflammatory [2], anticancer [6], antimicrobial [7], antifungal [8], anti-allergic [9] and anti-depressant [10]. Therefore, to improve the current research and improve the reliability of the results obtained, this study should be further developed to reveal more interesting aspects in the fields covered by this research as well as in other scientific and industrial areas in the coming year. In this regard, access to specific coumarin through more direct and selective synthetic procedures is of vital importance for future works.

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