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Synthesis, Ft-Ir Characterization and Anti-Bacterial Activity of 5-Bromo-8-Quinolinoxyacetic Acid

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ABSTRACT

This paper involves the synthesis, FT-IR characterization and anti-bacterial activity of 5-bromo-8-quinolinoxylacetic acid. The synthesized compound was prepared by bromination of 8-hydroxyquinoline with the addition of bromine to give a mono brominated compound, 5-bromo-8-hydroxyquinoline and coupling the 5-bromo-8-hydroxylquinoline compound with chloro-acetic acid in the presence of NaOH, 5-bromo-8-quinolinolinoxylacetic acid was produced. The compound was analyzed by infra-red spectroscopy while anti-bacterial activity was done by standard method. The synthesized compound had a milky green color, with a solid state and powdery in nature, with a melting point of 206^{o}C. The anti-bacterial activity gave zones of inhibition of 9 mm (Actinobacter), 29 mm (Staphylococcus aureus) at doses less than100 mg/ml showed a lesser zone of inhibition which suggest a dose dependent activity. The IR bands were observed at 1049.31cm^{-1} (C-O stretch) for carbonyl group; 1797.72cm^{-1}(C=O stretch) for acid halide, 794.7cm^{-1}(C-H) bend for 1, 3 –disubstituted benzenes among others. Thus, the IR results confirm the presences of functional groups present in the synthesized compound. The compound showed a promising activity as anti- bacterial agent.

1. Introduction

Heterocyclic compounds play an important role in designing new classes of structural entities of medicinal importance with potentially new mechanisms of action. These heterocyclic compounds are well known to possess diverse pharmacological properties such as, antimicrobial, anticancer, anticonvulsant, antimalarial activities etc [1]. One important class of these heterocyclic compounds is quinoline and it derivatives. Quinoline is characterized by a double ring structure composed of benzene and pyridine ring fused at two adjacent carbon atoms. The benzene ring contains six carbon atoms, while the pyridine ring contains five carbon atoms and a nitrogen atom having molecular formula of C_9H_7N [2]. Quinoline nucleus has been well demonstrated as shown by a high number of patents employing such species as chemotherapeutic agents**.** Quinoline nucleus (quinoline derivatives) occurs in several natural compounds *isolated from sources such as plants, animals and bacteria* and pharmacologically active substances displaying a broad range of biological activity [3, 4]. Quinolines exhibits wide range of activity such as antiprion [5], antimicrobial [6, 7, 8, 9], anti-bacterial [10], anti-tubercular [11, 12, 13], and anticancer activities [13, 14, 15, 16]. Quinoline ring plays an important role in new anti-cancer agents development as their derivatives have shown

excellent results through different mechanism of action such as growth inhibitors by cell cycle arrest, apoptosis, inhibition of angiogenesis, disruption of cell migration, and modulation of nuclear receptor responsiveness [17,18,19]. A review on anticancer potential of bioactive heterocyclic quinolone was published recently revealing the significance of quinoline [20]. 8-Hydroxquinoline, which is one of the most popular and versatile quinoline derivatives and a starting material to several important and bioactive compounds is an organic crystalline bicyclic compound derived from quinolone and consist of two rings system: carboxylic ring and pyridine ring as in quinoline with hydroxyl group substituted at position 8. It has typical phenolic properties, for example, it give violet colour with ferric chloride, couple with diazonium cations, and participate in Reimer-Tiemann and Bucherer reactions; its acetate ester usually undergo the Fries rearrangement with aluminium chloride to give acetyl derivative [21] . Several reactions including halogenation can take place with 8-hydroxyquinoline using suitable reagents, under the right conditions.8-Hydroxyquinoline and derivatives can be synthesized by diazotization of 8-aminoquinoline or from 8-sulphonic acid by alkali fusion [22). Different substitutions (groups) can be introduced to 8-hydroxyquinoline by several methods. The most used method in this category is Suzuki cross-coupling reaction in which a new substitution can be introduced at position 5 only or at positions 5 and 7 of the 8-hydroxyquinoline moiety [22].

Owing to the distinctive chemical properties of 8-Hydroxyquinoline and its derivatives, many of these compounds nowadays have application in agricultural and medical fields. 8-Hydroxyquinoline and numerous of its derivatives exhibit potent activities against several strains of insects, fungi and bacteria which make them good candidates for the treatment of many parasitic and microbial infection diseases. In addition, other 8-Hydroxyquinoline derivatives have showed antitumor and antioxidant activities [22]. The reaction such as bromination will be very essential in this synthesis. Bromination is more selective than chlorination because the reaction is less exothermic. Most commonly bromination is conducted by the addition of Br_2 to alkenes. An example of bromination is the organic synthesis of the anesthetic halothane from trichloroethylene [23]. Thus this study aimed at synthesizing bromo derivative of 8-hydroxylquinoline with proving antimicrobial activity.

2. Materials and Method

2.1. Materials

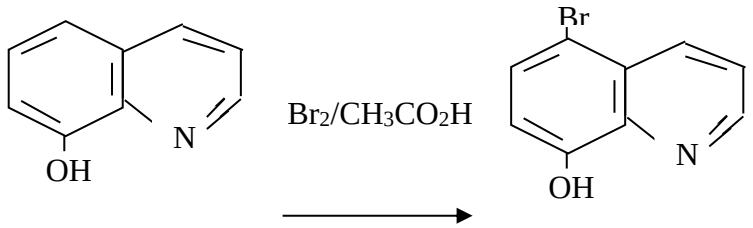
The apparatus and reagent used for the experiment includes: Volumetric Flask, Dropping Pipette, Measuring Cylinder, Starring Rods, Funnels, Separating Funnel, Buckner Funnel, Funnel, Capillary, Conical Flask, Beaker, Glass, Retort Stand, Petri Dishes, Test Tubes, Pipette. 8-Hydroxyquinoline,Glacial Acetic Acid**,** Bromine**,** Ethyl Acetate**,** Chloroacetic Acid**,** Sodium Hydroxide**,** Hydrochloric Acid**,** Ethanol**,** Distilled Water**,** *S. Aureus***,** *Acinobacter* Nutrient Broth**,** Nutrient agar and some equipment such as fume cupboard, vacuum pump, oven, melting point apparatus, FT-IR spectrophotometer, weighing balance, heating mantle, mechanical shaker.

2.2. Method

2.2.1. Synthesis of compound I (5-bromo, 8-hydroxylquinoline)

Five (5) grams of 8-hydroxylquinoline was measured into a volumetric flask and 20ml of glacial acetic acid was added and shaken together (a yellow coloration was formed from the mixture). Three (3) grams of bromine was weighed into a 100ml volumetric flask and placed

on a weighing balance in a fume-cupboard and 30ml of glacial acetic acid was added drop wise using a dropping pipette. The mixture above was poured into a separating funnel and set on a retort stand inside the fume cupboard. The separation was opened to allow the dropping of the mixture into the 8-hydroxylquinoline and glacial acetic acid mixture drop wise and shaken gently on dropping and a cloudy yellowish solution (milky yellow crystal) was form at the end of the reaction. The mixture was filtered with a vacuum pump. A yellow filtrate was gotten and the milky yellow residue (crystals) was dried and weighed. The reaction scheme is shown in Figure 1:



8-hydroxylquinoline

5-bromo-8-hydroxylquinoline

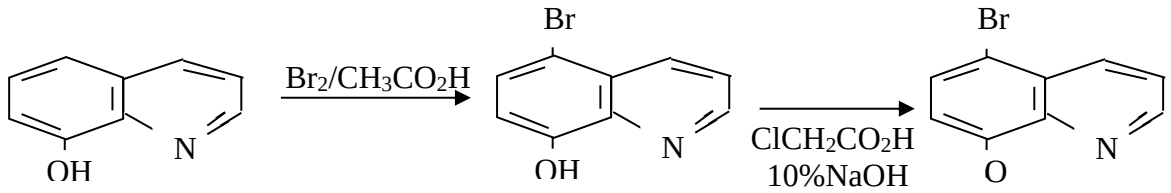
Figure 1: Synthesis of 5-bromo-8-hydroxylquinoline

2.2.2. Recrystallization of 5-bromo-8-hydroxylquinoline

The dried residue of 5-bromo-8-hydroxlquinoline was dissolved in 40ml ethylacetate and heated for few minutes for complete dissolution, then allowed to cool .The crystals formed were filtered and dried.

2.2.3. Synthesis of compound II (5-bromo-8-quinolinoxlacetic acid)

One (1) gram of the previously synthetized 5-bromo-8-hydroxylquinoline was weighed into a beaker and 0.450g of chloroacetic acid was added directly and immediately transferred into a beaker containing 25ml of 10% sodium hydroxide. The mixture was placed in a cold water to cool so that the temperature will not exceed 10^oC at room temperature. It was stirred and heated for 30minutes and allowed to cool, then placed on a shaker for 3hours and hydrochloric acid was added at interval while shaking. The mixture was then filtered using filter paper (Whitman filter paper no.1) and the residue (greenish and milky) was dried and weighed. The reaction scheme is in Figure 2:



8-hydroxylquinoline **5-bromo-8-hydroxylquinoline** **5-bromo-8-quinolinoxylacetic acid**

Figure 2: Synthesis of 5-bromo-8-quinolinoxyl acetic acid

The compound synthesized was made to undergo recrystallization in order to purify the compound and the meting point and solubility was determined.

Antimicrobial activity was determined using Agar well diffusion assay via which determination of MIC (minimum inhibitory concentration) was carried out.

The MIC values of the synthesized compound was determined using two-fold micro-dilution to prepare concentration of 100mg/ml, 50mg/ml, 25mg/ml, 12.5mg/ml. 1ml of each extract and a drop of the bacterial suspension that had been previously diluted to about 10^6cfu/ml was aseptically inoculated into a molten nutrient agar and allowed to set. The plate was incubated at a temperature of 37^0C for 24hours. The lowest concentration preventing visible growth for each of the test organism was recorded as the MIC. The experiment was carried out in triplicate for each synthesized compound concentration and control against the bacterial isolates. Amoxicillin, pefloxacin, septrin and ciprofloxacin were used as the positive control while distilled water was used as the negative control and determination of minimum bactericidal concentration was also carried out, were Minimum bactericidal concentration was determined from the least values of MIC contents was poured into fresh plates inoculated from the MIC and incubated at a temperature of 37^0C for 24hours. The MBC was measured using a graduated measuring ruler. The least value is the MBC (minimum bactericidal concentration) and was recorded.

3. Results and Discussion

3.1. Physical Properties

The physical properties of the standing compounds (reactants) and the synthesized product which includes colour, state, nature, and melting points are shown in Table 1:

Table 1: Physical properties determination of the starting material (8-hydroxylquinoline) and that of the synthesized compounds

Compounds	Colour	State	Nature	Melting point
8-hydroxylquinoline	Orange	Liquid	Solution	
5-bromo-8-hydroxylquinoline	Milky yellow	Solid	Powder	127^{o}C
5-bromo-8-quinolinoxylacetic acid	Milky green	Solid	Powder	206^{o}C

3.2. Antimicrobial Activity

3.2.1. The Antimicrobial Test of Standard Antibiotic Drugs.

The Minimum Inhibitory concentration (MIC) and Minimum Bacteriocidal Concentration (MBC) of synthesized compounds are shown in Tables 2, 3, and 4 respectively.

Table 2: Sensitivity test of bacterial isolates to standard antibiotic drugs

Standard antibiotics	**Strength(mg)**	**Bacteria isolates**	
		Actinobacter	***S. aureus***
Refloxacin	10	S	S
Ciproflaxin	10	S	S
Amoxalin	30	S	S
Septrin	30	S	S

S – Sensitive

R – Resistant

A pathogen is said to be sensitive, if the infection it has caused is likely to respond to that susceptible substance at the high dose(s).

Table 3: Result of antibacterial activity (minimum inhibitory concentration) of the synthesized compound on Actinobacter and Staphylococcus aureus and their zone of inhibition in mm

Bacteria isolates	Concentration of 5-bromo-8-quinolinoxylacetic acid			
	100mg/ml	50mg/ml	25mg/ml	12.5mg/ml
Actinobacter	9mm	8.0mm	0.0mm	0.0mm
S. aureus	29.0mm	12.0mm	10.0mm	8.0mm

Table 4: Result of antibacterial activity (minimum bacteriocidal concentration) of the synthesized compound on *Actinobacter* and *Staphylococcus aureus*

Bacterial isolates	Concentration of 5-bromo-8-quinolinoxylacetic acid	
	12.5mg/ml	50mg/ml
Actinobacter	0.0mm	7.5mm
S. aureus	11.0mm	0.0mm

Table 5: showing the absorption frequencies of the synthesized compound

S/n	Wave Number(cm^{-1})	Appearance	Bond	Suspected functional Group
1	794.7	Strong	C-H bond	1,3-disubstituted Benzene
2	1049.31	Strong	C-O stretch	Carbonyl group
3	1141.9	Strong	C-O stretch	Carbonyl group
4	1195.91	Strong	C-O stretch	Carbonyl group
5	1265.35	Strong	C-O stretch	Acid, ester, anhydride
6	1327.07	Strong	C-O stretch	Acid, ester, anhydride
7	1381.08	Medium	C-H bond	Methyl
8	1481.38	Variable	C=C stretch	Arenes
9	1573.97	Variable	C=C stretch	Arenes
10	1643.41	Variable	C=C stretch	Alkenes
11	1797.72	Very strong	C=O stretch	Acid Halide
12	2823.88	Medium	C-H Stretch	Aldehyde
13	2885.60	Medium	C-H Stretch	Alkyl group
14	3425.69	Strong	O-H Stretch	Alcohol

3.3. Physical properties

Results obtained from the determination of the physical properties of the synthesized compounds shows that the synthesized compounds are 5-bromo-8-hydroxylquinoline and 5-bromo-8-quinolinoxylacetic acid having colour of milky yellow and milky green as well as melting point of 127^0C and 206^0C respectively, since the retention factors (rf) values were different when monitored with thin layer chromatography (TLC). It was observed that the bromination of 8 hydroxylquinoline gave a mono-brominated product in scheme 1/Figure 1 and the brominating of compound 1 in glacial acetic acid in an alkaline medium of NaOH gave a single crystal in a high percent yield which quite agree with Gerhard *et al* (2012) were aqueous acetic acid 96% ,glacial acetic acid and other aquous mixtures was used and it was still observed to have given a mono–brominated compound of high percentage yield with glacial acetic acid. The bromination of the starting material, 8-hydroxylquinoline yielded a stable intermediate 5-bromo-8-hydroxylquinoline under the experimental condition and upon acetylation with acetic acid yield the compound, 5-bromo-8-quinolinoxylacetic acid. Which quite agree with Gerhard *et al* (2012) were treatment of the 2,4,5-triphenyl derivative with bromine “in alkaline medium” reportedly gave stable radicals.

3.4. Antimicrobial Activity

Results obtained from the determination of antimicrobial activity of the synthesized compound (5-bromo-8-quinolinoxylacetic acid), shows that the compound posse a very good antibacterial activities against both gram positive and gram negative bacteria such as *Staphylococcus aureus* and *Actinobacter*. The result also shows that the synthesized compound have antibacterial activity that is almost competitive with those of standard antibiotic drugs. The 5-bromo-8-quinolinoxylacetic acid exhibited growth inhibition activity against *Acinetobacter* with minimum inhibitory concentration of 9.0mm at 100mg/ml, 8.0mm at 50mg/ml and no growth inhibition at both 25mg/ml and 12.5mg/ml and *Staphylococcus aureus* with minimum inhibitory concentrations of 29.0mm at 100mg/ml, 12.0mm at 50mg/ml, 10.0mm at 25mg/ml and 8.0mm at 12.5mg/ml after 24 hours of incubation at 37^0C.

In addition, the 5-bromo-8-quinolinoxyacetic acid exerted antibacterial activity against *Acinetobacter* with Minimum bacteriocidal concentration of 7.5mm at 50mg/ml and no growth inhibition at 12.5mg/ml, and against *Staphylococcus aureus* with minimum bacteriocidal concentration of 11.0mm at 12.5mg/ml and no growth inhibition at 50mg/ml after 24 hours of incubation at 37^0C. The I.R results indicates the functional groups, which are present in the synthesized compounds, the infra-red band for the synthesized compound indicated 794.7cm^{-1} (C-H bend) a disubstituted benzene which suggest the presence of the benzene ring in 8-hydroxylquinoline, peak1049.31cm^{-1}(C-O stretch),1141.9cm^{-1}(C-O stretch),1195.91cm^{-1}(C-O stretch) suggest the presence of carbonyl group in the compound synthesized .the presence of the acid halide functional group observed at peak 1797.72cm^{-1}(C=O stretch) suggest success of the bromination of the 8-hydroxylqinoline in the compound. The peak 1265.35cm^{-1}(C-O stretch),1327.07cm^{-1}(C-O stretch),suggest the presence of acid, esters ,and anhydride in the compound ,peak1381.08cm^{-1}(C-H bend) suggest the presence of methyl group in the compound ,peak 1481.38cm^{-1}(C=C stretch), 1573.97cm^{-1}(C=C stretch), 1643.41cm^{-1} (C=C stretch) suggest the presence of double bond(Arenes and Alkenes) group which is present in the benzene ring of the 5-bromo-8-quinolinoxylacetic acid. Peak 2823.88cm^{-1}(C-H stretch) suggest the presence of aldehyde functional group, peak 2885.6cm^{-1}(C-H stretch) suggest the presence of alkyl group and peak 3425.69cm^{-1}(O-H stretch) also suggest the presence of phenolic group in the 5-bromo-8-quinolinoxylacetic acid. Thus, the synthesized compound possesses the needed functional group in 5-bromo-8-quinolinoxylacetic acid.

4. Conclusion and Recommendation

At the end of the research, the synthesis of 5-bromo-8-quinolinoxyacetic acid was achieved. It was discovered from the work that the derivative of 8-hydroxyquinoline, 5-bromo-8-quinolinoxyacetic acid is a potential antibiotics against *Staphylococcus aureus* (Gram- positive) and *Acinetobacter* (Gram-negative) which were comparable to the known standard drugs such as Ciproflaxicin and Amoxalin. It was also proved that 5-bromo-8-quinolinoxylacetic acid was active against *Staphylococcus aureus* and *Acinetobacter* at varying concentrations. This proves the high therapeutic value of this compound and encourages further study to explore their biological potential. However, further characterization with respect to mass spectrometer, scanning electron microscope (SEM), NMR, proton NMR and carbon 13 NMR should be done to ascertain the product synthesized, while microbial activity should be tested on other microbes to know the product potency.

5. Acknowledgment

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6. Conflict of Interest

There is no conflict of interest associated with this work.

References

[1] Ilango, K., Valentina, P., Subhakar, K. and Kathiravan, M. K. (2015). Design, Synthesis and Biological Screening of 2, 4- DisubstitutedQuinolines.*Austin Journal of Analytical and Pharmaceutical Chemistry*.2(4): 1-4.

[2] Peter, J. C. (2002). Antibiotic resistance. *MJA Practice Essentials*. 177: 325-329.

[3] *Heeb, S., Fletcher, M. P., Chhabra, S. R., Diggle, S. P., Williams, P. and Cámara, M. (2011).* Quinolines: from Antibiotics to autoinducers. *FEMS Microbiology Reviews. **35** (2): 247-274*

[4] Al-juboory, S. B. and Kubba, A. R. M. (2016). Synthesis, characterization and antifungal evaluation of some novel quinolone derivatives derived from ethyl *p*-aminobenzoate. *Der PharmaChemica*. **8**(4):63-66.

[5] Cope, H., Mutter, R., Heal, W., Pascoe, C., Brown, P. and Pratt, S. (2006). Synthesis and SAR study of acridine, 2-methylquinoline and 2-phenylquinazoline analogues as anti-prion agents. *European Journal of Medicinal Chemistry*. 41: 1124-1143.

[6] Mamladesai, S. N., Katagi, M. S., Khare, P. V., Maddi, V. S. andBhat, A. R. (2008). Synthesis and antimicrobial activity of 4-hydroxy-1-metnyl/phenyl-3-substituted quinolin-2- (1H)-ones.Indian Journal of Heterocyclic Chemistry. 17: 381-382.

[7] Kamel, M. A., Lobna,A. M., El-Sayed, L. M., Mohamed, H. I. and Rania, B. H. (2006). Hydrazones of 2-aryl-quinoline-4-carboxylic acid hydrazides: Synthesis and preliminary evaluation as antimicrobial agents. *Biorganic and Medicinal Chemistry*. 14: 8675-8682.

[8] Ola, E. I., Sayed, A., Fatma, E. M., Shada, E. I., Badr, A. A. and Maher, H. E. (2005). Synthesis of 2,4-disubstituted pyrimido[4,5-b] quinolines as potential antimicrobial agents. Indian Journal of Heterocyclic Chemistry. 14: 327-330.

[9] Kansagra, B. P., Bhatt, H. H. and Parikh, A. R. (2000). Synthesis and antimicrobial activity of substituted 4-thiazolidinones bearing 2-chloro quinoline nucleus. Indian Journal of Heterocyclic Chemistry. 10: 5-8.

[10] Santhosh, K. S., Ajay, N., Tiwari, R. P. and Praveen, J. (2006). Synthesis of novel substituted/unsubstituted-(2,8-bis-triflouromethyl-quinolin-4-yloxy)-acetic acid: derivatives of cephalosphorin and their antibacterial activity. *Indian Journal of Chemistry*. 45: 1734-1739.

[11] Amit, N. and Rahul, J. (2008).Synthesis and anti-tuberculosis activity of 2, 4-disubstituted quinolines.Indian Journal of Chemistry.47: 117-128.

[12] Vangapandu, S., Jain, M., Jain, R., Kaur, S. and Singh, P. P. (2004). Ring-substituted quinolines as potential anti-tuberculosis agents. *Bioorganic and Medicinal Chemistry*. **12**: 2501- 2508.

[13] Vikramdeep, M., Amit, N., Balasubramanian, V., Prakash, P. B., Sarbjit Singh. J. and Sukhraj, K. (2004). Synthesis and antimycobacterial activities of ring-substituted quinolinecarbohydrazide and ring-substituted quinolinecarboxamide analogues. *Biorganic and Medicinal Chemistry*. **12**: 6465-6472.

[14] Tseng, C. H., Chen, Y. L., Lu, P. J., Yang, C. N. andTzeng, C. C. (2008). Synthesis and antiproliferative evaluation of certain indeno[1,2-c]quinoline derivatives. *Bioorganic and Medicinal Chemistry*. **16**: 3153-3162.

[15] Katarzyna, S., Lukasz, K. S., Wojciech, S. J., Joanna, W., Marta, S. and Wanda, P. C. (2007). Synthesis and antiproliferative activity of diacetylenicthioquinolines. *Institute of Immunology and Experimental Therapy*. **61**: 41-200.

[16] Zhao, Y. L., Chen, Y. L., Chang, F. S. and Tzeng, C. C. (2005). Synthesis and cytotoxic evaluation of certain 4-anilino-2-phenylquinoline derivatives. *Eurpean Journal of Medicinal Chemistry*. **40**: 792-797.

[17] Firestone, G. L. and Sundar, S. N. (2009). Anticancer activities of artemisinin and its bioactive derivatives. *Expert Reviews in Molecular Medicine*. **11**: 32.

[18] Lu, J. J., Meng, L. H., Cai, Y. J., Chen, Q., Tong, L. J.and Lin, L. P. (2008). Dihydroartemisinin induces apoptosis in HL-60 leukemia cells dependent of iron and p38 mitogen-activated protein kinase activation but independent of reactive oxygen species.*Cancer Biology and Therapy*. **7**: 1017-1023.

[19] Kouznetsov, V. V., Rojas Ruíza, F. A., Vargas Méndeza, L. Y. and Gupta, M. P. (2012).Simple C-2-Substituted Quinolines and their Anticancer Activity. *Letters in Drug Design and Discovery*. **9**: 680-686.

[20] Afzal, O., Kumar, S., Haider, M. R., Ali, M. R., Kumar, R. andJaggi, M. (2015).A review on anticancer potential of bioactive heterocyclequinoline.*European Journal Medicinal Chemistry*. **97**: 871-910.

[21] Godard, A., Robin, Y. and Queguiner G. (1987). Etude de la métallation des carbamates d'hydroxy-5,-6,-7et-8 quinoéine. *Journal Organometallic Chemistry*. **336**(1-2): 1.

[22] Al-Busafi, S. N., Suliman, F. E. O. and Al-Alawi, Z. R. (2013). 8-Hydroxyquinoline and its Derivatives: Synthesis and Applications. *Research and Reviews: Journal of Chemistry*. **3**(1): 1-10.

[23] Vardanyan, R. and Hruby, V. (2005). Synthesis of essential drugs. Elsevier. **4**(1): 1-10.