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Synthesis of 2,3-dihydroquinazoline -4(H)-one Derivatives by Intramolecular Oxidative Coupling Reaction as Cytotoxic Agent

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Abstract:

A pair of 2,3-dihydroquinazoline-4(H)-one derivatives having fused with 1,2-dihydro-3,4-benzoquinoline moiety were prepared by a three component condensation reaction of isatoic anhydride, primary amines and aromatic aldehydes followed by the intramolecular oxidative coupling reaction in the presence of nontoxic $FeCl_3$. This reaction involves dehydrogenative coupling of a various of 1,2-diarylethylene derivatives at temperature 0-5 ^oC. NMR and IR spectroscopy were used to characterize all the synthesized compounds and studied their cytotoxic property by Brine Shrimp Lethality Bioassay. Among these compounds, compound **2b** and **3b** showed moderate cytotoxicity with LC_{50} values 76.16 and 70.70 µg/mL respectively.

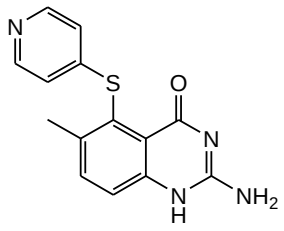
Key words:

2,3-dihydroquinazoline-4(H)-one, Isatoic anhydride, There component condensation reaction, Intramolecular oxidative coupling, Cytotoxicity, Brine Shrimp Lethality Bioassay.

Introduction:

Nitrogen containing heterocyclic compounds have been attracting significant research interest for their natural abundance, structural variety and potential biological activities. Their ability to form the hydrogen bond or other interaction with the various biological target such as enzymes and receptors with sufficient stability make them crucial unit in various drug design.

The 2,3-dihydroquinazolin-4(1H)-one derivatives belong to an vital class of fused nitrogenous heterocyclic compounds that exhibit a wide range of biological activities including, antibacterial, antihypertensive, antitumor, mono amine oxidase inhibitor, and also plant growth regulator [1-6]. Moreover, 2,3-dihydroquinazolin-4(1H)-one derivatives are the key intermediate for the synthesis of quinazolin-4(1H)-one compounds[7-8].



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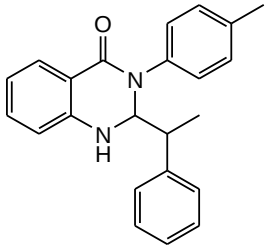

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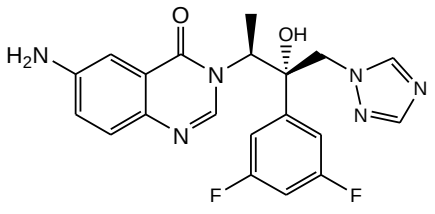

III

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A variety of DHQs derivatives have been reported to have some diverse biological activities and currently using as drugs for the treatment of different diseases [9-11]. For example, the compound **I** is used as antineoplastic agent whereas compound **II** and compound **III** were reported as neurotransmitter and antifungal drugs.[9-10].

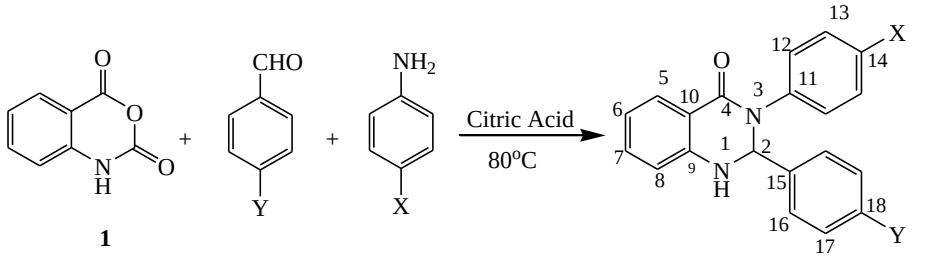
Intramolecular oxidative reaction introduce a new ring which increase the rigidity of the molecule. As a results the activity may increase as well as reduce the risk of adverse effect. In this context, this article mainly focus on the synthesis 2,3-dihydroquinazoline-4(H)-ones derivatives having fused with 9,10- dihydrophenanthrene by green condensation method followed by the intramolecular oxidation derivatives to study their cytotoxic properties.

Experimental:

General: All the solvents used in the reactions were used after purification by distillation. The completion of the reaction was checked with thin layer chromatography (TLC) containing silica gel, 60 GF254 (Merck). Melting point of the products was measured in Fisher John electro thermal melting point apparatus in 300 ^{0}C. The IR spectrum of the products was recorded on a Shimadzu Prestige-21 Fourier Transform Infrared Spectrophotometer in KBr disk. The NMR spectrum of the products was recorded with Bruker-400 MHz using deuterated solvents.

Preparation of compound 2a-2c:

To a round-bottom flask, isatoic anhydride (1eq.) was added in water. Then *p*-substituted benzaldehydes (1eq.) and *p*-substituted anilines (1eq.) were added into the round bottom flask containing isatoic anhydride. Finally citric acid was added into the mixture. The temperature was maintained at 80 ^{o}C for a duration around 7-8 hours [11]. The crude products were recrystallized from a mixed solvent, water and ethanol (1:1).

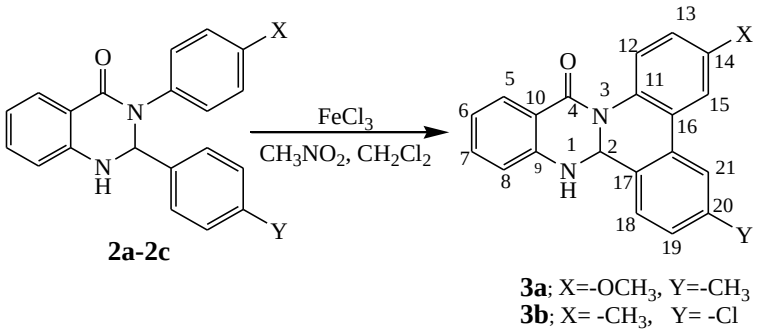


Scheme-1: Synthesis of 2,3-dihydroquinazoline-4(H)-ones derivatives

Preparation of compound 3a-3c:

To a round-bottom flask, starting compound (**2a-2c**) (1eq) was dissolved in dichloromethane. The solution was then placed into an ice bath to reduce the temperature around 0^o C. Meanwhile, ferric chloride (4eq.) was dissolved in nitromethane and added to the round-bottom flask containing compound **2a-2c**. The temperature is maintained at 0-5 ℃for 2 hours [12]. Upon completion, the reaction mixture was passed through a short silica gel column and then purified by another column

chromatography using the solvent *n*-hexane: ethyl acetate = 3:1. The product was recrystallized from *n*-hexane.



Scheme-2: Synthesis of oxidized 2,3-dihydroquinazoline-4(H)-ones derivatives(**3a-3b**).

All the compounds were characterized using ^{1}H-NMR and FTIR data.

Compound 2a: After recrystallization, the compound **2a** was obtained as white solid with the yield of 59%, R_f = 0.23(*n*-hexane: ethyl acetate=3:1) and melting point = 242-243℃. **FTIR (KBr/cm^{-1}) υ:** 3296(N-H), 3057 (C-H,aromatic), 2963-2839 (C-H, alkane), 1636(C=O, amide), 1608 and 1487(C=C, aromatic), 1441 and 1391(C-H, bend), 1315(C-N) ,1242(C-O) cm^{-1}, **^{1}H NMR (400MHz, DMSO-d$_6$) δ$_H$:** 2.23 (s, 3H, CH_3), 3.709 (s, 3H, OCH_3), 6.12(s, 1H, H_2), 6.70(t, *J* = 7.2 Hz, 1H, H_6), 6.72(d, *J* = 7.2 Hz, 1H, H_8), 6.87(d, *J* = 8.0 Hz, 2H, H_{13}), 7.09 (d, *J* = 8.0 Hz, 2H, H_{16}), 7.14 (*J* = 8.0 Hz, 2H, H_{17}), 7.24 (d, *J* = 8.0 Hz, 2H, H_{12}), 7.27 (t, *J* = 7.2 Hz, 1H, H_7), 7.46 (s, 1H, H_1, NH), 7.70 (d, *J* = 7.2 Hz, 1H, H_5).

Compound 2b: The compound **2b** was obtained as white solidwith the yield of 65%, R_f = 0.43(*n*-hexane: ethyl acetate=3:1) and melting point =234-235 ℃. **FTIR (KBr/cm^{-1}) υ:** 3302(N-H), 3059 (C-H, aromatic), 2922 (C-H, alkane), 1636(C=O, amide), 1609 and 1487(C=C, aromatic), 1391(C-H, bend), 1315(υ_{C-N}), 783(C-Cl) cm^{-1}, **^{1}H NMR (400MHz, DMSO-d$_6$) δ$_H$:** 2.23 (s, 3H, CH_3), 6.27 (s, 1H, H_2), 6.73 (t, *J* = 7.6 Hz, 1H, H_6), 7.75 (d, *J* = 7.6 Hz, 1H, H_8), 7.14 (s, 4H, H_{12}, H_{13}), 7.28 (t, *J* =7.6 Hz, 1H), 7.38 (s, 4H, H_{16}, H_{17}), 7.59 (s, 1H, H_1, NH), 7.71(d, *J* =7.6 Hz, 1H, H_5).

Compound 2c: The compound **2c** was obtained as white solid with the yield of 61%, R_f = 0.47 (*n*-hexane: ethyl acetate=3:1) and melting point 250-252℃. **FTIR (KBr/cm^1) υ:** 3306(N-H), 3049(C-H, aromatic), 2922-2826(C-H, alkane), 1636(C=O, amide), 1609 and 1489 (C=C, aromatic), 1441and 1387(C-H, bend), 1315(C-N), 604(C-Br) cm^{-1}, **^{1}H NMR (400MHz, DMSO-d$_6$) δ$_H$:** 2.23 (s, 3H, CH_3), 6.26 (s, 1H, H_2), 6.71(t, *J* = 7.2 Hz, 1H, H_6), 6.74 (d, *J* = 7.2 Hz, 1H, H_8), 7.11(d, *J* = 7.6 Hz, 2H, H_{17}), 7.22 (d, *J* = 7.6 Hz, 2H, H_{16}), 7.24 (d, *J* = 7.6 Hz, 2H, H_{12}), 7.28 (d, *J* = 7.2 Hz, 1H, H_7), 7.51(d, *J* = 7.6 Hz, 2H, H_{13}), 7.64 (s, 1H, H_1,NH), 7.71 (d, *J* = 7.2 Hz, 1H, H_5).

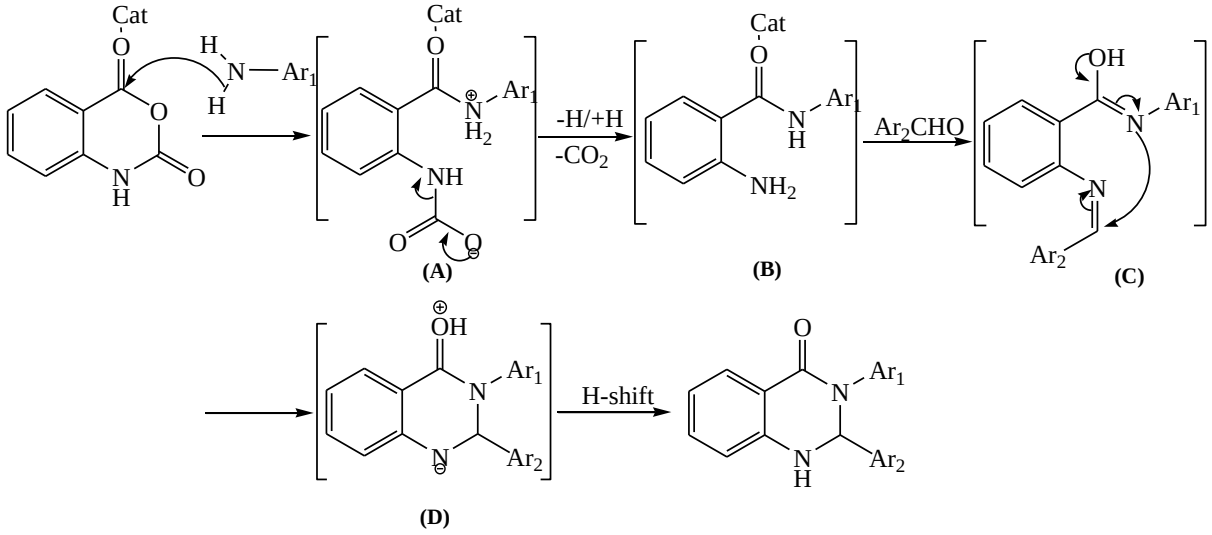
Compound 3a: The compound **3a** was obtained as white solid with yield of 33%, R_f = 0.47(*n*-hexane:ethyl acetate=3:1), melting point 146-147 ℃. **FTIR (KBr/cm^{-1}) υ:** 3466 (N-H), 3123(C-H, aromatic), 2922, 2853 (C-H, alkane), 1636 (C=O, amide), 1609 and 1487(C=C, aromatic), 1391(C-H, bend), 1248(C-N), 1153(C-O) cm^{-1}, **^{1}H NMR (400MHz, DMSO-d$_6$) δ$_H$:** 2.30 (s, 3H,

-CH_3), 3.77 (s, 3H, -OCH_3), 6.06(s, 1H, H_2), 6.64(d, *J* = 8.0 Hz, 1H, H_8), 6.73 (s, 1H, H_{15}), 6.75 (s, 1H, H_{21}), 6.90 (t, *J*= 8.0 Hz, 1H, H_6), 7.05 (d, *J* = 8.4 Hz, 1H, H_{13}), 7.10 (d, *J* = 8.4 Hz, 1H, H_{19}), 7.19 (d, *J* = 8.4 Hz, 1H, H_{18}), 7.46 (d, *J* = 8.4 Hz, 1H, H_{12}), 7.49 (t, *J* = 8.0 Hz, 1H, H_7), 7.72 (s, 1H, H_1, NH), 8.04(d, *J* = 8.0 Hz, 1H, H_5).

Compound 3b: The compound **3b** was obtained as white solid with yield of 15%, R_f = 0.49(*n*-hexane:ethyl acetate=3:1), melting point 124-125 ℃.**FTIR (KBr/cm^{-1}) υ:** 3364(N-H), 3028(C-H, aromatic), 2922, 2853(C-H, alkane), 1636(C=O, amide), 1597and 1491(C=C, aromatic), 1396(C-H, bend), 1248(C-N), 752(C-Cl) cm^{-1}, **^{1}H NMR (400MHz, DMSO-d$_6$) δ$_H$:** 2.30 (s, 3H, -CH_3), 6.30 (s, 1H, H_2), 6.58 (t, *J*=8.0 Hz, 1H, H_6), 6.74(d, *J* = 8.0 Hz, 1H, H_7), 6.74 (s, 1H, H_{15}), 6.79 (s, 1H, H_{21}), 7.05 (d, *J* = 8.4 Hz, 1H, H_{13}), 7.11 (d, *J* = 8.4 Hz, 1H, H_{19}), 7.17 (d, *J* = 8.4 Hz, 1H, H_{18}), 7.19 (t, *J* = 8.0 Hz, 1H, H_7), 7.48 (d, *J* = 8.4 Hz, 1H, H_{12}), 7.74 (s, 1H, H_1,NH), 8.03(d, *J* = 8.0 Hz, 1H, H_5).

Result and Discussion:

The compounds **2a-2c** were synthesized by one pot multicomponent condensation reaction using nontoxic citric acid as a catalyst with an acceptable yield. A plausible mechanism of this reaction is illustrated in scheme-3 [13].



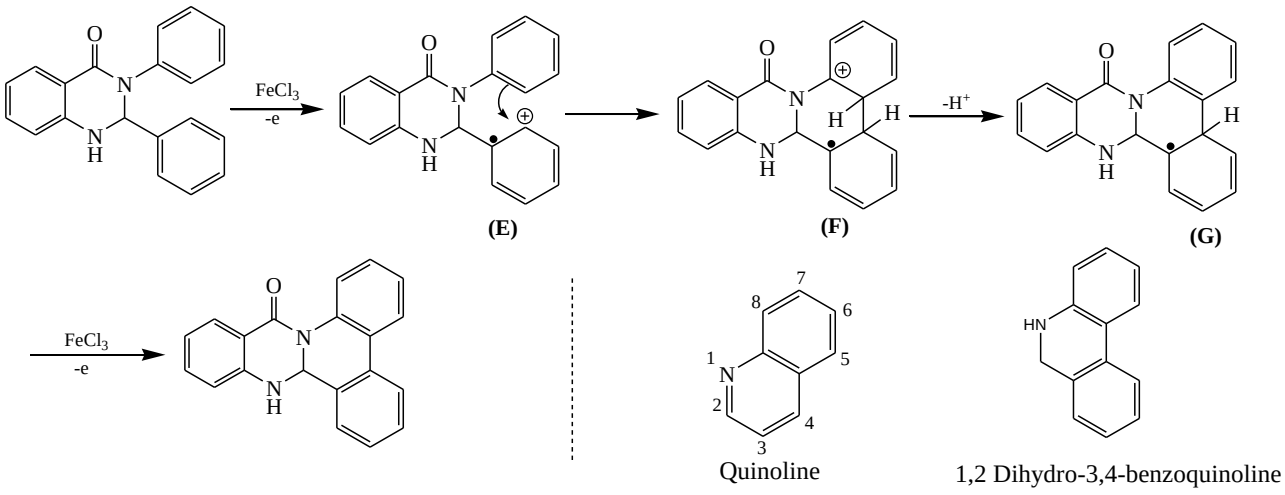
Scheme-3: A plausible mechanism of three components condensation reaction.

Activation of isatoic anhydride **1** by catalyst followed by the *N*-nucleophilic attacks of amine on the carbonyl produced the intermediate (A). Then, decarboxylation generate the intermediate 2-amino-*N*-substitued-benzamide (B). Subsequently, the reaction of aldehyde and intermediate B afford the intermediate C which converted to D *via* an intramolecular cyclization. Finally, disubstituted 2,3-dihydro-4(1H)-quinazolinones **2a-2c** were formed by a 1,5-proton transfer of intermediate D.

The structures of these compounds were confirmed by different spectroscopic data. In the IR spectrum of the compound **2a-2c**, the bands at 3296-3306 are due to υ_{N-H} whereas the bands at 3049-3059 are assigned to υ_{C-H}, aromatic. The absence of $\upsilon_{C=O}$(carbonyl) indicates the formation of compounds **2a-2c** which were supported by the presence of aromatic proton of newly introduced rings in the ^{1}H-NMR spectra which appeared at δ_H 6.87-7.50 . The other signals in the ^{1}H NMR spectra complies with structures of the compounds **2a-2c.**

The intramolecular oxidative coupling reaction in the presence of iron (III) chloride afford the compounds **3a-3c** having fused 1,2-dihydro-3,4-benzoquinoline moiety. The intramolecular oxidative coupling reaction may causes some decomposion which lead to the low yield of the products. Though the IR spectrum of these compounds (**3a-3b**) are very similar to that the precursor, ^{1}HNMR spectrum is quite different. The signals for NH proton appeared at δ_H 7.64-7.74 ppm. In addition, proton of CH between two nitrogen showed a sharp singlet at 6.06-6.30 ppm. The absence of the signal for the protons of the carbons connected by the new bond confirm the formation of the products.

The intramolecular oxidative coupling reaction proceed through the transfer of a pair of electron. Firstly, the treatment with $FeCl_3$ generated a radical cation (E). Then the new C-C bond formed when radical cation was attacked by another electron rich benzene ring (F). Finally, under the same effect of $FeCl_3$, dehydrogenation restore the aromaticity of the benzene ring of the desired oxidized compounds [14].



Scheme-4: The mechanism of intramolecular oxidative coupling reactions

Brine Shrimp Lethality test:

The cytotoxicity of the synthesized compounds were studied and compared with the standard vincristine sulphate [15]. None of these compound showed the cytotoxicity to the satisfactory level. Among these compounds, compound **2b** and **3b** showed moderate cytotoxicity whereas compound **2a**, **2c** and 3a showed very weak cytotoxicity.

Table-1: LC_{50} of the synthesized compounds

Compounds No	LC_{50}	Remarks
vincristine sulfate	3.501	Standard
2a	132.34	Weakly toxic
2b	76.31	Moderately toxic
2c	128.05	Weakly toxic
3a	242.99	Weakly toxic
3b	70.70	Moderately toxic

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