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Synthesis of Amino Acid and Aniline Derivatives of Quinolinediones

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Successful synthesis of amino acid and aniline derivatives of 6,7-dibromo-5,8-quinolinedione is reported. 6,7-Dibromo-5,8-quinolinedione was prepared by nitrosation of 8-hydroxyquinoline, followed by subsequent amination and oxidation of the resulting intermediates. Thereafter, addition of amino acids and anilines supplied the desired products. Effect of solvent on reaction yield and time showed pyridine as the best amongst the studied solvents. Structural elucidation was done using proton NMR and mass spec.

Keywords: Amination; bioactivities; 6,7-dibromo-5,8-quinolinequinone; structural modification.

1. INTRODUCTION

The Chemistry of quinolinedione has been known for over a century ago [1]. Since then, they have been an area of interest to large number of researchers because of their vast spectrum of bioactivities, like potent antifungal, antibacterial [2], antimalarial [3] and antineoplastic [4] properties. Since the discovery of quinolinedione, several variations have been done to it not only to obtain molecules of enhanced properties, but also to find new scope of applications [4]. As a result, modifications in the parent structure have resulted in a good

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number of compounds of medicinal and industrial applications.

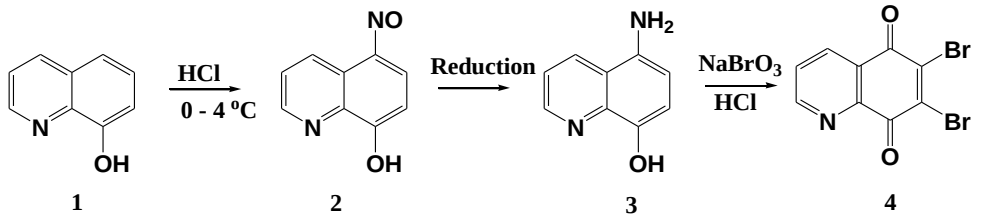
Despite the several modifications, the Chemistry of quinolinediones remains poorly developed [4]. Furthermore, nitrogen, oxygen and sulphur containing compounds are known to be essentially used in medicine for the treatment of different infections and ailments [5], because of their high efficiency against diseases [6].

Amino acids are known to display diverse range of biological and pharmacological properties like anticancer [7] and antitumur activities [7].

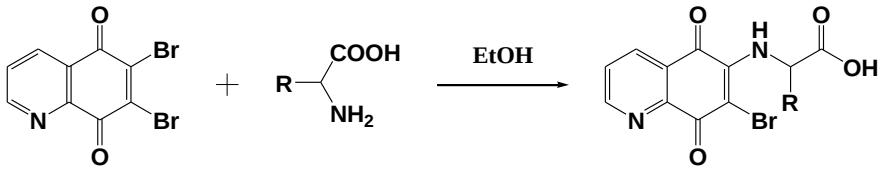
As a result of the aforementioned and extension of our interest in the synthesis of quinolinedione derivatives [8, 9, 10], this research reports synthesis of amino acid and aniline derivatives of quinolinediones with the hope of obtaining compounds of improved activities and new areas of applications.

2. RESULTS AND DISCUSSION

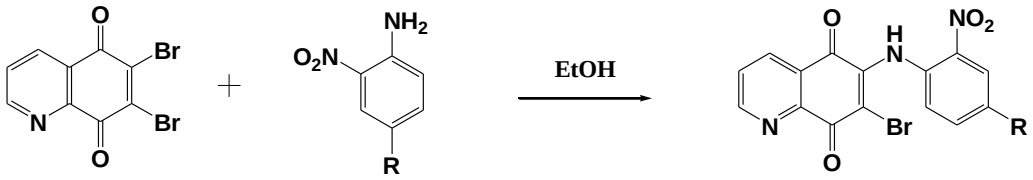
Synthesis of key intermediate 6,7-dibromo-5,8-quinolinequinone was achieved in a three-step reaction (Equ. 1).



Equation 1. Synthesis of 6,7-dibromo-5,8-quinolinequinone



Equation 2. Synthesis of amino acid derivatives of 6,7-dibromo-5,8-quinolinequinone

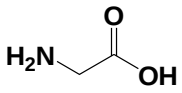
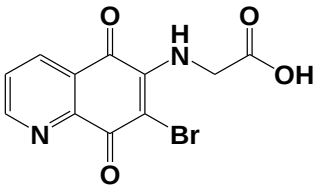
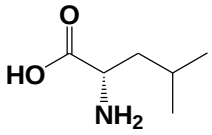
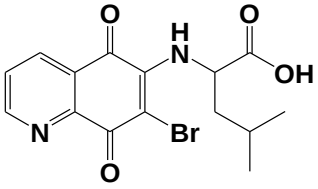
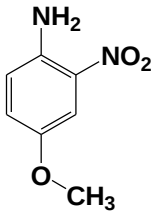
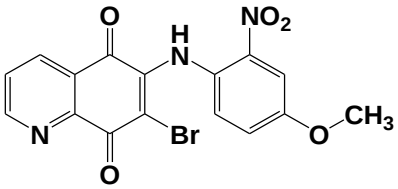
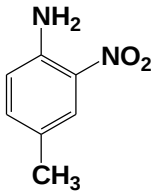
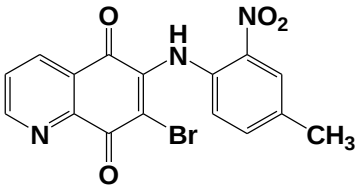


Equation 3. Synthesis of aniline derivatives of 6,7-dibromo-5,8-quinolinequinone

Table 1. Solvent effect on reaction yield and time

Entry	Reaction Conditions	Yield (%)	Reaction time (h)
1	MeOH	20	48
2	EtOH	80	3
3	CH_3CN	Trace	24
4	Pyridine	80	2

Table 2. Synthesized quinolinedione derivatives

Entry	Amino acid/Aniline	Product	Reaction time (h)
1			80
2			82
3			73
4			78

The reaction between aqueous solution of 8-hydroxoyquinoline, **1** and concentrated hydrochloric acid stirred with aqueous sodium nitrite solution over 1.5 h and 0-4 °C furnished 8-hydroxy-5-nitrosoquinoline hydrochloride, 2 as a yellow solid product which melted at 178 °C. Under basic and hot conditions, and in a nitrogen atmosphere, sodium dithionite reduces 8-hydroxy-5-nitrosoquinoline hydrochloride, 2 to the corresponding amine which in the presence of 6 M sulphuric acid precipitates as the sulphate of 5-amino-8-hydroxyquinoline, 3. The brownish red solid melted at 218-220 °C. 5-Amino-8-hydroxyquinoline sulphate 3 was converted to 6,7-dibromo-5,8-quinolinequinone 4 by sodium bromate in 24 % hydrobromic acid at 50-60 °C for 0.5 h. The resulting yellow compound melted at 242-243 °C. Thereafter, 6,7-dibromo-5,8-quinolinequinone was reacted with some amino acids and anilines to provide the desired products (Equ. 2 and Equ. 3).

Effect of solvent of reaction yield and time was also studied. The results revealed that ethanol and pyridine had better yields and times. Pyridine had the best result probably due to its dual role as both solvent and base which could facilitate abstraction of proton from the amine group to form C-N bond.

3. EXPERIMENTAL

3.1 Procedure A

1mmol each of 6,7-dibromo-5,8-quinolinequinone and amino acid, and 10 mL EtOH were charged into a flask. The mixture was refluxed while stirring vigorously. After completion as determined by TLC, it was allowed cool, filtered and recrystallized using water/ acetone mixture to give the product of interest.

3.2 Procedure B

1mmol each of 6,7-dibromo-5,8-quinolinequinone and aniline acid, and 10 mL EtOH were charged into a flask. The mixture was refluxed while stirring vigorously. After completion as determined by TLC, it was allowed cool, filtered and recrystallized using water/ acetone mixture to give the product of interest.

3.2.1 2-(7-Bromo-5,8-dihydro-5,8-dioxoquinolin-6-ylamino)acetic acid (5)

248 mg, 80 %, Mp: 259 ^{o}C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.47 (s, OH, 1H) 7.93 (dd, J = 7.5 Hz, 1H, H-1); 7.66 (d, J = 4.5 Hz, 1H, H-2); 7.57 (dd, J = 8.5 Hz, J = 3.5 Hz, 1H, H-3); 4.46 (m, CH_2); 2.49 (s, NH, 1H). EIMS *m/z*: 309 (M^+, 100).

3.2.2 2-(7-Bromo-5,8-dihydro-5,8-dioxoquinolin-6-ylamino)-4-methylpentanoic acid 6

303 mg, 82 %, Mp: 272 ^{o}C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.93 (s, OH, 1H) 8.76 (dd, J = 7.5 Hz, 1H, H-1); 8.52 (d, J = 4.5 Hz, 1H, H-2); 8.49 (s, NH_2); 7.90 (dd, J = 8.67 Hz, J = 3.5 Hz, 1H, H-3); 4.5 (s,CH_2, 1H); 2.4 (s, $(CH_3)_2$ 6H). EIMS *m/z*: 367 (M^+, 100).

3.2.3 6-(4-Methoxy-2-nitrophenylamino)-7-bromoquinoline-5,8-dione 7

292 mg, 73 %, Mp: 298 ^{o}C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.60 (s, 1H), 7.75 (dd, 1H), 7.57 (d, 1H), 7.3 (dd, 1H), 7.21 (s, 1H), 4.78 (m, 1H), 4.18 (dd, 1H), 3.3 (OCH_3). EIMS *m/z*: 404 (M^+, 100).

3.2.4 6-(4-Methyl-2-nitrophenylamino)-7-bromoquinoline-5,8-dione 8

304 mg, 78 %, Mp: 288 ^{o}C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.6 (s, 1H), 7.90 (dd, 1H), 7.67 (d, 1H), 6.9 (dd, 1H), 7.2 (s, 1H), 7.01 (dd, 1H), 7.0 (dd, 1H), 2.1 (CH_3). EIMS *m/z*: 388 (M^+, 100).

4. CONCLUSION

This study provides easy and facile routes to novel heterocycles thereby extending methods available for obtaining quinolinequinone derivatives. Thus, it will generate new vistas for further research. The new compounds synthesized will potentially be useful as anticancer and antimicrobial agents in medicine making the research a worthwhile venture.

DISCLAIMER

The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by Kogi State University, Anyigba – Institutional Based Research (IBR) Fund.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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