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# Synthesis of piperazine propyl 4-oxo-3,4-dihydroquinazoline-2-carboxylate derivatives

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**ABSTRACT**

An efficient method have been developed for the synthesis of a series of piperazine propyl 4-oxo-3,4-dihydroquinazoline-2-carboxylate derivatives (**8a-e**) with various piperazines **7a-e** in the presence of potassium carbonate in DMF. The synthesized compounds were characterized by spectral data.

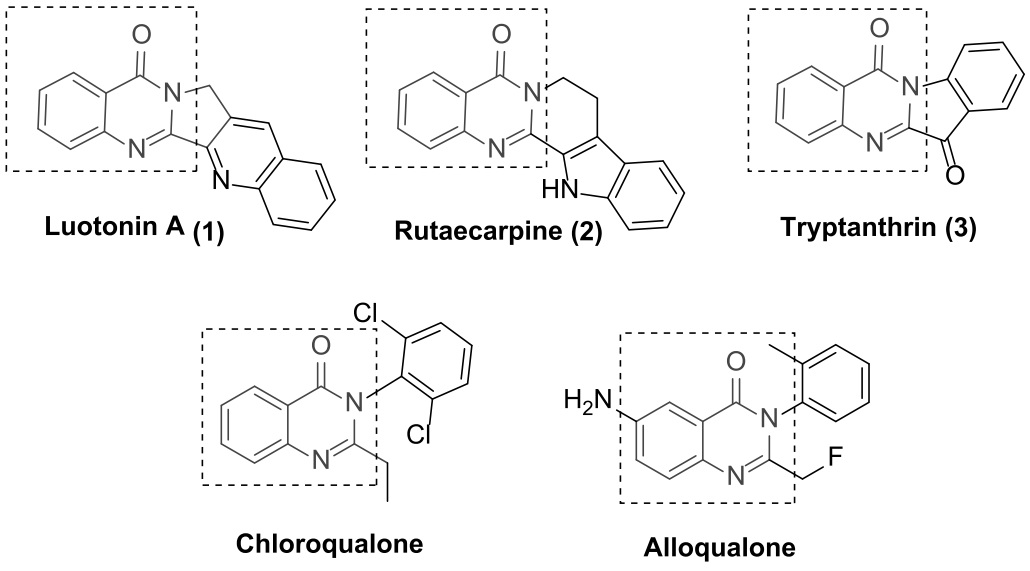
## INTRODUCTION

The quinazolinone moiety contained in natural products (Luotonin, Rutaecarpine, Tryptanthrin, Chloroqualone, Alloqualone, etc) represents medicinally and pharmaceutically important class of compounds [**1-2**] because of their diverse range of biological activities such as anti-cancer, diuretic, anti-inflammatory, anti-convulsant and anti-hypertensive [**3-4**]. In recent years, quinazolinone embedded numerous natural products have been identified [**5**]. Several other quinazolinone derivatives have been identified with anticancer, mPTP modulators, EGFR and VEGFR-2 inhibitors [**6-8**]. The cytotoxic alkaloid Luotonin-A (1) and its derivatives infused with quinazolinone moiety is clinically proved as anti-cancer agents (Figure 1) [**9-11**].

In this paper we describes the synthesis of novel piperazine propyl 4-oxo-3,4-dihydroquinazoline-2-carboxylate derivatives as shown in Scheme 1.

## EXPERIMENTAL

All the commercial reagents and solvents were used without further purification unless otherwise stated. Melting points were recorded on a Buchi 535 melting point apparatus and are uncorrected. All the reactions were monitored by thin layer chromatography performed on precoated silica gel $60F_{254}$ plates (Merck). Compounds were visualized with UV light at 254 nm and 365 nm, $I_2$ and heating plates after dipping in 2% phosphomolybdic acid in 15% aq. $H_2SO_4$ soln. IR spectra were recorded on a Perkin-Elmer 683 or a 1310 FT-IR spectrometers with KBr pellets. NMR spectra

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were recorded on a Varian Unity-400 MHz and BRUKER AMX 300 spectrometers using TMS as an internal standard. Mass spectra were recorded on a VG. Micromass 7070H and a Finnigan Mat 1020B mass spectrometers operating at 70eV.

**Preparation of 4-oxo-3,4-dihydroquinazoline-2-carboxylic acid (4)**

To the solid compound, 2-aminobenzamide (5 g, 0.037 mol), an excess of diethyl oxalate (15 mL, 0.11 mol) was added carefully and the mixture was stirred at reflux temperature for 8h. After completion of the reaction (TLC analysis), the solution was allowed to cool to room temperature and the excess diethyl oxalate was removed under vacuum. The remaining solid was suspended in EtOH and filtered to produce **ethyl-4-oxo-3,4-dihydroquinazoline-2-carboxylate (3),** white solid, Yield 90%; mp 191-193°C; $^1$H NMR (300 MHz, $CDCl_3$): δ 1.40 (t, *J* = 7.1 Hz, 3H, $CH_3$), 4.29-4.43 (q, *J* = 7.1 Hz, 2H, $CH_2$), 7.19 (t, *J* = 7.5 Hz, 1H, Ar-H), 7.45-7.60 (m, 1H, Ar-H), 7.89 (d, *J* = 7.7 Hz, 1H, Ar-H), 8.24 (br, 1H, NH), 8.60 (d, *J* = 8.1 Hz, 1H, Ar-H).

The intermediate **3** converted into **4** by treating with 1N KOH : EtOH (30 mL, 1:1) under reflux condition for 1h. After completion of the reaction (TLC analysis), the solution was allowed to cool to room temperature and ethanol was removed under vacuum, the obtained solid was filtered to give 4-oxo-3,4-dihydroquinazoline-2-carboxylic acid (3.45 g, 65%) as white solid.

**Preparation of 3-bromopropyl 4-oxo-3,4-dihydroquinazoline-2-carboxylate (6)**

To a compound of quinazoline acid **(**3g, 0.012 moles) and anhydrous $K_2CO_3$ (4.14g, 0.03 moles) in dry DMF (5 mL), 1,3-dibromopropane (2.25ml, 0.012 moles) was added and stirred at room temperature until the disappearance of the starting material which was confirmed by TLC (13–17 h), the solvent was removed under vacuum. The solid residue was poured into ethyl acetate (15 mL) and extracted with water (35 mL), the organic layer was dried over $Na_2SO_4$. Then, the crude was purified by flash column chromatography with hexane/EtOAc (85:15) to afford the desired bromo compound **6**. Yield: 76%, $^1$H NMR: δ 2.37-2.42 (m, $CH_2$, 2H), 3.45 (t, *J*=6.1, 12.3 Hz, $CH_2$, 2H), 4.19 (t, *J*=6.5, 13.2 Hz, $CH_2$, 2H), 7.52 (t, *J*=8.0, 16.1 Hz, ArH), 7.72-7.73 (m, 1H, ArH), 7.78 (t, *J*=8.3, 15.3 ArH), 8.12 (s, 1H, ArH), 8.31 (d, *J*=8.3Hz, 1H, ArH).

**General Procedure for the preparation of piperazine propyl 4-oxo-3,4-dihydroquinazoline-2-carboxylate derivatives (8a-e)**

To a compound of quinazolinone bromo ester, **(**3g, 0.021 moles) and anhydrous $K_2CO_3$ (4.21g, 0.03 moles) in dry DMF (5 mL), respective piperazine (1.25 mL, 0.012 moles) was added and stirred at room temperature until the disappearance of the starting material which was confirmed by TLC (13–17 h), the solvent was removed under vacuum. The solid residue was poured into ethyl acetate (15 mL) and extracted with water (35 mL), the organic layer was dried over $Na_2SO_4$. Then the crude was purified by flash column chromatography with hexane/EtOAc (85:15) to afford the following piperazine propyl-4-oxo-3,4-dihydroquinazoline-2-carboxylate derivatives **8a-e**:

**3-Morpholinopropyl-4-oxo-3,4-dihydroquinazoline-2-carboxylate (8a):**

Yield: 68%, $^1$H NMR: δ 1.59-1.80 (m, $CH_2$, 6H), 3.61-3.64 (m, $CH_2$, 4H), 3.89 (t, *J*=5.6, 9.7 $H_Z$ ,$CH_2$, 2H), 4.51-4.56 (m, CH, 2H), 7.56-7.63 (m, 2H, ArH), 7.78-7.83 (m, 2H, Ar H). MS m/z = 317 [M+H].

**3-Thiomorpholinopropyl-4-oxo-3,4-dihydroquinazoline-2-carboxylate (8b):**

Yield: 72%, $^1$H NMR: δ 2.05 (s, $CH_2$, 2H), 2.45 (t, *J*=7.2, 14.7 $H_Z$ ,$CH_2$, 2H), 2.66-2.74 (m ,$CH_2$, 8H), 4.28-4.32 (m , $CH_2$, 2H), 7.49-7.61 (m, 2H, ArH), 7.70-7.79 (m, 2H, ArH). MS m/z = 334 [M+H].

**3-(4-(Ethoxycarbonyl)piperazin-1-yl)propyl-4-oxo-3,4-dihydroquinazoline-2-carboxylate (8c):**

Yield: 70%, $^1$H NMR : δ 1.25-1.29 (m, $CH_3$, 3H), 2.02-2.07(m, $CH_2$, 2H), 2.39-2.44(m, $CH_2$ , 4H), 2.51(t,J=6.8, 13.9 HZ ,$CH_2$, 2H), 3.46-3.51 (m, $CH_2$, 4H), 4.10-4.18 (m, $CH_2$, 4H), 7.51-7.57 (m, 1H, Ar-H), 7.71-7.78 (m, 1H, Ar-H). MS m/z = 389 [M+H].

**3-(4-Benzylpiperazin-1-yl)propyl-4-oxo-3,4-dihydroquinazoline-2-carboxylate (8d):**

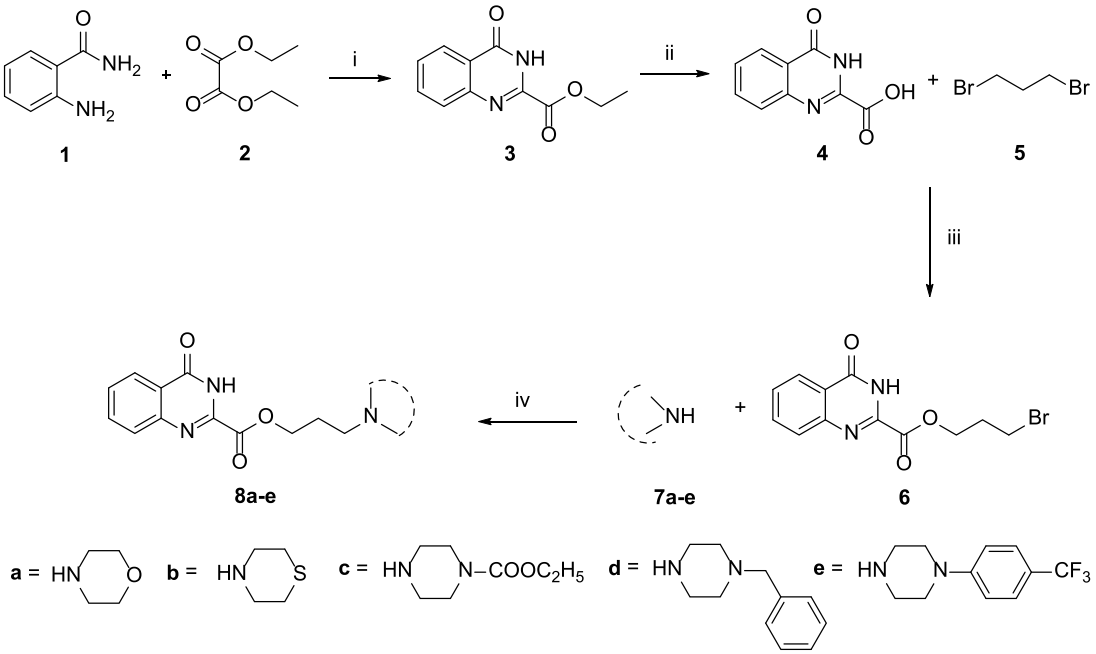
Yield: 78%, $^1$H NMR: δ 2.0-2.15 (m, $CH_2$, 9H), 2.49-2.56(m, $CH_2$, 2H), 2.64(t,J=6.9, 14.4 HZ ,$CH_2$, 2H), 3.14(d,J=11.2HZ ,1H, CH), 4.49-4.54 (m, $CH_2$, 2H), 7.10-7.13 (m, 2H, Ar-H), 7.17-7.21 (m, 2H, Ar-H), 7.51-7.58 (m, 2H, Ar-H), 7.69-7.81 (m, 3H, Ar-H), 8.29 (d,J=13HZ, 1H, Ar-H). MS m/z = 407 [M+H].

**3-(4-(4-(Trifluoomethyl)piperazin-1-yl)propyl-4-oxo-3,4-dihydroquinazoline-2-carboxylate (8e):**

Yield: 76%, $^1$H NMR: δ 2.20-2.24 (m, $CH_2$, 2H), 2.43-2.50 (m, $CH_2$, 2H), 2.57 (t, *J*=4.8, 9.7$H_Z$ , $CH_2$, 4H) 2.62 (t, *J*=4.8, 9.7 $H_Z$, $CH_2$, 2H), 2.67-2.69 (m, $CH_2$, 2H), 4.26 (t, *J*=5.7, 11.9$H_Z$, $CH_2$, 2H), 7.69-7.79 (m, 4H, ArH), 8.07 (s, 1H, ArH), 8.14 (s, 1H, ArH), 8.31(d, *J*=7.9$H_Z$, 2H, ArH). MS m/z = 461[M+H].

## RESULTS AND DISCUSSION

4-Oxo-3,4-dihydroquinazoline-2-carboxylic acid (**4**) was synthesized by treating anthranilamide (**1**) with excess of diethyl oxalate (**2**) under reflux temperature for 8 h followed by treatment with 1N KOH : EtOH (1:1) for 1h to produce compound **4** in good yields. The reaction of carboxylic acid **4** with 1,3-dibromo propane (**5**) in the presence of potassium carbonate in DMF furnished 3-bromopropyl-4-oxo-3,4-dihydroquinazoline-2-carboxylate (**6**). Treatment of bromo compound **6** with various piperazines **7a-e** in the presence




**Scheme 1**

of potassium carbonate in DMF, resulted corresponding targeted compounds 8**a-e** respectively as shown in Scheme 1.

***Reagents &Conditions*:**

i) Reflux, 8 h. ii) 1N KOH : EtOH (1: 1), reflux, 1 h. iii) $K_2CO_3$, DMF, RT. iv) $K_2CO_3$, DMF, 0 °C, RT.

In conclusion, we have synthesized a series novel derivatives of piperazine propyl 4-oxo-3,4-dihydroquinazoline-2-carboxylate derivatives in good to excellent yields with a milder conditions. Docking studies and anti-proliferative activity under progress.

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