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# SYNTHESIS, PRELIMINARY QSAR STUDY AND ANTIMICROBIAL ACTIVITY OF SOME NOVEL 2, 3-DISUBSTITUTED QUINAZOLINONE DERIVATIVES

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## ABSTRACT

A series of novel quinazolinone derivatives have been synthesized by the condensation of 2-substituted benzoxazine /6, 8-dibromo-2-substituted benzoxazine with p-amino containing compounds. Structures of the newly synthesized compounds have been established on the basis of their melting point, thin layer chromatography, IR and $^1$H-NMR data. All the newly synthesized quinazolinone derivatives were evaluated for their anti-bacterial activity by disc diffusion method by measuring the zone of inhibition and the results were compared to standard.

## KEYWORDS

Synthesis, Quinazolinone derivatives, Anti-bacterial activity, p-amino compounds.

## INTRODUCTION

Heterocyclic chemistry comprises at least half of all organic chemistry research worldwide. In particular, heterocyclic structures form the basis of many pharmaceutical, agrochemical and veterinary products. Among a wide variety of nitrogen heterocycles that have been explored for developing pharmaceutically important role in medicinal chemistry and subsequently have emerges as a pharmacophore[1]. Quinazolinones are classes of fused heterocycles that are of considerable interest because of the diverse range of their biological activities such as anticancer[2, 3], anti-tubercular[4], anti-bacterial[5], antifungal[6], anti-HIV[7], anthelmintic[8], analgesic[9], antiinflammatory[10], antihypertensive[11], anti-diabetic [12] and anti-oxidant[13] activities. In view of these facts, the present study involves the synthesis of compounds containing quinazolinone ring system and to evaluate their anti-bacterial potency.

The synthetic strategy to synthesize the target compounds is depicted in scheme 1. In step 1, disubstituted anthranilic acid (1) ($R^1$, $R^2$= H, Br), were allowed to react with acetic anhydride/Benzoyl chloride in dry pyridine to produce 6, 8-disubstitued (R1, R2= H, Br)-2-methyl/phenyl-4H-Benzoxazine-4-one (2)[14, 15]. In step 2, 6, 8-disubstitued-2-methyl/phenyl-4H-Benzoxazine-4-one were reacted with o-toludine (A) and pyridine-4-carbohydrazide (B) to yield the title compounds. The physico chemical properties of the synthesized compounds are given in Table 1.

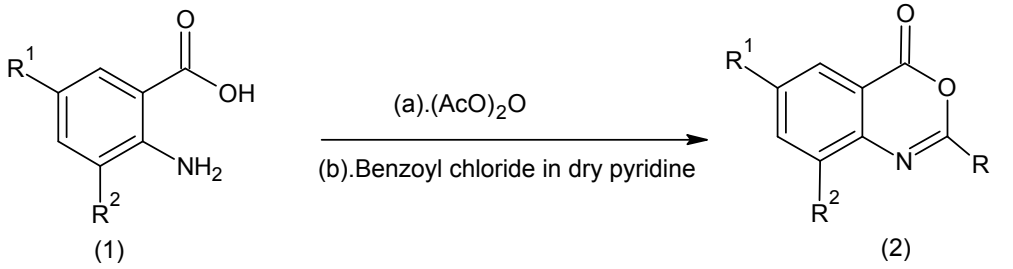
**Table 1**
***Physico-chemical parameters of the synthesized compounds:***

| Sl.No | Compound | R | $R^1$ | $R^2$ | Molecular Formula | Molecular Weight | % yield | Melting Point °C | Rf value | Log P Value |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 3a | $CH_3$ | H | H | $C_{16}H_{14}N_2O$ | 250.29 | 62 | 84 | 0.54 | 2.5 |
| 2 | 3b | $C_6H_5$ | H | H | $C_{21}H_{16}N_2O$ | 312.36 | 68 | 78 | 0.64 | 4.44 |
| 3 | 3c | $C_6H_5$ | Br | H | $C_{21}H_{15}BrN_2O$ | 391.26 | 72 | 94 | 0.61 | 5.21 |
| 4 | 3d | $CH_3$ | Br | Br | $C_{16}H_{12}Br_2N_2O$ | 408.08 | 70 | 98 | 0.64 | 4 |
| 5 | 3e | $C_6H_5$ | Br | Br | $C_{21}H_{14}Br_2N_2O$ | 470.08 | 71 | 90 | 0.53 | 5.94 |
| 6 | 4a | $CH_3$ | H | H | $C_{15}H_{12}N_4O_2$ | 280.28 | 58 | 170 | 0.58 | 0.4 |
| 7 | 4b | $C_6H_5$ | H | H | $C_{20}H_{14}N_4O_2$ | 342.35 | 68 | 64 | 0.68 | 2.16 |

# MATERIALS AND METHODS

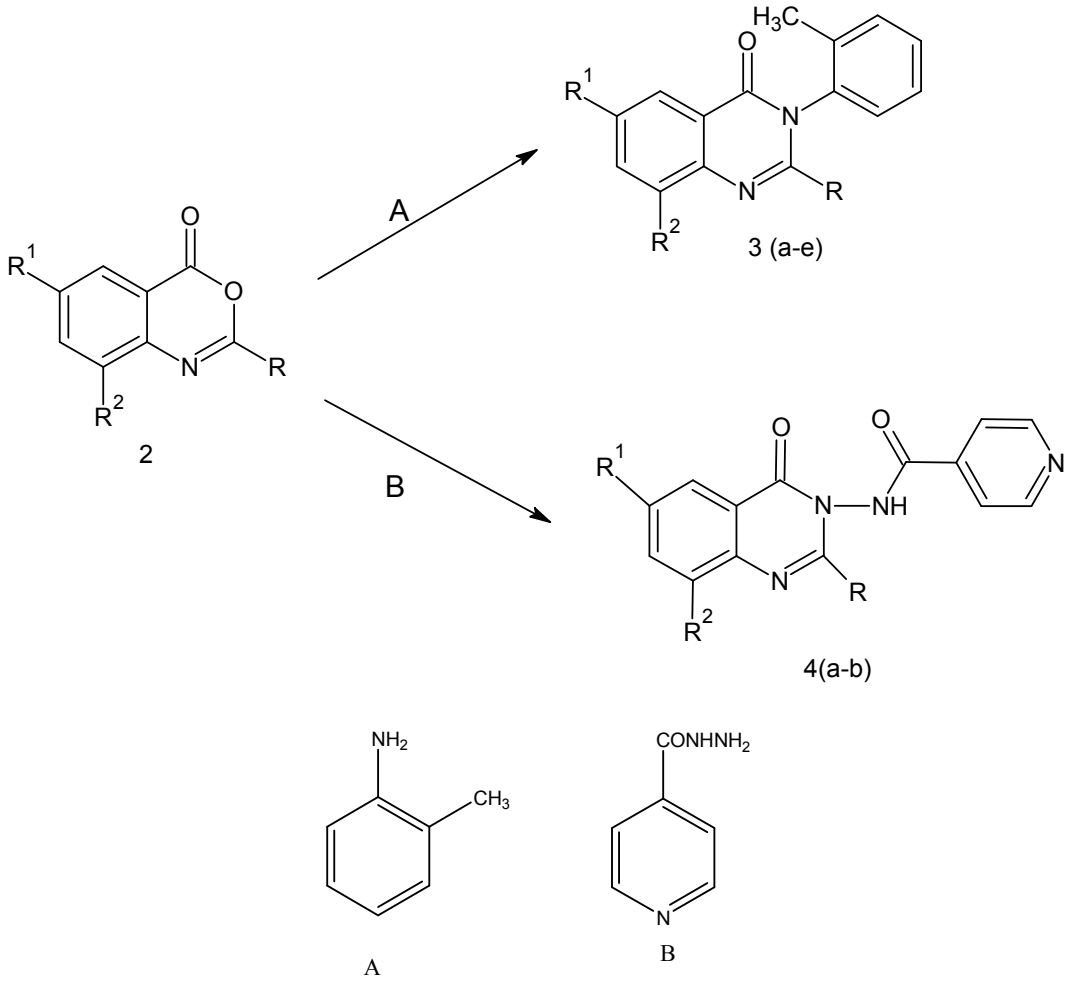
Melting points were determined using an open ended capillary tube method and are uncorrected. FT-IR spectra were recorded on a Perkin-Elmer 1800 FT-IR in KBr disc. $^1$H-NMR spectra were recorded at 400 MHZ on a Brucker FT-NMR spectrophotometer using TMS as internal standard. Completion of the reaction and purity of the compounds were checked by TLC using Silica gel G as stationary phase using chloroform and methanol (9:1) as mobile phase and the spot is visualized by UV-Chamber.

***Scheme 1***




(1) 6,8-disubstituted anthranilic acid

(2) 6,8-disubstituted methyl/phenyl benzoxazine-4-one




$R^1$, $R^2$ = H, Br
R= $CH_3$, $C_6H_5$

***Synthesis of 2-methyl-4H-Benzoxazine-4-one:***

A mixture of disubstitued anthranilic acid ($R^1$, $R^2$= H, Br) (0.12 mol) in Acetic anhydride (0.2 mol) was refluxed for 4 Hrs. The excess solvents were then distilled off under reduced pressure. The reaction mixture was filtered, washed, dried and recrystallized with absolute ethanol.

***Synthesis of 2-phenyl-4H-Benzoxazine-4-one:***

A mixture of disubstitued anthranilic acid ($R^1$, $R^2$= H, Br) (0.1 mol) was dissolved in 50 ml of dry pyridine. To this solution, Benzoyl chloride (0.2 mol) was added dropwise with constant stirring at low temperature. The reaction mixture was cooled. When the addition of Benzoyl chloride was completed, the resultant mixture was treated with 10% sodium bicarbonate. The reaction mixture was filtered and washed repeatedly with water to remove inorganic materials. The crude product obtained was recrystallized from ethanol.

***General synthetic method for the preparation of title compounds:***

***Synthesis of 2-methyl-3-(2-methylphenyl) quinazolin-4(3H)-one (3a):***

Equimolar mixture of 2-methyl benzoxazine-4-one and o-Toludine (0.01mol) was refluxed for 3 hours in the presence of 1-2ml glacial acetic acid. The reaction mixture was allowed to cool to room temperature. The crude product was recrystallized using absolute alcohol. IR ($cm^{-1}$): 1672 (C=O str), 1152.7 (C=C), 1604.5(C=N), $CH_3$ (1448.8); $^1$H-NMR ($CDCl_3$): δ 6.64 (s, 1H, Ar-H), 6.6 (s, 1H, Ar-H), 7.4-8 (m, 6H, Ar-H), 2.8(s, 3H, $CH_3$), 2.23 (s, 3H, CH3).

***Synthesis of 3-(2-methylphenyl)-2-phenyl quinazolin-4-(3H)-one (3b):***
A mixture of 2-phenyl-benzoxazine (0.013mol) and o-Toludine (0.013mol) were refluxed for 3 hrs in the presence of 1-2 ml glacial acetic acid. The reaction mixture was kept overnight and the solid obtained was recrystallized by using absolute alcohol. IR ($cm^{-1}$) :1666 (C=O str), 1517.3(C=C), 1595.5(C=N), 1026 (C-N); $^1$H-NMR ($CDCl_3$): δ 7.0 (s, 1H, Ar-H), 7.1 (s, 1H, Ar-H), 7.2-7.8 (m, 11H, Ar-H), 2.3(s, 3H, $CH_3$).

***Synthesis of 6-bromo-3-(2-methylphenyl)-2-phenylquinazolin-4(3H)-one (3c):***
A mixture of 6-bromo-2-phenyl benzoxazine (0.014mol) and o-toludine (0.014mol) were refluxed for 3 hrs in the presence of glacial acetic acid. The reaction mixture was cooled to room temperature. The solid obtained was recrystallized using absolute alcohol. IR ($cm^{-1}$): 1666.6 (C=O str), 1594, 1515 (C=C), 1447.3(C-H), 531(Br).

***Synthesis of 6, 8-dibromo-2-methyl-3-(2-methylphenyl) quinazolin-4(3H)-one (3d):***
A mixture of 6, 8 -dibromo-2-methyl benzoxazine (0.01mol) and o-toludine (0.01mol) were refluxed for 3 hrs in the presence of glacial acetic acid. The reaction mixture was cooled to room temperature, the product obtained was collected by filtration, dried and crystallized from ethanol to give 3d. IR ($cm^{-1}$): 1672(C=O str), 1493(C=C), 2535(C-H), 1617(C=N), 530,656(Br).

***Synthesis of 6, 8-dibromo-3-(2-methylphenyl)-2-phenylquinazolin-4(3H)-one (3e):***
A mixture of 6, 8-dibromo-2-phenyl benzoxazine (0.01mol) and o-toludine (0.01mol) were refluxed for 3 hrs in the presence of glacial acetic acid. The reaction mixture was cooled to room temperature, the product obtained was collected by filtration, dried and crystallized from ethanol to give 3e. IR ($cm^{-1}$) :1671(C=O str), 1512(C=C), 1447(C-H), 1603(C=N), 548, 699(Br).

***Synthesis of N-(2-methyl-4-oxoquinazolin-3(4H)-yl) pyridine-4-carboxamide (4a):***
2-methyl benzoxazine and pyridine-4-carbohydrazide (0.02 mol) was refluxed for 3 ½ hrs in the presence of glacial acetic acid. The reaction mixture was kept at overnight and the product obtained was recrystallized using ethanol. IR ($cm^{-1}$): 1669(C=O str), 1543(C=C), 1605(C=N), 3428(N-H str).

***Synthesis of N-(4-oxo-2-phenylquinazolin-3(4H)-yl) pyridine-4-carboxamide (4b):***
2-phenyl benzoxazine and pyridine-4-carbohydrazide (0.02 mol) was refluxed for 3 ½ hrs in the presence of glacial acetic acid. The reaction mixture was kept at overnight and the product obtained was recrystallized using ethanol. IR ($cm^{-1}$): 1685(C=O str), 1526(C=C), 1452(C-H), 1599(C=N), 1239(C-N), 3502(N-H str); $^1$H-NMR ($CDCl_3$): δ 7.3-7.4 (m, 5H, Ar-H), 7.41 (s, 1H, Ar-H), 7.53-7.57 (m, 3H, Ar-H), 7.6-7.72 (m, 5H, Ar-H).

## PHARMACOLOGICAL ACTIVITY

***Anti-bacterial activity:***
All the synthesized compounds were screened for their anti-bacterial activity against *Staphylococcus aureus* (Gram positive bacteria) and *Escherichia coli* (Gram negative bacteria) by paper disc diffusion technique using streptomycin as a standard.

***Paper Disc Diffusion Technique:***
The sterilized (autoclaved at 120 $^o$C for 30 min) medium was inoculated with the suspension of the microorganism and poured into a petridish to give a depth of 3-4 mm. the paper impregnated with the test compounds (10, 20, 50 and 100 microgram per ml in DMSO) was placed on the solidified medium. The plates were pre-incubated for 1 hr at room temperature and incubated at 37$^o$C for 24 hrs using Streptomycin as standard at a concentration of 10 microgram per ml. DMSO as a negative control showed no zone of inhibition. The antimicrobial activity of the synthesized compounds was recorded in table 2.

**Table 2**
***Antimicrobial activity of the synthesized compounds:***

| Sl.NO | Compound | Name of the organism | Zone of inhibition in mm | | | | |
|---|---|---|---|---|---|---|---|
| | | | Std | 10mcg | 20mcg | 50mcg | 100mcg |
| 1 | 3a | *S.aureus* | 24mm | 8mm | 9mm | 10mm | 11mm |
| | | *E.coli* | 16mm | 8mm | 9mm | 9.5mm | 10mm |
| 2 | 3b | *S.aureus* | 24mm | 6mm | 7mm | 8mm | 9mm |
| | | *E.coli* | 16mm | 9mm | 9mm | 9.5mm | 10mm |
| 3 | 3c | *S.aureus* | 24mm | 8mm | 9mm | 10mm | 10mm |
| | | *E.coli* | 16mm | 10mm | 11mm | 11mm | 12mm |
| 4 | 3d | *S.aureus* | 24mm | 9mm | 10mm | 11mm | 11mm |
| | | *E.coli* | 16mm | 8mm | 9mm | 9mm | 10mm |
| 5 | 3e | *S.aureus* | 24mm | 9mm | 9mm | 10mm | 11mm |
| | | *E.coli* | 16mm | 7mm | 7mm | 9mm | 10mm |
| 6 | 4a | *S.aureus* | 24mm | 9mm | 9mm | 10mm | 11mm |
| | | *E.coli* | 16mm | 9mm | 9mm | 10mm | 10mm |
| 7 | 4b | *S.aureus* | 24mm | 8mm | 9mm | 10mm | 11mm |
| | | *E.coli* | 16mm | 7mm | 7.5mm | 9mm | 10mm |

## RESULTS AND DISCUSSION

Novel Quinazolinone derivatives were synthesized by condensing 2-methyl/phenyl benzoxazine-4-one/ 6, 8-dibromo-2-methyl/phenyl benzoxazine-4-one with o-toludine / pyridine-4-carbohydrazide. The structures of the synthesized compounds were characterized by IR and $^{1}$HNMR. The purity of the compounds were checked by melting point and TLC. All the synthesized compounds were tested for their invitro antibacterial activity. The results showed that tested compounds showed mild to moderate activity against the tested bacteria (*S.aureus and E.coli)* compared with standard.

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