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Research Article

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Studies on Some Novel Benzoxazinone Derivatives with Potential Antibacterial and Antifungal Activity

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Abstract Recent trends in the medicines and related chemical sciences are directed towards the synthesis of novel heterocycles with good and profound biological activities, because of this reason there is a continuous study and research is going on for the newer heterocycles. This work of research is an attempt to show and present the importance of benzoxazin-4-one in medicinal chemistry and so that it can lead the way for newer drugs. Benzoxazin-4-one is a heterocyclic aromatic organic compound. It consist of fusion of benzene and 1, 3-oxazinan-6-one. The molecule has been studied for its affectivity and enormous biological activities with the suitable modifications in the structure. This work is a sincere effort made to direct the attention of the researchers across the globe towards the Benzoxazin-4-one ring for the development of novel chemical entities which are quite useful in the treatment of various life threatening diseases and disorders. Structures of the newly synthesized compounds were established by elemental analysis and spectral data. All new prepared compounds were subjected to antimicrobial and antifungal activity evaluation where many compounds exhibited good activities against *E. coli*, *Staphylococcus aureus, Bacillus subtilis, P. chrysogenum, Aspergillus niger*.

Keywords heterocycles, benzoxazin-4-one, antimicrobial, antifungal

Introduction

Compounds containing benzoxazinone moieties have great significance and importance and application in medicinal chemistry due to its pharmacological properties. Benzoxazinone derivatives fused with other heterocyclic and aromatic ring system were reported to possess various activities such as antimicrobial, antifungal, anti-inflammatory, analgesic. The isosteric replacements of other rings such as pyrido, oxazolo, derivatives have already been reported to possess antimicrobial activity. The Benzoxazinone are an important group of secondary metabolites occurring in gramineae, acanthaceae, and ranunculaceae. Their role as defense compounds towards pests like bacteria fungi and insects is documented. Novel 1, 4-benzoxazin-3-one derivative have been synthesized which would have inhibitory activities against tyrosine kinases and the inhibitory activities against KDR and ABL which are closely related to chronic disease such as cancer [1-6]. The structures of the newly synthesized compounds were elucidated through their IR, ^{1}H NMR, ^{13}C NMR and mass spectroscopic data. The new products showed remarkable antibacterial and antifungal activities upon screening for biological activity tests.

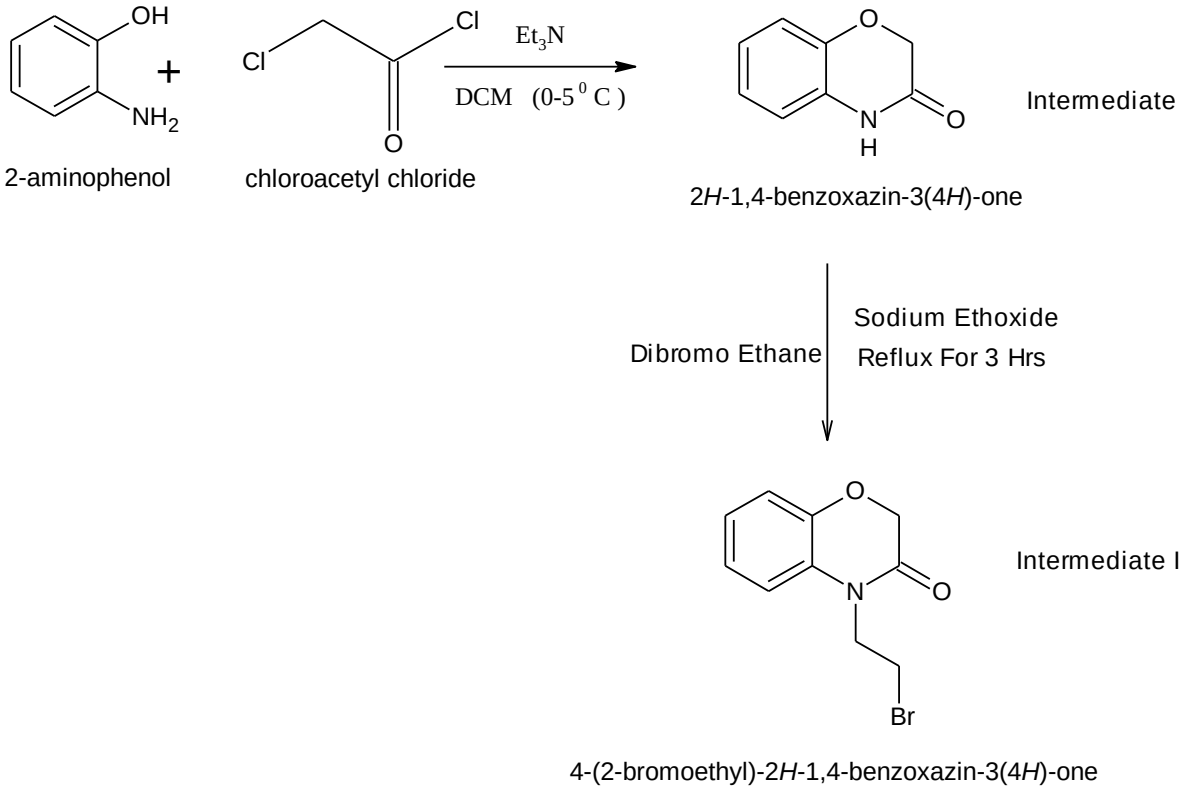
Material and Methods

All the melting points reported in this research work were determined by open capillary method and are uncorrected. The synthesis and analytical studies of compounds were carried out using laboratory grade and analytical grade

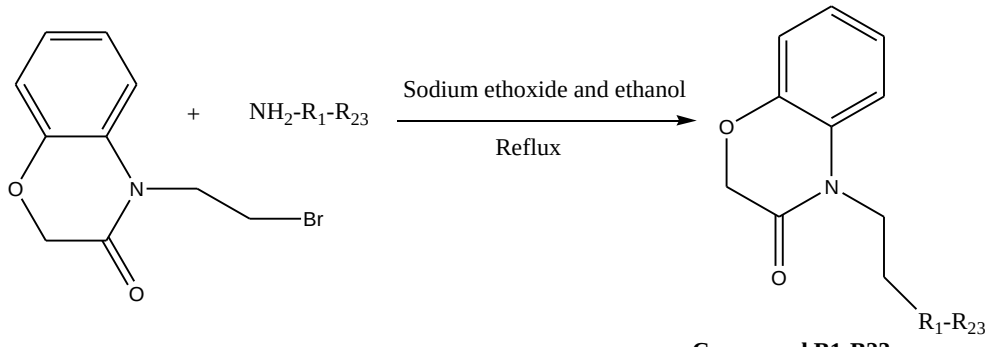
reagents as the case may be standard procedure or reported methods were followed with or without modification appropriately as and were required. The IR absorption spectra of the compounds were recorded on FTIR Bruker Tensor-27 model. The constitution of the synthesized products have been characterized by using elemental analysis and ^{1}H NMR spectroscopy and further supported by mass spectroscopy. All the compounds have been evaluated for their in vitro biological assay like antibacterial activity towards Gram positive and Gram negative bacterial strains and antifungal activity towards *A. niger*, and *C. albicans* at a different concentration. The biological activities of synthesized compounds were compared with standard drugs [7-10].

The synthetic route of the compounds is outlined in Scheme 1. For the synthesis of the title compounds [11-14].

A. Starting Synthetic Route of Intermediate Compounds

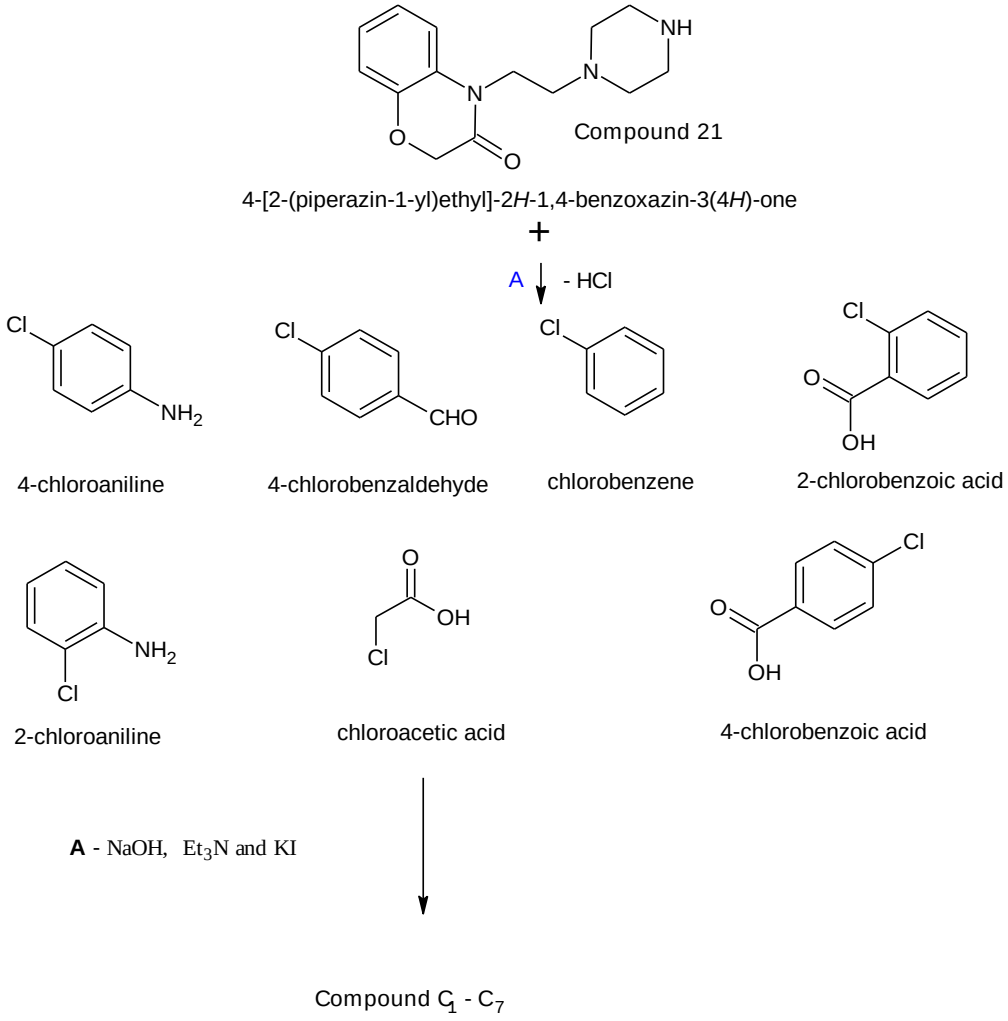


B. Synthetic Protocoalof Phase I Compounds



Compound B1-B23

C. Synthetic Protocol of Phase II Compounds



B. Synthesis of Phase I compounds

1. Synthesis of 4-{2-[(2,4-dichlorophenyl)amino]ethyl}-*2H*-1,4-benzoxazin-3(*4H*)-one (B 1)

1 gm. 4-(2-bromoethyl)-*2H*-1,4-benzoxazin-3(*4H*)-one was taken in a round bottom flask with 20ml of ethanol, 5 grams of 2,4-dichloroaniline and stirred at room temperature with 5 grams of sodium ethoxide. Then the reaction mixture was refluxed for 3hrs on water bath. The reaction was monitored by TLC for completion. The solution was cooled, poured into ice cold water (50ml). The product precipitated out and was filtered, dried and recrystallized from ethanol to give solid compound.

Solubility: - Methanol

Solvent system: - chloroform: methanol (9.5:0.5)

2. Synthesis of 4-{2-[(2-chlorophenyl) amino] ethyl}-*2H*-1,4-benzoxazin-3(*4H*)-one (B 2)

1 gm. 4-(2-bromoethyl)-*2H*-1, 4-benzoxazin-3(*4H*)-one was taken in a round bottom flask with 20ml of ethanol, 5 ml of 2-chloroaniline and stirred at room temperature with 5 grams of sodium ethoxide. Then the reaction mixture was refluxed for 3hrs on water bath. The reaction was monitored by TLC for completion. The solution was cooled, poured into ice cold water (50ml). The product precipitated out and was filtered, dried and recrystallized from ethanol to give solid compound.

Solubility: - Methanol

Solvent system: - chloroform: methanol (9.5:0.5)

3. Synthesis of 4-{2-[(3-chlorophenyl) amino] ethyl}-*2H*-1, 4-benzoxazin-3(*4H*)-one (B 3)

1 gm. 4-(2-bromoethyl)-*2H*-1, 4-benzoxazin-3(*4H*)-one was taken in a round bottom flask with 20ml of ethanol, 5 ml of 3-chloroanilineand stirred at room temperature with 5 grams ofsodium ethoxide. Then the reaction mixture was refluxed for 3hrs on water bath. The reaction was monitored by TLC for completion. The solution was cooled, poured into ice cold water (50ml). The product precipitated out and was filtered, dried and recrystallized from ethanol to give solid compound.

Solubility: - Methanol

Solvent system: - chloroform: methanol (9.5:0.5)

4. Synthesis of 4-{2-[(4-chlorophenyl)amino]ethyl}-*2H*-1,4-benzoxazin-3(*4H*)-one (B 4)

1 gm. 4-(2-bromoethyl)-*2H*-1, 4-benzoxazin-3(*4H*)-one was taken in a round bottom flask with 20ml of ethanol, 5 grams of 4-chloroaniline and stirred at room temperature with 5 grams of sodium ethoxide. Then the reaction mixture was refluxed for 3hrs on water bath. The reaction was monitored by TLC for completion. The solution was cooled, poured into ice cold water (50ml). The product precipitated out and was filtered, dried and recrystallized from ethanol to give solid compound.

Solubility: - Methanol

Solvent system: - chloroform: methanol (9.5:0.5)

5. Synthesis of 4-{2-[(3-methylphenyl)amino]ethyl}-*2H*-1,4-benzoxazin-3(*4H*)-one (B 5)

1 gm. 4-(2-bromoethyl)-*2H*-1, 4-benzoxazin-3(*4H*)-one was taken in a round bottom flask with 20ml of ethanol, 5 ml of 3-methylaniline (m-toluidine) and stirred at room temperature with 5 grams of sodium ethoxide. Then the reaction mixture was refluxed for 3hrs on water bath. The reaction was monitored by TLC for completion. The solution was cooled, poured into ice cold water (50ml). The product precipitated out and was filtered, dried and recrystallized from ethanol to give solid compound.

Solubility: - Methanol

Solvent system: - chloroform: methanol (9.5:0.5)

6. Synthesis of 4-{2-[(2-methylphenyl)amino]ethyl}-*2H*-1,4-benzoxazin-3(*4H*)-one (B 6)

1 gm. 4-(2-bromoethyl)-*2H*-1, 4-benzoxazin-3(*4H*)-one was taken in a round bottom flask with 20ml of ethanol, 5 ml of 2-methylaniline (o-toluidine) and stirred at room temperature with 5 grams of sodium ethoxide. Then the reaction mixture was refluxed for 3hrs on water bath. The reaction was monitored by TLC for completion. The solution was cooled, poured into ice cold water (50ml). The product precipitated out and was filtered, dried and recrystallized from ethanol to give solid compound.

Solubility: - Methanol

Solvent system: - chloroform: methanol (9.5:0.5)

7. Synthesis of 4-{2-[(4-methylphenyl) amino] ethyl}-*2H*-1,4-benzoxazin-3(*4H*)-one (B 7)

1 gm. 4-(2-bromoethyl)-*2H*-1, 4-benzoxazin-3(*4H*)-one was taken in a round bottom flask with 20ml of ethanol, 5 grams of 4-methylaniline (p-toluidine) and stirred at room temperature with 5 grams of sodium ethoxide. Then the reaction mixture was refluxed for 3hrs on water bath. The reaction was monitored by TLC for completion. The solution was cooled, poured into ice cold water (50ml). The product precipitated out and was filtered, dried and recrystallized from ethanol to give solid compound.

Solubility: - Methanol

Solvent system: - chloroform: methanol (9.5:0.5)

8. Synthesis of 4-{2-[(3,5-dimethylphenyl)amino]ethyl}-*2H*-1,4-benzoxazin-3(*4H*)-one (B 8)

1 gm. 4-(2-bromoethyl)-*2H*-1, 4-benzoxazin-3(*4H*)-one was taken in a round bottom flask with 20ml of ethanol, 5 ml of 3,5-dimethylaniline (3,5-xylidine) and stirred at room temperature with 5 grams of sodium ethoxide. Then the reaction mixture was refluxed for 3hrs on water bath. The reaction was monitored by TLC for completion. The solution was cooled, poured into ice cold water (50ml). The product precipitated out and was filtered, dried and recrystallized from ethanol to give solid compound.

Solubility: - Methanol

Solvent system: - chloroform: methanol (9.5:0.5)

9. Synthesis of 4-{2-[(2-nitrophenyl)amino]ethyl}-*2H*-1,4-benzoxazin-3(*4H*)-one (B 9)

1 gm. 4-(2-bromoethyl)-*2H*-1, 4-benzoxazin-3(*4H*)-one was taken in a round bottom flask with 20ml of ethanol, 5 grams of 2-nitroanilineand stirred at room temperature with 5 grams of sodium ethoxide. Then the reaction mixture was refluxed for 3hrs on water bath. The reaction was monitored by TLC for completion. The solution was cooled, poured into ice cold water (50ml). The product precipitated out and was filtered, dried and recrystallized from ethanol to give solid compound.

Solubility: - Methanol

Solvent system: - chloroform: methanol (9.5:0.5)

10. Synthesis of 4-{2-[(3-nitrophenyl) amino] ethyl}-*2H*-1,4-benzoxazin-3(*4H*)-one (B 10)

1 gm. 4-(2-bromoethyl)-*2H*-1, 4-benzoxazin-3(*4H*)-one was taken in a round bottom flask with 20ml of ethanol, 5 grams of 3-nitroanilineand stirred at room temperature with 5 grams of sodium ethoxide. Then the reaction mixture was refluxed for 3hrs on water bath. The reaction was monitored by TLC for completion. The solution was cooled, poured into ice cold water (50ml). The product precipitated out and was filtered, dried and recrystallized from ethanol to give solid compound.

Solubility: - Methanol

Solvent system: - chloroform: methanol (9.5:0.5)

11. Synthesis of 4-{2-[(4-nitrophenyl)amino]ethyl}-*2H*-1,4-benzoxazin-3(*4H*)-one (B 11)

1 gm. 4-(2-bromoethyl)-*2H*-1, 4-benzoxazin-3(*4H*)-one was taken in a round bottom flask with 20ml of ethanol, 5 grams of 4-nitroanilineand stirred at room temperature with 5 grams of sodium ethoxide. Then the reaction mixture was refluxed for 3hrs on water bath. The reaction was monitored by TLC for completion. The solution was cooled, poured into ice cold water (50ml). The product precipitated out and was filtered, dried and recrystallized from ethanol to give solid compound.

Solubility: - Methanol

Solvent system: - chloroform: methanol (9.5:0.5)

12. Synthesis of 4-{2-[(2-bromophenyl)amino]ethyl}-*2H*-1,4-benzoxazin-3(*4H*)-one (B 12)

1 gm. 4-(2-bromoethyl)-*2H*-1, 4-benzoxazin-3(*4H*)-one was taken in a round bottom flask with 20ml of ethanol, 5 ml of 2-bromoanilineand stirred at room temperature with 5 grams of sodium ethoxide. Then the reaction mixture was refluxed for 3hrs on water bath. The reaction was monitored by TLC for completion. The solution was cooled, poured into ice cold water (50ml). The product precipitated out and was filtered, dried and recrystallized from ethanol to give solid compound.

Solubility: - Methanol

Solvent system: - chloroform: methanol (9.5:0.5)

13. Synthesis of 4-{2-[(4-bromophenyl)amino]ethyl}-*2H*-1,4-benzoxazin-3(*4H*)-one (B 13)

1 gm. 4-(2-bromoethyl)-*2H*-1, 4-benzoxazin-3(*4H*)-one was taken in a round bottom flask with 20ml of ethanol, 5 grams of 4-bromoanilineand stirred at room temperature with 5 grams of sodium ethoxide. Then the reaction mixture was refluxed for 3hrs on water bath. The reaction was monitored by TLC for completion. The solution was cooled, poured into ice cold water (50ml). The product precipitated out and was filtered, dried and recrystallized from ethanol to give solid compound.

Solubility: - Methanol

Solvent system: - chloroform: methanol (9.5:0.5)

14. Synthesis of 4-{2-[(2,4,6-tribromophenyl)amino]ethyl}-*2H*-1,4-benzoxazin-3(*4H*)-one (B 14)

1 gm. 4-(2-bromoethyl)-*2H*-1, 4-benzoxazin-3(*4H*)-one was taken in a round bottom flask with 20ml of ethanol, 5 grams of 2, 4, 6-tribromoanilineand stirred at room temperature with 5 grams of sodium ethoxide. Then the reaction mixture was refluxed for 3hrs on water bath. The reaction was monitored by TLC for completion. The solution was cooled, poured into ice cold water (50ml). The product precipitated out and was filtered, dried and recrystallized from ethanol to give solid compound.

Solubility: - Methanol

Solvent system: - chloroform: methanol (9.5:0.5)

15. Synthesis of 4-{2-[(4-methoxyphenyl)amino]ethyl}-*2H*-1,4-benzoxazin-3(*4H*)-one (B 15)

1 gm. 4-(2-bromoethyl)-*2H*-1, 4-benzoxazin-3(*4H*)-one was taken in a round bottom flask with 20ml of ethanol, 5 grams of 4-methoxyaniline (p-Anisidine) and stirred at room temperature with 5 grams of sodium ethoxide. Then the reaction mixture was refluxed for 3hrs on water bath. The reaction was monitored by TLC for completion. The solution was cooled, poured into ice cold water (50ml). The product precipitated out and was filtered, dried and recrystallized from ethanol to give solid compound.

Solubility: - Methanol

Solvent system: - chloroform: methanol (9.5:0.5)

16. Synthesis of 4-{2-[(2-methoxyphenyl)amino]ethyl}-*2H*-1,4-benzoxazin-3(*4H*)-one (B 16)

1 gm. 4-(2-bromoethyl)-*2H*-1, 4-benzoxazin-3(*4H*)-one was taken in a round bottom flask with 20ml of ethanol, 5 ml of 2-methoxyaniline (o-Anisidine) and stirred at room temperature with 5 grams of sodium ethoxide. Then the reaction mixture was refluxed for 3hrs on water bath. The reaction was monitored by TLC for completion. The solution was cooled, poured into ice cold water (50ml). The product precipitated out and was filtered, dried and recrystallized from ethanol to give solid compound.

Solubility: - Methanol

Solvent system: - chloroform: methanol (9.5:0.5)

17. Synthesis of 4-[2-(propan-2-ylamino)ethyl]-*2H*-1,4-benzoxazin-3(*4H*)-one (B 17)

1 gm. 4-(2-bromoethyl)-*2H*-1, 4-benzoxazin-3(*4H*)-one was taken in a round bottom flask with 20ml of ethanol, 5 ml of N-methylmethanamineand stirred at room temperature with 5 grams of sodium ethoxide. Then the reaction mixture was refluxed for 3hrs on water bath. The reaction was monitored by TLC for completion. The solution was cooled, poured into ice cold water (50ml). The product precipitated out and was filtered, dried and recrystallized from ethanol to give solid compound.

Solubility: - Methanol

Solvent system: - chloroform: methanol (9.5:0.5)

18. Synthesis of 4-[2-(pentan-3-ylamino)ethyl]-*2H*-1,4-benzoxazin-3(*4H*)-one (B 18)

1 gm. 4-(2-bromoethyl)-*2H*-1, 4-benzoxazin-3(*4H*)-one was taken in a round bottom flask with 20ml of ethanol, 5 ml of N-ethylethanamine (Diethylamine) and stirred at room temperature with 5 grams of sodium ethoxide. Then the reaction mixture was refluxed for 3hrs on water bath. The reaction was monitored by TLC for completion. The solution was cooled, poured into ice cold water (50ml). The product precipitated out and was filtered, dried and recrystallized from ethanol to give solid compound.

Solubility: - Methanol

Solvent system: - chloroform: methanol (9.5:0.5)

19. Synthesis of 4-[2-(diphenylamino) ethyl]-*2H*-1,4-benzoxazin-3(*4H*)-one (B 19)

1 gm. 4-(2-bromoethyl)-*2H*-1, 4-benzoxazin-3(*4H*)-one was taken in a round bottom flask with 20ml of ethanol, 5 grams of N-phenylaniline (Diphenylamine) and stirred at room temperature with 5 grams of sodium ethoxide. Then the reaction mixture was refluxed for 3hrs on water bath. The reaction was monitored by TLC for completion. The solution was cooled, poured into ice cold water (50ml). The product precipitated out and was filtered, dried and recrystallized from ethanol to give solid compound.

Solubility: - Methanol

Solvent system: - chloroform: methanol (9.5:0.5)

20. Synthesis of 4-[2-(morpholin-4-yl)ethyl]-*2H*-1,4-benzoxazin-3(*4H*)-one (B 20)

1 gm. 4-(2-bromoethyl)-*2H*-1, 4-benzoxazin-3(*4H*)-one was taken in a round bottom flask with 20ml of ethanol, 5 ml of morpholineand stirred at room temperature with 5 grams of sodium ethoxide. Then the reaction mixture was refluxed for 3hrs on water bath. The reaction was monitored by TLC for completion. The solution was cooled, poured into ice cold water (50ml). The product precipitated out and was filtered, dried and recrystallized from ethanol to give solid compound.

Solubility: - Methanol

Solvent system: - chloroform: methanol (9.5:0.5)

21. Synthesis of 4-[2-(piperazin-1-yl)ethyl]-*2H*-1,4-benzoxazin-3(*4H*)-one (B 21)

10 gm. 4-(2-bromoethyl)-*2H*-1, 4-benzoxazin-3(*4H*)-one was taken in a round bottom flask with 200ml of ethanol, 50 grams of piperazineand stirred at room temperature with 50 grams of sodium ethoxide. Then the reaction mixture was refluxed for 3hrs on water bath. The reaction was monitored by TLC for completion. The solution was cooled, poured into ice cold water (50ml). The product precipitated out and was filtered, dried and recrystallized from ethanol to give solid compound.

Solubility: - Methanol

Solvent system: - chloroform: methanol (9.5:0.5)

22. Synthesis of 4-[2-(piperidin-1-yl)ethyl]-*2H*-1,4-benzoxazin-3(*4H*)-one (B 22)

1 gm. 4-(2-bromoethyl)-*2H*-1, 4-benzoxazin-3(*4H*)-one was taken in a round bottom flask with 20ml of ethanol, 5 ml of piperidineand stirred at room temperature with 5 grams of sodium ethoxide. Then the reaction mixture was refluxed for 3hrs on water bath. The reaction was monitored by TLC for completion. The solution was cooled, poured into ice cold water (50ml). The product precipitated out and was filtered, dried and recrystallized from ethanol to give solid compound.

Solubility: - Methanol

Solvent system: - chloroform: methanol (9.5:0.5)

23. Synthesis of 4-[2-(2-methylpiperazin-1-yl) ethyl]-*2H*-1,4-benzoxazin-3(*4H*)-one (B 23)

1 gm. 4-(2-bromoethyl)-*2H*-1, 4-benzoxazin-3(*4H*)-one was taken in a round bottom flask with 20ml of ethanol, 5 ml of 2-methylpiperazineand stirred at room temperature with 5 grams of sodium ethoxide. Then the reaction mixture was refluxed for 3hrs on water bath. The reaction was monitored by TLC for completion. The solution was cooled, poured into ice cold water (50ml). The product precipitated out and was filtered, dried and recrystallized from ethanol to give solid compound.

Solubility: - Methanol

Solvent system: - chloroform: methanol (9.5:0.5)

C. Synthesis of Phase II compounds

1. Synthesis of 4-{2-[4-(4-aminophenyl) piperazin-1-yl] ethyl}-*2H*-1,4-benzoxazin-3(*4H*)-one (C 1)

1 g of 4-[2-(piperazin-1-yl) ethyl]-*2H*-1, 4-benzoxazin-3(*4H*)-one was taken in a round bottom flask and dissolved in 15 ml of 15 % Sodium Hydroxide Solution, 5 ml 4-Chloro aniline was added and stirred well and kept for 5 min. and 3 g of Potassium iodide was added stirred well and few ml of HCl was added and refluxed for 3 hrs. The hot mixture was poured in ice cold water and the precipitate of the respective substitute was obtained and was recrystallized with the ethanol. The completion of reaction was monitored by running TLC.

Solubility: - dimethylformamide

Solvent system: - chloroform: methanol (9.5:0.5)

2. Synthesis of 4-{4-[2-(3-oxo-2,3-dihydro-*4H*-1,4-benzoxazin-4-yl)ethyl]piperazin-1-yl}benzaldehyde (C 2)

1 g of 4-[2-(piperazin-1-yl) ethyl]-*2H*-1, 4-benzoxazin-3(*4H*)-one was taken in a round bottom flask and dissolved in 15 ml of 15 % Sodium Hydroxide Solution, 5 ml 4-Chloro benzaldehyde was added and stirred well and kept for 5 min. and 3 g of Potassium iodide was added stirred well and few ml of HCl was added and refluxed for 3 hrs. The hot mixture was poured in ice cold water and the precipitate of the respective substitute was obtained and was recrystallized with the ethanol. The completion of reaction was monitored by running TLC.

Solubility: - dimethylformamide

Solvent system: - chloroform: methanol (9.5:0.5)

3. Synthesis of 4-[2-(4-phenylpiperazin-1-yl)ethyl]-*2H*-1,4-benzoxazin-3(*4H*)-one (C 3)

1 g of 4-[2-(piperazin-1-yl) ethyl]-*2H*-1, 4-benzoxazin-3(*4H*)-one was taken in a round bottom flask and dissolved in 15 ml of 15 % Sodium Hydroxide Solution, 5 ml Chloro benzene was added and stirred well and kept for 5 min. and 3 g of Potassium iodide was added stirred well and few ml of HCl was added and refluxed for 3 hrs. The hot

mixture was poured in ice cold water and the precipitate of the respective substitute was obtained and was recrystallized with the ethanol. The completion of reaction was monitored by running TLC.

Solubility: - dimethylformamide

Solvent system: - chloroform: methanol (9.5:0.5)

4. Synthesis of 2-{4-[2-(3-oxo-2,3-dihydro-*4H*-1,4-benzoxazin-4-yl)ethyl]piperazin-1-yl}benzoic acid (C 4)

1 g of 4-[2-(piperazin-1-yl) ethyl]-*2H*-1, 4-benzoxazin-3(*4H*)-one was taken in a round bottom flask and dissolved in 15 ml of 15 % Sodium Hydroxide Solution, 5 grams 2-Chloro benzoic acid was added and stirred well and kept for 5 min. and 3 g of Potassium iodide was added stirred well and few ml of HCl was added and refluxed for 3 hrs. The hot mixture was poured in ice cold water and the precipitate of the respective substitute was obtained and was recrystallized with the ethanol.The completion of reaction was monitored by running TLC.

Solubility: - dimethylformamide

Solvent system: - chloroform: methanol (9.5:0.5)

5. Synthesis of 4-{2-[4-(2-aminophenyl)piperazin-1-yl]ethyl}-*2H*-1,4-benzoxazin-3(*4H*)-one (C 5)

1 g of 4-[2-(piperazin-1-yl) ethyl]-*2H*-1, 4-benzoxazin-3(*4H*)-one was taken in a round bottom flask and dissolved in 15 ml of 15 % Sodium Hydroxide Solution, 5 ml 2-Chloro aniline was added and stirred well and kept for 5 min. and 3 g of Potassium iodide was added stirred well and few ml of HCl was added and refluxed for 3 hrs. The hot mixture was poured in ice cold water and the precipitate of the respective substitute was obtained and was recrystallized with the ethanol. The completion of reaction was monitored by running TLC.

Solubility: - dimethylformamide

Solvent system: - chloroform: methanol (9.5:0.5)

6. Synthesis of {4-[2-(3-oxo-2,3-dihydro-*4H*-1,4-benzoxazin-4-yl)ethyl]piperazin-1-yl}acetic acid (C 6)

1 g of 4-[2-(piperazin-1-yl) ethyl]-*2H*-1, 4-benzoxazin-3(*4H*)-one was taken in a round bottom flask and dissolved in 15 ml of 15 % Sodium Hydroxide Solution, 5 grams Chloro acetic acid was added and stirred well and kept for 5 min. and 3 g of Potassium iodide was added stirred well and few ml of HCl was added and refluxed for 3 hrs. The hot mixture was poured in ice cold water and the precipitate of the respective substitute was obtained and was recrystallized with the ethanol. The completion of reaction was monitored by running TLC.

Solubility: - dimethylformamide

Solvent system: - chloroform: methanol (9.5:0.5)

7. Synthesis of 4-{4-[2-(3-oxo-2,3-dihydro-*4H*-1,4-benzoxazin-4-yl)ethyl]piperazin-1-yl}benzoic acid (C 7)

1 g of 4-[2-(piperazin-1-yl) ethyl]-*2H*-1, 4-benzoxazin-3(*4H*)-one was taken in a round bottom flask and dissolved in 15 ml of 15 % Sodium Hydroxide Solution, 5 grams 4-Chlorobenzoic acid was added and stirred well and kept for 5 min. and 3 g of Potassium iodide was added stirred well and few ml of HCl was added and refluxed for 3 hrs. The hot mixture was poured in ice cold water and the precipitate of the respective substitute was obtained and was recrystallized with the ethanol. The completion of reaction was monitored by running TLC.

Solubility: - dimethylformamide

Solvent system: - chloroform: methanol (9.5:0.5)

Table 1: Antibacterial Activity of Synthesized Compounds (mean of Zone of Inhibition)

Compound No.	Conc. (ppm)	*E. coli* (Gram –ve Bacteria)		*P. aeruginosa* (Gram –ve Bacteria)		*Staphylococcus aureus* (Gram +ve Bacteria)		*Bacillus subtilis* (Gram +ve Bacteria)	
		Zone of inhibition (in mm)	% inhibition	Zone of inhibition (in mm)	% inhibition	Zone of inhibition (in mm)	% inhibition	Zone of inhibition (in mm)	% inhibition
B1	500	06	21.42	04	16	05	22.75	06	21.42
B2	500	08	28.57	06	24	07	31.85	06	21.42
B3	500	10	35.71	10	40	08	36.32	10	35.70
B4	500	10	35.71	08	32	11	49.94	10	35.70
B5	500	18	64.28	14	56	13	59.02	18	64.26
B6	500	19	67.85	15	60	16	72.64	13	46.41

B7	500	20	71.42	17	68	18	81.72	18	64.26
B8	500	10	35.71	09	36	08	36.32	04	14.28
B9	500	08	28.57	06	24	05	22.75	08	28.26
B10	500	09	32.14	06	24	08	36.32	07	24.99
B11	500	10	35.71	08	32	08	36.32	07	24.99
B12	500	08	28.57	06	24	06	27.24	09	32.13
B13	500	09	32.14	07	28	07	31.85	06	21.42
B14	500	05	17.85	03	12	03	13.62	02	7.14
B15	500	19	67.85	14	56	15	68.10	18	64.26
B16	500	18	64.28	15	60	16	72.64	14	49.98
B17	500	20	71.42	18	72	18	81.72	17	60.69
B18	500	21	74.99	18	72	18	81.72	19	67.83
B19	500	20	71.42	19	76	19	86.26	17	60.69
B20	500	21	74.99	17	68	15	68.10	15	53.55
B21	500	23	82.14	20	80	17	77.18	19	67.83
B22	500	22	78.57	19	76	18	81.72	19	67.83
B23	500	24	85.71	21	84	19	86.26	18	64.26
C1	500	26	92.85	21	84	20	90.80	19	67.83
C2	500	24	85.71	20	80	20	90.80	20	71.40
C3	500	22	78.57	18	72	16	72.64	18	64.26
C4	500	23	82.14	19	76	16	72.64	17	60.69
C5	500	24	85.71	20	80	18	81.72	19	67.83
C6	500	25	89.28	22	88	20	90.80	18	64.26
C7	500	24	85.71	21	84	21	95.34	19	67.83
Standard- I (ciprofloxacin)	**500**	**28**	**100**	**25**	**100**	**22**	**100**	**28**	**100**

Table 2: Antifungal Activity of Synthesized Compounds

Compound No.	**Conc. (ppm)**	***C. albicans***		***A. niger***	
		Zone of inhibition (in mm)	**% inhibition**	**Zone of inhibition (in mm)**	**% inhibition**
B1	500	04	21.04	04	22.20
B2	500	06	31.56	05	27.75
B3	500	07	36.82	06	33.30
B4	500	06	31.56	04	22.20
B5	500	14	73.64	11	61.05
B6	500	12	63.12	14	77.70
B7	500	15	78.90	14	77.70
B8	500	08	42.08	06	33.30
B9	500	04	21.04	05	27.75
B10	500	04	21.04	06	33.30
B11	500	11	57.86	09	49.95
B12	500	06	31.56	04	22.20
B13	500	05	26.30	06	33.30
B14	500	02	10.52	02	11.10
B15	500	10	52.60	11	61.05
B16	500	14	73.64	13	72.15
B17	500	16	84.16	13	72.15
B18	500	16	84.16	15	83.25
B19	500	17	89.42	16	88.80
B20	500	17	89.42	15	83.25
B21	500	18	94.68	14	77.70
B22	500	18	94.68	16	88.80
B23	500	14	73.64	15	83.25
C1	500	18	94.68	15	83.25
C2	500	16	84.16	15	83.25

C3	500	16	84.16	17	94.35
C4	500	15	78.90	16	88.80
C5	500	17	89.42	16	88.80
C6	500	14	73.64	14	77.70
C7	500	16	84.16	15	83.25
Standard- I (Griseofulvin)	**500**	**19**	**100**	**18**	**100**

Table 3: Minimum Inhibitory Concentration (MIC) of the Most Potent Compounds

Compound No.	MIC (µg/mL)			
	***E. coli* (Gram –ve Bacteria)**	***P. aeruginosa* (Gram –ve Bacteria)**	***Staphylococcus aureus* (Gram +ve Bacteria)**	***Bacillus subtilis* (Gram +ve Bacteria)**
B19	60	70	50	50
B21	50	50	50	50
C1	50	50	50	50
C2	60	50	60	50
C4	50	50	50	40
C5	50	60	40	50
C6	50	50	50	50
C7	50	50	50	50

Result and Discussion

The benzoxazinones are an important class group of secondary metabolite occurring in Gramineae, Acanthaceae, Ranunculaceae, and scrophulariaceae. Their role as defense compounds towards pests like bacteria, fungi and insects were reported for different cereals (Gramineae) including corn wheat and rye.

Chemistry of benzoxazinone is as old as recorded history. The compounds encompassing benzoxazinone moiety are of great interest and have been extensively used in pharmaceutical chemistry and agriculture division. Heterocycles bearing a benzoxazinone ring residue are reported to show anticancer, anti-inflammatory, analgesic, muscle-relaxant, sedative, antitubercular, antimicrobial, anticonvulsant, antimalerial, antiviral, antioxidant, CNS depressant, and plant growth regulatory activity etc. In addition, benzoxazinone forms an important pharmacaphore in fungicidal, herbicidal and insecticidal, agents.

Novel 1,4-benzoxazinone-3-one derivative has been synthesized which would have inhibitory activities against tyrosine kinases and the inhibitory activities against KDR and ABL which are closely related to chronic disease such as cancer.

1,4-benzoxazinone has wide application in medicinal chemistry due to its pharmacological properties. The members of this family are used for treating Parkinson's disease, ischemia, reperfusion, selective potassium channel openers, antidepressants, and antifungal agent in addition properties of 1,4-benzoxazinone are valuable as laser dyes and coupling agent for oxidative hair dyes. Moreover, 1,4-benzoxazinone used as intermediates for the synthesis of aza sugar.

First of all the Synthesis of *2H*-1, 4- benzoxazin-3(*4H*)-one was carried out by reacting 2- amino phenol with chloro acetyl chloride in dichloromethane in presence of triethylamine and then the bromo substitution was done by reacting with dibromoethane. Piperazine substituents were prepared in laboratory and then the title compounds were synthesized. One additional benzoyl substitution was also done.

The entire synthesized compounds were primarily characterized by running T.L.C. and melting point analysis.

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