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Synthesis and Screening of some benzoxazinone derivatives

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ABSTRACT

Benzoxazinone derivatives fused with other heterocyclic and aromatic ring system were reported to possess various activities such as anti-inflammatory, analgesic, antimicrobial. The Benzoxazinone are an important group of secondary metabolites occurring in gramineae, acanthaceae, and ranunculaceae. 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. 1,4- Benzoxazinones has wide application in medicinal chemistry due to its pharmacological properties. The members of this family are used for treating parkinsons disease, ischemia reperfusion, selective potassium channel openers, antinociceptive, antidepressant and anti-fungal agent.

Keywords: Benzoxazinone, secondary metabolites, tyrosine kinases, bantinociceptive.

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INTRODUCTION

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 for different cereals (Gramineae) including corn, wheat, and rye. 2H-1, 4-Benzoxazin-3(4H)-one has been identified as an intermediate in the biosynthesis of cyclic hydroxamic acids in maize by showing that the deuterium labeled compound is incorporated into DIMBOA with high retention of deuterium and high efficiency, by trapping radioactivity from [14C] anthranilic acid in a pool of unlabelled benzoxazinone administered to maize shoots, and by showing that benzoxazinone is oxidized to DIBOA by maize microsomes in an NADPH- and oxygen-dependent reaction.[1]

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. A number of new 1-phenyl-(a),1-(3-chlorophenyl)-(b) and 1-(2-methoxyphenyl), (c) piperzine derivatives containing 1,4-benzoxazin-3(4H)-one (2-4), 2,4- benzoxazin-3(4H)-one (5), 1,2-benzoxazolin-3-one (6) and 1,3-benzoxazolin-2,4-dione were synthesized.[2]

1,4- Benzoxazinones has wide application in medicinal chemistry due to its pharmacological properties .the members of this family are used for treating parkinsons disease, ischemia reperfusion , selective potassium channel openers, antinociceptive, antidepressant and anti-fungal agent . Moreover 1, 4- Benzoxazinone used intermediates for the synthesis of aza sugers.[3]

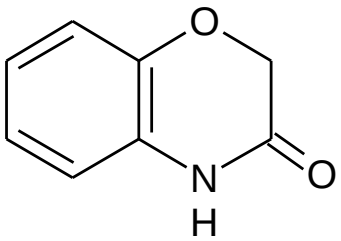

Figure1: Molecular structure- 2 H-1, 4- BENZOXAZIN-3(4H)-one

Pharmaceutical chemistry occupies the most important place among the related sciences but at the same time it is dependent on other chemical and biological disciplines. The approach to practice medicinal chemistry has developed from an empirical one, which involves organic synthesis of new compounds, largely based on modification of structures of known activity. For more than a century, heterocyclic have constituted one of the largest areas of research in organic chemistry. Heterocyclic compounds plays an important role in biological process because the side group of the most typical and essential constituent of living cells, DNA and RNA are based on aromatic heterocyclic.

Among the approximately 20 million chemical compounds identified by the end of the second millennium, more than two third are fully or partially aromatic and approximately half are heterocyclic, so we have chosen the heterocyclic compound benzoxazinones. Resistance to antimicrobial agents has become an increasingly important and pressing global problem. Structural modification of antimicrobial drugs to which resistance has developed has proven to be an effective means of extending the lifespan of antifungal agents such as the azoles, antiviral agents such as the non-nucleoside reverse transcriptase inhibitors, and various antibacterial agents.[5]

Despite of tremendous progress in human medicines, infectious diseases caused by bacteria, fungi, viruses and parasites are still a major threat to public health. Their impact is particularly large in developing countries due to relative unavailability of medicines and the emergence of widespread drug resistance. During the last two decades, the development of drug resistance as well as the appearance of undesirable side effects of certain antibiotics has led to the search of new antimicrobial agents mainly among plant extracts with the goal to discover new chemical structures, which overcome the above disadvantages. Current research on natural molecule and products primarily focuses on plants since they can be sourced more easily and be selected based on their ethno-medicinal uses.[6]

Humankind has been subject to infection by microorganism since before the dawn of recorded history. One presumes that mankind has been searching for suitable therapy for nearly as long. This was a desperately difficult enterprise given the acute nature of most infections and the nearly total lack of understanding of their origins prevalent until the last century. Although one can find indications in old medical writing of folkloric use of plant and animal preparations, soybean curd, moldy bread and cheese, counter infection with other microbes, the slow development of public health measures, and an understanding of the desirability of personal cleanliness, these factors were erratically and inefficiently applied and often failed. Until after the discovery of bacteria 300 years ago, and subsequent understanding of their role in infection about 150 years ago, there was no hope for rational therapy.[7]

Microbes of soil origin remain to this day the most fruitful source of antibiotics, although the specific means employed for their discovery are infinitely more sophisticated today than those employed 50 years ago. Initially extracts of fermentation were screened simply for their ability to kill pathogenic microorganisms in vitro. Those that did were pushed along through ever more complex pathogenic and toxicological tests in attempts to discover clinically useful agents. Today many thousands of such extracts of increasingly exotic microbes are tested each week and the test now includes sophisticated assays for agents operating through particular biochemical mechanism or possessing desirable properties. The impact of genomics is expected to have very substantial impact on this effort. As a consequence of this work mankind has now many choices for powerful, effective and specific therapy for some of its most ancient and common bacterial infections.[8]

MATERIAL AND METHODS

All the melting points reported in this dissertation progress report 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.

1. Synthesis of 2 *H*-1, 4- benzoxazin-3(4*H*)-one

A mixture of 2-aminophenol (mol. Wt. 109; 30g) (dichloromethane 80ml) and triethylamine (20ml) was taken in round bottom flask, in ice cool condition , stirred well using magnetic stirrer with simultaneous drop wise addition of chloroacetylchloride which was also maintained in ice cold condition. The crude product was obtained by evaporating dichloromethane. The dried product was boiled in water with pinch of decolorizing charcoal until solubilized and filtered while hot. The solution thus obtained was allowed to cool at 10° C for 30 minutes, filtered and dried. The completion of reaction was monitored by running TLC. [9]

2. Synthesis of 4-(2-bromoethyl)-2*H*-1,4-benzoxazin-3(4*H*)-one

A mixture of benzoxazinone (mol. Wt. 149; 45g) sodium ethoxide was taken in round bottom flask, stir well using magnetic stirrer, distilled to remove ethanol , then N,N-dimethylformamide was added mix well ,then 20 ml of 1,2 dibromoethane was added slowly. Then reflux for 3 hours. The crude product was obtained by evaporating N, N dimethylformamide on rotary evaporator. The dried product was boiled with pinch of decolorizing charcoal until solubilized and filtered while hot. The solution thus obtained was allowed to cool at 10° C for 30 minutes, filtered and dried. The completion of reaction was monitored by running TLC.[10]

3. Synthesis of substituted piperazine derivatives

a. Benzyl substitution.(1-phenylcarbonyl)piperazine

10 g of piperazine was taken in a round bottom flask and was dissolved in 15 % of sodium hydroxide and small excess of benzoyl chloride was added and shaken vigorously benzoylation takes place and small crystal of benzoyl derivative separates. Recrystalization was done by methanol. The completion of reaction was monitored by running TLC.[11]

b. Other substitutions

10 g of piperazine was taken in a round bottom flask and dissolved in 15 ml of ethyl methyl ketone,5 g of the respective substituent (ex. 4-Chloro aniline) was added and stirred well and kept for 5 min. and 3 g of sodium iodide 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 ppt of the respective substitute was obtained.The ppt was recrystalized with the rectified spirit. The completion of reaction was monitored by running TLC.[12]

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

1g of (1-phenylcarbonyl)piperazine was taken in a round bottom flask and was dissolved in dimethylformamide,1gm of 4-(2-bromoethyl)-2*H*-1,4-benzoxazin-3(4*H*)-one was added into it and small quantity of triethylamine was also added and refluxed for three hrs. The hot solution was poured in to ice cold water and the precipitate of the final product was collected and dried in the air. Completion of reaction was monitored by running TLC.[13]

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

1g of 4-Chloro aniline substituted piperazine was taken in a round bottom flask and was dissolved in dimethylformamide, 1 g of 4-(2-bromoethyl)-2*H*-1,4-

benzoxazin-3(4*H*)-one was added into it and small quantity 0f triethylamine was also added and refluxed for three hrs. The hot solution was poured in to ice cold water and the precipitate of the final product was collected and dried in the air. Completion of reaction was monitored by running TLC.[14]

RESULTS AND DISCUSSIONS

First of all the Synthesis of 2 *H*-1, 4- benzoxazin-3(4*H*)-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. The data which were revealed during the experimental work are summarized in tables 1, 2 and 3.

Table 1: The Physicochemical Data of Synthesized Intermediate Compounds

Compound	Mol. formula	Mol. Wt.	Rf	Color (Appearance)	M.P. (°C)
1	$C_8H_7NO_2$	149	0.40	Pale brownish (crystalline)	108-110
2	$C_{10}H_{10}BrNO_2$	256	0.72	Light brown (crystalline)	120-122
3	$C_{11}H_{14}N_2O$	190	0.91	Brown Amorphous	134-138

Table 2: The Physicochemical Data of Synthesized Compounds

Compound	Mol. formula	Mol. Wt.	R_f	Color (Appearance)	M.P. (°C)
4a	$C_{21}H_{23}N_3O_3$	365	0.96	Pale yellow (Crystalline)	188-190
4b	$C_{20}H_{24}N_4O_2$	352	0.91	Light Brown (Crystalline)	58-60
4c	$C_{21}H_{23}N_3O_3$	365	0.89	Pale orange (Crystalline)	193-195
4d	$C_{20}H_{23}N_3O_2$	337	0.93	Pale orange (Crystalline)	189-191
4e	$C_{21}H_{23}N_3O_4$	381	0.93	Pale yellow (Crystalline)	207-209

Table 3: IR Spectra Data of Synthesized Compounds

Compound No.	Wave No.{cm^{-1}}
1	3367(NH Str.), 2875(C-H), 1656(C=O), 1515(NH bend.), 1195(C-O-C), 744(Ar-H)
2	2902(C-H), 1697,1647 (C=O), 1406(C-N.), 1114(C-C), 1218(C-O), 744(Ar-H)
3	3359 (NH Str.), 3056 (Ar-H str.), 2902(C-H), 1697, 1650(C=O), 1604 (C=C Ar.), 1500, 1361(C-N.), 744(Ar-H bend.)
4a	3313(NH Str.), 3132 (Ar-H str.), 2843(C-H Str.), 1703(C=O), 1632 (C=CAr.) 1505(NH bend.), 1351(C-N.)
4b	3050,742(Ar-H), 1642(C=O), 1403(C-H Bend),1195 (C-O), 1105 (C-N.),
4c	3128(NH Str.), 3128,873(Ar-H), 2993,1401(C-H),1196 (C-N.), 1690(C=O), 1640(NH bend.), 1640 (C= CAr)
4d	3059,742(Ar-H), 2902,1492(C-H) 1721(C=O), 1555, 1382(C-N.)
4e	3055,732(Ar-H),1639(C=O),1109 (C-N.), 1402(C-H Bend),1189 (C-O)

CONCLUSION

The research work was aimed to synthesize novel benzoxazinone derivatives, review of literature reveals various biological activities for the chemical compounds containing benzoxazinone nucleus based on these observation it was planned to synthesize such derivatives of benzoxazinone that may be of interest.

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. Heterocyclic bearing a benzoxazinone ring residue are reported to show anticancer, anti-inflammatory, analgesic, muscle-relaxant, sedative, antitubercular, antimicrobial, anticonvulsant, antimalarial, antiviral, antioxidant, CNS depressant, and plant growth regulatory activity etc. In addition, benzoxazinone forms an important pharmacaphore in fungicidal, herbicidal and insecticidal, agents.

REFERENCES

1. Niemeyer HM, Hydroxamic acids (4-hydroxy-14-benzoxazin-3-ones) defense chemicals in the gramineae. Phytochemistry 1988; 27:3349–3358.
2. Zunig GE, Massardo F, Hydroxamic acid content in undifferentiated and differentiated tissues of wheat. Phytochemistry 1991; 30:3281–3283.
3. www.arkat-usa.com
4. http://www.chemicalbook.com/chemicalproductproperty_EN_CB5111761.htm
5. Williams DA, Lemke TL. Foye's principles of medicinal chemistry. 5thed. Philadelphia (USA): Lippincott Williams and Wilkins; 2002.

6. Tripathi KD. Essential of medical pharmacology. 5th ed. New Delhi (India): Jaypee brothers medical publishers; 2003

7. Critically Important Antimicrobials for Human Medicine: Categorization for the Development of Risk Management Strategies to contain Antimicrobial Resistance due to Non-Human Antimicrobial Use Report of the Second WHO Expert Meeting Copenhagen, 29–31 May 2007

8. www.safewater.org

9. http://www.slideshare.net/majid4uonly/antimicrobial-presentation-885004

10. Janez I, Petra S, Tefanic A, Marija SD, and Danijel K, Recent advances in the synthesis of 2H-1,4-benzoxazin-3-(4H)-ones and 3,4-dihydro-2H-1,4-benzoxazines. Tetrahedron 2005; 61:7325–7348.

11. Kumar P, Donald M, and Milliam SC, 2h-1,4-benzoxazjn-3(4h)-one, An intermediate in the biosynthesis of cyclic Hydroxamic acids in Maize. Phymhemistry 1994; 36(4):893498

12. Seckin O, Aydin MO, Hakan G, Nurten A, Synthesis and antimicrobial activity of some new 4-hydroxy-2*H*-1,4-benzoxazin-3(4*H*)-ones Il Farmaco 2000; 55:715–718.

13. Piao ZT, Guan LP, Zhao LM, Hu RP, Quan ZS, Synthesis of novel 7-benzylamino-2H-1,4-benzoxazin-3(4H)-ones as anti-convulsant agents European Journal of Medicinal Chemistry 2008; 43:1216-1221.

14. Moussavi Z,Plancke MO, Olivier P, Lesieur D, Fruchart JC, and Sauzieres J, Lipid lowering actions of 7-(2-methylene butyryl) - (2H) -1,4-benzoxazin-3-(4H) -one derivatives in mice, rats and Syrian hamsters. CIinica Chimica Acta, 1989; 180: -44.

15. Holger H and Dieters S, 2(R)-2-β-D-Glucopyranosyloxy 4-hydroxy-2h-1,4-benzoxazin-3(4h)-one from secale cereal. Phytochemwry. 1994; 35(3):827-828.