International Journal of Pharmacy and Industrial Research (IJPIR)

ISSN:2231-6567

IJPIR |Volume 13 | Issue 1 | Jan - Mar - 2022
Available online at: www.ijpir.com

Reserch article Pharmaceutical Chemistry

Design, synthesis, and anti-microbial activity of some novel benzoxazole derivatives

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ABSTRACT

Advances in Organic Chemistry have made possible the synthesis of complex molecule. Today the chief source of agents for cure, the mitigation or prevention of diseases are organic, natural or synthetic, together with so called organometallics. The derivatives bearing fluoro-substituted benzoxazole nucleus presented here; up to a great extent have proved to be potent antibacterial agents. It is much clear that the use of electron-withdrawing functional groups in the final derivatives as substituents has influenced the biological property of the synthesized motifs. This concept of utilizing electron-withdrawing substituents will be kept in mind while undertaking other scientific work of the same kind.

Keywords: Benzoxazole, Anti-Microbial.

INTRODUCTION

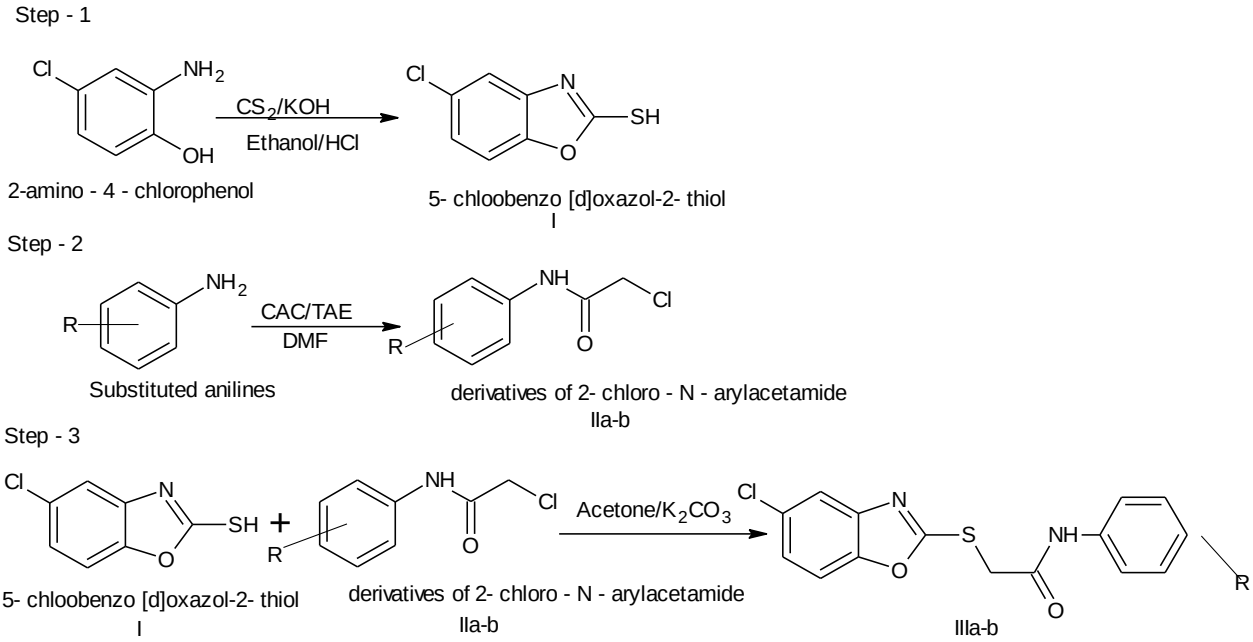
Organic Chemistry is the area of chemistry that involves the study of carbon and its compounds. Carbon is now known to form a seemingly unlimited number of compounds. The uses of organic compounds impact our lives daily in medicine, agriculture, and general life. Organic Chemistry erupted as an important branch in chemical science around 1900, until which the subject, chemistry remained undivided. The unprecedented number of factual research enforced a progressive segmentation of the subject into sub disciplines. Organic Chemistry is one of a special branch in chemistry and is concerned with the synthesis of organic compounds via use of several reactions and reagents. Organic synthesis has emerged as a subject of interest and centre of attraction for many scientists because of its ability to produce several beneficial products artificially, for the smooth functioning of human life.

Scientists believed that organic chemical found in nature contained a special "vital force" that directed their natural synthesis, and therefore, it would be impossible to accomplish a laboratory synthesis of the chemicals. Fortunately, Frederich Wohler (1828) that urea, a natural component in urine, could be synthesized in the laboratory by heating ammonium cyanate.His discovery meant that the natural "vital force" was not required to synthesis of organic compounds, and paved the way for many chemists to synthesize organic compounds.Organic Chemistry has helped to construct many different useful drugs and also insynthesizing other compounds, what a basic human needs. A keen investigation in the Organic Chemistry has helped to serve the mankind with lifesaving molecules – drugs and medicines and other basic necessities. Along with the development of Organic Chemistry, the advances in the interdisciplinary knowledge of relationship between biological activity and chemical structures has made a remarkable appearance in the support of synthesizing novel and useful organic molecules, thus ensuring a limitless scope for the development of structurally novel organic compounds with wide range of biological applicability.

Advances in Organic Chemistry have made possible the synthesis of complex molecule. Today the chief source of agents for cure, the mitigation or prevention of diseases are organic, natural or synthetic, together with so called

organometallics. Along with the development of Organic Chemistry; a great improvement in structural and functional development occurred, which helped the researchers to undertake their research and reach the conclusions more effectively. The instruments developed for characterizing organic molecules were much advanced technologically and were able to produce high quality results in less time span.

Present work



Experimental

All reagents and solvents were used as obtained from the supplier or recrystallized/redistilled and dried as necessary. Melting points of the synthesized compounds were determined in open capillaries and were uncorrected. The purity of the compounds was checked by TLC on silica gel G (Merck). IR spectra were recorded on Shimadzu FT-IR Affinity-1 spectrometer using KBr. The 1H-NMR and 13C-NMR spectra were recorded on Varian mercury plus 300 MHz spectrophotometer in CDCl3 and DMSO-*d6* as solvent and TMS as internal standard with 1H resonant frequency of 300 MHz and 13C resonant frequency of 75 MHz. The Mass spectra (ESI-MS) were recorded on VG AUTOSPEC mass spectrometer and on Varian Inc. 410 prostar binary LC with 500 MS IT mass spectrometer. High-resolution mass spectra (HRMS) were obtained by using ESI-QTOF mass spectrometry.

Synthesis of 5-chlorobenzo[d]oxazole-2-thiol

Ethanol (40 ml) and potassium hydroxide (0.01 mol, 56.11 gm/mol, 0.56 gm in 2 ml H2O) were taken in a dry round bottom flask. 2-amino-4-chlorophenol (0.01 mol, 143.57gm/mol, 1.43gm) was added to it and stirred well to get a clear solution. Carbon disulfide (0.02 mol, 76.14 gm/mol, 1.2 ml) was added to the clear solution obtained above and refluxed for 12 -15 h. The ethanol was distilled off and then cooled to room temperature. The content was poured into water and acidified with diluted HCl till the precipitates were separated. The separated solid was washed with cold water and dried to get the desired product. The completion of the reaction was monitored on TLC using ethyl acetate: benzene (6:4) as mobile phase. m.p.:258°C; Yield: 72%.

Synthesis of 2-chloro-N-(aryl) acetamide derivatives IIa-1b

Various substituted amines (0.01 mol) were added to a solution of DMF (35ml) containing TEA (3-4 drops). The mixture was stirred for 10 minutes at room temperature. CAC (0.015 mol, 113gm/mol, 1.19 ml) was added to the above mixture, maintaining the temperature between 0 to 5°C. The obtained solution was then stirred at room temperature for 4-6h. The completion of reaction was monitored with TLC using toluene: acetone (8:2) as mobile phase. The solution was then added onto crushed ice and the separated precipitates were filtered and dried. The product was crystallized from methanol.

Synthesis of 2-(5-chlorobenzo[d]oxazol-2-ylthio)-N-arylacetamide derivatives IIIa-b

5-chlorobenzo[d]oxazole-2-thiol ***I*** (0.01 mol, 172.61gm/mol, 1.7gm) was made soluble in acetone. To this well stirred solution different 2-chloro-N-arylacetamide derivatives **IIa-b**(0.01 mol) were added to the above solution. K2CO3 (0.02 mol, 138 gm/mol, 2.76 gm) was added to the solution containing mixture of *5- chlorobenzo[d]oxazole-2-thiol****I*** and different acetamide derivatives. The mixture was allowed to stir for 4h at room temperature. The completion of reaction was monitored using TLC plate with mobile phase ethyl acetate: n-hexane (6:4). The final products thus obtained were poured into ice cold water and stirred for 30 min. The

precipitates were filtered and washed occasionally. The final products **IIIa-b**obtained were crystallized from alcohol.

BIOLOGICAL EVALUATION

Antimicrobial assay

Broad panels of bacterial and fungal strains were used for testing the antimicrobial properties of the synthesized molecules. The results obtained were depicted in the form of Minimum Inhibitory Concentration (MIC) values for the synthesized derivatives. The samples were tested by standard protocols like micro dilution/broth titer method. The screening for antimicrobial activity was carried out by diluting the solution and preparing the sets consecutively from 1000, 500, 250, 125, 62.5, 31.25, 15.62 up to 7.8 µg/ml. Ciprofloxacin was used as a standard drug for antibacterial activity tests and fluconazole was used as a standard for antifungal activity tests. The MIC values for standards fluconazole against *C. albicans* and *A. niger* were recorded 125 µg/ml and 62.5 µg/ml respectively. On the other hand, the MIC values obtained for the standard ciprofloxacin against gram-positive bacteria *S. aureus* and *E. faecalis*were62.5 µg/ml and 125 µg/ml respectively; similarly, the MIC value was recorded 125 µg/ml when tested against both the gram-negative bacteria *E. coli* and *P. aeruginosa* for the same standard drug ciprofloxacin. The antibacterial and antifungal details for each compound synthesized are discussed below.

RESULT AND DISCUSSION

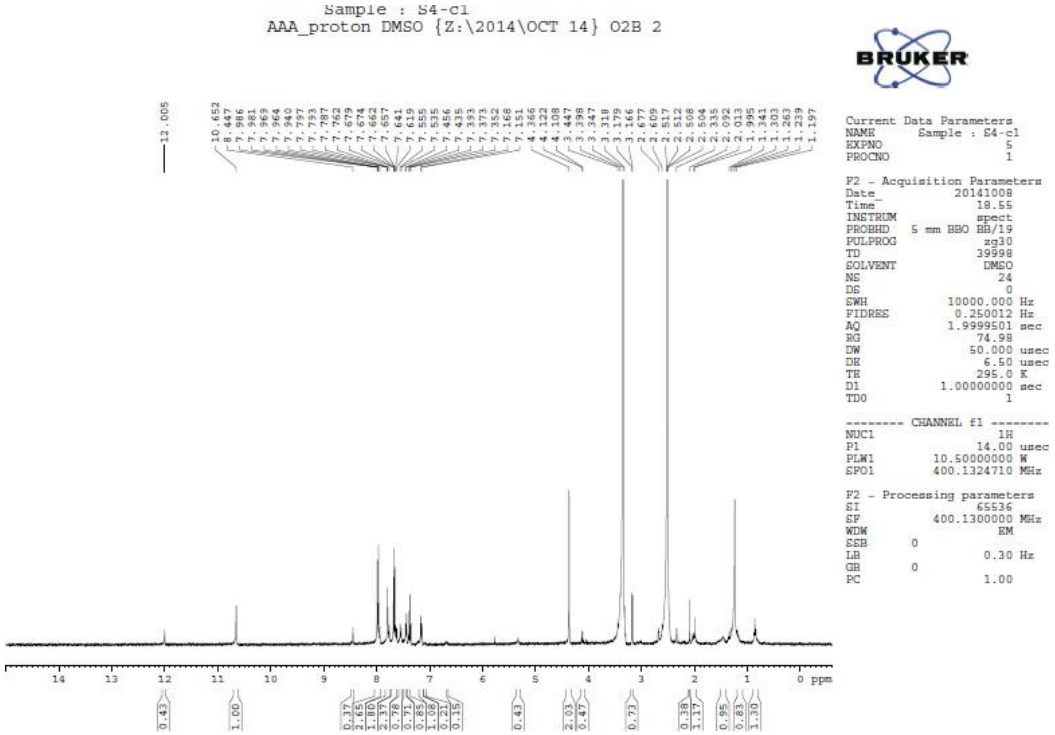
Spectral analysis of synthesized compound 2-(5-chlorobenzo[d]oxazol-2-ylthio)-N-arylacetamide (IIIa)

IR spectra

Table 1: Physical data for derivatives IIIa-b

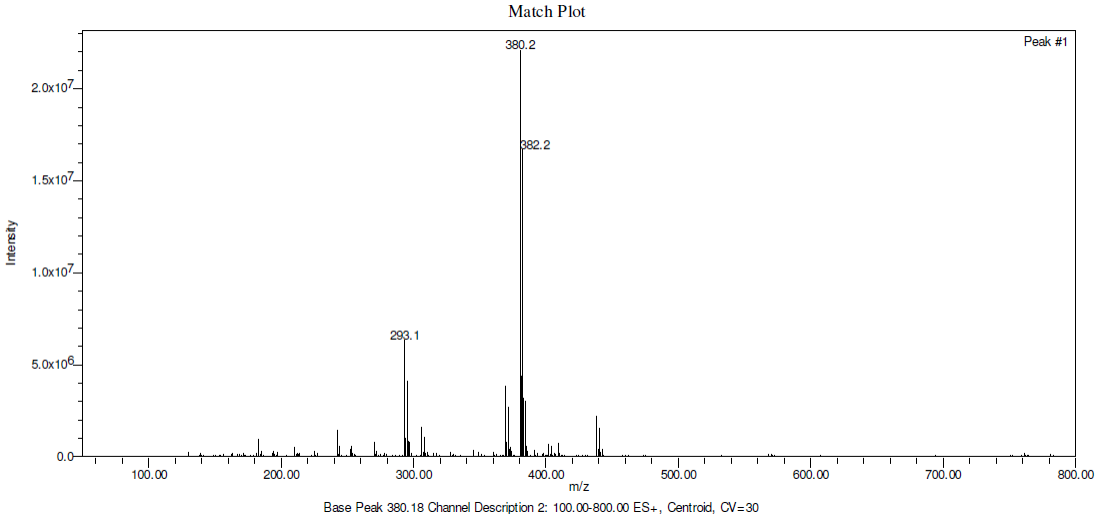
Functional group	Frequency (Cm^{-1})	Functional group	Frequency (Cm^{-1})
-N-H sec. amine (str.)	3239	-C=C- aromatic ring (str.)	1422
-C-H aromatic ring (str.)	3081	-C-Cl (str.)	682
-CH2 methylene group (str.)	2511	-C-O-C- ring (str.)	1013, 1277
-C=O carbonyl group (str.)	1671	-Nil-	-Nil-

^{1}H NMR spectra



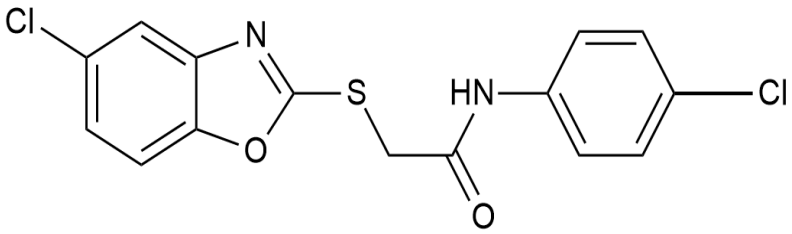
Assignment	No. of protons	Multiplicity	□ value (ppm)
-NH	1	singlet	10.652
-CH2	2	singlet	4.36
Ar-H	8	multiplet	7.35-7.98

Mass spectra

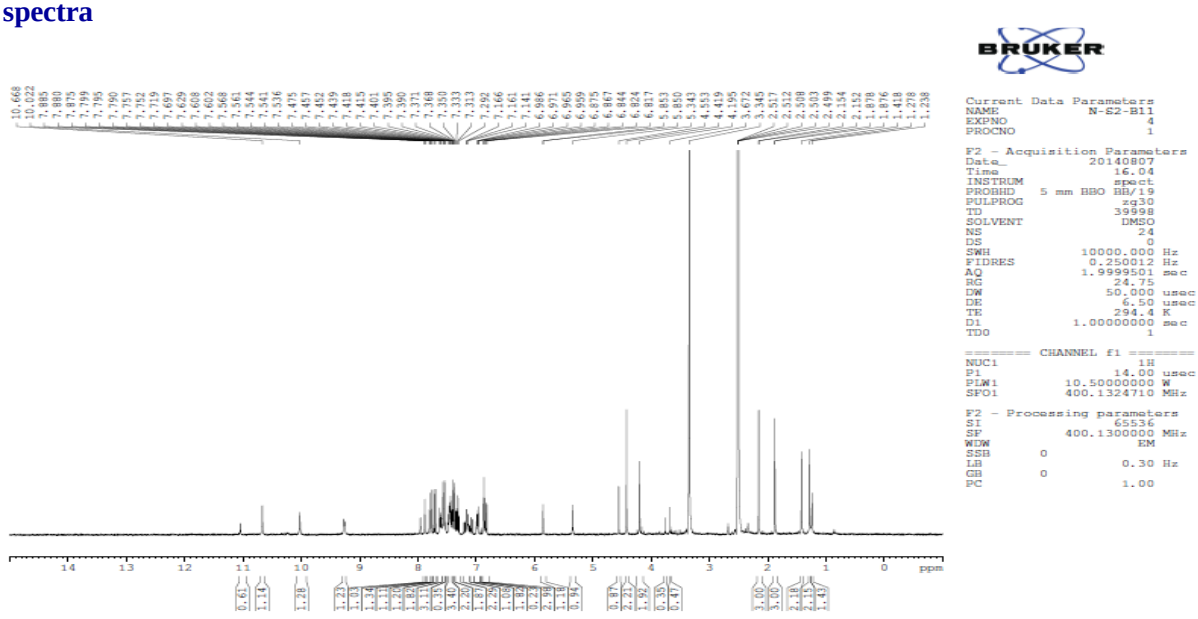


Peak assignment	m/z value
M+1 peak	380.2

2-(5-chlorobenzo[d]oxazol-2-ylthio)-N-(3-chlorophenyl)acetamide (IIIb)

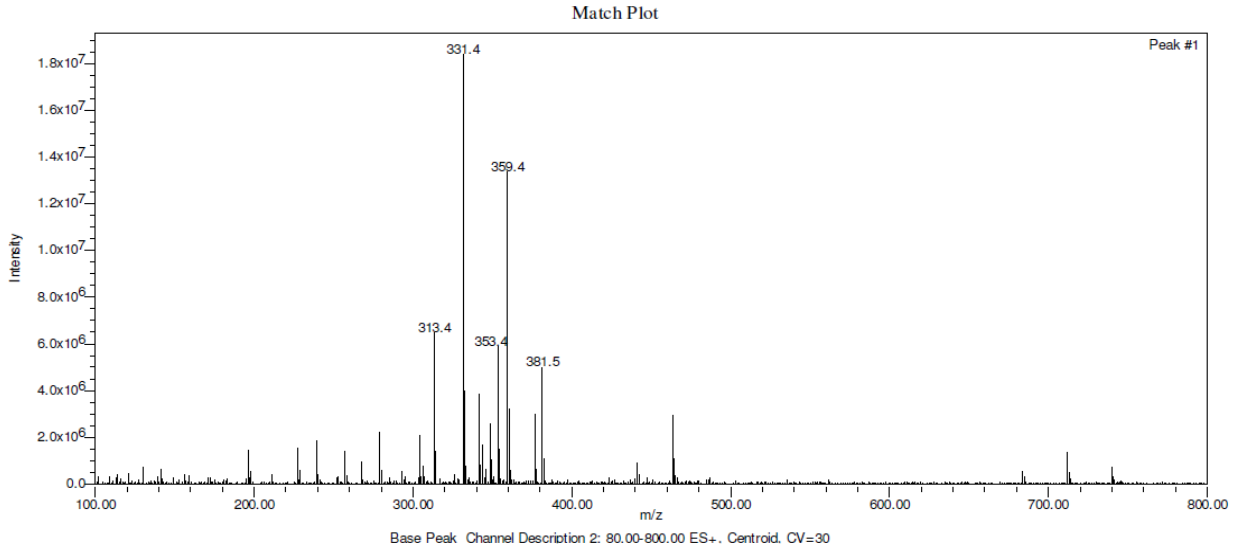


^{1}H NMR spectra



Assignment	No. of protons	Multiplicity	□ value (ppm)
-NH	1	singlet	10.66
-CH2	2	Singlet	4.38
Ar-H	7	Multiplet	7.141-7.395

Mass spectra



Peak assignment	m/z value
M+1 peak	353.4

Antibacterial activity for compounds III1-14

It was found that from the synthesized, compounds IIIb, exhibited activity excellent to that of the compound IIIa on compare to standard ciprofloxacin (62.5 µg/ml). The synthesized compounds were tested against both gram-positive and gram-negative bacterial strain.

Antifungal activity for compounds III1-13

The antifungal tests were carried against two fungal strains *C. albicans* and *A. niger*, where fluconazole was used as a standard drug for comparison and evaluation of antifungal activity of the synthesized molecules. Compound IIIb shows more potent antifungal activity than IIIa.

CONCLUSION

From the antimicrobial results, it can be concluded that the derivatives possessing electron with-drawing substituent were found to exhibit excellent antimicrobial property. On the basis of above results, attempts are made to optimize the lead structure to obtain more potent antimicrobial molecules. The derivatives bearing fluoro-substituted benzoxazole nucleus presented here; up to a great extent have proved to be potent antibacterial agents. It is much clear that the use of electron-withdrawing functional groups in the final derivatives as substituents has influenced the biological property of the synthesized motifs. This concept of utilizing electron-withdrawing substituents will be kept in mind while undertaking other scientific work of the same kind.

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