Section: Research Paper

SYNTHESIS AND ANTIMYCOBACTERIAL EVALUATION OF 2-[(E)-2-SUBSTITUTED-ETHENYL]-1,3-BENZOXAZOLES

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Abstract
"A set of six 2-[(E)-2-substituted-ethenyl]-1,3-benzoxazoles was synthesized and characterized". Three types of mycobacteria were used to test all of the compounds that were made. "2-[4-(methylsulfanyl) phenyl] ethenyl-1,3-benzoxazole was the most effective against M. tuberculosis, M. avium, and M. kansasii". It was also much more effective than isoniazid against M. avium as well as M. kansasii. "The most powerful ortho-substituted compound, 2-[(E)-2-(2-methoxyphenyl) ethenyl]", is able to stop PET from working. The relationships between structure and action are also talked about.

Key words: *Antimycobacterial, benzoxazole, bacterial, fungal.*

Introduction

One of those most crucial aspects in the study of antibiotics right now is coming up with new compounds that can kill bacteria, mycobacteria, and fungus that are resistant to antibiotics. This is because dangerous germs are quickly becoming immune to the antimicrobial drugs that are already on the market. "Tuberculosis (TB)", the number of cases of Mycobacterium tuberculosis that are immune to multiple drugs ("MDR-TB"), and "infections by mycobacteria" that don't cause tuberculosis (NTM) are all on the rise. This is because there are more people with weak immune systems and some types of mycobacteria are becoming more resistant to antimycobacterial chemotherapies [1,2]. People took a long time to understand that other NTM could also be dangerous to humans because M. tuberculosis is so well-known. For example, "M. kansasii", which is one of the most dangerous nontuberculous mycobacteria, is causing more and more nontuberculous mycobacterial lung illnesses [3,4]. Because of this, it is very important to find new antimycobacterial agents that can fight not only "TB/MDR-TB but also NTM forms".

The structure of benzoxazole is different from that of its "isosteres, benzimidazole and benzothiazole". This means that they can work as compounds with multiple binding or the enzyme targets, as long as their structures are only slightly changed. They are important building blocks not only in the pharmaceutical business, but also in agriculture, electronics, polymer chemistry, and many other fields. The benzoxazole system is used to make a lot of antibiotic medicines. Also, it was found that benzoxazoles and benzothiazoles are very effective against algae and fungus. In this

study, "2-[(E)-2-substituted-ethenyl]-1,3-benzoxazoles" derivatives were made and studied to see if they could stop the growth of different types of bacteria and fungi.

Material and method

Processes involved in synthesis: For the overall purpose of the "synthesis of 2-[(E)- 2-substituted-ethenyl]-1,3-benzoxazoles (1–6): Dry THF (10 mL) and t-BuOH (2 mL)" were combined in a container with 6.78 mmol of 2-methylbenzo[d]oxazole and 1.695 mmol of the appropriate aldehyde. The container was then sealed and placed in an argon environment. "The mixture was then cooled to 50 degrees Celsius, and 2 milliliters of a potassium tert-butoxide solution diluted in THF" at a concentration of one million was added slowly while maintaining a "temperature below 50 degrees Celsius". The reaction mixture initially seemed light yellow, but when more was added, its hue shifted to green. Stirring the alteration stream for two hours at a temperature of 50 degrees Celsius. After that, the temperature was raised to around 26 degrees Celsius and maintained there for three hours.

All of the produced compounds were put to the test against a strain of Mycobacterium tuberculosis (MTB) called CNCTC. The tests were performed in the "Laboratory for Mycobacterial Diagnostics and TB". It was necessary to monitor both the sterility and the growth of the inoculum, so each strain was simultaneously seeded into Petri dishes with "Lowenstein-Jensen media". The substances that were being investigated were initially dissolved in DMSO and then added to the medium. Warming was maintained at 37 degrees Celsius for microtone bags containing plates that had been infected.

The spectral data of the synthesized compounds is given below:

"2-[(E)-2-Phenylethyl]-1,3-benzoxazole (1). Only white. 41% yield; melting point of 81.6–82.5°C (86–88°C [46]). (KBr, cm1): 3062, 3040, 2343, 1642, 1454, 1350, 1237, 1178, 1004, 967, 933, 863, 840, 764, 743, 7014, 684, 497, 434. 1H NMR (300 MHz, CDCl3), 7.80 (1H, d, J = 16.2 Hz), 7.72 (1H, m), 7.60 (2H, m), 7.41 (3H, m), 7.34 (2H, m)".

"2-[(E)-2-(2-Methoxyphenyl) ethenyl]-1,3-benzoxazole (2). Only white. 14% yield; melting point of 67–68°C. IR (KBr, cm−1): 3061, 3001, 2949, 2842, 1924, 1884, 1811, 1637, 1596, 1577, 1545, 1532, 1485, 1453, 1468, 1320, 1305, 1286, 1249, 1183, 1163, 1103, 1053, 1025, 1003, 932, 894, 855, 844, 786, 760, 626, 603, 576, , 478, 428. 1H NMR (500 MHz, CDCl3), : 8.11 (d, J = 15 Hz), 7.11 (m), 7.53 (m), 7.33 (m), 7.23 (d, J = 20 Hz), 6.94 (d, J = 10 Hz), 3.93 (s)".

"2-[(E)-2-(4-Methoxyphenyl)ethenyl]-1,3-benzoxazole (3). Yel-lowish strong. 56% yield; melting point of 133.2–134.7°C (138–139°C [48]). IR (KBr, cm−1): 3403, 2973, 2839, 1774, 1600, 1506, 1350, 1254, 1207, 1145, 1117, 1030",

1007, 962, 933, 893, 823, 760, 721, 573, 534, 439. "1H NMR (500 MHz, CDCl3), : 7.75 (1H, d, J = 16.4 Hz), 7.71 (1H, m), 7.53 (3H, m), 7.32 (2H, m), 6.94 (3H, m)"

"2-(E)-2-[4-(Methylsulfanyl)phenyl]ethynyl-1,3-benzoxazole (4). Solid and yellowish. 15% yield; melting point 143.0–144.1°C. IR (KBr, cm−1): 3446, 3064, 2920, 1639, , 1556,1491, 1472, 1453, 1407, 1349, 1290, 1244, 1119, 1053, 1002, 972, 931, 894, 865, 843, 812,747, 622, 530, 507, 436. 1H NMR (500 MHz, CDCl3), : 7.83 (1H, d, J = 15 Hz), 7.78 (1H, m), 7.58 (3H, m), 7.40 (2H, m), 7.33 (2H, m), 7.10 (1H, d, J = 16.8 Hz)"

"2-[(E)-2-(4-Methylphenyl) ethenyl]-1,3-benzoxazole (5). Yel-lowish strong. 25% yield; melting point of 130–132°C (130–132°C [48]). IR (KBr, cm−1): 3446, 3051, 2917, 1639, 1606, 1534, 1508, 1455,1350, 1291, 1260, 1243, 1197, 1178, 1157, 1118, 1004, 976, 929, 894, 879, 865,777, 760, 740,

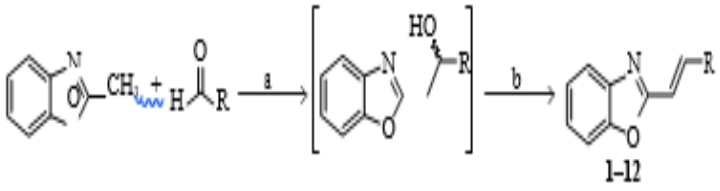
532, 486, 1H NMR (500 MHz, CDCl3), : 7.79 (1H, d, J = 16.4 Hz), 7.52 (3H, m), 7.35 (2H, m), 7.25 (2H, m), 7.05 (1H, d, J = 16.3 Hz), and 2.41 (3H, s)".

"2-[(E)-2-(4-Chlorophenyl) ethenyl]-1,3-benzoxazole (6). Yel-lowish strong. Yield: 43%; melting point: 144–145°C (148–150°C [48]). IR (KBr, cm−1): 3404, 1773, 1698, 1864, 1594, 1570, 1530, 1490, 1453, 1407, 1349, 1304, 1289, 1189, 1177, 1106, 1089, 1013, 1003, 930, 893, 843, 813, 760, 739, 721, 669, 622, 531, 503, 435. 1H NMR (500 MHz, CDCl3), : 7.74 (2H, m), 7.54, 7.38 (4H, m), and 7.05 (1H, d, J = 16.4 Hz)".

Result and discussion

It is possible to draw the conclusion that heterocycles showed lower lipophilicity than phenyl (1) based on the findings, with compound 5 being the sole one to demonstrate higher lipophilicity than that of 1. The following are the steps that improved the lipophilicity of these compounds: OCH3 SCH3 CH3 Cl CF3 is the formula. The 2-methoxy moiety, which was found in compound 2, exhibited a lower level of lipophilicity when contrasted with the 4-methoxy moiety, which was found in compound 3.

The effectiveness of benzoxazoles (1–6) was evaluated using three different mycobacterial strains: M. TB, M. avium, and M. kansasii. In the in vitro testing, M. tuberculosis was resistant to all of the chemicals that were tried, and none of them were effective against it. However, the activity of several benzoxazole derivatives against M. kansasii and particularly against M. avium was significantly higher than that of the gold standard medication, which is known as isoniazid (INH). Compound number 6 had the lowest level of activity, but 2-[(E)-2-(4-methoxyphenyl)ethenyl]- 1,3-benzoxazole (3) had the highest level of activity when tested against all three types of tuberculosis and mycobacterial strains., 2,3-dihydro-1-benzofuran-5-yl, is a cyclic analogue of the 4-methoxyphenyl moiety (compound 3), and this group is also isosteric to the methylsulfanyl moiety (compound 4), which is another possibly suitable alternative., 2,3-dihydro-1-benzofuran-5-yl is a chemical that contains the formula. In spite of the fact that there aren't a lot of compounds that can kill mycobacteria and some of them don't dissolve very well in the testing medium, there are connections that may be identified between log(1/MIC (mol/L)) and lipophilicity, which is represented by the log k notation. It is safe to state that lipophilicity has a significant impact on the antitubercular and antimycobacterial action of a substance, despite the fact that MIC values might vary quite a little.



Scheme 1 Synthesis of 2-[(E)-2-Substituted-ethenyl]-1,3-benzoxazoles 1-6. Reagents and condition a: t-BuOK, THF, -50 ˚C b: ambient temperature.

Table 1 Antimicrobial activity of six derivatives of benzoxazole.				
Serial number	Compound name	MTB MIC (µmol/L)	MA MIC (µmol/L)	MK MIC(µmol/L)

1.	2-[(E)-2-Phenylethyl]-1,3-benzoxazole (1)	125	62.5	125
2.	"2-[(E)-2-(2-Methoxyphenyl) ethenyl]-1,3-benzoxazole (2)"	125	62.5	125
3.	"2-[(E)-2-(4-Methoxyphenyl) ethenyl]-1,3-benzoxazole (3)"	62.5	62.5	125
4.	"2-(E)-2-[4-(Methylsulfanyl) phenyl] ethynyl-1,3-benzoxazole (4)"	62.5	125	500
5.	"2-[(E)-2-(4-Methylphenyl) ethenyl]-1,3-benzoxazole (5)"	250	500	250
6.	"2-[(E)-2-(4-Chlorophenyl) ethenyl]-1,3-benzoxazole (6)"	250	250	500

Conclusion

In the course of this research, employing the tried-and-true method, six different "2-[(E)-2-substituted-ethenyl]-1,3-benzoxazoles" derivatives were produced. In order to investigate the antimicrobial properties of compounds such as "2-[(E)-2-(4-Methoxyphenyl)ethenyl]", antimicrobial strains were utilized in the research.-"1,3-benzoxazole(3), 2-(E)-2-[4-(methylsulanyl)phenyl]-ethenyl.-1,3-benzoxazole(4)", which was produced after the fact. The effectiveness of 1,3-benzoxazole against Mycobacterium avium and Mycobacterium kansasii was significantly higher than that of the gold standard isoniazid.It is possible to say that lipophilicity, the type of substitution, and the position of substitution are the most critical criteria in determining how effectively a chemical kills mycobacterium.

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