Journal of Advanced Zoology
ISSN: 0253-7214
Volume 44 Issue 5 Year 2023 Page 1310:1315

Evaluating 2-[(E)-2-Substituted-Ethenyl]-1,3-Benzoxazoles Against Photosynthesis Inhibition Activity

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Abstract

The total twelve compounds 2-[(E)-2-substituted-ethenyl]-1,3-benzoxazoles[1-12] were tested for the capacity to block photosynthetic electrons transport (PET) in chloroplasts of spinach. 2, 8, and 4 had the strongest activity against M. TB, M. kansasii, and M. avium, and it was much more effective against M. avium than isoniazid. The most potential ortho-substituted molecule, 2-[(E)-2-(2-methoxyphenyl)ethenyl], inhibited PET. It took 76.3 mol/L of -1,3-benzoxazole to block PET, but much less of the para-substituted compounds were able to do this. The inhibitory location of the investigated chemicals is on the donor side of photosystem II. The links between structure and their activity are examined.

Keywords: Antibacterial, bacterial, Photosynthesis inhibition, benzoxazole

Introduction

As the development of novel chemicals to target mycobacteria, fungi, and resistant bacteria has become one of the most critical study fields pertaining to antimicrobials, the development of novel chemicals to combat pathogenic bacteria resistance to currently available antimicrobial medications is swiftly becoming a global health crisis.

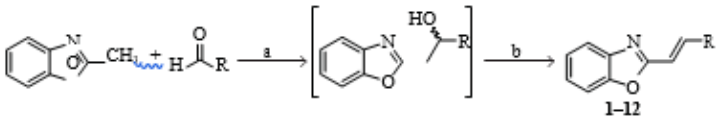
Benzoxazoles are nucleotide-structural bioisosteres such as guanine and adenine. This improves their interaction with the biopolymers found in living systems. Furthermore, it has been discovered that benzoxazoles block important bacterial enzymes such as isocitrate lyase [1] and hyaluronan lyase, as well as bacterial two-component systems [2]. While certain herbicidal benzoxazoles and benzothiazoles can inhibit fatty acid synthesis, more than half of commercially available herbicides inhibit photosynthesis via reversible binding to photosystem II (PS II), which is a complex of embrane proteins found inside the membranes of thylakoids. PS II catalyzes two functions: the reduction of plastoquinone and the oxidation of water [3]. Both medications and pesticides, "including herbicides, are intended to impede particular biological activities, and the cellular sites of action of these two types of substances are frequently identical to one another. Almost every pharmaceutical company maintained an agrochemical division for many years. Occasional lead times for pesticides and medications result in the use of identical chemicals for vegetation control and human health. Herbicides of diverse classes and with multiple activities exhibit potential medicinal properties, functioning as anti-infective agents and therapeutic medications that target human molecular targets [4]. Moreover, a robust correlation was observed between herbicidal effects and antibacterial activity [5]. As prospective antimycobacterial agents, the synthesized 2-styrylbenzoxazole-like chemicals were evaluated against 3

mycobacterial species. In spinach chloroplasts, each of the chemicals that were produced was examined to see whether or not they have the capacity to impede photosynthetic electrons transport, as various antimicrobial compounds have photosynthesis-suppressing activity [6] via bonding to PS II. The structures and antimycobacterial or inhibitory effects of the new compounds on photosynthetic electrons transport in spinach chloroplasts are discussed.

Material and method

Synthesis of compounds

All the chosen compounds were synthesized using the below scheme.



Scheme 1 Synthesis of comp. [1-12], 2. Reagents and condition, t-BuOK, -50 ˚C, THF, ambient temperature.

Determination of Lipophilicity via HPLC (calculated log k/capacity factor k)

Utilized were a Waters Photodiode Array Detector HPLC separation module. A Symmetry C18 chromatographic column, was utilized Using Empower 2 Chromatography Data Software, Waters 2009, the HPLC separation procedure was monitored. The mobile phase utilized was a combination of 70% MeOH p.a. and 30% H_2O-HPLC Mili-Q Grade. The column's overall flow rate was 1.0 mL/min, with an injection volume of 30 L, a temperature of 45°C for the column, and a sample temperature of 10°C. A 210-nanometer detection wavelength was selected.

The KI methanolic solution was employed to determine the dead of time (t_D). Retention of times (t_R) were measured in minutes. The capacity factors, denoted ask, were computed utilizing the Empower 2 Chromatography Data Software in accordance with the formula $k = (t_R - t_D)/ t_D$. In this context, t_R represents the retention time of the solute, and t_D signifies the dead time acquired with an analyte. Table 1 contains a listing of the logarithmic values of each compound.

Investigation of Spinach Chloroplast Inhibition activity of Photosynthetic Electronss Transport (PET)

chloroplasts of Spinach were generated in accordance with the methodology outlined by Masarovicova and Kralova [51]. Spectrophotometric analysis was employed to ascertain the inhibition activity of photosynthetic electrons transport in spinach chloroplasts. In order to accomplish this, methodology called for the use of an artificial electron's acceptor known as DCPIP. The rate of photosynthetic electrons transport was monitored through the photoreduction of DCPIP.

Phosphate buffer (0.03 mol/L, pH 7.2) supplemented with sucrose (0.5 mol/L), MgCl2 (0.006 mol/L), and NaCl (0.016 mol/L) was utilized for the experiments. In order to prevent the samples from heating (suspension temperature of 23°C), they were irradiated (approximately 100 W/m2 at a distance of 10 cm) with a halogen lamp (251 W) through a 4cm water filtration. The chlorophyll concentration in these experiments was 30 mg/L. The compounds under investigation were dissolved in DMSO on account of their poor solubility in water. In spinach chloroplasts, the photochemical activity was unaffected by DMSO concentrations as high as 4%.

IC_{50} values were used to measure how well the compounds under study blocked oxygen evolution. These values show the molar concentration of the compound at which the rate of oxygen evolution drops by 50% compared to the control that wasn't treated. Analogous to DCMU (Diuron), the IC_{50} value for the selective herbicide 3-(3,4-dichlorophenyl)-1,1-dimethylurea was approximately 1.9 moll/L. The findings are presented in Table 1.

Investigation of the Fluorescence of Aromatic Amino Acids in Spinach Chloroplasts. The emission spectra of AAA (aromatic amino acids) present in spinach chloroplasts were measured using a fluorescence spectrophotometer model F-2000. The excitation wavelength and emission slit were both set to 10 nm. The wavelength of excitation was set to 275 nm. To dilute the chloroplast solution, the same phosphate buffer that was employed in the prior description was used. To compensate for the compounds' limited solubility in water, they were introduced to the chloroplast suspension in DMSO solution. The concentration of DMSO in each sample was the same as the concentration in the control (10%). The concentration of chlorophyll in the chloroplast suspension was ten micrograms per liter.

Result and discussion

Table 1 Antimicrobial activity of twelve derivatives of benzoxazole.

Serial number	Compound name	PET IC50	MIC OF MTB (unit µmol/L)	MIC OF MA (unit µmol/L)	MIC OF MK (unit µmol/L)
1.	2-[(E)-2-Phenylethyl]-1,3-benzoxazole[1]	148.4	125	62.5	125
2.	2-[(E)-2-(2-Methoxyphenyl)ethenyl]-1,3-benzoxazole[2]	76.6	62.5	125	125
3.	2-[(E)-2-(4-Methoxyphenyl)ethenyl]-1,3-benzoxazole[3]	216.5	62.5	62.5	125
4.	2-(E)-2-[4-(Methylsulfanyl)phenyl]ethynyl-1,3-benzoxazole[4]	199.5	62.5	125	500
5.	2-[(E)-2-(4-Methylphenyl)ethenyl]-1,3-benzoxazole[5]	102	250	500	250
6.	2-[(E)-2-(4-Chlorophenyl)ethenyl]- 1,3-benzoxazole[6]	516	250	250	500
7.	*2-{(E)-2-[4-(Trifluoromethyl)phenyl] ethenyl}-1,3-benzoxazole[7]*	b	125	125	250
8.	*2-[(E)-2-(2,3-Dihydro-1-benzofuran-5-yl)ethenyl]-1,3-benzoxazole[8]*	131.4	62.5	32	62.5
9.	*2-[(E)-2-(Furan-2-yl)ethenyl]-1, 3-benzoxazole[9]*	224.1	62.5	62.5	125
10.	*2-[(E)-2-(5-Ethylfuran-2-yl)ethenyl]-1 ,3-benzoxazole[10]*	122.3	250	250	62.5
11.	*2-[(1E,3E)-4-Phenylbuta-1,3-dien-1-yl]-1 ,3-benzoxazole[11]*	777.5	125	250	500
12.	*2-[(1E,3E)-4-(4-Methoxyphenyl)buta-1, 3-dien-1-yl]-1,3-benzoxazole[12]*	351	125	125	125
13.	*INH*	0.5	>250	>250	-

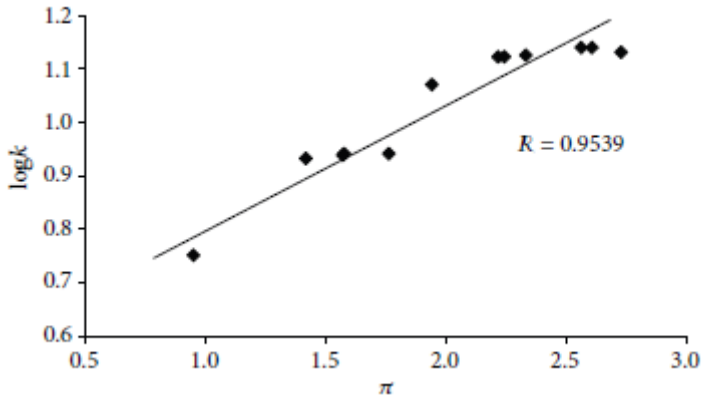
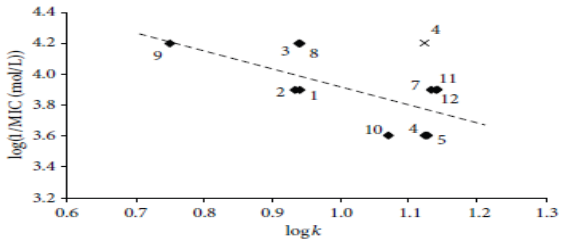
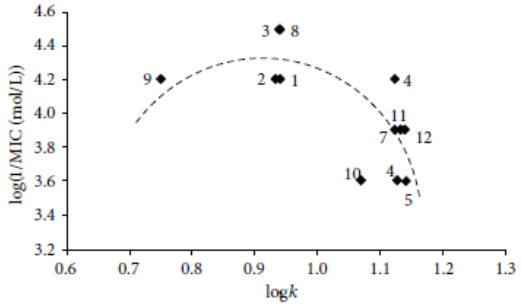


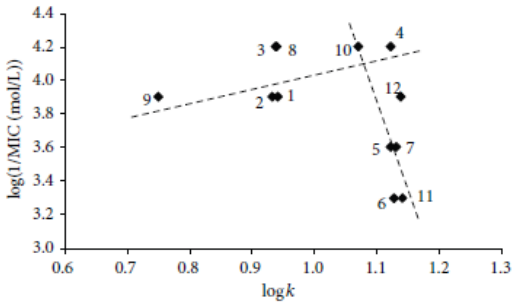
Figure 1. A comparison of the experimentally discovered log k values and the computed distributive parameter π of substitutes of 2-[(E)-2-substituted-ethenyl-1,3-benzoxazole 1-12.



(a)

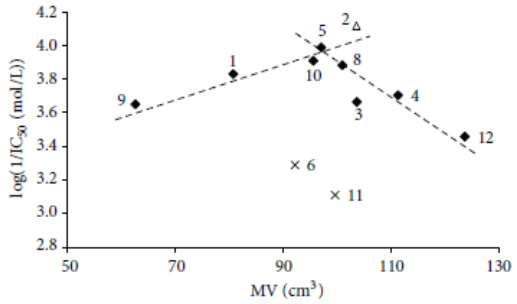


(b)



(c)

Figure 2. In vitro antitubercular/antimycobacterial activity against three strains after 14 days depended on lipophilicity (log k) of 2-[(E)-2-substituted-ethenyl-1,3-benzoxazole 1-12) after 14 days. My 331/88 is M. TB, M. avium My 330/88 (b) My 235/80 is (c)



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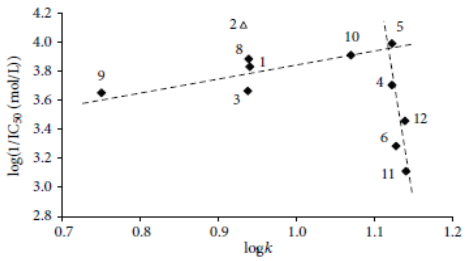

(b)

Figure 3. The relationship of PET of inhibition log(1/MIC (mol/L) in spinach chloroplasts and the molar volume of various substituents benzoxazole compounds , (a) lipophilicity (log k), and (b) of selected investigated compounds.

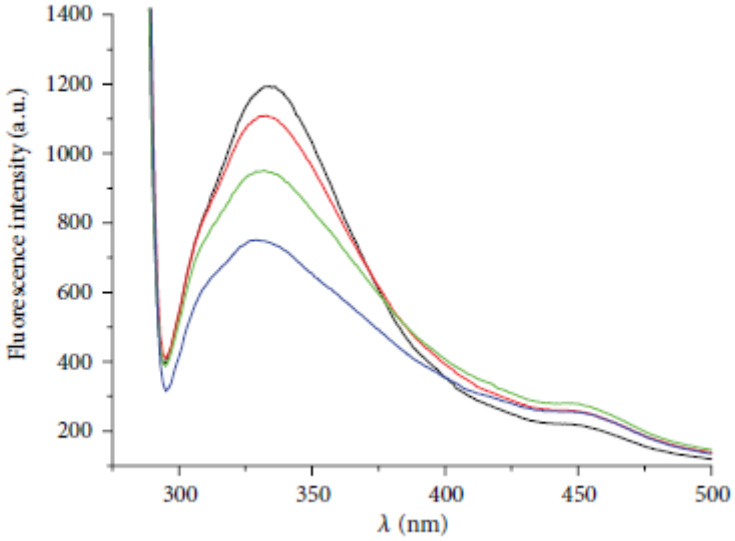

Figure 4. Emissions fluorecene spectrum of aromatic amino acids in spinach chloroplast suspension without and with 3 (c = 0,2.2,6.5,9.7 mol/L curves from top to bottom)

Pept (photosynthesis electrons transport) inhibition

within the chloroplasts of spinach. As previously stated, agrochemicals and drugs, being biologically active compounds, can target comparable locations of action. Thus, molecular sites of action for herbicides can also be found in mammals and nonplant organisms. However, it is important to note that the biological responses of plants and animals can be entirely dissimilar when targeting compounds to biological systems that share similar physicochemical properties. As an illustration, fluconazole was initially identified as a highly effective pesticide before its classification as an antifungal medication was confirmed.

Furthermore, it is recommended and necessary to conduct extensive screening of novel compounds prior to their release into the environment so that the impact of these compounds on various nontarget organisms can be estimated. In contrast to the standard, the observed activity of the substituted benzoxazoles in inhibiting photosynthetic electrons transport in the chloroplasts of spinach (Spinacia oleracea L.) was either moderate or low (refer to Table 1). The compounds' ability to inhibit PET was determined using the negative logarithm of the IC50 value, which represents the concentration of the compound in mol/L that caused 50% inhibition of PET. 2-ethenyl 2-[(E)-2-(2-Methoxyphenyl)The sole ortho-substituted compound, -1,3-benzoxazole (2), exhibited the most pronounced inhibitory activity against PET (IC_{50} = 76.3**H**mol/L).

On the basis of the results obtained (see Table 1), it can be concluded that the molar volume of substituents affects the PET-inhibiting activity. Upon eliminating derivatives 6 and 11, which exhibit the least amount of PET-inhibiting activity, one can observe the bilinear relationship between log(1/IC_{50} (mol/L)) and molar volume. Biological activity, conversely, is also influenced by lipophilicity. Generally, heterocyclic and/or para-substituted 2-[(E)-ethenyl derivatives The inhibitory activity of -1,3-benzoxazole on PET increases linearly with lipophilicity up to log k ca.

where the relationship between log k and log (1/IC_{50} (mol/L)) is depicted.Nevertheless, the succeeding rise in lipophilicity is accompanied by a swift deterioration in the inhibitory activity of PET, potentially due to a reduction in the compounds' solubility.

Using 2,5-diphenylcarbazide (DPC), an artificial donor of electrons that operates in the Z/D intermediate on the donor side of PS II, a study was conducted with the purpose of determining the specific location within the photosynthetic apparatus where the chemicals under investigation exerted their effects. The chemical compounds that were investigated were able to significantly recover the photochemical activity of chloroplasts, which had been impaired in the past (up to 93% of the control). It can be deduced from this discovery that the chemicals are directed towards the donor side of PS II.

The relationship between the chemicals under investigation and aromatics The AAA fluorescence at 334 nm had to be turned off to see if amino acids (AAA) were present in spinach chloroplasts, which are photosynthetic proteins found in PS II. The fluorescence emission spectra of AAA generated by untreated spinach chloroplasts and compound 3 are depicted in Figure 4. The fact that AAA fluorescence drops exponentially as concentration

3 increases indicates that it interacts with the above-mentioned elements of the photosynthetic machinery, preventing PET from operating.

Conclusion

During this study, twelve distinct 2-[(E)-2-substituted-ethenyl]-1,3-benzoxazoles derivatives were synthesized using the tried-and-true method. The compounds were tested to see how well they stopped PET in the chloroplasts of Spinacia oleracea L. spinach. They were also tested to see if they were effective against Mycobacterium tuberculosis, Mycobacterium kansasii, and Mycobacterium avium. The compound 2 had the strongest effect on blocking PET of all the ones tested. On the other hand, the para-substituted compounds had much weaker effects on blocking PET. The location of the analyzed compounds' site of action was identified as the donor side of photosystem II. The compound (3), (2), (4), (8) exhibited markedly greater efficacy in inhibiting the growth of bacteria in comparison to the standard isoniazid.

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