Review

Pyridazinic Bioisosteres with Potential Applications in Medicinal Chemistry and Agriculture

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Abstract: Bioisosteres are substituents or groups (atoms, ions, or molecules) with similar chemical or physical properties, and which usually have similar biological properties. Pyridazine and its derivatives are invaluable scaffolds in medicinal chemistry, having a large variety of activities such as antibacterial, antifungal, antimalarial, anticancer, antituberculosis, antihypertensive, etc. Also, the pyridazine core is of high interest in agriculture, being used as a growth factor for plants, herbicides, etc. This study aims to review our previous contributions related to antimicrobials and the germination and seedling capabilities of some seeds and plants of some pyridazine classical and nonclassical bioisosteres. So, we present herein the synthesis (under conventional thermal heating and microwave irradiation) and spectral characterization of seven series of pyridazine bioisosteres, the in vitro antimicrobial activity (against different strains of Gram-positive and Gram-negative bacteria and fungi), and the biologic effect on wheat germination and seedling growth. Some pyridazine bioisosteres proved to have very good activity against pathogenic bacterial strains, with some spectacular results. Overall, nonclassical bioisosteres prove to have better antibacterial and antifungal activity compared with classical bioisosteres. The pyridazine bioisosteres may influence the wheat germination rate, seedling growth, height, and weight of the plantlets. Feasible explanations for this behaviour were furnished.

Keywords: classical and nonclassical bioisosteres; pyridazine compounds; synthesis; microwave; spectral characterisation; stereochemistry; antibacterial and antifungal activity; wheat germination; seedling growth; height and weight of plantlets

1. Introduction

In drug design, bioisosterism [1–4] is used to enhance the desired biological or physical properties of a compound without making significant changes in its chemical structure. Also, bioisosterism is used to reduce toxicity, change bioavailability, or modify the activity of the lead compound and may alter the metabolism of the lead. The success of this strategy in developing new substances that are therapeutically attractive has experienced a significant growth in distinct therapeutic classes. The pharmaceutical industry is making extensive use of it to find new, commercially appealing analogous therapeutic innovations as well as a tool useful in molecular modification.

Pyridazine (1,2-diazine) and its derivatives have demonstrated interesting potential applications in different fields of science, being highly valuable materials in medicinal chemistry, opto-electronics, agriculture, etc. [4–13]. The compounds derivatives from pyridazine are invaluable scaffolds in medicinal chemistry, possessing a large range of biological activities: antibacterial, antifungal, antiplasmodial, antitubercular, antiviral, anticancer, antihypertensive, diuretic, antithrombic, anticoagulant, etc. Our group has

made significant contributions in these fields [14–28]. In opto-electronics, pyridazine scaffolds are of huge importance for their highly fluorescent properties, with potential as sensors and biosensors, electroluminescent materials, lasers, and semiconductor devices. Our group has also made significant contributions in this field [29–34]. Finally, it was proven that pyridazine derivatives are compounds of great importance in agriculture, having potential as herbicides and growth factors for plants, and again, our group has made contributions in these fields [13,35–38].

With these things in mind, the main goal of this review was to give information about the synthesis, structure, and biological activity (antimicrobial and biological effect on wheat germination and seedling growth) of classical bioisosteres derived from the pyridazine-4-R-acetophenone moiety and replaced in the para(4) position of the acetophenone moiety with the methyl group, fluorine, or chlorine. In equal measure, we were interested to see the influence of nonclassical isosteres derived from pyrrolo-pyridazine derivatives substituted with trifloromethyl groups (which are nonclassical isosteres with halogen atoms) against the same above-described parameters.

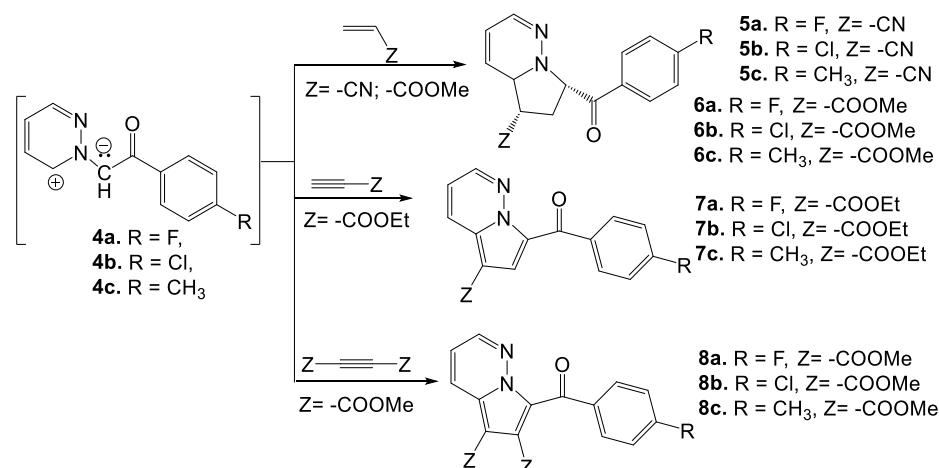## 2. Synthesis of Pyridazine Bioisosteres

The medicinal chemistry literature indicates that the methyl group (-CH3), the fluorine atom (-F), and the chlorine atom (-Cl) are classical bioisosteres because the peripheral layers of electrons can be considered to be identical [1–4]. On the other hand, the halogen atoms are described as typical nonclassical isosteres with a trifluoromethyl group (-CF3). Also, in medicinal chemistry, it is well established that the incorporation of trifluoromethyl groups in a bioactive compound is an usual tool in order to improve the pharmacological properties of these compounds, especially metabolic stability [39,40].

In order to study the classical bioisosterism phenomena in the series of pyridazine-4-R-acetophenone (R = -CH3, -Cl, -F) derivatives and the nonclassical bioisosterism phenomena in the series of pyrrolo-pyridazine derivatives substituted with trifloromethyl groups, the group of Mangalagiu synthesised and further determined the antimicrobial activity [19,25,26,37] and biologic effect on wheat germination and seedling growth [13,35,36,38]. The author chose for the synthesis of pyridazine-4-R-acetophenone classical bioisosteres a straight and efficient method in two steps. The first step is an N-alkylation reaction to the pyridazine nitrogen with α-bromacetophenone (substituted in para position with the classical bioisosteres methyl group, the fluorine, and the chlorine atom), and when the corresponding α-bromacetophenone pyridazine salts **3a–c** are obtained; see Scheme 1.
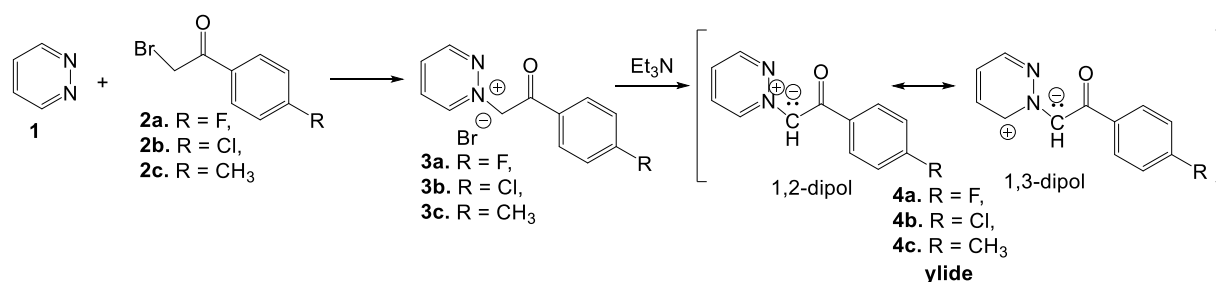
Scheme 1. The synthesis of α-bromacetophenone pyridazine salts **3a–c** classical bioisosteres and their ylides **4a–c,** generated in situ.

In the second step, pyridazinium ylides **4a–c** [generated in situ from the corresponding salts **3a–c** in alkaline medium by triethylaine (Et3N)] react via a Huisgen 3 + 2 dipolar cycloaddition reaction with variously dipolarophiles (symmetrically and non-symmetrically substituted Z-alkene and Z-alkyne), leading to the corresponding pyridazine bioisostere cycloadducts **5a–c** to **11a–c**; see Schemes 2 and 3.

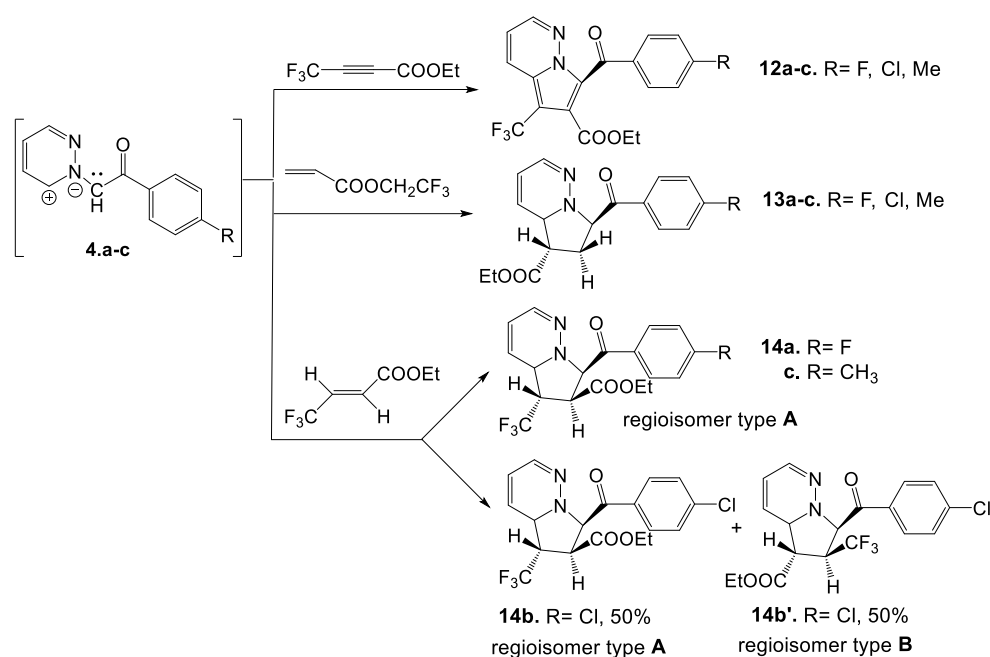**Scheme 2.** The synthesis of pyridazine classical bioisostere cycloadducts **5a–c** to **8a–c** (via cycloaddition reactions with symmetrically substituted dipolarophiles).
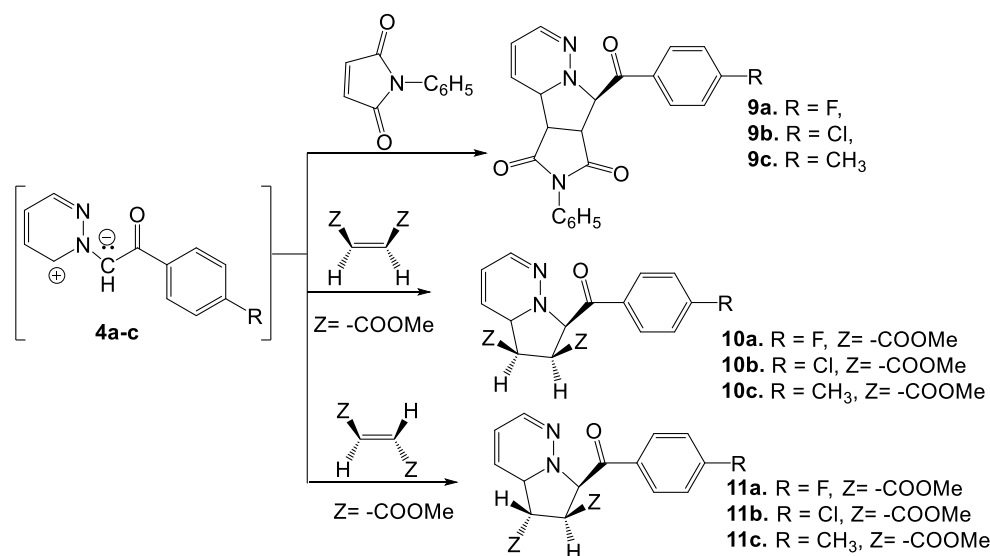
Scheme 3. The synthesis of pyridazine classical bioisosteres cycloadducts **9a–c** to **11a–c** (via cycloaddition reactions with non-symmetrically substituted dipolarophiles).

According to the nature of dipolarophiles, six series of pyridazine bioisostere cycloadducts are obtained: Z-tetrahydro-pyrrolo-pyridazine-4-R-acetophenone **5a–c** and **6a–c**, Z-pyrrolo-pyridazine-4-R-acetophenone **7a–c**, Z,Z-pyrrolo-pyridazine-4-R-acetophenone **8a–c**, tetrahydro-tetrahydro-pyrrolo-pyridazine-4-R-acetophenone **9a–c**, cis-Z,Z-tetrahydro-pyrrolo-pyridazine-4-R-acetophenone **10a–c**, trans-Z,Z-tetrahdro-pyrrolo-pyridazine-4-R-acetophenone **11a–c**.

In order to synthesise the pyrrolo-pyridazine derivatives substituted with trifloromethyl groups (nonclassical bioisosteres), the authors have used a similar strategy as described above, Scheme 4. In the case of the 3 + 2 dipolar cycloaddition reaction, the authors used dipolarophiles containing trifloromethyl groups (non-symmetrically substituted Z-alkenes and Z-alkynes).

Scheme 4. The synthesis of trifluoromethyl-pyrrolo-pyridazine nonclassical bioisostere cycloadducts **12a–c** to **14a–c** (via cycloaddition reaction with symmetrically and non-symmetrically substituted dipolarophiles containing trifloromethyl groups).

The cycloaddition reactions of pyridazinium ylides **4a–c** with alkyne dipolarophile ethyl 4,4,4-trifluorobutinoate lead to the trifloromethyl-pyrrolo-pyridazine cycloadducts **12a–c.** The cycloaddition reactions of ylides **4a–c** with 2,2,2-trifluoroethyl acrylate occur highly regioselectively, a single regioisomer with a trifloromethyl-tetrahydro-pyrrolo-pyridazine structure (**13a–c**) being obtained. The cycloaddition reactions of ylides **4a–c** with ethyl 4,4,4-trifluorocrotonate (*E*-isomer, non-symmetrically dipolarophile) involve a more complicated chemistry, the reactions involve additional stereo- and regiochemical problems, called chorochemistry [19]. In the case of ylides **4a** (R = F) and **4c** (R = Me) the cycloaddition reactions occur chorospecifically, a single type of regioisomer being obtained, those with trifloromethyl-tetrahydro-pyrrolo-pyridazine structure type **A** (**14a**, **14c**). In the case of ylides **4b** (R = Cl), the cycloaddition reactions occur choroselectively, resulting in a mixture of two regisomers, those with trifloromethyl-tetrahydro-pyrrolo-pyridazine structures type **A** (**14b**) and type **B** (**14b′**), in a molar ratio of 1:1.

All these syntheses were performed both under conventional thermal heating (TH) and nonconventional methods using microwave (MW) technology. The literature [7] data indicate that the use of MW in chemical reactions has some undeniable advantages compared with conventional TH such as shorter reaction times, higher yields, spectacular accelerations of chemical reactions, higher product purities, and, in many cases, being environmentally friendly (using small amounts or no organic solvents, having milder reaction conditions, and having no side reactions). Having in view these considerations, the authors studied the reactions described above under microwave irradiation, in liquid phase, solid phase (using KF–Al$_2$O$_3$ support), and interphasic transfer catalysis (PTC, using KF-Aliquat). The obtained results reveal that, under MW irradiation, the consumed energy decreases considerably, reaction times decrease dramatically, in some cases yields are higher, and the amount of solvent used in the liquid phase is several times (at least five-fold) less compared with conventional TH, while the solid phase and PTC did not use solvents. Taking into consideration these aspects, the authors claim that these reactions could be considered environmentally friendly.

The structure of the compounds was proved by elemental and spectral analysis (FT-IR and NMR mono- and bi-dimensional). The ^{1}H and ^{13}C NMR spectra were recorded on a

Bruker Avance 400 DRX spectrometer at 400/100 MHz in DMSO-d6. The IR spectra were recorded on an FT-IR Shimadzu Prestige 8400s spectrophotometer in KBr.

The antimicrobial assay was performed using the disc diffusion Kirby–Bauer method; for antibacterial tests, Müeller Hinton agar was used, and Sabouraud environment was used for antifungal tests. The in vitro antibacterial activities of the pyridazine-4-R-acetophenone classical bioisosteres and the trifloromethyl-pyrrolo-pyridazine nonclassical bioisosteres, were investigated using Gram-positive bacteria, Gram-negative bacteria, and fungi. Chloramphenicol (an antibiotic) and Nysatin (an antimycotic) were used as control drugs. The bioisosteres were dissolved in dimethylformamide (DMF) 5% (*v/v*) and a witness solvent sample has been taken. The plates with the test sample were incubated immediately at 34 °C for bacteria and at 37 °C for *Candida albicans* for 24 h. Activity was determined by measuring the diameter of zones showing complete inhibition (mm). Growth inhibition was compared with the standard antibacterial drug. A compound is considered active when the difference between the inhibition diameter zone of the compound and the witness is up to 2 mm (3–4 mm is moderately active and up to 5 mm is very active). In order to clarify any participating role of DMF in the biological screening, separate studies were carried out with the solutions alone of DMF and they showed no activity against any bacterial strains.

The experiments to determine the effects of pyridazine-4-R-acetophenone classical bioisosteres and trifloromethyl-pyrrolo-pyridazine nonclassical bioisosteres on seed germination and growth of wheat seedlings were performed in Petri dishes on double Watmann no. 1 filter paper at room temperature. Fifty seed samples of wheat were treated with 5 mL of each $5 \cdot 10^{-3}$ molar solution of bioisosteres for 1 h. A blank with redistilled water was also carried out (**W**), and all the determinations were performed in triplicate or duplicate. Then, the seeds were taken out and put into Petri dishes on double filter paper together with their treatment solutions. The seeds were periodically watered, and the percent of germinated seeds was reported 3 days later (energy of germination, **EG**) and 7 days later (germination rate, **GR**), respectively. A seed with visible coleorhizae was considered to have germinated. Young wheat plants were harvested from their seeds, measured (**H**, expressed as cm), and weighed (**W**, expressed as grammes).

3. Characterization of Pyridazine Bioisosteres and Investigation of Their Effects

3.1. The Spectral Characterization of Pyridazine Bioisosteres

The structure of the obtained pyridazine-4-R-acetophenone classical bioisosteres **3a–c** to **11a–c** and trifloromethyl-pyrrolo-pyridazine nonclassical bioisosteres **12a–c** to **14a–c** was proven by elemental (C, H, N) and spectral analysis: FT-IR and NMR [1-H and 13-C NMR spectra and two-dimensional 2D-COSY, 2D-HETCOR (HMQC), and long range 2D-HETCOR (HMBC) experiments]. All the elemental and spectral data correspond with the proposed structures and could be found in the previously published papers of our team [19,25,26,37].

3.2. The Biological Activity of Pyridazine Bioisosteres

The in vitro antibacterial and antifungal activities of the pyridazine-4-R-acetophenone classical bioisosteres **3a–c** to **11a–c** and trifloromethyl-pyrrolo-pyridazine nonclassical bioisosteres **12a–c** to **14a–c**, were determined against five Gram-positive and Gram-negative bacterial strains (*Staphylococcus aureus ATCC 25923*, *Sarcina lutea ATCC 9341*, *Bacillus subtillis*, *Pseudomonas aeruginosa*, *Escherichia coli ATCC 25922*), and one fungus (*Candida albicans ATCC 10231*). Tables 1 and 2 summarise the antibacterial and antifungal activity of the bioisosteres and control drugs, expressed as inhibition zone diameters (mm).

Table 1. The antibacterial and antifungal activity of pyridazine-4-R-acetophenone in classical bioisosteres **3a–c** to **11a–c** *.

Comp.	S. aureus [1]	S. Lutea [2]	B. subtillis [3]	P. aeruginosa [4]	E. coli [5]	C. albicans [6]
Chloramphenicol 30 µg/disc	30	40	26	19	25	-
Nystatin, 100 µg/disc	-	-	-	-	-	29
3a.	**38**	**61**	**31**	20	**31**	19
3b.	**36**	**57**	**32**	20	**36**	29
3c.	**47**	**81**	**40**	20	25	27
5a.	26	**50**	27	14	20	23
5b.	30	**57**	29	14	28	**35**
5c.	**46**	**67**	**39**	19	23	30
7a.	27	**48**	22	20	23	22
7b.	25	**48**	25	20	**33**	30
7c.	**40**	**56**	**37**	18	25	28
8a.	27	**52**	23	15	21	21
8b.	30	**57**	26	18	**31**	24
8c.	46	65	26	19	25	29
9a.	27	**63**	28	16	25	25
9b.	28	**54**	28	18	28	**34**
9c.	31	**73**	**37**	18	24	29
10a.	29	**60**	**37**	18	**35**	24
10b.	33	**56**	**39**	18	**32**	25
10c.	**41**	**62**	**39**	19	**37**	30
11a.	29	**51**	**35**	17	**35**	27
11b.	23	**54**	**36**	15	**31**	27
11c.	**47**	**59**	**38**	17	**37**	29

(*) the series 'a' of compound is related to F, the series 'b' of compound is connected to Cl and the series 'c' of compound involve CH_3. [1] *Staphylococcus aureus*. [2] *Sarcina lutea*. [3] *Bacillus subtillis*. [4] *Pseudomonas aeruginosa*. [5] *Escherichia coli*. [6] *Candida albicans*; Bold and underline means very active compound.

Table 2. The antibacterial and antifungal activity for trifloromethyl -pyrrolo-pyridazine nonclassical bioisosteres **12a–c** to **14a–c**.

Comp.	S. aureus	S. lutea	B. subtillis	P. aeruginosa	E. coli	C. albicans
Chloramphenicol 30 µg/disc	25	30	25	19	29	-
Nystatin, 100 µg/disc	-	-	-	-	-	29
12a.	**30**	**41**	**31**	16	**34**	29
12b.	29	**44**	**38**	18	**42**	26
12c.	**49**	**60**	**36**	19	**40**	**32**
13a.	28	**55**	**31**	19	26	27
13b.	**30**	**58**	**33**	20	**35**	**37**
13c.	**30**	**59**	**39**	20	28	30
14a.	**88**	**58**	**38**	21	31	29
14b, b'	**35**	**61**	**42**	19	**38**	**39**
14c.	29	**61**	**38**	21	27	**31**

Bold and underline means very active compound.

3.3. Tables

The most active compounds are listed in bold and underlined.

In Table 3, the effect of the pyridazine-4-R-acetophenone classical bioisosteres on wheat germination is summarised.

Table 3. The effect of pyridazine-4-R-acetophenone classical bioisosteres **3a–c** to **11a–c** on wheat germination.

Compound	Germination Rate (GR, %)	Number of Plantlets in the Lot
3a.	64 ± 5	26 ± 1
3b.	38 ± 4	14 ± 5
3c.	69 ± 4	9 ± 2
5a.	61 ± 4	26 ± 4
5b.	54 ± 5	20 ± 3
7a.	81 ± 3	34 ± 4
7b.	54 ± 4	20 ± 4
8a.	73 ± 5	32 ± 2
8b.	80 ± 4	24 ± 3
9a.	72 ± 4	34 ± 3
9b.	72 ± 4	25 ± 1
10a.	73 ± 5	30 ± 3
10b.	61 ± 5	17 ± 2
10c.	59 ± 6	22 ± 1
11a.	0 ± 0	0 ± 0
11b.	79 ± 4	26 ± 6
11c.	40 ± 5	28 ± 5

In Table 4, the effect of the pyridazine-4-R-acetophenone classical bioisosteres on wheat germination and seedling growth is summarised. The main parameters used are the total height of plantlets in the lot, **H**, the mean height of plantlets in the lot, **Hm**, the weight of plantlets in the lot, **W**, and the mean weight of plantlets in the lot, **Wm**. The blank control was water, **W**.

Table 4. The effect of pyridazine-4-R-acetophenone classical bioisosteres **3a–c** to **11a–c** on wheat germination and seedling growth.

Compound	H, cm	Hm, cm	W, g	Wm, mg
3a.	121 ± 15	5 ± 1	0.89 ± 0.12	40 ± 5
3b.	52 ± 13	5 ± 0.4	0.47 ± 0.19	42 ± 17
3c.	52 ± 13	5 ± 0.9	0.47 ± 0.41	40 ± 3
5a.	178 ± 17	6 ± 0.6	1 ± 0.12	34 ± 2
5b.	120 ± 15	7 ± 0.8	0.8 ± 0.13	44 ± 0.07
7a.	239 ± 17	6 ± 0.4	1.38 ± 0.16	35 ± 4
7b.	117 ± 6	27 ± 0.4	0.75 ± 0.07	43 ± 4
8a.	233 ± 26	7 ± 0.7	1.37 ± 0.14	37 ± 4
8b.	133 ± 3	6 ± 0.1	0.87 ± 0.17	42 ± 8
9a.	198 ± 7	5 ± 0.6	1.11 ± 0.15	29 ± 13
9b.	149 ± 8	7 ± 0.3	0.95 ± 0.14	45 ± 4
10a.	186 ± 32	6 ± 0.9	1.11 ± 0.19	32 ± 5
10b.	77 ± 10	6 ± 0.7	0.64 ± 0.30	42 ± 2
10c.	11 ± 0.3	0.55 ± 0.01	0.08 ± 0.01	40 ± 0.01
11a.	0 ± 0	0 ± 0	0 ± 0	0 ± 0
11b.	185 ± 19	8 ± 0.8	1.06 ± 0.19	47 ± 8.48
11c.	136 ± 31	6 ± 1.3	0.98 ± 0.08	42 ± 3.36
W (water)	224 ± 23	7 ± 0.7	1.42 ± 0.19	42 ± 6

H—the total height of plantlets in the lot; Hm—the mean height of plantlets in the lot; W—the weight of plantlets in the lot; Wm—the mean weight of plantlets in the lot.

The data presented in Tables 1–4, allow interesting correlations and conclusions related to the antibacterial, antifungal and biologic effect on wheat germination and seedling growth to be obtained.

3.4. Antibacterial Activity

Analysis of the data from Table 1 reveals some interesting structure-activity correlations in the series of pyridazine-4-R-acetophenone classical bioisosteres **3a–c** to **11a–c**. The authors notice a certain significative influence of the isosteres substituent **R** from the para(4)-position of the acetophenone moiety, with the bioisosteres compounds in which **R** is a methyl (-CH$_3$) moiety being far more active than those in which the substituent **R** is fluorine (-F) or chlorine (-Cl) atoms. The authors also notice that all bioisosteres, no matter to what class they belong, have excellent antibacterial activity against the Gram-positive strain *Sarcina lutea*, some results being spectacular, with an activity twice as high as that of the reference drug Chloramphenicol. The authors notice that the pyridazine-4-R-acetophenone salts **3a–c** have excellent nonselective antibacterial activity against all Gram-positive and Gram-negative bacteria. A comparative analysis of the series of pyridazine-4-R-acetophenone bioisosteres **3a–c** to **11a–c** reveals that the bioisostere salts **3a–c** are significantly more active than the bioisostere cycloadducts **5a–c** to **11a–c** (the authors explain this behaviour due to the complementary action of the bromine anion). In the series of bioisosteres cycloadducts **5a–c** to **11a–c**, the comparative analysis reveals that saturated structures (the tetrahydropyrrolo one) are more active compared with the others.

Analysis of the data from Table 2 reveals that trifloromethyl-pyrrolo-pyridazine nonclassical bioisosteres (**12a–c** to **14a–c**) have an analogous behaviour with classical bioisosteres, with some particularities. All nonclassical bioisosteres, no matter the class to which they belong, have excellent antibacterial activity against two Gram-positive strains, *Bacillus subtilis* and *Sarcina lutea.* The authors notice that the trifloromethyl-pyrrolo-pyridazine nonclassical bioisosteres **13a–c** and **14a–c** have better activity compared with **12a–c**, which leads them to the conclusion that a saturated tetrahydro-pyrrolo-pyridazine structure (bioisosteres **13a–c** and **14a–c**) is more favourable for antibacterial activity compared with an aromatized pyrrolo-pyridazine structure (bioisostere **12a–c**).

3.5. Antifungal Activity

The data from Table 1 indicate that the synthesised pyridazine-4-R-acetophenone classical bioisosteres **3a–c** to **11a–c** have no significant antifungal activity. The data from Table 2 reveal that in the case of trifloromethyl-pyrrolo-pyridazine nonclassical bioisosteres **12a–c** to **14a–c**, there are two compounds (**13b** to **14b**) that manifest a very good antifungal activity against the fungus *Candida albicans*; this fact led them to the conclusion that the combining presence of a trifloromethyl moiety (on the pyrrolo-pyridazine motif) and a chlorine atom (on the 4-R-acetophenone scaffold) is favourable for antifungal activity.

3.6. The Biologic Effect on Wheat Germination and Seedling Growth

Statistics. The data were validated by the Tukey test [41].

The data from Tables 3 and 4 indicate that the pyridazine-4-R-acetophenone bioisosteres **3a–c** to **11a–c** have a significant influence on the germination process of the wheat seeds and also on the seedling growth process. From a bioisosterism point of view, the data from Table 3 indicate a certain influence of the substituent **R** from the para(4)-position of the acetophenone moiety, the bioisosteres having a chlorine (-Cl) atom having the most noxious effect on wheat germination. A comparative analysis of the series of pyridazine-4-R-acetophenone bioisosteres **3a–c** to **11a–c** reveals that the bioisostere salts **3a–c** manifest a more toxic effect on wheat germination than the bioisostere cycloadducts **5a–c** to **11a–c**. Once again, the authors explain this behaviour as due to the complementary action of the bromine anion. The pyridazine-4-R-acetophenone bioisosteres also have an influence on the number of plantlets in the seedling process. The bioisostere compounds having a chlorine (-Cl) atom or a methyl (-CH$_3$) moiety have the most noxious effect, killing more than 50% of the seeds.

The data from Table 4 reveal that both the height and weight of the plantlets are significantly affected by pyridazine-4-R-acetophenone bioisosteres, with a significant decrease. Once again, the authors notice a certain influence of the isosteres substituent **R** from the

para (4)-position of the acetophenone moiety, the bioisosteres having a chlorine (-Cl) atom have the most noxious effect, decreasing the significant height and weight of the plantlets; for instance, in the case of bioisostere salt **3c**, the height is reduced to 52 cm (compared with 223 for blank) while the weight decreases to 0.47 g (compared with 1.42 g for blank). A comparative analysis of the series of pyridazine-4-R-acetophenone bioisosteres **3a–c** to **11a–c** revealed that the bioisostere salts **3a–c** manifest a more toxic effect on the height and weight of the plantlets compared with the bioisostere cycloadducts **5a–c** to **11a–c**, roughly by about 50%.

4. Conclusions

In conclusion, a comprehensive study concerning the synthesis, structure, and biological activity of classical and nonclassical pyridazine bioisostere derivatives is reported. Using a simple and straightforward method of synthesis (an N-alkylation reaction followed by a Huisgen 3 + 2 dipolar cycloaddition reaction), the authors were able to make seven series of classical pyridazine-4-R-acetophenone bioisosteres. Six of the series are cycloadducts, and one is a salt. By using a similar strategy, three other classes of nonclassical bioisosteres with trifloromethyl-pyrrolo-pyridazine structures have been obtained. The reactions were performed both using conventional thermal heating and microwave irradiation, revealing some certain advantages of MW irradiation. The antimicrobial activity of pyridazine classical and nonclassical bioisosteres was determined, revealing some interesting structure–activity correlations. The authors notice that the isostere substituent R from the para(4)-position of the acetophenone moiety has a significant effect. The bioisostere compounds where R is a methyl (-CH$_3$) moiety are much more active than those where R is a fluorine (-F) or chlorine (-Cl) atom. The classical pyridazine bioisostere salts are significantly more active than bioisostere cycloadducts. In the series of bioisostere cycloadducts, the comparative analysis reveals that saturated structures (the tetrahydropyrrolo one) are more active compared with the others. The nonclassical bioisosteres are active in a higher number of bacterial strains compared with the classical bioisosteres. The influence of pyridazine-4-R-acetophenone bioisosteres on the germination process of the wheat seeds and also on the seedling growth process was determined. It was observed that the substituent **R** from the para(4)-position of the acetophenone moiety, the bioisosteres having a chlorine (-Cl) atom, had the most noxious effect on wheat germination and decreased the significant height and weight of the plantlets. Also, the bioisostere salts manifest a more toxic effect on wheat germination and on the height and weight of the plantlets compared with bioisostere cycloadducts. Overall, the results obtained by the authors suggest that the research in the pyridazine bioisosteres class should be continued, with interesting results expected both in the field of antimicrobial derivatives and on the germination process of crop plant seeds and seedling growth processes.

Author Contributions: All authors have equal contributions. All authors have read and agreed to the published version of the manuscript.

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