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Original article

Synthesis, antifungal activity and QSAR study of 2-arylhydroxynitroindoles

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ABSTRACT

A series of 2-arylhydroxynitroindoles were prepared and tested for antifungal activity *in vitro*. The preliminary bioassays indicated that some compounds are comparable to the commercial fungicide (triadimefon). To further explore the structure–activity relationships, the data set of the seventeen structures and their quantitative values of antifungal activities were used for QSAR modeling. Based on the obtained QSAR models four new chemical compounds were designed, synthesized and tested in fungicidal assays. Reasonable correspondence between the experimental and predicted values of antifungal activity was observed.

1. Introduction

Substituted 2-arylindoles are known to be biologically active molecules. They inhibit *aldose reductase*(*H*), which is important for diabetes treatment [1], combat against multidrug resistance strains of *Staphilococcus aureus* [2], and in the form of 2-pyridylindoles inhibit the micelial growth of some fungi [3].

Furthering our researches on the conversion of aromatic explosives (TNT, TNB, etc.) and their transformation to multipurpose synthons for organic chemistry [4,5] we developed a method for the synthesis a number of new 2-arylindoles with hydroxyl and nitro groups in 4- and 6-positions, respectively [6]. As follows from the results of the initial studies, some of them have high fungicidal activity dramatically exceeding that of the conventional commercial fungicide–triadimefon [7]. This research deals with the synthesis of substituted 2-aryl-4-hydroxy-6-nitroindoles, study of their fungicidal properties and elucidation of the structure–fungicidal activity relations within a series of such compounds.

2. Results and discussion

2.1. Chemistry

For broadening a scope of 2-aryl-4-hydroxy-6-nitroindoles with a view to investigate an impact of substituents in the aryl ring on the fungicidal properties we used the synthetic method (Scheme 1 [6]) having been developed by us earlier.

At first sight, the generation of indoles **3** seems unexpected. However it can be explained on the basis of the cyclization mechanism of *O*-arylketoximes to benzo[*b*]furans [8].

In case of *O*-(3-amino-5-nitrophenyl)ketoximes **2**, the [3,3]-sigmatropic rearrangement (**2** → **C**) may equally probable occur both to the *ortho*-position to NO_2 (Scheme 2, a) and to the *ortho*-position to NH_2 (Scheme 2, b) with the generation of corresponding intermediates **C′** and **C″** and, further on, intermediates **D′** and **D″**. For intermediates **D′**, cyclization proceeds in a common way to produce 6-amino-4-nitrobenzo[*b*]furans **4** (**D′** → **E′** → **F′**, Scheme 2, a). As regards intermediates **D″**, intramolecular addition is likely to be implemented to the C=NH_2^+ bond of the NH_2 group rather than of the OH group (**D″** → **G**) followed by the ammonium ion split-off and generation of 4-hydroxy-6-nitroindoles **3** (**G** → **H**, Scheme 2, b).The OH group here can not compete with the NH_2 group (NH_2 is much more nucleophilic than unionized OH), otherwise 4-amino-6-nitrobenzofurans would be formed, what actually does not happen.

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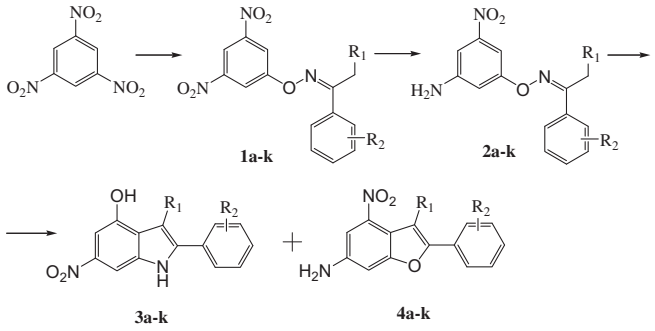


R_1=CH_3, R_2=H(**a**); R_1=R_2=H(**b**); R_1=H, R_2=2-Cl(**c**); R_1=H, R_2=2,4-Cl_2(**d**); R_1=H, R_2=4-OH(**e**); R_1= H_2C⌒N⌒N R_2=4-F(**f**); R_1=H, R_2=4-Br(**g**); R_1=H, R_2=4-CF_3(**h**); R_1=H, R_2=4-F(**i**); R_1=H, R_2=4-OCH_3(**j**); R_1=H, R_2=2-OCH_3(**k**).

Scheme 1.

To assess the molecular structure influence on fungicidal activity we studied a possibility of synthesizing 2-aryl-4-hydroxy-6-nitroindole derivatives alkylated by oxygen and nitrogen. As found for compound **3a**, O-alkylation of the 4-hydroxyl group runs first, and only after that N-alkylation of the nitrogen indole atom occurs. All further attempts to demethylate the methoxy group using various reagents (HBr, $AlCl_3$, HI, BBr_3, PhSH) in order to afford indole **7a** did not yield positive results: either the reaction does not run or it is accompanied by resinification (Scheme 3).

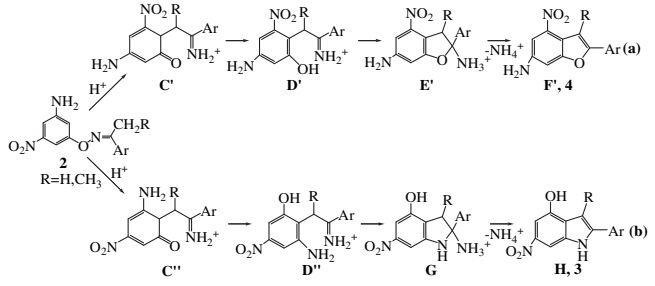
Indole **3b** behaves in a similar manner. In this case, in a pure form we managed to isolate merely a bismethylation product.

As an alternative, we looked at a possibility to synthesize hydroxynitroindoles substituted by nitrogen from *N*-monoalkyl-substituted derivatives of ketoximes **7b**–**d** through the Scheme 4.

It appeared that in this case reductive alkylation proceeded with a good yield, and at the same time the C=N bond of the oxime moiety was not impacted. Of note is that the alkylation conditions for formaldehyde and for aromatic aldehydes differ significantly. The rearrangement of oximes **7** proceeds by analogy with non-substituted oximes **2a**–**k**, though indole yields are much lower.

2.2. Fungicidal activity testing and discussion

The 2-aryl-4-hydroxy-6-nitroindoles were tested *in vitro* for the fungicidal activity according to a very common conventional procedure [9–11] with six phytopathogenic fungi from different taxonomic classes: *Sclerotinia sclerotiorum* (*S.s.*), *Fusarium oxysporum* (*F.o.*), *Fusarium moniliforme* (*F.m.*), *Bipolaris sorokiniana* (*B.s.*), *Rhizoctonia solani* (*R.s.*), and *Venturia inaequalis* (*V.i.*) (Table 1). The effect of the tested compounds on the mycelium radial growth in the potato-saccharose agar with widely used fungicide triadimefon as a reference compound was measured in a concentration 30 μg mL^{-1}. The tests in the concentration range 1–100 μg mL^{-1} let evaluate EC_{50} for the two most potent fungicidal substances (Table 2).



Scheme 2.

The first members (**3a** and **3b**) in the sequences of 2-aryl-4-hydroxy-6-nitroindoles displayed the strongest fungicidal action. Their potency exceeds those of the commercial fungicide (*triadimefon*) with respect to all phytopathogens – they inhibit the mycelium growth in the majority of fungi at concentration 30 μg mL^{-1}. The introduction of halogen into the aryl ring led to a considerable activity decrease, for the exception of 2-chlorophenyl-substituted indole **3c**. This compound equivalent in activity to its non-substituted analog **3b**, whereas its impact on the scab pathogen of apple tree *V. inaequalis* is twice lower than that of **3b**. The modification of the structure of the most active 4-hydroxy-6-nitro-2-phenylindole by alkylation showed that antifungal action decreased to medium values in the transition to N-methylation product **8b**, mean while *N*-(4-chloro-benzyl) derivative **8d** exerted just moderate activity. The fungicidal properties disappear almost completely in the transition to O-alkylation products **5a**, **6a** and **6b**, what allows assuming that 4-hydroxyl groups play an important pharmacophoric role for fungicidal 2-aryl-6-nitroindoles **3** at large. The introduction of the 1,2,4-triazolylethyl moiety to the indole 3rd position should be admitted as a failing modification option – here fungicidal activity declines to moderate. It is worth pinpointing that only indole products of heterocyclization of ketoximes **2a**–**j** exhibit fungicidal activity, whereas substituted benzofurans **4a**–**j**, e.g., benzofuran **4b**, do not actually affect the mycelium growth in pathogenic fungi.

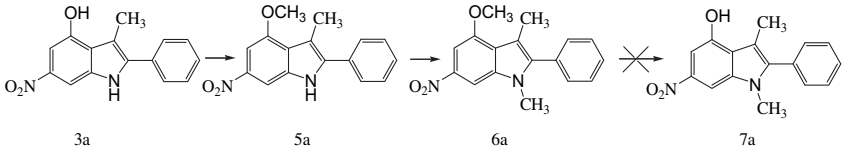
2.3. Quantitative structure–activity relationships (QSAR)

2.3.1. Data sets

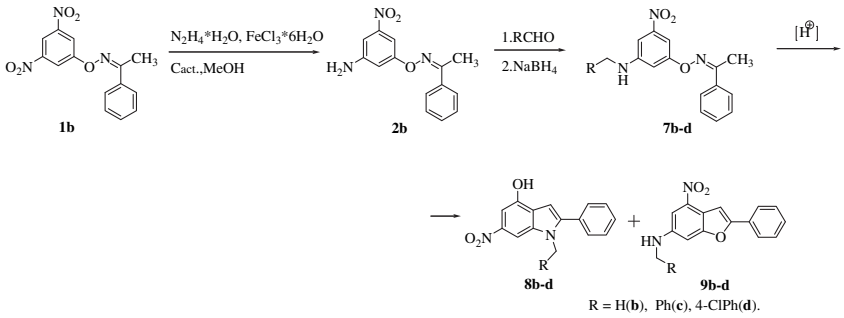
The data set of the seventeen structures and their quantitative values of antifungal activities were used for QSAR modeling with the end-points similar to those published in the paper [12]. The end-points were presented in percent of inhibition at 30 μg mL^{-1} concentration for six different taxonomic classes of fungi: *B.s.*, *F.m.*, *F.o.*, *R.s.*, *S.s.*, *V.i.* Thus, six different modeling sets were obtained. Each sets correspondent to the appropriate end-point was randomly divided onto the training and test sets in the ratio of 70% and 30%, respectively. The training set was used for creation of QSAR models and test set for the assessment of external predictive accuracy. QSAR models were developed using GUSAR program, which based on Multilevel and Quantitative Neighborhoods of Atoms (MNA, QNA) descriptors [13,14] and self-consistent regression (SCR) algorithm [15].

2.3.2. QSAR modeling on the basis of QNA descriptors

QNA descriptors are *P* and *Q* values calculated for each atom of molecule. The calculation of *P* and *Q* values is based on the



Scheme 3.



Scheme 4.

connectivity matrix (C) and the standard values of ionization potential (IP) and electron affinity (EA) of atoms in a molecule [13]. The estimation of a target property of chemical compound is calculated as the mean value of the function of P and Q values of the atoms of a molecule in QNA descriptors' space. We have proposed to use two-dimensional Chebyshev polynomials for approximation of the function of P and Q values. So, the independent regression variables are calculated as average values of particular two-dimensional Chebyshev polynomials of P and Q values for molecule atoms.

QNA descriptors and their polynomial transformations do not provide information on the shape and volume of a molecule although this information may be important for determination of the structure–activity relationships. Therefore, these parameters were added to the variables obtained from Chebyshev polynomials. Topological length of a molecule is the maximal distance calculated in the number of bonds between any two atoms (including hydrogen). The volume of a molecule is the sum of each atom's volume.

GUSAR algorithm uses three randomly chosen procedures for generation of different QSAR models based on QNA descriptors: (a) calculation of QNA descriptors for all atoms or for those molecule atoms, which have two or more immediate neighbors; (b) changing of the coefficient before the connectivity matrix (c) changing of parameters of Chebyshev polynomials. The final QSAR model is the consensus of built in this way different QNA based models.

Table 1
Fungicidal activity of some synthesized compounds.

№	Mycelium growth inhibition, % (C = 30 μg mL^{-1})					
	V.i.	*R.s.*	*F.o.*	*F.m.*	*B.s.*	*S.s.*
3a	93	100	87	100	89	100
3b	89	100	88	100	100	100
3c	44	100	88	100	100	100
3d	26	36	25	54	22	29
3e	20	38	27	39	18	19
3f	2	31	28	30	52	17
3g	15	11	12	21	5	14
3h	53	82	71	84	74	70
3i	60	96	58	73	35	48
3k	26	8	15	36	20	20
4b	16	3	9	5	3	7
5a	2	13	11	7	7	5
6a	12	4	8	8	12	0
6b	21	7	7	23	7	8
8b	46	77	56	51	77	23
8d	12	34	27	18	11	2
10a	41	91	34	54	83	51
10b	48	89	63	71	95	94
10c	70	100	73	84	83	51
10d	65	100	91	88	87	54
Triadimefon	42	66	60	79	71	47

V.i. – *Venturia inaequalis*, *R.s.* – *Rhizoctonia solani*, *F.o.* – *Fusarium oxysporum*, *F.m.* – *Fusarium moniliforme*, *B.s.* – *Bipolaris sorokiniana*, *S.s.* – *Sclerotinia sclerotiorum*.

2.3.3. QSAR modeling on the basis of biological activity profiles prediction using MNA descriptors

GUSAR allows creating QSAR models based on biological activity profiles of chemical compounds. Each chemical compound represented as a list of MNA descriptors, which are used as input parameters [14] for obtaining the prediction of biological activity profiles. PASS algorithm is used for calculation of this profile [15–17]. The results of PASS prediction are given as a list of biological activities, for which the difference between probabilities to be active (Pa) and to be inactive (Pi) was calculated. The activities from the list of predicted biological activities are randomly selected as the input independent variables for regression analysis to obtain different QSAR models. The latest version of PASS (10.1) predicts 4130 kinds of biological activity with the mean prediction accuracy about 95%. The list of predictable biological activities currently includes 501 pharmacotherapeutic effects (e.g., Antihypertensive, Hepatoprotectant, Nootropic, etc.), 3295 mechanisms of action (e.g., 5 Hydroxytryptamine antagonist, Acetylcholine M1 receptor agonist, Cyclooxygenase inhibitor, etc.), 57 adverse and toxic effects (e.g., Carcinogenic, Mutagenic, Hematotoxic, etc.), 199 metabolic terms (e.g., CYP1A inducer, CYP1A1 inhibitor, CYP3A4 substrate, etc.) 49 transporter proteins (e.g., P-glycoprotein 3 inhibitor, Nucleoside transporters inhibitors) and 29 activities related to gene expression (e.g., TH expression enhancer, TNF expression inhibitor, VEGF expression inhibitor).

2.3.4. Self-consistent regression

GUSAR uses self-consistent regression for building of (Q)SAR models. Self-consistent regression (SCR) is based on the regularized least-squares method [13,18]. Unlike the stepwise regression and other methods of combinatorial search, the initial SCR model includes all regressors. The basic result of application of SCR method is a removal of variables, which are worse for the description of an appropriate value [18]. The number of the final variables in QSAR equation selected after the self-consistent regression procedure is significantly less comparing to the number of the initial variables. However, as was shown in [13] the

Table 2
Fungicidal activity (EC_{50}) of 2-phenyl-4-hydroxy-6-nitroindoles **3a** and **3b**.

Compound	EC_{50}, μg mL^{-1}					
	V.i.	*R.s.*	*F.o.*	*F.m.*	*B.s.*	*S.s.*
3a	15.4	5.86	18.0	3.48	13.0	8.65
3b	16.9	11.2	21.5	6.84	26.6	17.2
Triadimefon	20.0	20.6	3.25	2.41	11.0	6.18

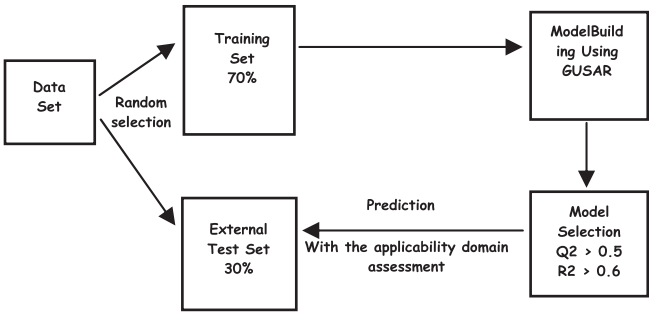


Fig. 1. QSAR modeling workflow.

final model contains a set of variables, correctly representing the existing relationship.

2.3.5. Nearest neighbor's correction

It is well known that the combining global and local models for non-congeneric sets one can improve the quality of QSAR models [19]. We used the experimental data of the nearest neighbors (NN) for the correction of prediction values obtained from the regression model. The correction value was estimated by taking an average of the 3 chemicals values in the training set that are the most similar to the chemical under prediction. The similarity of any chemical compounds' pairs is estimated as Pirson's coefficient calculated in the space of independent variables obtained after SCR. The average value of the nearest neighbors was averaged with the predicted value for the test compound calculated by the regression model.

2.3.6. Applicability domain

Three nearest neighbors from the training set are calculated for each tested chemical compound using a similarity value. Similarity of two chemical compounds is estimated as Pirson's coefficient calculated in the space of independent variables obtained after SCR. The average similarity of three nearest neighbors is used for assessment of the applicability domain (AD) of the model. If the average similarity exceeds a certain threshold then the chemical compound under prediction falls in AD of the model and vice-versa. The higher value of the threshold was selected the more similar compounds fell in AD of the model. In this study we used the threshold for AD equal to 0.7.

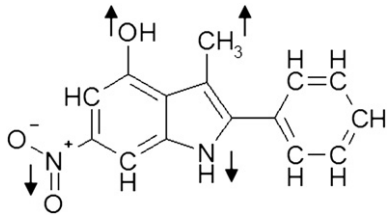


Fig. 2. Atom contribution into the antifungal activity.

2.3.7. Consensus modeling

The final predicted value is estimated by taking into account a weighted average of the predicted values from each obtained QSAR model (QSAR models provide the predictions that are within the respective applicability domains). The predicted value obtained from each developed model is weighted on similarity value calculated during the evaluation of applicability domain. General scheme of the algorithm combined the result of QSAR modeling on the basis of QNA descriptors and PASS predicted biological activity profiles, is represented in Fig. 1.

2.3.8. Interpretation of the obtained QSAR models

Simultaneously with the estimation of activity value for the entire structure, GUSAR calculates the contribution of each particular functional group into the activity. At the user's display these contributions are reflected by different colors: "green" – no significant contribution; "red" – increase in the activity; "blue" – decrease in the activity. This provides the hints to medicinal chemist concerning the further modification of the structure. If she/he wants to increase the activity, it is necessary to modify the groups reducing the activity. If she/he wants to decrease the activity (e.g., for toxicity), it is necessary to modify the groups elevating the activity. In Fig. 2 we present an example of structure, where "↑" marks the groups elevating the activity; and "↓" marks the groups reducing the activity.

2.3.9. QSAR modeling and validation of antifungal end-points

For each training set of antifungal end-point one hundred QSAR models were generated. Models that satisfied the following criteria were considered as acceptable for prediction: I) $R^2 > 0.6$, II) $Q^2 > 0.5$. Selected models were used for consensus prediction of appropriate test sets taking into account of applicability domain. Prediction results and characteristics of models are presented in the Table 3.

R^2 values for three antifungal activities exceed 0.80, for two – 0.60 and for one 0.50. For all antifungal activities average error of prediction is 27%; it means that the obtained models successfully identify active and inactive compounds in the test sets. All compounds from the test sets fall in applicability domain of models for five antifungal end-points. Only *BS* antifungal end-point was predicted with coverage 80%.

The obtained QSAR models were used for analysis of atoms' contribution of chemical compounds from the training set into the antifungal activity and for selection of fragments with significant contribution to the activity. It was found that hydroxyl and methyl groups increase the activity against all six fungi. Nitro group in the meta-position has a negative influence to antifungal activity (Fig. 2). According to the analysis it was considered to consider 2-phenylindole derivates with nitro and hydroxyl groups placed in

Table 3
QSAR modeling of antifungal activities results.

Activity name	Number of compounds training set/test set	Number of models	R^2 Training set	Q^2 Training set	R^2 Test set	Coverage, %	RMSE test
B.s.	12/5	4	0.89	0.72	0.57	80	35.74
F.m.	12/5	21	0.89	0.77	0.80	100	28.01
F.o.	12/5	3	0.85	0.68	0.66	100	17
R.s.	12/5	20	0.91	0.79	0.72	100	27.58
S.s.	12/5	11	0.89	0.79	0.81	100	37.29
V.i.	12/5	2	0.83	0.61	0.82	100	20.37

R^2 – determination coefficient.
Q^2 – determination coefficient calculated for leave-one-out cross validation procedure.
RMSE – root mean square error.

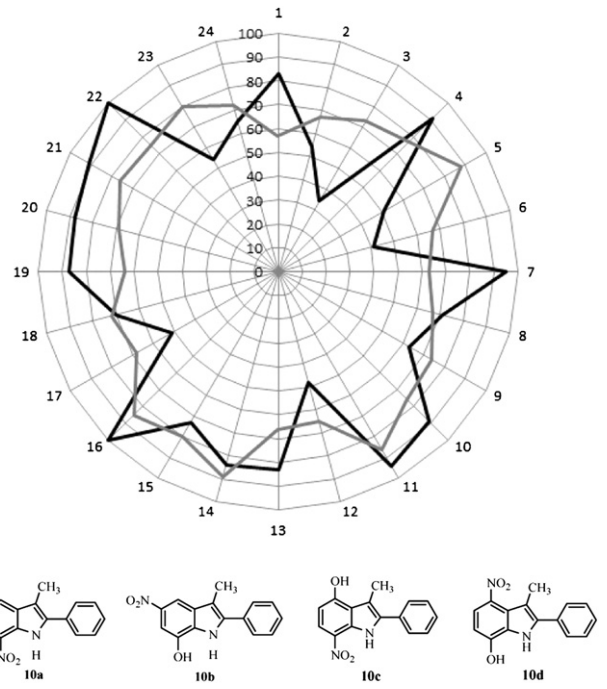


Fig. 3. Comparison of the experimental (black line) and predicted (gray line) antifungal activities for compounds **10a** (1–6), **10b** (7–12), **10c** (13–18), **10d** (19–24). 1–6, 7–12, 13–18 and 19–24 are activities against *B.s.*, *F.m.*, *F.o.*, *R.s.*, *S.s.* and *V.i.*, respectively. Average RMSE values calculated for each activity vary from 12 to 25; for each compound – from 12 to 28. All values are given in percent of inhibition at 30 μg mL^{-1} concentration of the compound.

the *ortho*- and *para*-position. Several dozen structures were designed by chemists *in silico*, and based on the GUSAR estimation four structures **10a**–**d** (Fig. 3) were selected for synthesis [20] and tested on their antifungal activity against *B.s.*, *F.m.*, *F.o.*, *R.s.*, *S.s.*, *V.i.* The observed values of antifungal activity for compounds **10a**–**d** reasonably corresponds to those calculated on the basis of QSAR models (Fig. 3). All four compounds match to the applicability domain of the obtained QSAR models.

Compounds **10c** and **10d** were found to be the most active against all six fungi. All compounds shown high inhibition activity at 30 μg mL^{-1} concentration for *R.s.* The best predicted results were obtained for compound **10c** (RMSE = 12). This compound shows the potent inhibition activity against *B.s.*, *F.m.* and *R.s.* Three antifungal activities *F.m.*, *R.s.* and *V.i.* were predicted better than *B.s.* and *S.s.* These results correspond to accuracy of test sets prediction in terms of RMSE obtained during validation of QSAR models (see Fig. 3). Thus, application of validated QSAR models allowed finding new chemical compounds with high antifungal activity.

3. Conclusions

A series of hydroxynitroindoles possessing fungicidal activity were prepared by acid-catalyzed cyclization of ketoximes **2** and **7**. Among them, indoles **3a**–**c** and **3h**,**i** have the highest fungi toxicity and surpass the commercial fungicide (triadimefon) with respect to all phytopathogens – at concentration 30 μg mL^{-1} they substantially inhibit the mycelium growth in all fungi. 4-hydroxyl groups play an important pharmacophoric role for fungi toxic 2-aryl-6-nitroindoles **3**. Based on the QSAR estimates, from several dozen designed structures we selected and synthesized four chemical compounds. Two compounds **10c** and **10d** appeared to be the most active against all six fungi in comparison with triadimefon.

4. Experiment

4.1. General remarks

All reagents and solvents were used without further purification or drying. All reagents were purchased from Acros Organics. The ^{1}H NMR spectra were recorded by Bruker AM-300. The chemical shifts were given relative to Me_4Si in DMSO-d_6, δ, ppm, J, Hz. Melting points of the synthesized compounds were measured on a Boetius hot stage according to Koffler (heating rate 4 °C min^{-1}).

4.2. General procedure for the synthesis of O-(3,5-dinitrophenyl) ketoximes *1*

Trinitrobenzene (TNB), 0.1 mol (21.3 g), is added to a mixture of 0.1 mol of acetophenoneoxime substituted in an appropriate manner[1] and 0.1 mol (13.8 g) of K_2CO_3 in 1-methyl-2-pyrrolidone (120 mL). The reaction mixture is heated to 50 °C and stirred at this temperature until the TNB full conversion (3–8 h). The reaction mass is poured into 600 mL of water. The precipitate is filtered off, water-washed and dried. The residue is recrystallized from EtOH.

Reaction time, yields, melting points and ^{1}H NMR spectra of the synthesized compounds:

4.2.1. 1-(2,4-Dichlorophenyl)ethanone O-(3,5-dinitrophenyl)oxime (*1d*)

4 h, yield 84%, m.p. = 170–171 °C.

^{1}H NMR: δ 7.58–7.70 (m, 2H), 7.82 (d, 1H, J = 1.8 Hz), 8.42 (d, 2H, J = 1.9 Hz), 8.55 (t, 1H, J = 2.0 Hz). Anal. Found %: C, 45.12; H, 2.11; N, 11.70. Calcd. for $C_{14}H_9Cl_2N_3O_5$ %: C, 45.43; H, 2.45; N, 11.35.

4.2.2. 1-(4-Hydroxyphenyl)ethanone O-(3,5-dinitrophenyl)oxime (*1e*)

6 h, yield 49%,m.p. = 179–180 °C.

^{1}H NMR: δ 6.90 (d, 2H, J = 8.7 Hz), 7.73 (d, 2H, J = 8.7 Hz), 8.43 (d, 2H, J = 1.9 Hz), 8.50 (t, 1H, J = 2.0 Hz), 10.03 (s, 1H). Anal. Found %: C, 53.26; H, 3.76; N, 13.09. Calcd. for $C_{14}H_{11}N_3O_6$ %: C, 53.00; H, 3.49; N, 13.24.

4.2.3. 1-(4-Fluorophenyl)-4-(1H-1,2,4-triazol-1-yl)butan-1-one O-(3,5-dinitrophenyl)oxime (*1f*)

5 h, yield 58%, m.p. = 152–154 °C.

^{1}H NMR: δ 2.09–2.14 (m, 2H), 2.98–3.04 (m, 2H), 4.29–4.34 (m, 2H), 7.34–7.40 (m, 2H); 7.86–7.91(m, 2H), 7.98 (s, 1H), 8.40–8.41 (m, 2H), 8.52–8.53 (m, 2H). Anal. Found %: C, 52.32; H, 3.38; N, 20.63. Calcd. for $C_{18}H_{15}FN_6O_5$ %: C, 52.18; H, 3.65; N, 20.28.

4.2.4. 1-(4-Bromophenyl)ethanone O-(3,5-dinitrophenyl)oxime (*1g*)

3 h, yield 95%,m.p. = 175–176° C.

^{1}H NMR: δ 7.74 (d, 2H, J = 8.5 Hz), 7.83 (d, 2H, J = 8.6 Hz), 8.47 (d, 2H, J = 2.1 Hz), 8.54 (t, 1H, J = 2.0 Hz). Anal. Found %: C, 44.57; H, 2.31; N, 10.78. Calcd. for $C_{14}H_{10}BrN_3O_5$ %: C, 44.23; H, 2.65; N, 11.05.

4.2.5. 1-[4-(Trifluoromethyl)phenyl]ethanone O-(3,5-dinitrophenyl) oxime (*1h*)

4 h, yield 48%, m.p. = 149–151 °C.

^{1}H NMR: δ 2.50 (s, 3H), 7.89 (d, 2H, J = 8.3 Hz), 8.07 (d, 2H, J = 8.2 Hz), 8.47(d, 2H, J = 1.9 Hz), 8.52 (t, 1H, J = 2.0 Hz). Anal. Found %: C, 48.63; H, 2.51; F, 15.18; N, 11.42. Calcd. for $C_{15}H_{10}F_3N_3O_5$ %: C, 48.79; H, 2.73; F, 15.44; N, 11.38.

[1] For compound **1f**, corresponding 4-azobutyrophenone was prepared by the known procedure [21].

*4.2.6. 1-(4-Fluorophenyl)ethanone O-(3,5-dinitrophenyl)oxime (**1i**)*

4 h, yield 76%, m.p. = 163–164 °C.

^{1}H NMR: δ 2.50 (s, 3H), 7.33–7.40 (m, 2H), 7.91–7.96 (m, 2H), 8.45 (d, 2H, *J* = 2.0 Hz), 8.52 (t, 1H, *J* = 2.0 Hz). Anal. Found %: C, 52.43; H, 3.31; N, 13.29. Calcd. for $C_{14}H_{10}FN_3O_5$ %: C, 52.67; H, 3.16; N, 13.16.

*4.2.7. 1-(4-Methoxyphenyl)ethanone O-(3,5-dinitrophenyl)oxime (**1j**)*

8 h, Yield 71%, m.p. = 179–180 °C.

^{1}H NMR: δ 3.83 (s, 3H), 7.06 (d, 2H, *J* = 8.8 Hz), 7.82 (d, 2H, *J* = 8.7 Hz), 8.42 (d, 2H *J* = 2.0 Hz), 8.49 (t, 1H, *J* = 2.0 Hz). Anal. Found %: C, 54.06; H, 4.29; N, 12.53. Calcd. for $C_{15}H_{13}N_3O_6$ %: C, 54.38; H, 3.96; N, 12.68.

*4.3. General procedure for the synthesis of O-(3-amino-5-nitrophenyl)-ketoximes (**2**)*

Hydrazine hydrate 10 mL (0.2 mol) was added to a mixture of an appropriate *O*-(3,5-dinitrophenyl)ketoxime **1** (0.1 mol), $FeCl_3 \cdot 6H_2O$ (0.13 g, 0.5 mmol), and activated carbon (6 g) in methanol (700 mL). The reaction mixture was refluxed until the starting dinitro compound was completely consumed (monitoring by TLC with $CHCl_3$ as an eluent) and filtered hot. The carbon was washed with hot methanol (2 × 50 mL), the filtrate was cooled to 4 °C, and the precipitate that formed was filtered off.

Yields, melting points and ^{1}H NMR spectra of the synthesized compounds:

*4.3.1. 1-(2,4-Dichlorophenyl)ethanone O-(3-amino-5-nitrophenyl) oxime (**2d**)*

Yield 65%, m.p. = 151–152 °C.

^{1}H NMR: δ 2.40 (s, 3H), 5.95 (s, 2H), 6.83 (t, 1H, *J* = 2.0), 7.10–7.12 (m, 2H,), 7.58–7.59 (m, 2H), 7.80 (d, 1H, *J* = 1.8 Hz). Anal. Found %: C, 49.19; H, 3.69; N, 12.09. Calcd. for $C_{14}H_{11}C_{l2}N_3O_3$ %: C, 49.43; H, 3.26; N, 12.35.

*4.3.2. 1-(4-Hydroxyphenyl)ethanone O-(3-amino-5-nitrophenyl) oxime (**2e**)*

Yield 51%, m.p. = 159–162 °C.

^{1}H NMR: δ 2.39 (s, 3H), 5.91 (s, 2H), 6.85 (t, 1H, *J* = 1.9 Hz), 6.88 (d, 2H, *J* = 8.7 Hz), 7.10 (t, 1H, *J* = 2.0 Hz), 7.14 (t, 1H, *J* = 2.0 Hz), 7.67 (d, 2H, *J* = 8.6 Hz), 9.91 (s, 1H). Anal. Found %: C, 58.17; H, 4.79; N, 14.55. Calcd. for $C_{14}H_{13}N_3O_4$ %: C, 58.53; H, 4.56; N, 14.63.

*4.3.3. 1-(4-Fluorophenyl)-4-(1H-1,2,4-triazol-1-yl)butan-1-one O-(3-amino-5-nitrophenyl)oxime (**2f**)*

Yield 38%, m.p. = 97–99 °C.

^{1}H NMR: δ 2.03–2.08 (m, 2H), 2.90(m, 2H), 4.29 (m, 2H), 5.98 (s, 2H), 6.85(t, 1H, *J* = 1.9 Hz), 7.10–7.11 (m, 2H), 7.34 (m, 2H), 7.80–7.85 (m, 2H), 8.0 (s, 1H), 8.52 (s, 1H). Anal. Found %: C, 56.39; H, 4.24; N, 21.63. Calcd. for $C_{18}H_{17}FN_6O_3$ %: C, 56.25; H, 4.46; N, 21.86.

*4.3.4. 1-(4-Bromophenyl)ethanone O-(3-amino-5-nitrophenyl) oxime (**2g**)*

Yield 59%, m.p. = 156–158 °C.

^{1}H NMR: δ 2.44 (s, 3H), 5.94 (s, 2H), 6.90 (t, 1H, *J* = 1.9 Hz), 7.12–7.15 (m, 2H), 7.68–7.79 (m, 4H). Anal. Found %: C, 48.36; H, 3.60; N, 12.33. Calcd. for $C_{14}H_{12}BrN_3O_3$ %: C, 48.02; H, 3.45; N, 12.00.

*4.3.5. 1-[4-(Trifluoromethyl)phenyl]ethanone O-(3-amino-5-nitrophenyl)oxime (**2h**)*

Yield 59%, m.p. = 151–154 °C.

^{1}H NMR: δ 5.98 (s, 2H), 6.89 (t, 1H, *J* = 2.0 Hz), 7.13 (t, 1H, *J* = 2.1 Hz), 7.16 (t, 1H, *J* = 2.0 Hz), 7.86 (d, 2H, *J* = 8.2 Hz), 8.02 (d, 2H, *J* = 8.1 Hz). Anal. Found %: C, 53.46; H, 3.32; N, 12.54. Calcd. for $C_{15}H_{12}F_3N_3O_3$ %: C, 53.10; H, 3.57; N, 12.39.

*4.3.6. 1-(4-Fluorophenyl)ethanone O-(3-amino-5-nitrophenyl) oxime (**2i**)*

Yield 87%, m.p. = 136–137 °C.

^{1}H NMR: δ 2.44 (s, 3H), 5.95 (s, 2H), 6.90 (t, 1H, *J* = 1.9 Hz), 7.12(t, 1H, *J* = 1.9 Hz), 7.15 (t, 1H, *J* = 1.9 Hz), 7.30–7.38 (m, 2H), 7.85–7.90 (m, 2H). Anal. Found %: C, 58.38; H, 4.52; N, 14.80. Calcd. for $C_{14}H_{12}FN_3O_3$ %: C, 58.13; H, 4.18; N, 14.53.

*4.3.7. 1-(4-Methoxyphenyl)ethanone O-(3-amino-5-nitrophenyl) oxime (**2j**)*

Yield 70%, m.p. = 122–123 °C.

^{1}H NMR: δ 2.40 (s, 3H), 3.81 (s, 3H), 5.93 (s, 2H), 6.88 (t, 1H, *J* = 2.0 Hz), 7.03 (d, 2H, *J* = 8.8 Hz), 7.10 (t, 1H, *J* = 1.9 Hz), 7.13 (t, 1H, *J* = 1.9 Hz), 7.76 (d, 2H, *J* = 8.8 Hz). Anal. Found %: C, 59.36; H, 4.78; N, 13.81. Calcd. for $C_{15}H_{15}N_3O_4$ %: C, 59.79; H, 5.02; N, 13.95.

*4.4. General procedure for the synthesis of 4-hydroxy-6-nitroindoles (**3**) and 4-amino-6-nitrobenzofurans (**4**)*

An appropriate *O*-(3-amino-5-nitrophenyl)oxime **2**(0.01 mol) was added to a mixture of ethanol (10 mL) and 36% HCl (10 mL). The reaction mixture was refluxed 2 h. On cooling to ~20 °C, the precipitate was filtered off and neutralized in water (50 mL) with aqueous ammonia to weakly basic reaction. The precipitate of 6-amino-4-nitrobenzofuran **4** was filtered off and dried in vacuo. The filtrate was evaporated to dryness and the residue was neutralized in water (50 mL) with aqueous ammonia to weakly basic reaction. The precipitate of 4-hydroxy-6-nitroindole **3** was filtered off, recrystallized from a minimum amount of ethanol, and dried in vacuo.

Yields, melting points and ^{1}H NMR spectra of the synthesized compounds:

*4.4.1. 2-(2,4-Dichlorophenyl)-6-nitro-1H-indol-4-ol (**3d**)*

Yield 28%, m.p. = 279–281 °C.

^{1}H NMR: δ 7.10 (d, 1H, *J* = 1.5 Hz), 7.27 (d, 1H, *J* = 1.5 Hz), 7.58–7.64 (m, 1H), 7.76–7.82 (m, 2H), 7.87 (s, 1H), 10.55 (s, 1H), 12.16 (s, 1H). Anal. Found %: C, 51.78; H, 2.27; Cl, 22.83; N, 8.32. Calcd. for $C_{14}H_8C_{l2}N_2O_3$ %: C, 52.04; H, 2.50; Cl, 21.94; N, 8.67.

*4.4.2. 2-(2,4-Dichlorophenyl)-4-nitro-1-benzofuran-6-amine (**4d**)*

Yield 30%, m.p. = 252–253 °C.

^{1}H NMR: δ 6.04 (s, 2H), 7.16 (d,1H, *J* = 1.4 Hz), 7.55 (d, 1H, *J* = 1.5 Hz), 7.78–7.83 (m, 3H), 7.97–8.00 (m, 1H). Anal. Found %: C, 52.39; H, 2.13; N, 8.49. Calcd. for $C_{14}H_8C_{l2}N_2O_3$ %: C, 52.04; H, 2.50; N, 8.67.

*4.4.3. 2-(4-Hydroxyphenyl)-6-nitro-1H-indol-4-ol (**3e**)*

Yield 21%, m.p. = 262–263 °C.

^{1}H NMR: δ 6.92 (d, 2H, *J* = 8.6 Hz), 7.69 (s, 1H), 7.91 (d, 2H, *J* = 8.6 Hz), 8.37 (d, 1H, *J* = 1.5 Hz), 8.54 (d, 1H, *J* = 1.6 Hz), 10.16 (s, 1H), 11.76 (s, 1H). Anal. Found %: C, 62.48; H, 3.36; N, 10.21. Calcd. for $C_{14}H_{10}N_2O_4$ %: C, 62.22; H, 3.73; N, 10.37.

*4.4.4. 4-(6-Amino-4-nitro-1-benzofuran-2-yl)phenol (**4e**)*

Yield 26%, m.p. = 231–233 °C.

^{1}H NMR: δ 6.00 (s, 2H), 6.90 (d, 2H, *J* = 8.3 Hz), 7.32 (d, 1H, *J* = 1.4 Hz), 7.52 (d, 1H, *J* = 1.6 Hz), 7.60(s, 1H), 7.80 (d, 2H, *J* = 8.4 Hz). Anal. Found %: C, 62.03; H, 3.56; N, 10.48. Calcd. for $C_{14}H_{10}N_2O_4$ %: C, 62.22; H, 3.73; N, 10.37.

*4.4.5. 2-(4-Fluorophenyl)-6-nitro-3-[2-(1H-1,2,4-triazol-1-yl) ethyl]-1H-indol-4-ol (**3f**)*

Yield 23%, m.p. = 145–147 °C.

^{1}H NMR: δ 4.52–4.53 (m, 2H), 7.31–7.44 (m, 5H), 7.78–7.85 (m, 2H), 8.23 (s, 1H), 10.63 (s, 1H), 11.89 (s, 1H).Anal. Found %: C, 58.36; H, 3.56; F, 5.39; N, 19.23. Calcd. for $C_{18}H_{14}FN_5O_3$ %: C, 58.85; H, 3.84; F, 5.17; N, 19.07.

*4.4.6. 2-(4-Fluorophenyl)-4-nitro-3-[2-(1H-1,2,4-triazol-1-yl) ethyl]-1-benzofuran-6-amine (**4f**)*

Yield 30%, m.p. = 220–222 °C.

^{1}H NMR: δ 3.37–3.40 (m, 2H), 4.29–4.36 (m, 2H), 5.90 (s, 2H), 7.10 (d, 1H, *J* = 1.5 Hz), 7.28–7.36 (m, 2H), 7.44 (d, 1H, *J* = 1.6 Hz), 7.53–7.55 (m, 2H), 7.77 (s, 1H), 8.19 (s, 1H). Anal. Found %: C, 58.32; H, 3.69; N, 19.11. Calcd. for $C_{18}H_{14}FN_5O_3$ %: C, 58.85; H, 3.84; N, 19.07.

*4.4.7. 2-(4-Bromophenyl)-6-nitro-1H-indol-4-ol (**3g**)*

Yield 21%, m.p. = 298–300 °C.

^{1}H NMR: δ 7.72 (d, 2H, *J* = 8.3 Hz), 7.97(d, 2H, *J* = 8.2 Hz), 8.01 (d, 1H, *J* = 1.5 Hz), 8.41 (d, 1H, *J* = 1.4 Hz), 8.56 (s, 1H), 10.52 (s, 1H), 11.79 (s, 1H). Anal. Found %: C, 50.61; H, 2.78; N, 8.39. Calcd. for $C_{14}H_9BrN_2O_3$ %: C, 50.47; H, 2.72; N, 8.41.

*4.4.8. 2-(4-Bromophenyl)-4-nitro-1-benzofuran-6-amine (**4g**)*

Yield 27%, m.p. = 276–277 °C.

^{1}H NMR: δ 5.94 (s, 2H), 7.17 (d, 1H, *J* = 1.3 Hz), 7.52 (d, 1H, *J* = 1.3 Hz), 7.68 (d, 2H, *J* = 8.4 Hz), 7.74 (s, 1H), 7.89 (d, 2H, *J* = 8.3 Hz). Anal. Found %: C, 50.62; H, 2.93; N, 8.69. Calcd. for $C_{14}H_9BrN_2O_3$ %: C, 50.47; H, 2.72; N, 8.41.

*4.4.9. 6-Nitro-2-[4-(trifluoromethyl)phenyl]-1H-indol-4-ol (**3h**)*

Yield 16%, m.p. = 224–226 °C.

^{1}H NMR: δ 7.26–7.27 (m, 2H), 7.85–7.88 (m, 3H); 8.10–8.13 (m, 2H), 12.36 (s, 1H). Anal. Found %: C, 55.59; H, 2.46; N, 8.81. Calcd. for $C_{15}H_9F_3N_2O_3$ %: C, 55.91; H, 2.82; N, 8.69.

*4.4.10. 4-Nitro-2-[4-(trifluoromethyl)phenyl]-1-benzofuran-6-amine (**4h**)*

Yield 37%, m.p. = 218–221 °C.

^{1}H NMR: δ 6.06 (s, 2H), 7.19(d, 1H, *J* = 1.4 Hz), 7.54 (d, 1H, *J* = 1.3 Hz) 7.66 (s, 1H), 7.82 (d, 2H, *J* = 8.3 Hz), 7.90 (s, 1H), 8.12(d, 2H, *J* = 8.2 Hz). Anal. Found %: C, 55.66; H, 2.68; N, 8.86. Calcd. for $C_{15}H_9F_3N_2O_3$ %: C, 55.91; H, 2.82; N, 8.69.

*4.4.11. 2-(4-Fluorophenyl)-6-nitro-1H-indol-4-ol (**3i**)*

Yield 21%, m.p. = 283–284 °C.

^{1}H NMR: δ 7.07 (d, 1H, *J* = 1.5 Hz); 7.26 (d, 1H, *J* = 1.4 Hz), 7.33–7.40 (m, 2H), 7.83 (s, 1H), 7.94–7.96 (m, 2H), 10.40 (s, 1H), 12.15 (s, 1H). Anal. Found %: C, 61.62; H, 3.59; N, 10.52. Calcd. for $C_{14}H_9FN_2O_3$ %: C, 61.77; H, 3.33; N, 10.29.

*4.4.12. 2-(4-Fluorophenyl)-4-nitro-1-benzofuran-6-amine (**4i**)*

Yield 30%, m.p. = 203–204 °C.

^{1}H NMR: δ 5.92 (s, 2H), 7.18 (d, 1H, *J* = 1.7 Hz), 7.30–7.37 (m, 2H), 7.52 (d, 1H, *J* = 1.8 Hz), 7.68 (s, 1H), 7.96–8.04 (m, 2H). Anal. Found %: C, 61.42; H, 3.17; N, 10.27. Calcd. for $C_{14}H_9FN_2O_3$ %: C, 61.77; H, 3.33; N, 10.29.

*4.4.13. 2-(4-Methoxyphenyl)-6-nitro-1H-indol-4-ol (**3j**)*

Yield 30%, m.p. = 256–257°C.

^{1}H NMR: δ 3.82 (s, 3H), 6.97 (d, 1H, *J* = 1.5 Hz), 7.08(d, 1H, *J* = 8.7 Hz), 7.24 (d, 1H, *J* = 1.7 Hz), 7.81–7.85 (m, 3H), 10.36 (s, 1H), 12.06 (s, 1H). Anal. Found %: C, 63.62; H, 4.02; N, 9.31. Calcd. for $C_{15}H_{12}N_2O_4$ %: C, 63.38; H, 4.25; N, 9.85.

*4.4.14. 2-(4-Methoxyphenyl)-4-nitro-1-benzofuran-6-amine (**4j**)*

Yield 43%, m.p. = 209–210 °C.

^{1}H NMR: δ 3.83 (s, 3H), 5.86 (s, 2H), 7.06 (d, 2H, *J* = 8.7 Hz), 7.17 (d, 1H, *J* = 1.3 Hz), 7.49 (d, 1H, *J* = 1.3 Hz), 7.55 (s, 1H), 7.88 (d, 2H, *J* = 8.7 Hz). Anal. Found %: C, 63.02; H, 4.48; N, 9.69. Calcd. for $C_{15}H_{12}N_2O_4$ %: C, 63.38; H, 4.25; N, 9.85.

*4.5. Procedure for the synthesis of (**5a**), (**6a**,**b**)*

Dimethylsulfate (0.01 mol or 0.03 mol for the synthesis of **6**) was added to a mixture of an appropriate indole **3** (0.01 mol) and potassium carbonate (0.03 mol) in dry DMF (10 mL). The mixture was stirred for 2 h at ambient temperature and next, poured in water. The precipitate was collected, washed with water, and dried in vacuo.

Yields, melting points and ^{1}H NMR spectra of the synthesized compounds:

*4.5.1. 4-Methoxy-3-methyl-6-nitro-2-phenyl-1H-indole (**5a**)*

Yield 78%, m.p. = 234–235 °C.

^{1}H NMR: δ 2.57 (s, 3H), 3.99 (s, 3H), 7.19–7.25(m, 3H), 7.29 (d, 1H, *J* = 1.7 Hz), 7.56–7.69 (m, 2H), 7.95(d, 1H, *J* = 1.9 Hz). Anal. Found %: C, 68.43; H, 5.33; N, 9.87. Calcd. for $C_{16}H_{14}N_2O_3$ %: C, 68.07; H, 5.00; N, 9.92.

*4.5.2. 4-Methoxy-1,3-dimethyl-6-nitro-2-phenyl-1H-indole (**6a**)*

Yield 86%, m.p. = 132–133 °C.

^{1}H NMR: δ 2.34(s, 3H), 3.66(s, 3H), 3.98(s, 3H), 7.16–7.27 (m, 3H), 7.34 (d, 1H, *J* = 1.3 Hz), 7.46–7.58 (m, 2H), 8.13 (d,1H, *J* = 1.6 Hz). Anal. Found %: C, 68.46; H, 5.27; N, 9.79. Calcd. for $C_{17}H_{16}N_2O_3$ %: C, 68.91; H, 5.44; N, 9.45.

*4.5.3. 4-Methoxy-1-methyl-6-nitro-2-phenyl-1H-indole (**6b**)*

Yield 83%, m.p. = 106–108 °C.

^{1}H NMR: δ 3.86 (s, 3H), 4.01 (s, 3H), 6.74 (s, 1H), 7.41(d, 1H, *J* = 1.5 Hz), 7.48–7.59 (m, 3H), 7.64–7.66 (m, 2H), 8.22(d,1H, *J* = 1.4 Hz). Anal. Found %: C, 68.31; H, 4.73; N, 9.46. Calcd. for $C_{16}H_{14}N_2O_3$ %: C, 68.07; H, 5.00; N, 9.92.

*4.6. Synthesis of 1-phenylethanone O-[3-(methylamino)-5-nitrophenyl]oxime (**7b**)*

O-(3-Amino-5-nitrophenyl)methylphenylketoxime (**2b**) (0.013 mol) was added to a freshly prepared solution of sodium methylate (0.064 mol) in methanol (30 mL) containing para form (0.018 mol). The mixture was stirred for 5 h at ambient temperature. Next, sodium borohydride (0.013 mmol) was added at intensive stirring and the mixture was refluxed until gas evolving is over. The reaction was cooled to 20 °C, then 1 M NaOH was added until pH = 9–10. The precipitate was collected, washed with water, and dried, and recrystallized from methanol.

Yield 91%, m.p. = 142–144 °C.

^{1}H NMR: δ 2.45 (s, 3H); 2.75(d, 3H, *J* = 4.9 Hz), 6.50–6.55 (m, 1H), 6.81 (t, 1H, *J* = 1.9 Hz), 7.05 (t, 1H, *J* = 1.9 Hz), 7.21 (t, 1H, *J* = 2.0 Hz), 7.49–7.50 (m, 3H), 7.79–7.82 (m, 2H). Anal. Found %: C, 63.41; H, 5.63; N, 14.69. Calcd. for $C_{15}H_{15}N_3O_3$ %: C, 63.15; H, 5.30; N, 14.73.

*4.7. General procedure for the synthesis of (**7c**,**d**)*

A mixture of O-(3-amino-5-nitrophenyl)methylphenylketoxime (0.013 mol) and an appropriate benzaldehyde (0.018 mol) in acetic acid (11 mL) was stirred at ambient temperature for 30 min. To this sodium boronhydride (0.013 mol) was added slowly. The mixture was stirred at ambient temperate for 2 h. Next, 1 M NaOH was added

until pH = 9–10. The precipitate was collected, washed with water, and dried on the filter, and recrystallized from methanol.

Yields, melting points and ^{1}H NMR spectra of the synthesized compounds:

*4.7.1. 1-Phenylethanone O-[3-(benzylamino)-5-nitrophenyl]oxime (**7c**)*

Yield 69%, m.p. = 150–151 °C.

^{1}H NMR: δ 2.42 (s, 3H), 4.37 (d, 2H, *J* = 5.8 Hz), 6.88 (t, 1H, *J* = 2.0 Hz), 7.12–7.14 (m, 2H), 7.18(t, 1H, *J* = 2.0 Hz), 7.23–7.28 (m, 1H), 7.35 (t, 1H, *J* = 1.9 Hz), 7.37–7.40 (m, 2H), 7.48–7.50 (m, 3H), 7.75–7.78 (m, 2H). Anal. Found %: C, 69.35; H, 5.11; N, 11.19. Calcd. for $C_{21}H_{19}N_3O_3$ %: C, 69.79; H, 5.30; N, 11.63.

*4.7.2. 1-Phenylethanone O-{3-[(4-chlorobenzyl)amino]-5-nitrophenyl}oxime (**7d**)*

Yield 74%, m.p. = 132–134 °C.

^{1}H NMR: δ 2.42 (s, 3H), 4.38 (d, 2H, *J* = 5.8 Hz), 6.86 (t, 1H, *J* = 1.9 Hz), 7.12 (t, 1H, *J* = 1.9 Hz), 7.17–7.20 (m, 2H), 7.38–7.43(m, 4H), 7.47–7.51(m, 3H), 7.75–7.77(m, 2H). Anal. Found %: C, 63.46; H, 4.14; Cl, 9.03; N, 10.38. Calcd. for $C_{21}H_{18}ClN_3O_3$ %: C, 63.72; H, 4.58; Cl, 8.96; N, 10.62.

Compounds **8b**–**d**, **9b**–**d** were prepared by the same procedure as for **3**, **4**.

Yields, melting points and ^{1}H NMR spectra of the synthesized compounds:

*4.7.3. 1-Methyl-6-nitro-2-phenyl-1H-indol-4-ol (**8b**)*

Yield 9%, m.p. = 188–190 °C.

^{1}H NMR: δ 3.82 (s, 3H), 6.75 (s, 1H), 7.31 (d,1H, *J* = 1.6 Hz), 7.49–7.58 (m,3H), 7.62–7.65 (m, 2H), 8.04 (d, 1H, *J* = 1.5 Hz), 10.47 (s,1H).Anal. Found %: C, 67.32; H, 4.58; N, 10.12. Calcd. for $C_{15}H_{12}N_2O_3$ %: C, 67.16; H, 4.51; N, 10.44.

*4.7.4. N-Methyl-4-nitro-2-phenyl-1-benzofuran-6-amine (**9b**)*

Yield 77%, m.p. = 97–99 °C.

^{1}H NMR: δ 2.81 (s, 3H), 5.54 (s, 1H), 7.22 (d, 1H, *J* = 1.6 Hz), 7.41–7.43 (m,1H), 7.47–7.51 (m,3H), 7.70 (s,1H), 7.92–7.95 (m,2H). Anal. Found %: C, 67.48; H, 4.93; N, 10.21. Calcd. for $C_{15}H_{12}N_2O_3$ %: C, 67.16; H, 4.51; N, 10.44.

*4.7.5. 1-Benzyl-6-nitro-2-phenyl-1H-indol-4-ol (**8c**)*

Yield 0.5%, m.p. = 161–163 °C.

^{1}H NMR: δ 5.58 (s, 2H), 6.84 (s, 1H), 6.88–6.90 (m, 2H), 7.19–7.27 (m, 3H), 7.32 (d, 1H, *J* = 1.6 Hz), 7.45–7.55 (m,5H), 7.90 (d, 1H, *J* = 1.5 Hz), 10.58 (s,1H).Anal. Found %: C, 73.61; H, 4.36; N, 8.29. Calcd. for $C_{21}H_{16}N_2O_3$ %: C, 73.24; H, 4.68; N, 8.13.

*4.7.6. 2-N-Benzyl-4-nitro-2-phenyl-1-benzofuran-6-amine (**9c**)*

Yield 79%, m.p. = 183–185 °C.

^{1}H NMR: δ 4.42 (d, 2H, *J* = 5.8 Hz), 7.13–7.18(m, 2H), 7.23–7.51 (m, 8H), 7.59 (t, 1H, *J* = 1.5 Hz), 7.69 (s,1H), 7.90–7.92 (m,2H).Anal. Found %: C, 73.70; H, 4.77; N, 8.32. Calcd. for $C_{21}H_{16}N_2O_3$%: C, 73.24; H, 4.68; N, 8.13.

*4.7.7. 1-(4-Chlorobenzyl)-6-nitro-2-phenyl-1H-indol-4-ol (**8d**)*

Yield 6%, m.p. = 173–175 °C.

^{1}H NMR: δ 5.59 (s, 2H), 6.85–6.90 (m, 3H), 7.30–7.33(m, 3H), 7.47–7.51(m, 5H), 7.93(d, 1H, *J* = 1.6 Hz), 10.61(s, 1H). Anal. Found %: C, 66.19; H, 3.67; N, 7.21. Calcd. for $C_{21}H_{15}ClN_2O_3$ %: C, 66.58; H, 3.99; Cl, 9.36; N, 7.40.

*4.7.8. N-(4-Chlorobenzyl)-4-nitro-2-phenyl-1-benzofuran-6-amine (**9d**)*

Yield 70%, m.p. = 190–192 °C.

^{1}H NMR: δ 4.43 (d, 2H, *J* = 5.8 Hz), 7.13–7.18 (m, 2H), 7.23–7.28 (m, 1H), 7.33–7.51 (m, 6H), 7.59 (d, 1H, *J* = 1.5 Hz), 7.69 (s, 1H), 7.90–7.93 (m, 2H). Anal. Found %: C, 66.39; H, 3.53; Cl, 9.23; N, 7.52. Calcd. for $C_{21}H_{15}ClN_2O_3$ %: C, 66.58; H, 3.99; Cl, 9.36; N, 7.40.

4.8. Bioassays of fungicidal activites

The antifungal activities were tested according to the conventional procedure [9–11] with six phytopathogenic fungi from different taxonomic classes: *S. sclerotiorum* (*S.s.*), *F. oxysporum* (*F.o.*), *F. moniliforme* (*F.m.*), *B. sorokiniana* (*B.s.*), *R. solani* (*R.s.*), and *V. inaequalis* (*V.i.*). The effect of the chemicals on mycelial radial growth was determined by dissolving them at various concentration in acetone and suspending aliquots in potato-saccharose agar at 50 °C to give the required series of concentration (1–100 μg mL^{-1}). The final acetone concentration of both fungicide-containing and control samples was 10 mL L^{-1}. Petri dishes containing 15 mL of the agar medium were inoculated by placing 3-mm fungus-coated discs upside down on the agar surface. Plates were incubated at 25 °C and radial growth was measured after 72 h. The mixed medium without sample was used as the blank control. Three replicates of each test were carried out. The mycelium elongation diameter (mm) of fungi settlements was measured after 72 h of culture. The growth inhibition rates were calculated with the following equation: $I = [(D_C - D_T)/D_C]x100\%$. Here *I* is the growth inhibition rates (%), D_C is the control settlement diameter (mm), and D_T is the treatment group fungi settlement diameter (mm). The results are summarized in Tables 1 and 2.

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