SYNTHESIS AND ANTIFUNGAL ACTIVITY OF BENZOXAZOLE DERIVATIVES WITH THEIR SAR ANALYSIS BY SAS-MAP

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Abstract

A simple and efficient method has been developed for the synthesis of benzoxazole derivatives. In the first step, 2-aminophenols reacted with various aldehydes in the presence of titanium supported nano-silica to produce an imine intermediate. Then the imine was oxidized to get the final azole compounds. Eleven derivatives were synthesized (c)-(m) via this simple and environmentally friendly procedure with high yields. The simple methodology (only 2 steps) with high yields for the reactions and easy procedure are the advantages of the newly developed method. The identification and characterization of all the synthesized compounds were confirmed by melting point, thin layer chromatography, FT-IR, 1H NMR and 13C NMR spectral data. Also elemental analysis was applied for five compounds. All the compounds were screened for antimicrobial activity by broth microdilution methods as recommended by CLSI. Of the tested compounds 2-(2,4-dichlorophenyl)-1,3-benzoxazole (g), and 2-(4-chlorophenyl)-1,3-benzoxazole (f) inhibited the growth of all examined fungi, while 2-(4-nitrophenyl)-1,3-benzoxazole (e) exhibited inhibitory activities only against the tested yeasts.

Rezumat

A fost dezvoltată o metodă simplă și eficientă pentru sinteza derivaților de benzoxazol. În prima etapă, 2-aminofenolii au reacționat cu diferite aldehide, în prezența nano-silicii cu titan pentru a produce un intermediar iminic. Ulterior imina a fost oxidată pentru a obține azoli finali. Au fost sintetizați cu randamente ridicate, prin această procedură simplă și ecologică, unsprezece compuși. Identificarea și caracterizarea tuturor compușilor sintetizați au fost confirmate prin: punctul de topire, cromatografie în strat subțire, FT-IR, 1H RMN și 13C RMN. De asemenea, analiza elementară a fost aplicată pentru cinci compuși. Toți compușii au fost analizați din punct de vedere microbiologic prin metode microdiluțiilor. Dintre compușii testați, 2-(2,4-dichlorofenil)-1,3-benzoxazol (g) și 2-(4-clorofenil)-1,3-benzoxazol (f) au inhibat creșterea tuturor ciupercilor examinate, în timp ce 2-(4-nitrofenil)-1,3-benzoxazol (e) a prezentat activități inhibitoare numai împotriva drojdiilor testate.

Keywords: benzoxazole, synthesis, antifungal, SAR analysis, nano-TiCl3SiO2

Introduction

Systemic fungal infections increased dramatically in the past few decades, especially in immune-compromised individuals suffering from tuberculosis, cancer, AIDS, and in organ transplant recipients [1]. The widespread use of antifungal drugs and their resistance against fungal infections have led to serious health concerns. Although different drugs such as novel imidazoles, benzimidazoles and benzotriazoles have been developed including copper-catalysed cyclizations of o-halobenzenilides or cross-coupling of primary amines [13, 14] and direct condensation of o-aminophenol with carboxylic acid or aldehyde [15]. In our previous reports, we described the preparation procedure for a number of imidazole, benzimidazole and benzotriazole derivatives with biological interest [3-6]. In the current study, we have synthesized some new derivatives of benzoxazoles as antifungal agents. Usually, nitrogen and sulphur containing organic compounds display a wide range of biological activities. For example benzoxazole heterocycles display a broad spectrum of biological activities such as hypoglycaemic [7], antiulcer [8], antifungal [9], anticonvulsant [10], antitumor [11] and anti-inflammatory [12] activities. Different protocols for the synthesis of benzoxazoles have been developed including copper-catalysed cyclizations of o-halobenzenilides or cross-coupling of primary amines [13, 14] and direct condensation of o-aminophenol with carboxylic acid or aldehyde [15]. In most cases, more than one step is required to synthesize these heterocycles. To avoid these limitations,
Materials and Methods

Chemistry

The chemicals were purchased from Merck and used without any additional purification. The products were characterized by FT-IR (ATR), 1H-NMR, and a comparison of their physical properties with those reported in the literature was performed. FT-IR (ATR) spectra were acquired on a Bruker, Equinox 55 spectrometer. A Bruker (DRX-400 Avance) NMR was used to record the 1H NMR and 13C NMR spectra. The melting points were measured by a Buchi melting point B-540 apparatus. The elemental analysis was done by a Costech ECS 4010 CHNS-O analyser.

General procedure for synthesis of benzoxazole derivatives (a) - (m)

A mixture of 2-aminophenol derivatives (1.5 mmol) and substituted aldehydes (1 mmol) with Ti supported nano-SiO2 (0.1 g) in EtOH (2 mL) was stirred at room temperature for 1.5 h. Following completion of the reaction, the solvent was filtered and evaporated; small amounts of cold water were added and then dried. Our suggestion was that an imine intermediate is the product of this step. To make sure about the formation of this intermediate we isolated and identified the product of this step only for two compounds (intermediates (a) and (b) for compounds (c) and (d) respectively). Spectroscopic data confirmed our suggestion. Thus for other compounds (e) - (m) the reaction was performed in situ without any separation of the intermediate.

Subsequently, in the next step, by oxidation of the imine intermediate via KMnO4 (1.7 mmol) and CH3COOH (0.08 mL) in grinding, crude benzoxazole was formed. Purification of the crude compound was carried out by recrystallization from acetone (solid products) or by chromatography using silica gel and mixtures of n-hexane/ethyl acetate (70/30) of increasing polarity.

Table I

| Compounds | Spectral data |
|-----------|---------------|
| ![Image](image1.png) | Yield: 98%; Yellow Solid, Mp = 160 - 161°C; FT-IR, (ATR) = ν: 3365 (O-H stretch), 1587 (C=N stretch), 1509 (NO2 asym. stretch), 1480 (C=C stretch), 1335 (NO2 sym. stretch), 1287 (C=N stretch), 1241 (C-O stretch), cm⁻¹; 1H NMR (400 MHz, CDCl3), (ppm) = 6.95 (t, J = 8 Hz, 1H), 7.06 (d, J = 8 Hz, 1H), 7.18 (brs, 1H, OH), 7.37 (d, J = 8 Hz, 2H), 8.10 (d, J = 8 Hz, 2H), 8.37 (d, J = 8 Hz, 2H), 8.8 (m, 1H, =CH); 13C NMR (300 MHz, DMSO), (ppm) = 163.7 (C), 144.2 (C), 139.0 (C), 127.4 (C), 127.3 (C), 123.1 (C), 120.3 (C), 116.0 (C), 114.4 (C). |
| ![Image](image2.png) | Yield: 86%; Yellow Solid, Mp = 136 - 137°C; FT-IR, (ATR) = ν: 3345 (O-H stretch), 3046 (C-H stretch), 1630 (C=N stretch), 1587 (C=N stretch), 1509, 1476 (C=C stretch), 1513 (NO2 asym. stretch), 1345 (NO2 sym. stretch), 1286 (C=N stretch), 1239 (C-O stretch) cm⁻¹; 1H NMR (400 MHz, Acetone), (ppm) = 6.8 - 7.0 (m, 1H, OH), 7.2 (t, 1H), 7.5 (d, 1H), 7.85 (m, 1H), 8.3-8.4 (m, 2H), 8.5 (d, 1H), 8.8 (s, 1H), 9.04 (s, 1H, =CH); 13C NMR (300 MHz, DMSO), (ppm) = 164.9 (C), 145.4 (C), 139.7 (C), 131.2 (C), 129.6 (C), 128.7 (C), 126.1 (C), 131.2 (C), 123.1 (C), 122.4 (C), 117.0 (C), 116.1 (C). |
| ![Image](image3.png) | Yield: 92%; Brown Solid, Mp = 262 - 264°C [266 - 268°C] [25]; FT-IR, (ATR) = ν: 3112 (C-H stretch), 1598 (C=C stretch), 1555, 1451 (C=C stretch), 1519 (NO2 asym. stretch), 1348 (NO2 sym. stretch) cm⁻¹; 1H NMR (400 MHz, CDCl3), (ppm) = 7.26-8.1 (m, 4H, 4,5,6,7); 8.44 (brs, 2H, 4H, 5,6); 13C NMR (300 MHz, DMSO), (ppm) = 145.9 (C), 133.0 (C), 132.9 (C), 129.2 (C), 129.1 (C), 124.1 (C), 123.0 (C), 117.0 (C), 116.2 (C), 116.0 (C), 115.7 (C) ppm. |
| ![Image](image4.png) | Yield: 87%; Gray Solid, Mp = 210 - 212°C [211 - 212°C] [25]; FT-IR, (ATR) = ν: 3097 (C-H stretch), 1613 (C=C stretch), 1525 (NO2 sym. stretch), 1474, 1453 (C=C stretch), 1351 (NO2 asym. stretch), 1241 (C-O stretch) cm⁻¹; 1H NMR (400 MHz, Acetone), (ppm) = 7.48 - 8.98 (m, 8H, 4,5,6,7,8,9,10,11); 13C NMR (300 MHz, DMSO), (ppm) = 144.2 (C), 133.9 (C), 130.9 (C), 127.4 (C), 127.3 (C), 123.1 (C), 121.7 (C), 116.0 (C), 114.4 (C). |
Bacterial activity

Microorganisms. The antifungal activities of the synthetic compounds against some standard strains of fungi, including Candida albicans (ATCC 10261, 1905, 2730, 1912), C. tropicalis (ATCC 4344, 750), C. krusei (ATCC 6258), C. glabrata (ATCC 90030, 863, 2192), C. dubliniensis (ATCC 8500, 8501, 7988, 7987), C. neoformans (ATCC 9011), Aspergillus flavus (ATCC 64025), A. clavatus (CBS 514.65), A. fumigatus (ATCC 14110) and Exophiala dermatitidis (ATCC 157...
were determined. In addition, the antifungal activities of the compounds were tested against six clinical isolates of yeasts identified by polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) and three clinical isolates of dermatophytes (Epidermophyton floccosum, Microsporum canis and Trichophyton rubrum) identified by both morphological and molecular methods [26]. The antifungal susceptibility of the tested yeasts and Aspergillus species against fluconazole (Sigma, St. Louis, MO, USA) and dermatophytes against griseofulvin (Sigma) were examined by microdilution methods [27, 28].

**Determination of minimum inhibitory concentration.** MICs were determined by using the broth microdilution method recommended by the CLSI (Clinical & Laboratory Standards Institute) with some modifications. In order to determine the antimicrobial activities against fungi, serial dilutions of the synthetic compounds (1 - 1024 μg/mL) were prepared in 96-well microtiter plates using Roswell Park Memorial Institute medium (RPMI)-1640 media (Sigma, St. Louis, MO, USA) buffered with 3-(N-morpholino)propanesulfonic acid (MOPS) (Sigma). Stock inoculums were prepared by suspending three colonies of the examined yeast in 5 mL sterile 0.85% NaCl, and adjusting the turbidity of the inoculums to 0.5 McFarland standards at 530 nm wavelengths (this yields stock suspension of 1 - 5 × 10⁶ cells/mL). For moulds (Aspergillus spp. and dermatophytes), conidia were recovered from the 7-day old cultures grown on potato dextrose agar by a wetting loop with tween-20. The collected conidia were transferred in sterile saline and their turbidity was adjusted to OD = 0.09 - 0.11 that yields 0.4 - 5 × 10⁶ conidia/mL. The working suspension was prepared by making a 1/50 and 1/1000 dilution with RPMI of the stock suspension for moulds and yeasts, respectively. Working inoculums (0.1 mL) were added to the microtiter plates, which were incubated in a humid environment at 30°C for 24 - 48 h. Uninoculated medium (200 μL) was included as a sterility control. In addition, growth controls (medium with inoculums but without antibiotics or the synthetic compounds) were also included.

The growth in each well was compared with that of the growth in the control well. MICs were visually determined and defined as the lowest concentration of the compounds produced ≥ 95% growth reduction compared with the growth in the control well. Each experiment was performed in triplicate.

In addition, media from the wells with fungi showing no visible growth were further cultured on Sabouraud dextrose agar (Merck, Darmstadt, Germany) to determine the minimum fungicidal concentration (MFC). MFCs were determined as the lowest concentration yielding no more than 4 colonies, which resulted in mortality of 98% of the microbes in the initial inoculums.

**SAS map analysis**

To perform SAS analysis, the structures of the synthesized compounds were generated using MarvinSketch (Marvin 5.7, 2014, ChemAxon). Subsequently, **Open Babel 2.3.2** was used to calculate the MACCS fingerprints of all compounds. The resulted fingerprints were then entered in our in house application implemented in Visual.NET. The pairwise tanimoto distance calculation of compounds was done using the following equation:

\[ T_a = \frac{c}{a+b-c}, \]

where (a) and (b) represent the number of bit sets in fingerprint of compared compounds and c denotes the number of common bits [29]. Meanwhile, activity similarities were calculated according to the bellow equation.

\[ z_{\text{sim}}(i,j) = 1 - \frac{|activity_i - activity_j|}{|activity_{\text{max}} - activity_{\text{min}}|}, \]

where the two symbols activity max and activity min represent the MIC90 values for the most active and the least potent compounds, respectively [30]. Finally, the visualization of structure activity analysis was performed using a 2D plot.

**Results and Discussion**

Therefore, to optimize the reaction conditions we repeated the reactions in different situations in the point of solvents, catalysts and oxidizing agents (Table II). We have investigated the synthesis of N-2-hydroxyphenyl-4-nitrophenylimine(a) via the condensation of 4-nitrobenzaldehyde (1 mmol) and 2-aminophenol (1.5 mmol) with and without the nano-TiCl₄, SiO₂. We observed that the reaction did not continue in the absence of this catalyst (Table II, entry 1). Also we repeated the reaction with different amounts of the catalyst and we found that the most appropriate amount for catalyst was 0.1 g that gave 2-(4-nitrobenzylideneamino) phenol (imine intermediate) with 97% yield in 1 h (Table II, entry 4). On the other hand, we tried to repeat the reaction in different solvents such as ethanol, ethylacetate and chloroform (Table II, Entry 3, 6 and 7 respectively). Our results showed that ethanol was the best solvent for this type of reactions (Table II, entry 3). In the next step, for oxidizing the imine intermediate to 2-(4-Nitropheny1)-1,3-benzoaxole (e) various reagents were also tested, for example ceric ammonium nitrate (CAN), p-chloranil and aerobic oxidation (Table II, entry 9, 10 and 11), but according to our experiments the KMnO₄ along with CH₃COOH by the molar ratio, 1.7:1.4 for KMnO₄ and CH₃COOH respectively was the BEST oxidation agent via grinding for 1 minute (Table II, entry 4). This procedure for synthesis of benzoxazole was compared with different methods from literature (Table II, entry 12 and 13). Finally 2-aminophenol and its 4-chloro analogue reacted with various aldehydes in the optimized condition as substrates for the synthesis of benzoxazole derivatives and the results being presented in Table III.
Table I

| Entry | Catalyst (g) | Oxidant      | Solvent     | Condition | Time (h) | Yield (%) | Ref. |
|-------|--------------|--------------|-------------|-----------|----------|-----------|------|
| 1     | No catalyst  | KMnO₄/CH₃COOH| -           | RT        | -        | 0         | -    |
| 2     | Nano-TiCl₄.SiO₂ (0.15) | KMnO₄/CH₃COOH | - | RT | 3 | 57 | - |
| 3     | Nano-TiCl₄.SiO₂ (0.15) | KMnO₄/CH₃COOH | EtOH | RT | 1 | 92 | - |
| 4     | Nano-TiCl₄.SiO₂ (0.05) | KMnO₄/CH₃COOH | EtOH | RT | 1 | 97 | - |
| 5     | Nano-TiCl₄.SiO₂ (0.15) | KMnO₄/CH₃COOH | EtOH | RT | 3 | 85 | - |
| 6     | Nano-TiCl₄.SiO₂ (0.1) | KMnO₄/CH₃COOH | EtOAc | RT | 1 | 70 | - |
| 7     | Nano-TiCl₄.SiO₂ (0.1) | KMnO₄/CH₃COOH | CHCl | RT | 3 | 66 | - |
| 8     | Nano-TiCl₄.SiO₂ (0.1) | KMnO₄/CH₃COOH | EtOH | Reflux | 1 | 90 | - |
| 9     | Nano-TiCl₄.SiO₂ (0.1) | CAN | EtOH | RT | 1 | 72 | - |
| 10    | Nano-TiCl₄.SiO₂ (0.1) | p-chloranil | EtOH | RT | 1 | 80 | - |
| 11    | Nano-TiCl₄.SiO₂ (0.1) | - | EtOH | RT | 24 | 50 | - |
| 12    | Ni-SiO₂ | - | EtOH | RT | 1.5 | 90 | [22] |
| 13    | Molecular Iodine | - | - | MW | 10 min | 90 | [23] |

(a) The molar ratio of 2-aminophenol:4-nitrobenzaldehyde is 1.5:1; RT = room temperature, MW = microwave

Table II

| Entry | Catalyst (g) | Oxidant      | Solvent | Condition | Time (h) | Yield (%) | Ref. |
|-------|--------------|--------------|---------|-----------|----------|-----------|------|
| 1     | Nano-TiCl₄.SiO₂ (0.1) | KMnO₄/CH₃COOH | EtOH | Reflux | 1 | 90 | [22] |

Table III

| Entry | R | R’ | Products | yield (%) | Time (h) |
|-------|---|----|----------|-----------|----------|
| c     | H | 4-NO₂ | ![Image](159.png) | 92 | 1 |
| d     | H | 3-NO₂ | ![Image](159.png) | 87 | 1 |
| e     | H | 2-NO₂ | ![Image](159.png) | 90 | 1 |
| f     | H | 4-Cl | ![Image](159.png) | 85 | 1.5 |
| g     | H | 2,4-Cl | ![Image](159.png) | 88 | 1.5 |
| h     | H | 4-Br | ![Image](159.png) | 91 | 1.5 |
| i     | H | 4-COOCH₃ | ![Image](159.png) | 68 | 2.5 |
| j     | 4-Cl | 4-NO₂ | ![Image](159.png) | 83 | 2 |
| k     | 4-Cl | 3-NO₂ | ![Image](159.png) | 79 | 2 |
| l     | 4-Cl | 4-Cl | ![Image](159.png) | 81 | 2 |
| m     | 4-Cl | 2,4-Cl | ![Image](159.png) | 76 | 2 |

Reaction conditions: 2-aminophenol (1.5 mmol), substituted aldehydes (1 mmol), nano-TiCl₄.SiO₂(0.1 g), RT, EtOH. b) Isolated yields.
Antifungal activities of the synthetic compounds

Tables IVa and IVb summarizes the inhibitory activities of the synthetic compounds and control drugs against the tested fungi. By comparing MIC values of the synthetic compounds, (g) and (j) both exhibited strong inhibitory activities against all of the tested fungi, including both yeasts and filamentous fungi with MICs GM (geometric means) of 36.2 µg/mL and 46.3 µg/mL, respectively. Furthermore, (c) inhibited the growth of the both susceptible and resistant strains of Candida at concentrations ranging from 2 µg/mL to 256 µg/mL. Although, (k) and (j) showed no antifungal activities against the examined filamentous fungi, they both inhibited the growth of the tested yeasts, except those of azole-resistant strains. Of the synthetic compound, (f), (k), (c), (g) and (m) completely inhibited the growth of Crytococccus neoformance at concentrations ranging from 64 µg/mL to 256 µg/mL.

Table IVa

| Microorganism | (a) | (b) | (c) | (d) | (e) | (f) | (g) | (h) | (i) | (j) | (k) | (l) | (m) |
|---------------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Yeasts        |     |     |     |     |     |     |     |     |     |     |     |     |     |
| C. albicans (ATCC 10231) |     |     |     |     |     |     |     |     |     |     |     |     |     |
| C. albicans (ATCC 10412) |     |     |     |     |     |     |     |     |     |     |     |     |     |
| C. albicans (ATCC 519) |     |     |     |     |     |     |     |     |     |     |     |     |     |
| C. albicans (ATCC 1058) |     |     |     |     |     |     |     |     |     |     |     |     |     |
| C. albicans (ATCC 10412) |     |     |     |     |     |     |     |     |     |     |     |     |     |
| C. albicans (ATCC 519) |     |     |     |     |     |     |     |     |     |     |     |     |     |
| C. albicans (ATCC 10231) |     |     |     |     |     |     |     |     |     |     |     |     |     |
| C. albicans (ATCC 10412) |     |     |     |     |     |     |     |     |     |     |     |     |     |
| C. albicans (ATCC 519) |     |     |     |     |     |     |     |     |     |     |     |     |     |
| C. albicans (ATCC 10231) |     |     |     |     |     |     |     |     |     |     |     |     |     |
| C. albicans (ATCC 10412) |     |     |     |     |     |     |     |     |     |     |     |     |     |
| C. albicans (ATCC 519) |     |     |     |     |     |     |     |     |     |     |     |     |     |
| C. albicans (ATCC 10231) |     |     |     |     |     |     |     |     |     |     |     |     |     |
| C. albicans (ATCC 10412) |     |     |     |     |     |     |     |     |     |     |     |     |     |
| C. albicans (ATCC 519) |     |     |     |     |     |     |     |     |     |     |     |     |     |
| C. albicans (ATCC 10231) |     |     |     |     |     |     |     |     |     |     |     |     |     |
| C. albicans (ATCC 10412) |     |     |     |     |     |     |     |     |     |     |     |     |     |
| C. albicans (ATCC 519) |     |     |     |     |     |     |     |     |     |     |     |     |     |
| C. albicans (ATCC 10231) |     |     |     |     |     |     |     |     |     |     |     |     |     |
| C. albicans (ATCC 10412) |     |     |     |     |     |     |     |     |     |     |     |     |     |
| C. albicans (ATCC 519) |     |     |     |     |     |     |     |     |     |     |     |     |     |
| C. albicans (ATCC 10231) |     |     |     |     |     |     |     |     |     |     |     |     |     |
| C. albicans (ATCC 10412) |     |     |     |     |     |     |     |     |     |     |     |     |     |
| C. albicans (ATCC 519) |     |     |     |     |     |     |     |     |     |     |     |     |     |
| C. albicans (ATCC 10231) |     |     |     |     |     |     |     |     |     |     |     |     |     |
| C. albicans (ATCC 10412) |     |     |     |     |     |     |     |     |     |     |     |     |     |
| C. albicans (ATCC 519) |     |     |     |     |     |     |     |     |     |     |     |     |     |
| C. albicans (ATCC 10231) |     |     |     |     |     |     |     |     |     |     |     |     |     |
In comparison with the antifungal activities of the synthetic compounds based on variation of substitutions on 2,3 and 4-position of phenyl ring, we found that the compounds (f) and (g) with Cl residue in para and ortho-positions of phenyl ring respectively exhibited better antifungal activities against the tested fungi than the other compounds. In comparison to these mentioned compounds, addition of another Cl residue to the 5-position of benzoxazole ring resulted respectively (l) and (m) compounds with considerable lower antifungal activities. Replacement of Cl with NO2 residue in 4-position of phenyl ring of (c) reduced its antifungal activity compared to (f). Similarly, the addition of Cl residue to the 5-position of benzoxazole ring in (j) reduced its antifungal activity compared to (c). Moreover, exchanging of nitro group from para-position in c to ortho or meta-positions in (e) and (d) considerably decreased its activity on Candida sp. Of the examined synthetic compounds (f), (g) and (e) all were effective againstazole-resistant strains of Candida at concentrations ranging from 8 - 256 µg/mL, suggesting that the modes of action of this compound are different from the examined antibiotics.

Map analysis
The SAS analysis for all species was performed separately. For example the SAS map for Candida albicans is depicted in Figure 1.

Figure 1.
A plot of SAS-map for C. albicans ; where red dots depict “Cliffs”, or points which indicate a little difference in structure, but a great difference in activity between the two synthesized substance

As seen in Figure, the SAS plot can be divided into four regions. The bottom right area is presenting the pairwise comparisons of the compounds with similar structures but dissimilar activity values (activity cliffs). As an example an outstanding activity cliff in this series of compounds refers to compounds (f) and (l) wherein a chlorine atom was inserted at meta-position of benzoxazole ring. This modification led to a significant drop in the activity of the resulted compound (f), \( \text{MIC}_{50} = 8 \), and in case of (l) \( \text{MIC}_{50} > 256 \). Also as shown in Figure 1 the two compounds (l) and (g) are different considering a chlorine atom which is in the 2-phenyl position in compound (g) instead of meta-position of benzoxazole in compound (l). This difference caused such dissimilarity in effect so that the \( \text{MIC}_{50} \) value of compound (l) is more than 256 but for compound (g) is 8.

Conclusions
In conclusion, we have developed a novel and highly efficient method for the synthesis of benzoxazoles by treatment of 2-aminophenol and substituted aldehydes in the presence of Ni supported silica as an effective Lewis acid. This methodology may find widespread uses in organic synthesis for preparation of the benzoxazoles. In the present study, some of the synthetic compounds including (f) and (g) exhibited a great activity against tested Aspergillus, Candida and dermatophytes. Comparing the structure and activity of these two compounds with the others, revealed that the presence of Cl residue in para and ortho-position of phenyl ring, enhance the antifungal activity. Altogether, regarding the broad spectrum antifungal activities of some of the tested compounds even againstazole resistant strains, they might be good candidates
for further in vivo studies to elucidate their effects and toxicity as novel antifungal drugs.

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**Conflict of interest**

The authors declare no conflict of interest.

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