Synthesis and Antifungal Activity of Novel 2-Benzimidazolylimino-5-arylidene-4-thiazolidinones

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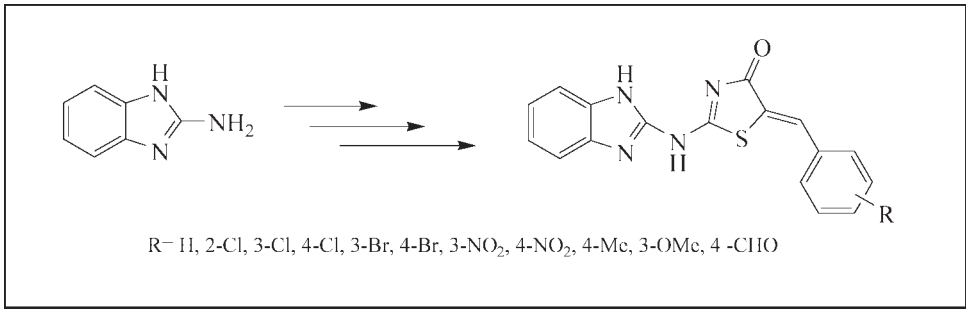

A series of 5-arylidene derivatives **3a-k**, as potential antifungal agents, were synthesized in good to high yields by the reaction of 2-benzimidazolylimino-4-thiazolidinone and corresponding aromatic aldehyde in a buffered medium. These compounds were evaluated for their antifungal activities against four agricultural fungi, *Botrytis elliptica*, *Fusarium graminearum, Phytophthora nicotianae*, and *Rhizoctonia solani*. Thereby, it was found that the compound **1** exhibits an antifungal effect against *P. nicotianae* and *B. elliptica*, comparable with carbendazim as a standard antifungal. Our results may provide some guidance for development of some novel benzimidazole-based antifungal lead structures.

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INTRODUCTION

Thiazolidin-4-ones constitute an important class of heterocyclic compounds because of their broad range of biological activities [1–5]. It is also well known that thiazolidin-4-ones have antifungal activity [6–9] and are used as a new class of potent anti-HIV-1 agents with marked reverse transcriptase (RT) inhibitory effects [10,11].

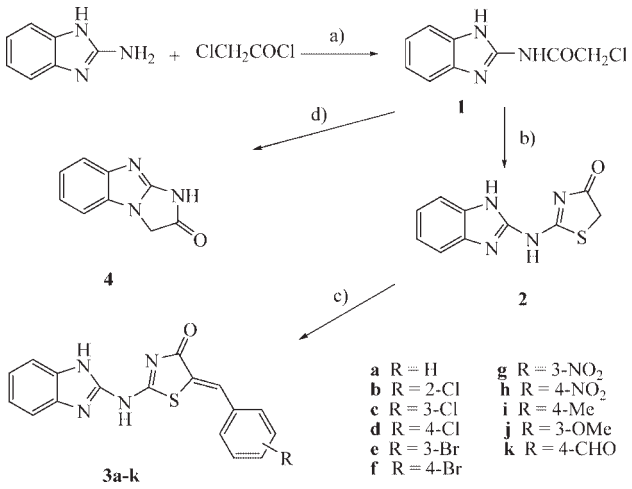
Benzimidazole derivatives are also of wide interest because of their diverse biological activities, such as anticancer, antiproliferative, antiviral, and platelet-anti-aggregating agents [12–16]. Benzimidazoles containing a subunit group, especially a methyl carbamate group on position C(2) (Carbendazim), are found as potential antifungal agent for plants [17]. Because of the aforementioned findings and also because of the incessant interest in the chemistry and antimicrobial activity of benzimidazoles, substantial attention should be paid to the synthesis of novel benzimidazole derivatives especially benzimidazolyl substituted 2-iminiothiazolidin-4-ones. In view of these reports, we extended our research for the synthesis of a novel class of benzimidazole substituted 2-iminiothiazolidin-4-ones resulting from the reaction of 2-(1H-benzimidazol-2-ylamino)-1,3-thiazol-4(5H)-one **2** with various aromatic aldehydes. The antifungal activity of these compounds was investigated against some agricultural fungi.

RESULTS AND DISCUSSION

Compound **1**, N-(1*H*-benzimidazol-2-yl)-2-chloroactamide, was synthesized from 2-amino benzimidazole using a variation of the reported procedure [9]. The compound **1** on heterocyclization in the presence of ammonium thiocyanate in refluxing ethanol (96%) efficiently produced compound **2** without any further purification [5]. Compounds **3a–k** were obtained by refluxing **2** with corresponding aromatic aldehydes in buffered glacial acetic acid (Scheme 1). Compound **3k** was selectively obtained by the reaction of **2** with an aromatic dialdehyde. The presence of an aldehyde group in the phenyl ring of the product was evidently confirmed by ^{1}H NMR, Ms, and infrared (IR) data. Finally, compound **4** was synthesized by refluxing **1** in the presence of K_2CO_3 in acetone. All new compounds were characterized using spectroscopy data (IR, ^{1}H, and ^{13}C NMR).

Compounds **2** and **3a–k** exist as lactam forms on the basis of the mechanism suggested by Vicini *et al.* [18]. This mechanism is more reasonable than that one led to

Scheme 1. Conditions: (a) Acetone, 2 h, reflux. (b) NH_4SCN, 96% EtOH, 8 h, reflux. (c) AcOH, AcONa, 3–10 h, reflux. (d) Acetone, K_2CO_3, 4 h, reflux.



the formation of an imine structure **5** as shown in Scheme 2 [9]. In ^{1}H NMR spectra of compounds **2** and **3a–k**, the resonance of two NH protons at 12.13 and 12.37–12.85 ppm are in support of the lactam form, because an imine proton appears at much higher field (about 9.70) [19,20]. The ^{1}H NMR and IR spectroscopy data (the absence signal of an OH group) is in agreement with a γ-lactam, confirm the $\mathbf{2}_a$ and $\mathbf{2}_b$ tautomeric forms in the solid and liquid states (Scheme 2).

Compounds (**1, 2, 3a–k, 4**) were tested for fungicidal activity against four agricultural fungi. The results (Table 1) show that the compounds **1** and **2** have higher antifungal activity than others and are comparable with carbendazim. The more interesting result could be observed in the treatment of compound **1**, which could completely inhibit the growth of *Phytophthora nicotianae* and *Botrytis elliptica* isolates. Compounds **3b** and **3f** also completely inhibit the growth of *B. elliptica*. Although, all of the compounds have the inhibiting effect against *B. elliptical*, no *Rhizoctonia solani* have. The other results are briefly mentioned in Table 1. It may also be noticed that introduction of benzylidene group at C-5 decreased the fungicidal activity.

Table 1

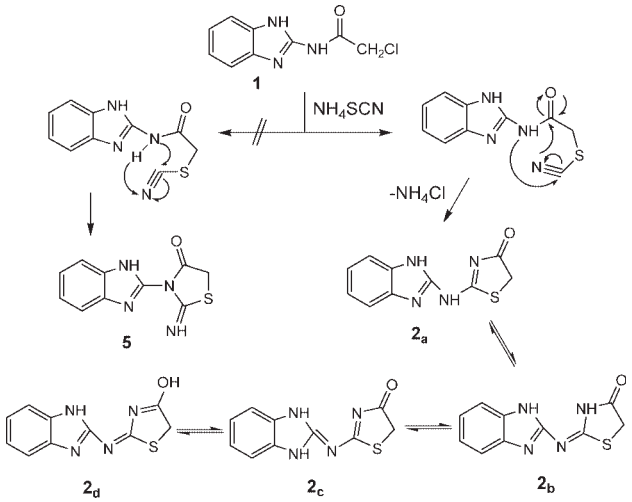
Antifungal activity studies by the agar growth medium poison technique.[a]

Compound	*Phytophthora nicotianae*	*Botrytis elliptica*	*Rhizoctonia solani*	*Fusarium graminearum*
1	100	100	0	40
2	58	50	0	0
3a	0	28	0	0
3b	0	100	0	0
3c	0	33	0	20
3d	15	50	0	0
3e	0	33	0	0
3f	5	100	0	30
3g	25	50	0	0
3h	0	33	0	0
3i	0	57	0	0
3j	0	57	0	6
3k	15	50	0	10
4	30	64	0	0
MBC[b]	0	100	100	100

[a] The results are reported as a percentage (%) inhibition of the fungi growth, and the concentration of the tested compounds was 50 ppm.
[b] Carbendazim as a reference.

In conclusion, we have described the synthesis of 2-benzimidazolylimino-5-arylidene-4-thiazolidinones, **3a–k** by the reaction of 2-benzimidazolylimino-4-thiazolidinone, **2** and corresponding aromatic aldehydes in a buffered medium with good to high yields. We also evaluated their antifungal activities against four agricultural fungi.

Scheme 2



EXPERIMENTAL

All used chemicals were prepared from Merck or Fluka Company. Melting points were determined using an electro thermal digital apparatus and are uncorrected. IR spectra were performed on a Galaxy series FT IR 5000 spectrometer using KBr discs. NMR spectra were recorded on a Bruker (300 MHz) spectrometer. Chemical shifts (ppm) were referenced to the internal standards tetramethylsilane. Elemental analyses were performed on a Vario EL III elemental analyzer. Reactions were monitored by thin layer chromatography (TLC).

Synthesis of N-(1H-benzimidazol-2-yl)-2-chloroactamide (1). A solution of 2-amino benzimidazole (4.0 g, 0.03 mole) in dry acetone (40 mL) was cooled to 0–5°C. A solution of chloroacetyl chloride (4.78 mL, 0.06 mole) in dry acetone (15 mL) was slowly added to it with vigorous stirring. The reaction mixture was refluxed for 2 h, and the solvent was removed under reduced pressure. The residue was washed with sodium bicarbonate (5%) and subsequently with water. The crude product was air dried and crystallized from ethanol to give the colorless crystals **1**, 4.1 g (65%), mp 219–222°C; R_f (ethyl

acetate/hexane 3:1) 0.65; IR (KBr): 3333 (NH), 3055 (CH), 2966 (CH$_2$), 1685 (C=O), 1633, 1583 (C=N), 1456 (C=C) cm^{-1}; ^{1}H NMR (DMSO-d$_6$, 300 MHz): δ 4.37 (s, 2H, CH$_2$), 7.09–7.13 (m, 2H, H-Ar), 7.43–7.46 (q, 2H, H-Ar), 12.08 (s, 2H, NH); ^{13}C NMR (DMSO-d$_6$, 75 MHz): δ 43.9 (CH$_2$), 114.3, 121.9, 135.7, 147.4 (C=N), 167.7 (C=O). Anal. Calcd. for $C_9H_8ClN_3O$: C, 51.56; H, 3.85; N, 20.04. Found: C, 51.45; H, 3.82; N, 20.14.

Synthesis of 2-(1H-benzimidazol-2-ylamino)-1,3-thiazol-4(5H)-one (2). A solution of compound **1** (3.0 g, 0.01 mole) and ammonium thiocyanate (1.96 g, 0.02 mole) in 50 mL of ethanol (96%) was refluxed for 8 h and allowed to stand for 2 h. The precipitate was filtered, washed with aqueous ethanol, and recrystallized from dioxane/water to give light yellow crystals **2** to yield 2.7 g (81%), mp 284°C; R_f (ethylacetate/hexane 3:1) 0.5; IR (KBr): 3138 (NH), 3065 (CH-Ar), 2926 (CH), 1697 (C=O), 1620, 1581 (C=N), 1352 (C=C) cm^{-1}; ^{1}H NMR (DMSO-d$_6$, 300 MHz): δ 3.96 (s, 2H, CH$_2$), 7.12–7.49 (m, 4H, H-Ar), 12.13 (br., 2H, NH); the NH protons disappeared on D$_2$O addition; ^{13}C NMR (DMSO-d$_6$, 75 MHz): δ 35.2 (CH$_2$), 112.7, 121.8, 142.6, 152.2 (C=N), 164.6 (C=N), 174.7 (C=O). Anal. Calcd. for $C_{10}H_8N_4OS$: C, 51.71; H, 3.47; N, 24.12; S, 13.81. Found: C, 51.58; H, 3.51; N, 24.22; S, 13.80.

General procedure for the synthesis of compounds (3). A well-stirred solution of compound **2** (0.2 g, 0.86 mmole) in 4–6 mL of acetic acid was buffered with sodium acetate (0.2 g, 2.58 mmole) and added the appropriate arylaldehyde (1.7 mmole). The solution was refluxed for desired time. The completion of the reaction was monitored by TLC (toluene/dioxane/acetic acid 18:2:1). The reaction mixture was then cooled to room temperature to produce the precipitate. The precipitate was filtered, abundantly washed with water, and then recrystallized from dioxane or dioxane/water to give the pure crystals (**3a**–**k**).

2-(1H-Benzimidazol-2-ylamino)-5-benzylidene-1,3-thiazol-4(5H)-one (3a). This compound was obtained by refluxing for 7 h to yield 0.26 g (96%), mp 326–327°C; IR (KBr): 3138 (NH), 3067 (CH-Ar), 1697 (C=O), 1618, 1581 (C=N), 1454, 1352, 1253 (C=C) cm^{-1}; ^{1}H NMR (DMSO-d$_6$, 300 MHz): δ 7.14–7.71 (m, 10H, H-Ar and C=CH-Ph), 12.38 (s, 1H, NH), 12.75 (s, 1H, NH); ^{13}C NMR (DMSO-d$_6$, 75 MHz): δ 112.9, 121.8, 124.1, 129.1, 129.6, 129.9, 130.5, 133.8, 134.1, 150.3 (C=N), 179.3 (C=N), 181.2 (C=O). Anal. Calcd. for $C_{17}H_{12}N_4OS$: C, 63.73; H, 3.78; N, 17.49; S, 10.01. Found: C, 64.01; H, 3.81; N, 17.39; S, 10.00.

2-(1H-Benzimidazol-2-ylamino)-5-(2-chlorobenzylidene)-1,3-thiazol-4(5H)-one (3b). This compound was obtained by refluxing for 6 h to yield 0.16 g (52%), mp 304°C; IR (KBr): 3151 (NH), 3063 (CH-Ar), 1695 (C=O), 1622, 1589 (C=N), 1471, 1352, 1255 (C=C) cm^{-1}; ^{1}H NMR (DMSO-d$_6$, 300 MHz): δ 7.15–7.68 (m, 8H, H-Ar), 7.87 (s, 1H, C=CH-Ar), 12.42 (s, 1H, NH), 12.92 (br., s, 1H, NH); ^{13}C-NMR (DMSO-d$_6$ (CD$_3$)$_2$SO, 75 MHz): 112.9, 123.8, 124.2, 128.4, 129.0, 129.7, 130.6, 131.1, 131.9, 132.9, 134.6, 150.1 (C=N), 179.3 (C=N), 180.7 (C=O). Anal. Calcd. for $C_{17}H_{11}ClN_4OS$: C, 57.55; H, 3.12; N, 15.79; S, 9.04. Found: C, 57.79; H, 3.16; N, 15.88; S, 9.13.

2-(1H-Benzimidazol-2-ylamino)-5-(3-chlorobenzylidene)-1,3-thiazol-4(5H)-one (3c). This compound was obtained by refluxing for 4 h to yield 0.26 g (85%), mp 320–322°C; IR (KBr): 3138 (NH), 3063 (CH-Ar), 1695 (C=O), 1618, 1581 (C=N), 1469, 1350, 1251 (C=C) cm^{-1}; ^{1}H NMR (DMSO-d$_6$, 300 MHz): δ 7.15–7.63 (m, 9H, H-Ar and C=CH-Ar), 12.40–12.85 (br., s, 2H, NH); ^{13}C NMR (DMSO-d$_6$, 75 MHz): δ 112.9, 122.3, 124.1, 127.3, 127.9, 129.2, 129.7, 131.3, 132.8, 134.2, 137.2, 150.3 (C=N), 179.2 (C=N), 180.9 (C=O). Anal. Calcd. for $C_{17}H_{11}ClN_4OS$: C, 57.55; H, 3.12; N, 15.79; S, 9.04. Found: C, 57.33; H, 3.17; N, 15.58; S, 9.14.

2-(1H-Benzimidazol-2-ylamino)-5-(4-chlorobenzylidene)-1,3-thiazol-4(5H)-one (3d). This compound was obtained by refluxing for 8 h to yield 0.16 g (52%), mp 337°C; IR (KBr): 3421, 3308 (NH), 3053 (CH-Ar), 1676 (C=O), 1618, 1574 (C=N), 1473, 1350, 1259 (C=C) cm^{-1}; ^{1}H NMR (DMSO-d$_6$, 300 MHz): δ 7.15–7.69 (m, 9H, H-Ar. and C=CH-Ph), 12.39 (s, 1H, NH), 12.75 (br., s, 1H, NH); ^{13}C NMR (DMSO-d$_6$, 75 MHz): δ 112.9, 124.1, 127.6, 129.6, 129.7, 131.5, 132.1, 133.8, 134.1, 150.3 (C=N), 179.3 (C=N), 181.1 (C=O). Anal. Calcd. for $C_{17}H_{11}ClN_4OS$: C, 57.55; H, 3.12; N, 15.79; S, 9.04. Found: C, 57.43; H, 3.07; N, 15.78; S, 9.09.

2-(1H-Benzimidazol-2-ylamino)-5-(3-bromobenzylidene)-1,3-thiazol-4(5H)-one (3e). This compound was obtained by refluxing for 5 h to yield 0.26 g (75%), mp 306–307°C; IR (KBr): 3192 (NH), 3068 (CH-Ar), 1699 (C=O), 1622, 1585 (C=N), 1481, 1251 (C=C) cm^{-1}; ^{1}H NMR (DMSO-d$_6$, 300 MHz): δ 7.16–7.88 (m, 9H, H-Ar. and C=CH-Ar), 12.79 (br., s, 2H, NH); ^{13}C NMR (DMSO-d$_6$, 75 MHz): δ 112.8, 122.8, 124.1, 127.2, 128.3, 129.7, 131.6, 132.1, 136.5, 137.4, 150.2, 153.1 (C=N), 179.2 (C=N), 180.8 (C=O). Anal. Calcd. for $C_{17}H_{11}BrN_4OS$: C, 51.14; H, 2.78; N, 14.03; S, 8.03. Found: C, 51.34; H, 2.76; N, 14.12; S, 7.99.

2-(1H-Benzimidazol-2-ylamino)-5-(4-bromobenzylidene)-1,3-thiazol-4(5H)-one (3f). This compound was obtained by refluxing for 10 h to yield 0.28 g (85%), mp 325–327°C; IR (KBr): 3217, 3136 (NH), 3026 (CH-Ar), 1691 (C=O), 1633, 1609 (C=N), 1487, 1350, 1257 (C=C) cm^{-1}; ^{1}H NMR (DMSO-d$_6$, 300 MHz): δ 7.02–7.95 (m, 9H, H-Ar and C=CH-Ar), 12.40 (s, 1H, NH), 12.78 (br., s, 1H, NH); ^{13}C NMR (DMSO-d$_6$, 75 MHz): δ 112.9, 123.0, 124.1, 127.7, 129.7, 131.7, 132.3, 132.5, 134.2, 150.3 (C=N), 179.3 (C=N), 181.0 (C=O). Anal. Calcd. for $C_{17}H_{11}BrN_4OS$: C, 51.14; H, 2.78; N, 14.03; S, 8.03. Found: C, 50.91; H, 2.75; N, 14.02; S, 8.05.

2-(1H-Benzimidazol-2-ylamino)-5-(3-nitrobenzylidene)-1,3-thiazol-4(5H)-one (3g). This compound was obtained by refluxing for 3 h to yield 0.28 g (90%), mp 333°C; IR (KBr): 3138 (NH), 3068 (CH-Ar), 1716 (C=O), 1655, 1620 (C=N), 1531, 1352 (NO2), 1464, 1265 (C=C) cm^{-1}; ^{1}H NMR (DMSO-d$_6$, 300 MHz): δ 7.17–8.55 (m, 9H, H-Ar and C=CH-Ar), 12.43 (s, 1H, NH), 12.85 (br., s, 1H, NH); ^{13}C NMR (DMSO-d$_6$, 75 MHz): δ 112.9, 123.8, 124.2, 126.4, 129.7, 131.0, 134.0, 135.7, 136.7, 148.6, 150.1, 172.5 (C=N), 178.9 (C=N), 180.8 (C=O). Anal. Calcd. for $C_{17}H_{11}N_5O_3S$: C, 55.88; H, 3.03; N, 19.17; S, 8.78. Found: C, 55.80; H, 3.05; N, 19.19; S, 8.75.

2-(1H-Benzimidazol-2-ylamino)-5-(4-nitrobenzylidene)-1,3-thiazol-4(5H)-one (3h). This compound was obtained by refluxing for 10 h to yield 0.30 g (96%), mp 353°C; IR (KBr): 3148 (NH), 3076 (CH-Ar), 1705 (C=O), 1631, 1599 (C=N), 1512, 1342 (NO$_2$) cm^{-1}; ^{1}H NMR (DMSO-d$_6$, 300 MHz): δ 7.16–8.32 (m, 9H, H-Ar and C=CH-Ar), 12.42 (s, 1H, NH), 12.92 (s, 1H, NH); ^{13}C NMR (DMSO-d$_6$, 75 MHz): δ 112.9, 124.1, 124.5, 126.2, 129.6, 130.6, 135.6, 141.4, 146.9, 150.1

(C=N), 178.9 (C=N), 180.7 (C=O). Anal. Calcd. for $C_{17}H_{11}N_5O_3S$: C, 55.88; H, 3.03; N, 19.17; S, 8.78. Found: C, 56.07; H, 3.02; N, 19.20; S, 8.80.

2-(1H-Benzimidazol-2-ylamino)-5-(4-methylbenzylidene)-1, 3-thiazol-4(5H)-one (3i). This compound was obtained by refluxing for 9 h to yield 0.15 g (52%), mp 331°C; IR (KBr): 3217, 3144 (NH), 3043 (CH-Ar), 2943 (Me), 1685 (C=O), 1620, 1533 (C=N), 1444, 1273 (C=C) cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz): δ 2.35 (s, 1H, CH_3), 7.15–7.67 (m, 9H, H-Ar and C=CH-Ar), 12.37 (s, 1H, NH), 12.70 (br., s, 1H, NH); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 21.5 (CH_3), 112.8, 118.5, 121.8, 124.1, 150.4, 129.8, 130.6, 131.8, 139.7, 157.4 (C=N), 179.5 (C=N), 181.2 (C=O). Anal. Calcd. for $C_{18}H_{14}N_4OS$: C, 64.65; H, 4.22; N, 16.75; S, 9.59. Found: C, 64.93; H, 4.23; N, 16.78; S, 9.56.

2-(1H-Benzimidazol-2-ylamino)-5-(3-methoxybenzylidene)-1,3-thiazol-4(5H)-one (3j). This compound was obtained by refluxing for 5 h to yield 0.24 g (80%), mp 271–272°C; IR (KBr): 3200, 3148 (NH), 3045 (CH-Ar), 2960 (Me), 1695 (C=O), 1640, 1620 (C=N), 1533, 1448, 1352 (C=C) cm^{-1}; 1273, 1228 (OMe); ^1H NMR (DMSO-d_6, 300 MHz): δ 3.81 (s, 3H, OMe), 6.98–7.68 (m, 9H, H-Ar and C=CH-Ar), 12.39 (s, 1H, NH), 12.74 (br., s, 1H, NH); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 55.6 (OMe), 112.8, 115.4, 116.2, 122.3, 124.1, 129.7, 129.0, 129.7, 130.8, 131.3, 150.3, 160.0 (C=N), 179.5 (C=N), 181.1 (C=O). Anal. Calcd. for $C_{18}H_{14}N_4O_2S$: C, 61.70; H, 4.03; N, 15.99; S, 9.15. Found: C, 62.02; H, 4.00; N, 15.87; S, 9.10.

4-{[2-(1H-Benzimidazol-2-ylamino)-4-oxo-1,3-thiazol-5(4H)-ylidene]methyl} benzaldehyde (3k). This compound was obtained by refluxing for 3 h to yield 0.27 g (90%). mp 339–341°C; IR (KBr): 3452, 3221 (NH), 3065 (CH-Ar), 2785, 2885 (CH, aldehyde), 1691 (C=O), 1622, 1589 (C=N), 1481, 1350, 1261 (C=C) cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz): δ 7.17–8.02 (m, 9H, H-Ar and C=CH-Ar), 10.03 (s, 1H, CHO), 12.85–12.94 (br., s, 2H, NH); MS (*m/z*, %): 348 (M^+, 100), 159 (92), 133 (15), 105 (12), 89 (24). Anal. Calcd. for $C_{18}H_{12}N_4O_2S$: C, 62.06; H, 3.47; N, 16.08; S, 9.20. Found: C, 62.37; H, 3.45; N, 16.17; S, 9.17.

Synthesis of 1H-imidazo[1,2-a]benzimidazol-2(3H)-one (4). To a well-stirred solution of compound **1** (0.4 g, 2 mmole) in dry acetone (30 mL), K_2CO_3 (0.32 g, 2 mmole) was added. The reaction mixture was refluxed for 4 h. The result solid was filtered, and water (5 mL) was added to the filtration to give compound **4,** which then filtered and washed with water and air dried to yield 0.16 g (50 %); mp 216–219°C; IR (KBr): 3358 (NH), 3051 (CH-Ar), 2991, 2930 (CH_2), 1666 (C=O), 1585, 1527 (C=N), 1448, 1336 (C=C) cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz): δ 4.90 (s, 2H, CH_2), 7.10–7.42 (m, 4H, H-Ar), 12.51 (br. s, 1H, NH); The NH proton disappeared on D_2O addition; ^{13}C NMR (DMSO-d_6, 75 MHz): δ 47.6 (CH_2), 110.6, 112.3, 121.8, 123.1, 129.4, 130.4, 147.6, 175.2 (C=O). Anal. Calcd. for $C_9H_7N_3O$: C, 62.42; H, 4.07; N, 24.27. Found: C, 62.22; H, 4.08; N, 24.32.

Antifungal assays. Fungicidal activity of compounds (**1**, **2**, **3a–k**, and **4**) were tested against four phytopathogenic fungal isolates, including *B. elliptica*, *Fusarium graminearum*, *P. nicotianae*, and *R. solani,* provided by Department of Plant diseases of Iranian Plant Protection Research Institute *in vitro*. Two negative controls: one with DMSO, the solvent of all tested compounds (no antifungal activity has been noted) and the other as untreated potato dextrose agar petri dishes used using the agar growth medium poison technique [8]. The medium was potato dextrose agar, and the concentration of the tested compounds was 50 ppm. After 5 days incubation at 25°C, the growth diameter of treatments was measured, and the percentage inhibition of growth for each compound was determined based on the negative control growth of each fungal species under the same incubation conditions. Carbendazim as a reference was included to compare with compounds (**1**, **2**, **3a–k**, and **4**). All tests were performed in triplicate and the average results, as a percentage (%) inhibition of growth, are shown in Table 1.

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