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Synthesis and Antifungal Activity of Diamidomethane Linked Oxazolyl / Thiazolyl / Imidazolyl Isoxazoles

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Abstract. Nitrogen containing heterocyclic compounds have great utility in synthetic, medicinal and material chemistry. Oxazole, isoxazole, thiazole, imidazole and their derivatives have gained prominence as they constitute the structural features of many bioactive compounds. In fact, amide functionality represents a privileged scaffold of biomolecules and many drugs. The combination of two or more heterocycles linked by amide functionality into one molecular framework would yield new chemical entities with enhanced pharmacological activities. Besides, development of environmentally benign methods with improved yields is highly desirable. In our continued interest to synthesize a variety of bioactive heterocycles, we planned to develop some new isoxazoles in combination with oxazoles / thiazoles / imidazoles adopting green methodologies and to study their antifungal activity. The results related to these aspects will be presented.

INTRODUCTION

Molecules having azole ring particularly oxazole, thiazole and imidazole as a privileged scaffold exhibits a wide range of applications in drug discovery as antimicrobials, antioxidants, antitumor and anticancer agents. Oxazole is one of the structural motifs in biologically active natural products such as phenoxan, hennoxazoles and leiodolides A and B [1]. Thiazole is the key component of alkaloids and pharmaceuticals [2]. The drugs sulfathiazole and tiazofurin constitute thiazole unit [3]. On the other hand, imidazoles are prominent players in pharmaceutical research. The antibiotic metronidazole, antifungals miconazole, econazole [4, 5] comprises of imidazole moiety. Besides, the combination of amide moieties with potential heterocycles is being used to develop novel formulation. Moreover, there is a quest for development of green methods to prepare heteroaromatic compounds. Based on the above and in continuation of our efforts to prepare biologically potential heterocycles [6, 7], the present work synthesis and antifungal activity of azolyl isoxazoles have been taken up.

Chemistry

The synthetic intermediates N-(2-oxo-2-((4-phenyloxazol-2-yl)amino)ethyl)cinnamamide (1), N-(2-oxo-2-((4-phenylthiazol-2-yl)amino)ethyl)cinnamamide (2) and N-(2-oxo-2-((4-phenyl-1H-imidazol-2-yl)amino)ethyl)-cinnamamide (3) were prepared as per the literature precedents [8]. The olefin functionality in 1, 2 and 3 was utilized to build isoxazole. The cycloaddition of nitrile oxide developed from benzaldoxime in the presence of PhiO
and CTAB to 1, 2 and 3 furnished N-(2-oxo-2-((4-phenyloxazol/thiazol/imidazol-2-yl)amino)ethyl)-3,5-diphenyl-4,5-dihydro-isoxazole-4-carboxamide (4/5/6). The $^1$H NMR spectra of 4a, 5a and 6a displayed a singlet at $\delta$ 3.78, 3.80, 3.72 (CH$_2$), two doublets at 5.10, 5.18, 5.21 (C$_4$-H), and at 5.32, 5.40, 5.45 (C$_5$-H) ppm respectively. The $J$ values 6.4, 6.9, 7.1 Hz revealed their cis geometry. Furthermore, two broad singlets were observed at $\delta$ 9.32, 9.46 & 9.28 due to NHCO and 8.95, 8.96 & 8.86 ppm (CH$_2$NH) respectively. Furthermore, N-(2-oxo-2-((4-phenyloxazol/thiazol/imidazol-2-yl)amino)ethyl)-3,5-diphenylisoxazole-4-carboxamide (7/8/9) were synthesized by the reaction of 4, 5 and 6 with iodine in dimethyl sulfoxide respectively (Scheme I). Absence of signals due to methine protons in the $^1$H NMR spectra of 7a, 8a and 9a confirmed the formation of isoxazole ring. The signal due to NH protons disappeared on deuteration. In fact, all the synthesized compounds obtained in higher yield and in shorter reaction times. The IR, $^{13}$C NMR, mass and microanalyses were also utilized to confirm the structures of all the title compounds.

![Synthesis of carboxamides 7, 8, 9](image)

**SCHEME 1.** Synthesis of carboxamides 7, 8, 9

**Antifungal Activity**

All the tested compounds inhibited the spore germination against both the tested fungi (Table 1). However, all the compounds displayed comparatively higher antifungal activity towards *Aspergillus niger* than *Penicillium chrysogenum*. The isoxazole derivatives 7-9 exhibited greater activity than the isoxazoline derivatives 4-6. The imidazolyl isoxazole (9) showed greater antifungal activity than oxazolyl isoxazole (7) and thiazolyl isoxazole (8). In general, it was observed that chloro substituted compounds presented higher activity than the methyl substituted ones. The compounds 9a and 9c exhibited promising antifungal activity among all other screened samples particularly against *A. niger*.

**TABLE 1.** The *in vitro* antifungal activity of compounds 4-9

<table>
<thead>
<tr>
<th>Compound</th>
<th>Zone of inhibition (mm)</th>
<th>Zone of inhibition (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>50 µg/well</td>
<td>100 µg/well</td>
</tr>
<tr>
<td>4a</td>
<td>13±1.1</td>
<td>17±1.7</td>
</tr>
<tr>
<td>4b</td>
<td>16±1.3</td>
<td>20±2.1</td>
</tr>
<tr>
<td>5a</td>
<td>15±2.1</td>
<td>17±2.5</td>
</tr>
<tr>
<td>5b</td>
<td>19±2.3</td>
<td>22±2.8</td>
</tr>
<tr>
<td>6a</td>
<td>14±2.2</td>
<td>17±2.6</td>
</tr>
<tr>
<td>6b</td>
<td>19±2.1</td>
<td>21±2.8</td>
</tr>
<tr>
<td>Ketoconazole</td>
<td>32±2.3</td>
<td>36±2.6</td>
</tr>
<tr>
<td>Control *</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

(-) No activity, (±) Standard deviation * DMSO
CONCLUSION

Some new amide-linked oxazolyl isoxazoles, thiazolyl isoxazoles, and imidazolyl isoxazoles were synthesized adopting green approaches. Thus, the cycloaddition of nitrile oxide developed from benzaldoxime in the presence of PhIO and CTAB to azolyl cinnamides followed by oxidation of azolyl isoxazolines with I2 in DMSO produced target compounds. The structures of all the synthesized compounds were established by spectral parameters and also assayed for antifungal activity. The azolyl isoxazoles exhibited greater antifungal activity than the azolyl isoxazolines. The presence of chloro substituent on phenyl ring enhances the activity. Among all the tested compounds, 9a and 9b exhibited pronounced antifungal activity.

EXPERIMENTAL SECTION

Melting points were determined in open capillaries on a Mel-Temp apparatus and are uncorrected. The IR spectra were run on a Thermo Nicolet FT 200 FTIR spectrometer as KBr pellets, and the wave numbers were given in cm⁻¹. The ¹H NMR and ¹³C NMR spectra were run in DMSO-d₆ on a Jeol JNM spectrometer operating at 400 and 100 MHz. All chemical shifts are reported in δ (ppm) using TMS as an internal standard. High resolution mass spectra were recorded on Micromass QTOF mass spectrometer using electrospray ionisation. The elemental analyses were carried out on a Perkin-Elmer 240C elemental analyzer.

General procedure for the synthesis of N-(2-oxo-2-((4-phenyl-(oxazol / thiazol / imidazol-2-yl) amino)ethyl)-3,5-diphenyl-4,5-dihydroisoxazole-4-carboxamide (4 / 5 / 6)

A mixture of 1 / 2 / 3 (2 mmol), benzaldoxime (1 mmol), water (8 mL) and CTAB (0.3 mmol) was stirred at room temperature for 8 min. To this, PhIO (2 mmol) was added and the stirred for 2-3 h at the same temperature. The progress of the reaction was checked by thin layer chromatography. The reaction mixture was extracted with ethyl acetate. The organic layer was washed with brine, dried and filtered. The solvent was removed under vacuum. The resultant residue was purified by column chromatography using ethyl acetate-hexane (1:3) as eluent.

N-(2-Oxo-2-((4-phenyloxazol-2-yl)amino)ethyl)-3-phenyl-4,5-dihydroisoxazole-4-carboxamide (4a). Yield 85%; white solid, mp 226-228 °C; IR (KBr) : 3294 (NH), 1667 (C=O), 1586 (C=N) cm⁻¹; ¹H NMR (400 MHz, DMSO-d₆): δ 2.21 (s, 3H, CH₃), 3.78 (s, 2H, CH₂), 5.10 (1H, Cₓ, J = 6.4 Hz ), 5.32 (d, 1H, Cₓ-H, J = 6.4 Hz), 7.01-7.67 (m, 15H, Ar-H), 8.95 (bs, 1H, CH₂-NH), 9.32 (bs, 1H, NH-CO) ppm; ¹³C NMR(100 MHz, DMSO-d₆): δ 22.6 (CH₃), 44.8 (CH₂), 58.7 (C-4'), 83.5 (C-5'), 136.5 (C-5), 141.4 (C-4), 151.9 (C-3'), 162.6 (C-2), 166.4 (CH₂NHCO), 167.5 (NHCO), 122.4, 123.8, 126.2, 126.9, 127.1, 128.0, 129.5, 132.0, 133.8, 134.6 ppm (aromatic carbons); HRMS: (m/z) 503.5147 [M+Na]. Anal. Calcd. for: C₂₈H₂₄N₄O₄: C, 69.99; H, 5.03; N, 11.66%. Found: C, 70.10; H, 5.02; N, 11.86%.

N-(2-Oxo-2-((4-phenyloxazol-2-yl)amino)ethyl)-3-phenyl-4,5-dihydro-5-(p-chlorophenyl)-isoxazole-4-carboxamide (5a). Yield 90%; white solid, mp 242-244 °C; IR (KBr) : 3304 (NH), 1676 (C=O), 1574 (C=N) cm⁻¹; ¹H NMR (400 MHz, DMSO-d₆): δ 3.82 (s, 2H, CH₂), 5.16 (d, 1H, Cₓ, J = 7.2 Hz ), 5.42 (d, 1H, Cₓ-H, J = 7.2 Hz), 7.18-7.74 (m, 15H, Ar-H), 8.88 (bs, 1H, CH₂-NH), 9.38 (bs, 1H, NH-CO) ppm; ¹³C NMR(100 MHz, DMSO-d₆): δ 45.2 (CH₃), 59.3 (C-4'), 84.6 (C-5'), 138.9 (C-4), 137.4 (C-5), 152.4 (C-3'), 163.2 (C-2), 165.3 (CH₂NHCO), 167.1 (NHCO), 120.6, 121.2, 121.8, 123.4, 124.7, 125.3, 126.6, 127.6, 128.8, 131.7, 133.9, 134.9 ppm (aromatic carbons); HRMS: (m/z) 523.9298 [M+Na]. Anal. Calcd. for: C₂₈H₂₃ClN₄O₄C, 69.99; H, 5.03; N, 11.18%. Found: C, 68.46; H, 4.24; N, 11.49%.

N-(2-Oxo-2-((4-phenylthiazol-2-yl)amino)ethyl)-3-phenyl-4,5-dihydro-5-(p-tolyl)-isoxazole-4-carboxamide (5b). Yield 86%; white solid, mp 276-278 °C; IR (KBr) : 3294 (NH), 1667 (C=O), 1581 (C=N) cm⁻¹; ¹H NMR (400 MHz, DMSO-d₆): δ 2.28 (s, 3H, CH₃), 3.80 (s, 2H, CH₂), 5.18 (1H, Cₓ, J = 6.9 Hz ), 5.40 (d, 1H, Cₓ-H, J = 6.9 Hz), 7.22-7.78 (m, 15H, Ar-H), 8.96 (bs, 1H, CH₂-NH), 9.46 (bs, 1H, NH-CO) ppm; ¹³C NMR(100 MHz, DMSO-d₆): δ 23.3 (CH₃), 45.4 (CH₂), 61.7 (C-4'), 84.7 (C-5'), 152.6 (C-3'), 164.5 (CH₂NHCO), 165.8 (C-2), 146.2 (C-4), 103.7 (C-5), 171.6 (NHCO), 121.9, 123.6, 124.8, 125.3, 126.2, 127.6, 129.7, 130.9, 131.5, 132.4, 133.2, 134.6 ppm (aromatic carbons); HRMS: (m/z) 519.5741 [M+Na]. Anal. Calcd. for: C₂₈H₂₃N₂O₄S, 67.72; H, 4.87; N, 11.28%. Found: C, 67.81; H, 4.90; N, 11.59%.

N-(2-Oxo-2-((4-phenylthiazol-2-yl)amino)ethyl)-3-phenyl-4,5-dihydro5-(p-chlorophenyl)-isoxazole-4-carboxamide (5c). Yield 90%; white solid, mp 242-244 °C; IR (KBr) : 3304 (NH), 1676 (C=O), 1574 (C=N) cm⁻¹; ¹H NMR (400 MHz, DMSO-d₆): δ 2.28 (s, 3H, CH₃), 3.80 (s, 2H, CH₂), 5.18 (1H, Cₓ, J = 6.9 Hz ), 5.40 (d, 1H, Cₓ-H, J = 6.9 Hz), 7.22-7.78 (m, 15H, Ar-H), 8.96 (bs, 1H, CH₂-NH), 9.46 (bs, 1H, NH-CO) ppm; ¹³C NMR(100 MHz, DMSO-d₆): δ 23.3 (CH₃), 45.4 (CH₂), 61.7 (C-4'), 84.7 (C-5'), 152.6 (C-3'), 164.5 (CH₂NHCO), 165.8 (C-2), 146.2 (C-4), 103.7 (C-5), 171.6 (NHCO), 121.9, 123.6, 124.8, 125.3, 126.2, 127.6, 129.7, 130.9, 131.5, 132.4, 133.2, 134.6 ppm (aromatic carbons); HRMS: (m/z) 519.5741 [M+Na]. Anal. Calcd. for: C₂₈H₂₃ClN₂O₄S, 67.72; H, 4.87; N, 11.28%. Found: C, 67.81; H, 4.90; N, 11.59%.
\( \text{C27H19ClN4O3S: C, 62.97; H, 3.72; N, 10.88\%} \). Found: C, 62.88; H, 3.75; N, 11.14\%.

1H NMR (400 MHz, DMSO-\( \text{d6} \)): \( \delta \) 2.32 (s, 3H, CH\(_3\)), 3.72 (s, 2H, CH\(_2\)), 5.21 (1H, CH\(_2\)), 6.21 (1H, C=C-H, J = 7.1 Hz), 7.28-7.88 (m, 15H, Ar-H), 9.86 (bs, 1H, CH\(_2\)-NH), 12.84 (bs, 1H, Imidazole-NH) ppm; \(^{13}\text{C}\) NMR (100 MHz, DMSO-\( \text{d6} \)): \( \delta \) 23.9 (CH\(_3\)), 44.6 (CH\(_2\)), 63.6 (C-4'), 82.4 (C-5'), 152.1 (C-3'), 161.7 (C-2), 135.3 (C-4), 114.2 (C-5), 166.4 (CH\(_2\)NHCO), 167.5 (NHCO), 126.6, 127.8, 128.4, 129.6, 131.4, 132.5, 133.4, 134.2, 135.6, 136.2, 137.2, 138.1 ppm (aromatic carbons); HRMS: (\( m/z \)) 502.5290 [M+Na].

Yield 86\%; white solid, mp 281-283 °C; IR (KBr): 3314 (NH), 1663 (C=O), 1620 (C=C), 1572 (C-N) cm\(^{-1}\);

\( \text{C28H25N5O3: C, 70.13; H, 5.26; N, 14.60\%} \). Found: C, 70.25; H, 5.29; N, 14.85\%.

1H NMR (400 MHz, DMSO-\( \text{d6} \)): 2.26 (s, 3H, CH\(_3\)), 3.76 (s, 2H, CH\(_2\)), 7.40-7.96 (m, 15H, Ar-H), 8.79 (bs, 1H, CH\(_2\)-NH), 9.50 (bs, 1H, NH-CO) ppm; \(^{13}\text{C}\) NMR (100 MHz, DMSO-\( \text{d6} \)): \( \delta \) 23.7 (CH\(_3\)), 45.6 (CH\(_2\)), 135.7 (C-4'), 150.5 (C-5'), 156.4 (C-3'), 161.7 (C-2), 138.2 (C-4'), 137.3 (C-5), 165.2 (CH\(_2\)NHCO), 168.9 (NHCO), 122.5, 123.2, 125.4, 126.6, 128.7, 129.5, 130.6, 131.4, 132.3, 133.3, 134.6, 135.4 ppm (aromatic carbons); HRMS: (\( m/z \)) 501.4985 [M+Na].

The 4/5/6 (0.1 mmol) in dimethyl sulfoxide (3 mL) was stirred for 8 min. To this iodine (1 mg, 2.2 mol %) was added while stirring and refluxed for 1-2 h. After completion of the reaction (checked by TLC), the reaction mixture was poured onto crushed ice. The solid obtained was separated by filtration, dried and recrystallized from 2-propanol.

\( \text{NH} \) (2-Oxo-2-((4-phenyl-1H-imidazol-2-yl)amino)ethyl)-3-phenyl-5-(p-tolyl)-4,5-dihydroisoxazole-4-carboxamide (6a). Yield 87\%; white solid, mp 270-272 °C; IR (KBr): 3288 (NH), 1667 (C=O), 1569 (C=N) cm\(^{-1}\);

\( ^{1}H\) NMR (400 MHz, DMSO-\( \text{d6} \)): \( \delta \) 2.32 (s, 3H, CH\(_3\)), 3.72 (s, 2H, CH\(_2\)), 5.21 (1H, CH\(_2\)), 6.21 (1H, C=C-H, J = 7.1 Hz), 7.28-7.88 (m, 15H, Ar-H), 9.86 (bs, 1H, CH\(_2\)-NH), 12.84 (bs, 1H, Imidazole-NH) ppm; \(^{13}\text{C}\) NMR (100 MHz, DMSO-\( \text{d6} \)): \( \delta \) 23.9 (CH\(_3\)), 44.6 (CH\(_2\)), 63.6 (C-4'), 82.4 (C-5'), 152.1 (C-3'), 161.7 (C-2), 135.3 (C-4), 114.2 (C-5), 166.4 (CH\(_2\)NHCO), 167.5 (NHCO), 126.6, 127.8, 128.4, 129.6, 131.4, 132.5, 133.4, 134.2, 135.6, 136.2, 137.2, 138.1 ppm (aromatic carbons); HRMS: (\( m/z \)) 522.9461 [M+Na].

General procedure for the synthesis of 2-Oxo-2-((4-phenyloxazol/thiazol-imidazol-2-yl)amino)ethyl)-3,5-diphenylisoxazole-4-carboxamide (7 / 8 / 9)

Yield 84\%; white solid, mp 285-287 °C; IR (KBr): 3301 (NH), 1669 (C=O), 1620 (C=C), 1572 (C=N) cm\(^{-1}\);

\( ^{1}H\) NMR (400 MHz, DMSO-\( \text{d6} \)): 2.34 (s, 3H, CH\(_3\)), 3.84 (s, 2H, CH\(_2\)), 7.32-7.83 (m, 15H, Ar-H), 8.82 (bs, 1H, CH\(_2\)-NH), 9.50 (bs, 1H, NH-CO) ppm; \(^{13}\text{C}\) NMR (100 MHz, DMSO-\( \text{d6} \)): \( \delta \) 23.7 (CH\(_3\)), 45.6 (CH\(_2\)), 135.7 (C-4'), 150.5 (C-5'), 156.4 (C-3'), 161.7 (C-2), 138.2 (C-4'), 137.3 (C-5), 165.2 (CH\(_2\)NHCO), 168.9 (NHCO), 122.5, 123.2, 125.4, 126.6, 128.7, 129.5, 130.6, 131.4, 132.3, 133.3, 134.6, 135.4 ppm (aromatic carbons); HRMS: (\( m/z \)) 501.4985 [M+Na].

Yield 86\%; white solid, mp 281-283 °C; IR (KBr): 3314 (NH), 1669 (C=O), 1620 (C=C), 1572 (C=N) cm\(^{-1}\);

\( ^{1}H\) NMR (400 MHz, DMSO-\( \text{d6} \)): 2.34 (s, 3H, CH\(_3\)), 3.84 (s, 2H, CH\(_2\)), 7.32-7.83 (m, 15H, Ar-H), 8.82 (bs, 1H, CH\(_2\)-NH), 9.50 (bs, 1H, NH-CO) ppm; \(^{13}\text{C}\) NMR (100 MHz, DMSO-\( \text{d6} \)): \( \delta \) 23.7 (CH\(_3\)), 45.6 (CH\(_2\)), 135.7 (C-4'), 150.5 (C-5'), 156.2 (C-3'), 164.6 (CH\(_2\)NHCO), 168.2 (C-2), 144.2 (C-4), 101.2 (C-5), 171.1 (NHCO), 123.8, 124.6, 126.7, 127.8, 128.5, 128.9, 129.5, 130.4, 131.6, 133.2, 134.2, 135.3 ppm (aromatic carbons); HRMS: (\( m/z \)) 517.5596 [M+Na].
NMR (400 MHz, DMSO-d$_6$): δ 2.32 (s, 3H, CH$_3$), 3.74 (s, 2H, CH$_2$), 7.30-7.86 (m, 15H, Ar-H), 7.96 (bs, 1H, CH$_2$-NH), 8.34 (bs, 1H, Imidazole-NH) ppm; $^{13}$C NMR(100 MHz, DMSO-d$_6$): δ 23.6 (CH$_3$), 45.4 (CH$_2$), 136.6 (C-4'), 148.7 (C-5'), 157.2 (C-3'), 158.8 (C-2), 134.6 (C-4), 113.4 (C-5), 165.5 (CH$_2$NHCO), 168.9 (NHCO), 125.2, 126.5, 127.4, 128.3, 129.5, 130.1, 131.3, 132.2, 134.5, 134.7, 136.4, 138.9 ppm (aromatic carbons); HRMS: (m/z) 500.5153 [M+Na]. Anal. Calcd. for: C$_{28}$H$_{23}$N$_5$O$_3$: C, 70.43; H, 4.86; N, 14.67%. Found: C, 70.49; H, 4.85; N, 14.92%.

$\text{N-(2-Oxo-2-((4-phenyl-1H-imidazol-2-yl)amino)ethyl)-3-phenyl-5-(p-chlorophenyl)-isoxazole-4-carboxamide (9b).}$ Yield 79%, white solid, mp 292-294 °C; IR (KBr) : 3312 (NH), 1676 (C=O), 1638 (C=C), 1574 (C=N) cm$^{-1}$; $^1$H NMR (400 MHz, DMSO-d$_6$): δ 3.76 (s, 2H, CH$_2$), 7.57-7.89 (m, 15H, Ar-H), 7.90 (bs, 1H, CH$_2$-NH), 9.54 (bs, 1H, Imidazole-NH) ppm; $^{13}$C NMR (100 MHz, DMSO-d$_6$): δ 44.8 (CH$_2$), 135.6 (C-4'), 149.5 (C-5'), 154.6 (C-3'), 158.1 (C-2), 133.8 (C-4), 110.7 (C-5), 165.1 (CH$_2$NHCO), 169.3 (NHCO), 123.6, 124.5, 125.3, 127.1, 127.9, 128.4, 129.3, 131.6, 135.5, 136.6, 137.8, 138.4 ppm (aromatic carbons); HRMS: (m/z) 520.9279 [M+Na]. Anal. Calcd. for: C$_{27}$H$_{20}$ClN$_5$O$_3$: C, 65.13; H, 4.05; N, 14.06%. Found: C, 65.25; H, 4.08; N, 14.32%.

**Antifungal Assays**

The compounds 4-9 were tested for antifungal activity using Ketocanazole as the standard drug [7].

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**REFERENCES**