Synthesis and Biological activities of 1,2-Benzisoxazoles and their N-Glucosides

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Keywords: 1,2-Benzisoxazole, Amino compounds, Pyrazoles, N-Glucosides and Polarography.

Abstract

2-oximinoacetyl-4-acetyl phenol 2 was prepared by the interaction of 2,4-diacetyl phenol 1 with hydroxylamine hydrochloride using suitable solvent. Cyclization of product 2 with acetic anhydride using N,N-Dimethylformamide afforded 3-methyl-5-acetyl-1,2-benzisoxazole 3. Nitration of compound 3 with nitration mixture produces 3-methyl-5-acetyl-7-nitro-1,2-benzisoxazole 4. 3-Methyl-5-acyl-7-amino-1,2-benzisoxazole 5 was prepared by the reduction of product 4 using tin and hydrochloric acid. Different 3-methyl-5-(3-aryl prop-2-enoyl)-7-amino-1,2-benzisoxazoles 6a-j have been synthesized by the interaction of appropriate 3-methyl-5-acyl-7-amino-1,2-benzisoxazole 5 with different aromatic aldehydes using piperidine. The reaction of 3-methyl-5-(3-aryl prop-2-enoyl)-7-amino-1,2-benzisoxazoles 6a-j with hydrazine hydrate in alcoholic KOH to obtained 3-methyl-5-(3-aryl-1H-pyrazol-5-yl)-7-amino-1,2-benzisoxazoles 7a-j. Condensation of tetra-O-acetylα-D-glucopyranosyl bromide with compounds 7a-j furnishes 3-methyl-5-(3-aryl-1H-pyrazol-5-yl)-7-amino-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-1,2-benzisoxazoles 8a-j which on deprotection to get 3-methyl-5-(3-aryl-1H-pyrazol-5-yl)-7-amino-(β-D-glucopyranosyl)-1,2-benzisoxazoles 9a-j. The synthesized compounds were characterized on the basis of IR, ¹H NMR, ¹³C NMR and Mass Spectroscopy, Elemental analysis, TLC, chemical properties and Polarographic studies. All compounds have been screened for antimicrobial activities and some compounds show potent activities.

Keywords: 1,2-Benzisoxazole, Amino compounds, Pyrazoles, N-Glucosides and Polarography.

Introduction

Heterocyclic chemistry is a vast and expanding area of chemistry because of the obvious applications of compounds derived from heterocyclic rings in pharmacy, medicine, agriculture and other fields. The chemistry of heterocyclic compounds is as relevant as that of alicyclic or aromatic compounds. Heterocyclic compounds used as pharmaceuticals, agrochemicals and veterinary products, used as optical brightening agents, as antioxidants, as corrosion inhibitors and as additives with a variety of other functions. Also, many dyestuffs and pigments have heterocyclic structures. A heterocyclic compounds such as isoxazole, pyrazoles, furans, pyrroles, thiazines, oxazines etc. exhibit diverse pharmacological activities such as potential anti-fungal agents, anti-bacterial agents, antiviral, anti-inflammatory, herbicidal, anticancer, cytotoxic, anaesthetics, insecticidal, pesticidal etc. The term pyrazole refers to the class of simple aromatic ring organic compounds of the heterocyclic series. The first natural pyrazole, 1-pyrazolyl-alanine, was isolated from seeds of watermelons in 1959. Pyrazole derivatives show application in agrochemicals as herbicides and in pharmaceutical industry as active pharmaceuticals; the COX-2 inhibitor has further highlighted the importance of these heterocyclic rings in medicinal chemistry. Many pyrazoles are used for the treatment of thyroid and leukaemia having possessed wide range of pharmacological activities like antioxidant, anti-inflammatory, anti-viral, anti-depressant, agrochemicals, and dyestuffs in sunscreen materials etc. The derivatives of 1,3,4-oxidiazole possess antibacterial, fungitoxic, insecticidal, herbicidal and anticancer activity. Coconcelli, et al, reported aryl azoles shows neuroprotective activity.

Benzisoxazoles have recently attracted attention as an important class of heterocyclic compounds in the field of drugs and pharmaceuticals. These compounds are widely used as analgesic, anticonvulsant, antipsychotic and antimicrobial agents. They are present in large number of pharmaceutical important products with antitumor, antithrombotic and cholinesererase-inhibiting properties. 1,2-Benzisoxazoles derivatives have been found to possess antidepressant and hypotensive activity, as potent and selective inhibitors of the enzyme acetyl cholinesererase, evaluated as a potential antipsychotic D2/5-HT2 antagonists. Two patents have claimed that substituted 3-(aminoalkylamino)-1,2-benzisoxazoles are useful for the treatment of various memory dysfunctions and as antidepressants by inhibiting monoamine oxidase. 6-fluro-4-piperidinyl-1,2-benzisoxazole-amides were synthesized and tested against antimicrobial agents and reported potent inhibition against antimicrobial stains.
Heterocyclic substituted chalcones were prepared by Bombardelli and Valenti reported some of them were introduced for the treatment of breast cancer, menopausal disorders and osteoporosis.

Chalcone derivatives have found a wide range of application in the pharmacological activities such as potential cytotoxic properties are reported by Bhatt, et al. Antiviral, anaesthetic, mydriatics, antimicrobial, anti-mitotic, antitumor, cytotoxicity, antipyretic, antifungal, anti-inflammatory, insecticidal and anti-HIV properties. Venkatachalam et al. reported anti-oxidant activity of substituted chalcone.

Glucosylation improves the solubility of various drugs without affecting their activities and attaching of the glucosidic moiety into the molecules increases its hydrophilicity than the respective aglycon. β-Glucosylation can improve the drug targeting to the cells due to their solubility in the membrane components. The carbohydrate moiety enhances the water and lipid solubility of the pharmacophoric group and the major active molecule is the aglycone which is responsible for its biological activities. The screening results indicate that glucosides showed moderate to excellent antibacterial activity against E. coli and S. aureus organisms as compared to aglycon.

In the view of pronounced biological and pharmacological applications of Chalcones, 1,2-Benzisoxazoles, Nitro, Amine derivatives, Pyrazoles and N-Glucosides. It was planned to synthesize new chemical entities having active pharmacological functions namely chalcones, benzisoxazoles, nitro, amine, pyrazoles and their N-glucosides moiety in a single molecular framework as a new biological active compounds.

Materials and Methods

Melting points were determined on a melting point apparatus and are uncorrected. IR spectra were recorded on Bruker infrared spectrometer. 1H NMR, 13C NMR spectra on Bruker Avance II 400 NMR spectrometer and MS spectra were recorded and polarograms were recorded on Elico CL-362 polarograph.

General Synthesis: Synthesis of 2,4-diacetyl phenol (1). It is prepared by Fries rearrangement reaction as reported in literature. The crude product 2,4-diacetyl phenol was crystallized from aqueous alcohol, decolourised with activated charcoal powder and pure colourless crystalline solid product was obtained. Yield 14.5g, 81.4%, MP 97ºC and its alcoholic solution gave violet colour with neutral FeCl3 solution.

IR: \( \nu_{\text{max}} \text{cm}^{-1}: 3353(\text{br. OH peak}), 2868-2972 \) (C-H str. In benzene), 1641 & 1670 (C=O two), 1489 (C=C str. in benzene); 1H-NMR: \( \delta \)2.69 (s, 1H, OH), \( \delta \)8.44 (d, J=2.04 Hz, 1H, Ar-H), \( \delta \)8.05-8.08 (m, 1H, Ar-H), \( \delta \)7.04 (d, J=8.76 Hz, Ar-H), \( \delta \)2.72 (s, 3H, CH), \( \delta \)2.69 (s, 3H, CH); 13C-NMR: \( \delta \)204.85 (C=O), \( \delta \)195.84 (C=O), \( \delta \)166.07 (C-1), \( \delta \)136.37 (C-5), \( \delta \)131.87 (C-4), \( \delta \)130.86 (C-3), \( \delta \)119.22 (C-2), \( \delta \)115.37 (C-1), \( \delta \)26.76 (CH3), \( \delta \)26.32 (CH3); MS: m/z 179, 164, 161, 137.

Synthesis of 2-oximinoacetyl-4-acetyl phenol (2): A mixture of 2,4-diacetyl phenol (17.8g, 0.1M), hydroxylamine hydrochloride (6.9g, 0.1M), sodium acetate (8.2g, 0.1M) and 50mL of EtOH/H2O (7:3) was refluxed for 2hrs. After cooling colourless solid were filtered, washed with water, dried and crystallised by aq. alcohol. (Yield 16.2g, 83.93%), MP 174ºC and its alcoholic solution gave violet colour with neutral FeCl3 solution.

Synthesis of 3-methyl-5-acetyl-1,2-Benzisoxazole (3): To a solution of 2-oximinoacetyl-4-acetyl phenol (19.3g, 0.1M) and N,N-dimethylformamide (8.0mL), sodium acetate (18.0g, 0.22M) and acetic anhydride (21.8mL, 0.23M) were added, the reaction mixture was refluxed for 4hr at which state all the starting material was consumed as indicated by TLC. After cooling the reaction mixture was poured into ice cold water. A brownish solid was filtered and dried. (Yield 13.1g, 74.81%), MP 112ºC and its alcoholic solution gave no violet colour with neutral FeCl3 solution.

IR: \( \nu_{\text{max}} \text{cm}^{-1}: 2862-3057 \) (C-H str. In benzene), 1467 (C=C str. in benzene). 1H-NMR: \( \delta \)8.03 (d, J=1.08 Hz, 1H, Ar-H), \( \delta \)7.96-7.99 (m, 1H, Ar-H), \( \delta \)7.57 (d, J=8.84 Hz, 1H, Ar-H), \( \delta \)2.69 (s, 3H, CH3), \( \delta \)2.47 (s, 3H, CH3); 13C-NMR: \( \delta \)194.15 (C-O), \( \delta \)168.66 (C-8), \( \delta \)155.50 (C-3), \( \delta \)130.56 (C-5), \( \delta \)128.83 (C-6), \( \delta \)122.70 (C-4), \( \delta \)120.83 (C-9), \( \delta \)110.10 (C-7), \( \delta \)24.79 (CH3), \( \delta \)14.77 (CH3).

Synthesis of 3-methyl-5-acetyl-7-nitro-1,2-benzisoxazole (4): Nitration of 3-methyl-5-acetyl-1,2-benzisoxazole (17.5g, 0.1M) in nitrating mixture [conc. H2SO4 (30mL) and conc. HNO3 (7mL)]. After addition was complete, the reaction mixture was warmed to room temperature and stirred. After the starting material was consumed as indicated by TLC the reaction mixture was poured slowly on ice with constant shaking. The resulting yellow solid was filtered and dried. Yield 20.40g, 86.44%, MP 66ºC.

Synthesis of 3-methyl-5-acetyl-7-amino-1,2-benzisoxazole (5): The appropriate 3-methyl-5-acetyl-7-nitro-1,2-benzisoxazole (23.6g, 0.1M) and tin granules (35.6g, 0.3M) were thoroughly ground together and then concentrated HCl (100 mL) was added slowly with vigorous stirring. After the addition of acid the reaction mixture was boiled for 30 min. and then allowed to cool to room temperature. The solution was diluted with water (50mL) cooled in an ice bath and made alkaline with 20 % NaOH solution added over 5-10 min. The resulting precipitate was filtered, washed with 2M NaOH and then water. (Yield 12.3g, 64.73%), MP 136ºC and functional group test i.e. Dye test was positive.

IR: \( \nu_{\text{max}} \text{cm}^{-1}: 3323 (-\text{NH}_2), 3261 (-\text{NH}_2), 2885-3054 \) (C-H str. In
benzene), 1637 (C=O), 1568 (benzene), 1637 (C=O), 1568 (C=N), 1615 (bend N-H); 1H-NMR: 88.36-8.39 (t, 1H, Ar-H), 88.11-8.18 (t, 1H, Ar-H), 6.42 (s, 2H, NH2), 6.26 (s, 3H, CH3), 6.56 (s, 3H, CH3); MS: m/z 190, 178, 173, 162, 160, 134, 131.

Synthesis of 3-methyl-5-(3-phenyl prop-2-enoyl)-7-amine-1,2-benzisoxazole (6a).
Condensation of 3-methyl-5-acetyl-7-amine-1,2-benzisoxazole (1.0g, 0.01M) in ethyl alcohol (25 mL) using a few drops of piperidine for 40 min. The reaction mixture was cooled to 0ºC, yellow solid compound formed was washed with water. (Yield 2.10g, 75.50%), MP 92ºC and its alcoholic solution turned red with conc. H2SO4.

In the same way, other chalcones 3-methyl-5-(3-aryl prop-2-enoyl)-7-amine-1,2-benzisoxazoles (6b-j) were prepared.

Synthesis of 3-methyl-5-(3-phenyl 1H-pyrazol-5-yl)-7-amine-1,2-benzisoxazole (7a).
A mixture of 3-methyl-5-(3-phenyl prop-2-enoyl)-7-amine-1,2-benzisoxazole (2.78g, 0.01M), hydrazine hydrate (0.5g), ethyl alcohol (15mL) and KOH (0.4g) was refluxed on water bath for 4hours. It was cooled and acidified with glacial acetic acid (1.5mL) and was poured on ice-cold water (50mL), dried and crystallized with aqueous alcohol. Yield 63%, MP 126ºC. It did not give dark red colour with conc. H2SO4.

IR: v_max cm⁻¹: 3243 (-NH2), 3198 (-NH2), 3064-2839 (C-H str. In benzene), 1734 (C=O). 1H-NMR: 88.79, (d, J=5.96, 1H, C=O-C=H=C-H), 88.47, (t, 1H, C=O-C=H=C-H), 88.21, (d, J=6.08 Hz, 1H, Ar-H), 88.07 (d, J=9.84 Hz, 1H, Ar-H), 87.45-7.82 (m, 4H, Ar-H), 87.03, (d, J=11.12 Hz, 1H, Ar-H), 86.22 (s, 2H, NH2), 8.69 (s, 3H, CH3); 13C-NMR: δ198.31 (C=O), δ125.18 (C-9), δ141.79 (ethylene CH), δ139.32 (C-1'), δ136.06(C-5), δ133.96 (C-7), δ131.80 (C-3'), δ129.27 (C-5'), δ127.39 (C-4'), δ126.97 (C-2'), δ125.98(C-6'), δ125.18 (C-9'), δ123.09 (ethylene CH), δ119.03 (C-6), δ114.43 (C-4), δ147.8 (CH3); MS: m/z 279, 262, 247, 184, 179, 164, 160, 136.

Following the above procedure, other 3-methyl-5-(3-aryl 1H-pyrazol-5-yl)-7-amine-1,2-benzisoxazoles (7b-j) were prepared. The characterization data of these compounds are summarised in Table-1.

<table>
<thead>
<tr>
<th>Comp</th>
<th>R</th>
<th>Molecular formula</th>
<th>Mol. Wt</th>
<th>MP C</th>
<th>Yield (%)</th>
<th>Found (Calculated) %</th>
</tr>
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<tbody>
<tr>
<td>7a</td>
<td>C₆H₅</td>
<td>C₁₇H₁₄N₂O</td>
<td>290.3</td>
<td>126</td>
<td>63</td>
<td>70.33 (72.12) 4.86 (4.90) 19.30 (19.05)</td>
</tr>
<tr>
<td>7b</td>
<td>4-ClC₆H₄</td>
<td>C₁₇H₁₃ClN₂O</td>
<td>334.7</td>
<td>110</td>
<td>68</td>
<td>62.87 (63.40) 4.03 (4.21) 17.25 (18.30)</td>
</tr>
<tr>
<td>7c</td>
<td>2-NO₂C₆H₄</td>
<td>C₁₇H₁₃N₂O</td>
<td>335.3</td>
<td>122</td>
<td>65</td>
<td>60.89 (61.80) 3.91 (4.10) 20.89 (22.30)</td>
</tr>
<tr>
<td>7d</td>
<td>4-NO₂C₆H₄</td>
<td>C₁₇H₁₄N₂O</td>
<td>335.3</td>
<td>112</td>
<td>70</td>
<td>60.89 (63.05) 3.91 (4.00) 20.89 (19.69)</td>
</tr>
<tr>
<td>7e</td>
<td>4-OHC₆H₄</td>
<td>C₁₇H₁₄N₂O</td>
<td>306.3</td>
<td>128</td>
<td>67</td>
<td>66.66 (69.78) 4.61 (4.65) 18.29 (19.57)</td>
</tr>
<tr>
<td>7f</td>
<td>2-OHC₆H₄</td>
<td>C₁₇H₁₄N₂O</td>
<td>306.3</td>
<td>133</td>
<td>55</td>
<td>66.66 (67.21) 4.61 (4.60) 18.29 (17.98)</td>
</tr>
<tr>
<td>7g</td>
<td>2-C₆H₅O</td>
<td>C₁₅H₁₃N₂O</td>
<td>280.2</td>
<td>166</td>
<td>58</td>
<td>64.28 (63.13) 4.32 (4.56) 19.99 (19.20)</td>
</tr>
<tr>
<td>7h</td>
<td>2-CH₃OC₆H₄</td>
<td>C₁₈H₁₆N₂O</td>
<td>320.3</td>
<td>101</td>
<td>56</td>
<td>67.49 (69.56) 5.03 (5.32) 17.49 (17.50)</td>
</tr>
<tr>
<td>7i</td>
<td>4-CH₃OC₆H₄</td>
<td>C₁₈H₁₆N₂O</td>
<td>320.3</td>
<td>98</td>
<td>48</td>
<td>67.49 (66.98) 5.03 (4.90) 17.49 (19.82)</td>
</tr>
<tr>
<td>7j</td>
<td>6-CH₃OC₆H₄</td>
<td>C₁₈H₁₆N₂O</td>
<td>320.3</td>
<td>109</td>
<td>62</td>
<td>67.49 (70.26) 5.03 (5.10) 17.49 (16.36)</td>
</tr>
</tbody>
</table>
Synthesis of 3-methyl-5-(3-phenyl-1H-pyrazol-5-yl)-7-amine-
(β-D-glucopyranosyl)-1,2-benzisoxazole (9a). It was prepared
from 3-methyl-5-(3-phenyl-1H-pyrazol-5-yl)-7-amino-1,2-
benzisoxazole (2.90g, 0.01M) refluxed with tetra-acetyl
glucopyranosyl bromide (TAGBr) (3.0g, 0.01M) in presence
of tetra butyl ammonium bromide (PTC) using dichloromethane
as a solvent. The deprotection of above obtained compound
3-methyl-5-(3-phenyl-1H-pyrazol-5-yl)-7-amino-(β-D-2,3,4,6-
tetra – O - acetyl glucopyranosyl)-1,2-benzisoxazole was done
by sodium methoxide in methanol and filtered from ion
exchange resin (Amberlite IR 120, H+, cation exchanger) to get
target molecules.

IR: v_{max}cm^{-1}: 3366 (str.OH), 3143 (N-H), 2929 (Ar-H str),
1634(C=N), 1H-NMR: δ8.38-7.03 (m, 7H, Ar-H), δ6.93 (s, 1H,
Pyrazole), δ4.51-4.47 (m, 1H in glucose), δ4.65 (s, 1H,
NH), δ3.81-2.70 (6H, glucose), δ2.55 (s, 3H, CH3); 13C-NMR:
δ152.0 (Pyrazole), δ151.3 (Pyrazole), δ156.7 (C-3), δ149.8 (C-
8), δ131.3 (C-5), δ130.2 (C-1'), δ129.1 (C-3'), δ127.9 (C-5'),
δ125.6 (C-4'), δ126.2 (C-7), δ 124.7 (C-2'), δ124.9 (C-6'),
δ123.7 (C-9), δ112.2 (C-6), δ110.5 (C-4), δ99.5 (Pyrazole),
δ81.3 (glucose C-1), δ73.9 (glucose C-5), δ72.3 (glucose C-3),
δ71.6 (glucose C-4), δ69.4 (glucose C-2), δ63.6 (glucose C-6),
δ18.4 (CH3). MS: m/z 453, 289, 274, 248, 180, 164, 143, 131.

Following the above procedure, other N-glucosides 3-methyl-5-
(3-aryl-1H-pyrazol-5-yl)-7-amino-(β-D-glucopyranosyl)-1,2-
benzisoxazoles (9b-j) were prepared. The characterization data
of these compounds are summarized in Table-2.

Table-2
Characterization data of 3-methyl-5-(3'-aryl-1H-pyrazol-5-yl)-7-amine-(β-D-glucopyranosyl)-1,2-benzisoxazoles (9a-j)

<table>
<thead>
<tr>
<th>Comp</th>
<th>R</th>
<th>Molecular formula</th>
<th>Mol. Wt.</th>
<th>Found (Calculated) %</th>
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</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>C6H5</td>
<td>C23H22N4O6</td>
<td>452.4</td>
</tr>
<tr>
<td>9a</td>
<td>C6H5</td>
<td>C23H22N4O6</td>
<td>486.9</td>
<td>56.74 (58.32)</td>
</tr>
<tr>
<td>9b</td>
<td>4-ClC6H5</td>
<td>C23H22ClN4O6</td>
<td>497.4</td>
<td>55.53 (56.80)</td>
</tr>
<tr>
<td>9c</td>
<td>2-NO2C6H4</td>
<td>C23H22N2O8</td>
<td>497.4</td>
<td>55.53 (54.20)</td>
</tr>
<tr>
<td>9d</td>
<td>4-NO2C6H4</td>
<td>C23H22N2O8</td>
<td>497.4</td>
<td>55.53 (54.20)</td>
</tr>
<tr>
<td>9e</td>
<td>4-OHC6H4</td>
<td>C23H22N2O7</td>
<td>468.4</td>
<td>58.97 (59.30)</td>
</tr>
<tr>
<td>9f</td>
<td>2-OHC6H4</td>
<td>C23H22N2O7</td>
<td>468.4</td>
<td>58.97 (60.20)</td>
</tr>
<tr>
<td>9g</td>
<td>2-C12H4</td>
<td>C21H22N2O7</td>
<td>442.1</td>
<td>57.01 (56.85)</td>
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<tr>
<td>9h</td>
<td>2-CH2OC6H4</td>
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<td>482.4</td>
<td>59.74 (60.58)</td>
</tr>
<tr>
<td>9i</td>
<td>4-CH2OC6H4</td>
<td>C23H26N2O7</td>
<td>482.4</td>
<td>59.74 (62.10)</td>
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<td>9j</td>
<td>6-CH2OC6H4</td>
<td>C23H26N2O7</td>
<td>482.4</td>
<td>59.74 (60.25)</td>
</tr>
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</table>

Polarographic studies: Polarographic studies of 3-methyl-5-(3-
phenyl-1H-pyrazol-5-yl)-7-amino-1,2-benzisoxazole and 3-
methyl-5-(3-phenyl-1H-pyrazol-5-yl)-7-amine-(β-D-
glucopyranosyl) -1,2-benzisoxazole were carried out using Elico
CL-362 polarograph based on microprocessor operation. The
electrode system consisted of dropping mercury electrode as
working electrode, platinum wire as auxiliary electrode and
saturated calomel electrode as reference electrode. The
supporting electrolyte used was 0.1 M KCl solution.

The supporting electrolyte solution was deaerated with nitrogen
for 15 minutes and polarograms were recorded in DC and DPP
modes. To this solution, various concentrations of ethanolic
solutions of 3-methyl-5-(3-phenyl-1H-pyrazol-5-yl)-7-amino-
1,2-benzisoxazole were added and polarograms were recorded
for each addition.

The DC polarogram shows a distinct polarographic wave with
half wave potential (E_{1/2}) -1.700V which matches with the
literature value for heterocyclic compounds such as pyrazole
group. The differential pulse polarogram shows a distinct peak
with peak potential -1.650V.

The supporting electrolyte solution was deaerated with nitrogen
for 15 minutes and polarograms were recorded in DC and DPP
modes. To this solution, various concentrations of ethanolic
solutions of 3-methyl-5-(3-phenyl-1H-pyrazol-5-yl)-7-amino-(β-
D-glucopyranosyl)-1,2-benzisoxazole were added and polarograms were recorded for each addition.
The DC polarogram shows a distinct polarographic wave with half wave potential (E_{1/2}) -1.600V which matches with the literature value for sugar group. The differential pulse polarogram shows a distinct peak with peak potential -1.550V\(^{32}\).

Results and Discussion

2,4-Diacetyl phenol (1) was synthesised as per reported work in the literature and the structure was confirmed by IR spectrum shows absorption band at 3353 cm\(^{-1}\), which indicates the presence of phenolic –OH group and two peaks shown in the range of 1670 cm\(^{-1}\) and 1641 cm\(^{-1}\), it proven two acetyl group in aforesaid compound. The \(^1\)HNMR spectra showed phenolic proton at δ12.69 ppm and the molecular mass of compound was confirmed by ion peak at m/z 179.2. The oximinoacetly-4-acetyl phenol (2) was prepared by the reaction with hydroxylamine hydrochloride and reflux for 1hr in ethanol and water\(^{43}\). The obtained product (2) are refluxed with DMF in presence of acetic anhydride afforded 3-methyl-5-acetyl-1,2-benzisoxazole (3). In IR and \(^1\)HNMR studies it is observed that the disappearance of phenolic –OH group also in \(^13\)CNMR spectra observed the peak at δ168.66 ppm and δ110.10 ppm it confirmed the cyclization and formation of compound (3). Nitrilation of (3) with nitrating mixture gives 3-methyl-5-acetyl-7-nitro-1,2-benzisoxazole\(^{44}\) (4) which on refluxed with reducing mixture tin metal granules and conc. hydrochloric acid to yield reduced product 3-methyl-5-acetyl-7-amine-1,2-benzisoxazole\(^{45}\) (5). The obtained compound 5 was confirmed by IR spectra and shown two peaks at 3359 cm\(^{-1}\) and 3253 cm\(^{-1}\). \(^1\)HNMR spectra indicates the peak of two protons at δ4.24 ppm and MS shows molecular ion peak at m/z 190.

The compounds 3-methyl-5-(3-aryl prop-2-enoyl)-7-amine-1,2-benzisoxazoles (6a-j) are prepared by the interaction of 5 with different aromatic and heterocyclic aldehydes using suitable solvent\(^{46}\). In IR spectrum the absorption band observed at 1734 cm\(^{-1}\) for >C=O group in chalcone. In \(^13\)CNMR spectra two peaks observed at δ141ppm and δ123 ppm for ethylenic (-CH) and for >C=O the peak appears at δ198 ppm. The reaction of 3-methyl-5-(3-aryl prop-2-enoyl)-7-amine-1,2-benzisoxazoles (6a-j) with hydrazine hydrate in alcoholic KOH obtained 3-methyl-5-(3-aryl-1H-pyrazol-5-yl)-7-amine-1,2-benzisoxazoles\(^{47}\) (7a-j). Mass spectra show the molecular ion peak at m/z 291. The 3-methyl-5-(3-aryl-1H-pyrazol-5-yl)-7-amine-(β-D-2, 3, 4, 6-tetra-O-acetyl glucopyranosyl)-1,2-benzisoxazoles (8a-j) have been prepared by Glucosylation of 3-methyl-5-(3-aryl-1H-pyrazol-5-yl)-7-amine-1,2-benzisoxazoles with tetra-O-acetyl glucopyranosyl bromide using PTC and dichloromethane as a solvent. All the synthesized compounds were deprotected by Sodium methoxide in methanol to obtained target molecules 3-methyl-5-(3-aryl-1H-pyrazol-5-yl)-7-amine-(β-D-glucopyranosyl)-1,2-benzisoxazoles\(^{47}\) (9a-j). The IR spectra of compound show strong band in the range of 3366 cm\(^{-1}\) due to glucosyl –OH. The \(^1\)HNMR spectra show a multiplet due to the glucosyl ring protons in the ranges of 6.81-2.70 ppm and the doublet of anomic proton of the glucose moiety within the region of δ4.51-4.47 ppm. The \(^13\)CNMR spectra show the signal for β-anomeric carbon is observed at δ81.3 ppm.

Antimicrobial activity: The antifungal screening of compounds 9a-9j were carried out against two fungi viz., Candida albicans and Aspergillus niger adopting the disc diffusion method. The comparison of results was done by using clotrimazole as a standard. The compounds 9b, 9c, 9g and 9h were active and 9a, 9d, 9e, 9f and 9i were moderately active against A. niger. The compounds 9a-9e, 9h and 9i were active and 9f, 9g and 9j was less active against fungi C. albicans at 800μg/mL concentration. Similarly, the compounds 9a-9j was screened for their antibacterial activity against Escherichia coli and Staphylococcus aureus by disc diffusion method. The standard Ciprofloxacin was used for the comparison of results. The screening result showed the entire compound active against both the bacteria tested at 800μg/mL concentration. Compounds 9b, 9e, 9h and 9j were active and 9a, 9c, 9d, 9f and 9i showed moderately active against bacteria E. coli and 9a, 9b, 9d, 9e, 9i and 9j were active and 9c, 9f, 9g and 9h showed less activity against bacteria S. aureus.

Conclusion

In this article, we have synthesized a new series of 1,2-benzisoxazoles and their derivatives like chalcones, pyrazoles, amines and their N-glucosides and evaluated for their antimicrobial activities. The compounds 9a-j was screened for anti-bacterial and anti-fungal activities. Compounds 9a-e, 9g, 9h and 9i were active against fungi while 9a, 9b, 9d, 9e, 9i and 9j was active against bacteria.

Thus novel benzisoxazoles derivatives can be incorporated to the family of bioactive heterocyclic compounds.

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