INTRODUCTION

In 2030, cancer is projected to be the leading cause of death globally, with an estimated death toll of about 17 million people. When discovered early and treated in accordance with best standards, some of the most prevalent cancer types, including breast cancer, cervical cancer, oral cancer and colorectal cancer, have high cure prospects. When the unfavourable side effects of chemotherapeutics limit their use, chemotherapy remains the most efficacious approach for cancer treatment, therefore, it is crucial for cancer research to look for safe and effective anticancer chemicals [1,2].

In medicinal chemistry, quinoline is a fascinating heterocyclic scaffold. Quinoline and its related compounds have a wide range of pharmacological effects, including antibacterial, antifungal, antitubercular, anticancer and choline esterase inhibitor properties [3-11]. Triazoles are desirable scaffolds among N-containing heterocycles because of their pharmacological importance. In the line of lactum antibiotics, synthetic triazoles tazobactum (1) and ceftrazidine (2) exist and CAI is available on the market, as shown in Fig. 1. 1,2,3-Triazoles have been found to exhibit antibacterial [12,13], antifungal [14], anticancer [15-17] and antitubercular [18] effects. Herein, the design and synthesis of new quinoline containing 1,4-disubstituted 1,2,3-triazole hybrids via click reaction based on their synthetic and biological activity.

EXPERIMENTAL

Unless otherwise specified, all solvents and reagents were purchased from well-known commercial sources. The Buchi melting point instrument was used to determine the melting points in open capillaries and are uncorrected. A F254 silica-gel precoated aluminum sheets were subjected to thin layer chromatography with hexane/ethyl acetate (7/3) as eluent to evaluate the reactions’ progress and the compounds’ purity. An automated elemental analyzer, Carlo-Erba EA 1108, was used for the element analysis. The absorption spectral studies were measured by UV-visible spectrometer. IR spectra were recorded on Perkin-Elmer 100S spectrometer using KBr pellet. NMR spectra were recorded on Bruker 400 MHz spectrometer using DMSO-d6 as solvent and TMS as an internal standard. Mass spectra (ESI) were recorded on a JEOL JMSD-300 spectrometer.

Synthesis of 2-chloroquinoline-3-carbaldehyde (2): To a cool solution of DMF (3.0 equiv.), phosphoryl chloride (4.5
equiv.) was added dropwise with stirring. In order to obtain 2-chloroquinoline-3-carbaldehyde (2), added acetonilide (1.0 equiv.) to the above mixture and stirred and stirred at 80-90 °C for 12 h. Following the completion of the reaction as shown by TLC, the mixture was poured into crushed ice, agitated for 5 min and the resultant solid was filtered, thoroughly washed with water, dried over anhydrous Na₂SO₄, and finally recrystallized with ethanol.

**Synthesis of 2-morpholinoquinoline-3-carbaldehyde derivatives (3):** A mixture of 2-chloroquinoline-3-carbaldehyde (1.0 equiv.), morpholine (1.1 equiv.) and anhydrous K₂CO₃ (2.0 equiv.) in DMF (10 mL) were charged in a 100 mL round bottom flask equipped with a mechanical stirrer and a condenser. The mixture underwent heating at 90 °C for 2 h. Once the reaction completed, as confirmed by TLC, the mixture was transferred into 100 mL of ice-water. It was then filtered, washed thoroughly with water, dried and finally recrystallized from ethanol to yield a yellow solid.

**Synthesis of (E)-2-chloroquinoline-3-carbaldehyde oxime (4):** An ethanolic solution containing 2-chloroquinoline-3-carbaldehyde (1 mmol), hydroxyl amine hydrochloride (1.5 mmol) and sodium acetate (1.5 mmol) was introduced into a round bottom flask and then the mixture was agitated at ambient temperature for 2 h. Following the reaction’s completion, as confirmed by TLC, 20 mL of ice-cold water was introduced to the mixture. The product was then extracted using 25 mL of chloroform, repeated twice. The chloroform was separated through distillation using a rota-evaporator under reduced pressure, in vacuo and the obtained crude product was purified by passing through silica gel column (elucent: 30% EtOAc in hexane) to get the desired pure substituted (E)-2-morpholinoquinoline-3-carbaldehyde oxime 4 in 85-90% yields (Scheme-I).

**Synthesis of (E)-2-morpholinoquinoline-3-carbaldehyde O-((1-phenyl-1,2,3-triazol-4-yl)methyl)oxime (8a-j):** To a mixture of (E)-4-(3-(2-prop-2-yn-1-yloxy)vinyl)quinolin-2-yl)morpholine (1.0 equiv.), substituted azidobenzenes 7a-j (1.2 equiv.) in dry DMF (30 mL) was added a solution of CuSO₄·5H₂O (0.01 equiv.) and sodium ascorbate (0.01 equiv.) and the reaction mixture was stirred at 0 ºC for 12 h. Following the completion of the reaction as indicated by TLC, the reaction contents were extracted from ice-cold water and ethyl acetate (3 × 50 mL). The organic layer was washed and dried using brine and dry Na₂SO₄, respectively. The solvent was removed in vacuo and the obtained crude product was purified by passing through silica gel column (eluent: 30% EtOAc in hexane) to get the desired pure substituted (E)-2-morpholinoquinoline-3-carbaldehyde O-((1-phenyl-1H-1,2,3-triazol-4-yl)methyl)oxime (8a-j) in 85-90% yields (Scheme-I).

**Fig. 1. Some biologically potent substituted triazole containing drug molecules in the market**
Scheme-I: Synthesis of a substituted (E)-2-morpholinoquinoline-3-carbaldehyde O-((1-(phenyl-1H-1,2,3-triazol-4-yl)methyl) oxime derivatives

(E)-2-morpholinoquinoline-3-carbaldehyde O-((1-(2-chloro phenyl)-1H-1,2,3-triazol-4-yl)methyl) oxime (8c): White solid, yield: 84%, m.p.: 198-200°C. 1H NMR (400 MHz, CDCl3) δ ppm: 8.40 (s, 1H), 8.32 (s, 1H), 7.89 (s, 1H), 7.73 (s, 1H), 7.67 (d, J = 8 Hz, 1H), 7.65-7.58 (m, 3H), 7.48-7.37 (m, 3H), 5.49 (s, 2H), 3.90 (s, 4H), 3.38 (s, 4H). 13C NMR (100 MHz, CDCl3) δ ppm: 168.2, 164.2, 163.1, 155.3, 144.5, 134.8, 132.5, 131.8, 130.5, 126.1, 125.1, 124.2, 122.6, 118.6, 70.2, 68.3, 55.1 ESI-MS: m/z: 449 (M+H)+. Anal. calcd. (found) % of C23H21N6O2Cl: C, 61.54 (61.52); H, 4.72 (4.76); Cl, 7.90 (7.85); N, 18.72 (18.74); O, 7.13 (7.19).

(E)-2-Morpholinoquinoline-3-carbaldehyde O-((1-(4-chloro phenyl)-1H-1,2,3-triazol-4-yl)methyl) oxime (8d): Pale brown solid, yield: 86%, m.p.: 190-192°C. 1H NMR (400 MHz, CDCl3) δ ppm: 8.40 (s, 1H), 8.32 (s, 1H), 8.05 (s, 1H), 7.85 (d, 1H, J = 8.1 Hz), 7.76-7.73 (m, 3H), 7.67-7.64 (m, 1H), 7.62-7.52 (d, J = 7.5 Hz, 2H), 7.39 (t, J = 7.42 Hz, 1H), 5.45 (s, 2H), 3.88 (s, 4H), 3.35 (s, 4H). 13C NMR (100 MHz, CDCl3) δ ppm: 156.4, 146.2, 142.3, 140.9, 135.7, 132.4, 128.2, 126.4, 125.2, 123.2, 122.4, 121.5, 118.6, 116.9, 76.1, 72.3, 52.2 ESI-MS: m/z: 449 (M+H)+. Anal. calcd. (found) % of C23H21N6O2Cl: 61.54 (61.52); H, 4.72 (4.76); Cl, 7.90 (7.85); N, 18.72 (18.74); O, 7.13 (7.19).

(E)-2-Morpholinoquinoline-3-carbaldehyde O-((1-(2-methoxyphenyl)-1H-1,2,3-triazol-4-yl)methyl) oxime (8e): Brown solid, yield: 86%, m.p.: 180-182°C. 1H NMR (400 MHz, CDCl3) δ ppm: 8.41 (s, 1H), 8.21 (s, 1H), 7.84-7.79 (m, 3H), 7.76 (t, J = 8.5 Hz, 1H), 7.64-7.43 (m, 2H), 7.41-7.10 (m, 2H), 5.49 (s, 2H), 3.88 (m, 7H), 3.34 (s, 4H). 13C NMR (100 MHz, CDCl3) δ ppm: 158.2, 147.1, 143.2, 141.3, 136.2, 135.3, 131.2, 128.1, 126.3, 124.2, 123.1, 121.1, 120.6, 119.6, 117.9, 76.5, 74.2, 53.2, 45.7 ESI-MS: m/z: 445 (M+H)+. Anal. calcd. (found) % of C24H24N6O3: C, 64.85 (64.89); H, 5.44 (5.47); N, 18.91 (18.92); O, 10.80 (10.85).
(E)-2-Morpholinoquinoline-3-carbaldehyde O-((1-(4-methoxyphenyl)-1H-1,2,3-triazol-4-yl)methyl)oxime (8f): Yield 83%, m.p.: 175-177 °C. 1H NMR (400 MHz, CDCl3) δ ppm: 8.40 (s, 1H), 8.33 (s, 1H), 7.90-7.84 (m, 2H), 7.73 (d, J = 7.1 Hz, 1H), 7.64 (t, J = 8.4 Hz, 1H), 7.42-7.36 (m, 5H), 5.48 (s, 2H), 3.88 (s, 4H), 3.36 (s, 4H), 2.24 (s, 3H). 13C NMR (100 MHz, CDCl3) δ ppm: 156.3, 146.3, 142.8, 140.4, 135.4, 134.2, 132.1, 127.2, 125.8, 122.2, 121.6, 120.5, 119.2, 118.2, 116.2, 78.2, 76.2, 56.2, 52.7 ESI-MS: m/z 445 (M+H)+. Anal. calcld. (found) % of C23H22N6O2: C, 64.77 (64.82); H, 5.47 (5.48); N, 10.80 (10.85).

(E)-Morpholinoquinoline-3-carbaldehyde O-((1-(2-methylphenyl)-1H-1,2,3-triazol-4-yl)methyl)oxime (8g): White solid, yield: 81%, m.p.: 170-172 °C. 1H NMR (400 MHz, CDCl3) δ ppm: 8.40 (s, 1H), 8.33 (s, 1H), 7.90-7.84 (m, 2H), 7.73 (d, J = 8.40 Hz, 1H), 7.64 (t, J = 8.42 Hz, 1H), 7.42-7.36 (m, 5H), 5.48 (s, 2H), 3.88 (m, 4H), 3.36 (s, 4H), 2.24 (s, 3H). 13C NMR (100 MHz, CDCl3) δ ppm: 152.4, 142.5, 141.8, 140.6, 136.9, 133.2, 131.9, 126.6, 124.3, 121.5, 121.1, 120.9, 119.1, 118.1, 117.2, 76.2, 71.2, 52.2, 32.6 ESI-MS: m/z: 429 (M+H)+. Anal. calcld. (found) % of C27H27N6O3: C, 64.85 (64.89); H, 5.44 (5.47); N, 18.91 (18.92); O, 10.80 (10.85).

(M)-2-Morpholinoquinoline-3-carbaldehyde O-((1-(4-methylphenyl)-1H-1,2,3-triazol-4-yl)methyl)oxime (8h): White solid, yield: 81%, m.p.: 170-172 °C. 1H NMR (400 MHz, CDCl3) δ ppm: 8.40 (s, 1H), 8.33 (s, 1H), 7.90-7.84 (m, 2H), 7.73 (d, J = 8.40 Hz, 1H), 7.64 (t, J = 8.42 Hz, 1H), 7.42-7.36 (m, 5H), 5.48 (s, 2H), 3.88 (m, 4H), 3.36 (s, 4H), 2.24 (s, 3H). 13C NMR (100 MHz, CDCl3) δ ppm: 152.4, 142.5, 141.8, 140.6, 136.9, 133.2, 131.9, 126.6, 124.3, 121.5, 121.1, 120.9, 119.1, 118.1, 117.2, 76.2, 71.2, 52.2, 32.6 ESI-MS: m/z: 429 (M+H)+. Anal. calcld. (found) % of C27H27N6O3: C, 64.85 (64.89); H, 5.44 (5.47); N, 18.91 (18.92); O, 10.80 (10.85).

RESULTS AND DISCUSSION

The initial screening study revealed that 6 out of the total 10 compounds exhibited significant anticancer activity with a range of 70-85% of cancer cell growth inhibition than the rest of the compounds (Table-1). Later, the selected compounds based on their anticancer activity were tested further with more number of concentrations so as to determine the IC50 value of the compounds which is a parameter used for the evaluation and comparison of the potency of the compounds with the standard drug used in this study. The IC50 values of the selected compounds were presented in Table-2 and found to be in the range of 2.85 µM, 4.07 µM and 3.35 µM against MCF-7, PC-3 and HeLa cancer cell lines respectively. Whereas the IC50 value of the standard drug, doxorubicin was found to be 2.71 µM (MCF-7), 4.01 µM (PC-3) and 3.21 µM (HeLa). These results showed that the selected compounds are more sensitive towards MCF-7 cancer cell lines than PC-3 and HeLa cancer cell lines. The synthesized stock solutions of the compound were diluted with culture medium. A density of 5 x 10^3 cells per well was used to seed the cells in 96-well plates. After incubation until confluency was achieved, each well was treated with 100 µL of media containing synthesized compounds as needed and left to incubate for 48 h. Then, after incubating for an additional 4 h, the MTT working solution (5 mg/mL) was applied to every well. Careful removal of the medium and addition of 200 µL of DMSO occurred at the end of incubation. This was followed by the measurement of the optical density at 490 nm and 630 nm using a microplate reader (MODEL). In order to determine the percentage of cell growth inhibition, the following equation was applied:

\[
\text{Inhibition} = \left(1 - \frac{\text{Sample group OD}_{490} - \text{Sample group OD}_{630}}{\text{Control group OD}_{490} - \text{Control group OD}_{630}}\right) \times 100
\]

The IC50 values were calculated with Graph pad prism software and standard deviation of the IC50 values were obtained from at least three independent experiments.
All the compounds shown good activity, however, compounds 8a, 8g and 8i had shown the excellent results.

**Conclusion**

Based on click reaction, novel quinoline containing 1,4-disubstituted 1,2,3-triazole hybrids e.g. ((E)-2-morpholinoquinoline-3-carbaldehyde O-((1-phenyl-1H-1,2,3-triazol-4-yl)-methyl)oxime derivatives) were successfully synthesized and characterized. The adopted method is believed to be effective and can contribute to the design of the new molecule for potential drug applications. The synthesized compounds were evaluated for their in vitro anticancer activity against pathogenic strains. All the compounds showed good activity, however, compounds 8a, 8g and 8i had shown the excellent results.

**ACKNOWLEDGEMENTS**

The authors are thankful to The Head, Department of Chemistry, Telangana University and Central of Facility Research and Development (CFRD), Osmania University for providing the NMR facilities. One of the authors, CH. Aruna Jyothi is thankful to UGC New Delhi, India for the financial support in the form of RGNF Fellowship.

**TABLE-1**

<table>
<thead>
<tr>
<th>Compd. No.</th>
<th>MCF-7 5 µM</th>
<th>MCF-7 10 µM</th>
<th>PC-3 5 µM</th>
<th>PC-3 10 µM</th>
<th>HeLa 5 µM</th>
<th>HeLa 10 µM</th>
</tr>
</thead>
<tbody>
<tr>
<td>8a</td>
<td>62</td>
<td>70</td>
<td>59</td>
<td>63</td>
<td>60</td>
<td>66</td>
</tr>
<tr>
<td>8b</td>
<td>90</td>
<td>95</td>
<td>79</td>
<td>86</td>
<td>80</td>
<td>88</td>
</tr>
<tr>
<td>8c</td>
<td>89</td>
<td>94</td>
<td>76</td>
<td>84</td>
<td>78</td>
<td>85</td>
</tr>
<tr>
<td>8d</td>
<td>87</td>
<td>92</td>
<td>74</td>
<td>80</td>
<td>76</td>
<td>82</td>
</tr>
<tr>
<td>8e</td>
<td>67</td>
<td>72</td>
<td>63</td>
<td>69</td>
<td>66</td>
<td>71</td>
</tr>
<tr>
<td>8f</td>
<td>68</td>
<td>74</td>
<td>64</td>
<td>70</td>
<td>67</td>
<td>72</td>
</tr>
<tr>
<td>8g</td>
<td>83</td>
<td>89</td>
<td>72</td>
<td>79</td>
<td>73</td>
<td>80</td>
</tr>
<tr>
<td>8h</td>
<td>74</td>
<td>81</td>
<td>67</td>
<td>73</td>
<td>69</td>
<td>75</td>
</tr>
<tr>
<td>8i</td>
<td>92</td>
<td>96</td>
<td>80</td>
<td>88</td>
<td>82</td>
<td>90</td>
</tr>
<tr>
<td>8j</td>
<td>63</td>
<td>71</td>
<td>60</td>
<td>65</td>
<td>61</td>
<td>67</td>
</tr>
<tr>
<td>Doxorubicin</td>
<td>93</td>
<td>98</td>
<td>76</td>
<td>86</td>
<td>82</td>
<td>90</td>
</tr>
</tbody>
</table>

(a) Values are average of three determinations and deviation of data results is 10-20%; (b) All compounds were dissolved in DMSO for testing; (c) MCF-7 breast cancer cell lines; (d) PC-3 prostate cancer cell lines; (e) HeLa cervical cancer cell lines.

**TABLE-2**

<table>
<thead>
<tr>
<th>Compd. No.</th>
<th>IC50 (µM ± SEM)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MCF-7</td>
</tr>
<tr>
<td>8b</td>
<td>2.98 ± 0.01</td>
</tr>
<tr>
<td>8c</td>
<td>3.14 ± 0.06</td>
</tr>
<tr>
<td>8d</td>
<td>3.28 ± 0.02</td>
</tr>
<tr>
<td>8g</td>
<td>3.47 ± 0.07</td>
</tr>
<tr>
<td>8h</td>
<td>3.85 ± 0.04</td>
</tr>
<tr>
<td>8i</td>
<td>2.85 ± 0.01</td>
</tr>
<tr>
<td>Doxorubicin</td>
<td>2.71 ± 0.03</td>
</tr>
</tbody>
</table>

**CONFLICT OF INTEREST**

The authors declare that there is no conflict of interests regarding the publication of this article.

**REFERENCES**