TRIAZOLOPHTHALAZINE INCORPORATING PIPERAZINE DERIVATIVES: SYNTHESIS AND IN VITRO ANTICANCER EVALUATION STUDY

Abdallah Turky¹, Ashraf H. Bayoumi¹, Adel Ghiaty¹, Hamada S. Abulkhair¹,²*

¹Department of Pharmaceutical Organic Chemistry, Faculty of Pharmacy, Al-Azhar University, Cairo, Egypt
²Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Horus University, New Damietta, Egypt

*Corresponding author: hamadaorganic@azhar.edu.eg

ABSTRACT

Cancer remains as one of the top leading causes of death worldwide in the last decade. In an attempt to develop a potent anticancer agent, herein we are reporting the synthesis of two novel series of piperazinyltriazolophthalazines as potential anticancer agents with potential inhibitory activity against PARP-1. All the newly synthesized compounds were evaluated for their anti-proliferative activity against four human cancer cell lines namely; Hepatocellular carcinoma (HePG-2), Mammary gland breast cancer (MCF-7), Human prostate cancer (PC3) and Colorectal carcinoma (HCT-116). The results of cytotoxicity evaluation showed that most of the synthesized compounds displayed moderate cytotoxic activity against the selected cell lines. Compound 23 showed the highest inhibitory effect followed by compound 24 against hepatocellular carcinoma (HePG2) with IC₅₀ values of 15.05 and 17.23 µM respectively. The same two compounds also showed moderate activity against colorectal carcinoma cell line (HCT-116) with IC₅₀ values of 21.93 and 24.06 µM respectively.

Keywords: anticancer, piperazinyltriazolophthalazines, Hepatocellular carcinoma, Mammary gland breast cancer, Human prostate cancer and Colorectal carcinoma.

Introduction

Phthalazine derivatives are biologically important heterocycles and are known to possess variety of biological activities such as antitumor (Fedorov et al. 2014), anticonvulsant (Sun et al. 2011; Sun, Wei, et al. 2010), anti-inflammatory (Abd alla et al. 2010; Liu et al. 2016; Sun, Hu, et al. 2010), antidiabetic (Awadallah, El-Eraky, and Saleh 2012), antihypertensive (Olmo et al. 2006), muscle relaxant (Haack et al. 2005) and antimicrobial (Holló et al. 2014; Khalil, Berghot, and Gouda 2009; Salvi et al. 2006). Phthalazine scaffold is in the core structure of many commercially available drugs (Asif 2012) like, zopolrestat, azelastine, hydralazine and budralazine, the first is antidiabetic, the second is antihistaminic while the third and the last are vasodilating. A promising class of anticancer agents with micromolar range of IC₅₀’s is the 1,2,4-triazoles (Lu et al. 2018). Triazolophthalazine rings presented in many anticancer agents
with potent bromodomain inhibitory effects (Almahli et al. 2018; Boraei et al. 2019; Moustakim, Peter G. K. Clark, et al. 2017). Few years ago, compound 1 (L-45) was discovered as the first potent [1,2,4]triazolo[3,4-a]phthalazine as anticancer with PCAF bromodomain inhibitory effect (Moustakim, Peter G. K. Clark, et al. 2017). Additionally, [1,2,4]triazolo[3,4-a]phthalazine is the pharmacophore ring system of certain anticancer agents (El-Helby et al. 2018; Moustakim, Peter G.K. Clark, et al. 2017; Xue et al. 2014). In the last decade, many synthetic [1,2,4]triazolo[3,4-a]phthalazines (Figure 1) have been reported to exhibit potent anticancer activities against hepatocellular carcinoma with IC\textsubscript{50} values range of 1.60-6.04 (El-Helby et al. 2017, 2018; Xue et al. 2014).

![Figure 1: Structures of selected triazolophthalazines with potent anticancer activity against hepatocellular carcinoma.](image)

On the other hand, piperazines are important class of compounds with diverse biological activities, particularly as anticancer (Chetan et al. 2010; Gurdal et al. 2015). Piperazine derivatives 5 & 6 (Figure 2) showed potent cytotoxic activity against NCIH460, HCT116 and U251 cell lines. Considering the above-mentioned facts and as an attempt to develop a new molecule with potent anticancer activity, molecular hybridization between triazolophthalazine scaffold and piperazine moiety was carried out. Here, inspired by the versatility of the [1,2,4]triazolo[3,4-a]phthalazine pharmacophoric ring skeleton of L-45 and the piperazine moiety mentioned above, nine novel compounds were synthesized to evaluate their anticancer activities. Different substitution patterns were introduced to both the C-3 of triazolophthalazine scaffold and the terminal pierazine ring to investigate the effect on cytotoxicity of the synthesized compounds. All the synthesized compounds were evaluated for their in vitro anticancer activity against four cancer cell lines namely; hepatocellular carcinoma (HePG-2), mammary gland breast cancer (MCF-7), human prostate cancer (PC3) and colorectal carcinoma (HCT-116).
Figure 2: Structures of some reported anticancer agents incorporating piperazine ring.

Results and discussion

Chemistry: The general route for the synthesis of starting triazolophthalazines is illustrated in Scheme 1. 4-Methylbenzoic acid converted into the ethyl ester by the action of ethanol in the presence of catalytic amount of sulfuric acid. The resulting ester allowed to react with hydrazine hydrate in refluxing ethanol to get 4-methylbenzohydrazide (9). In a parallel pathway, phthalic anhydride reacted with hydrazine hydrate in acetic acid to yield 2,3-dihydrophthalazine-1,4-dione (11). The latter reacted under reflux with phosphorus oxychloride to yield 1,4-dichlorophthalazine (12). Treating compound with 12 hydrazine hydrate at room temperature in ethanol to produce 1-chloro-4-hydrazinylphthalazine (13) (Abou-Seri et al. 2016). Reaction of the hydrazinyl derivative 13 with trifluoroacetic acid followed by chlorination with phosphorus oxychloride yielded 6-chloro-3-(trifluoromethyl)-[1,2,4]triazolo[3,4-a]phthalazine (14a). Alternatively, treating the dichlorophthalazine derivative 12 with 4-methylbenzohydrazide in refluxing ethanol produced the triazolophthalazine derivatives 14b.
Scheme 1: Synthetic route for preparation of starting triazolophthalazines

Reaction of the triazolophthalazine derivatives 14<sub>a,b</sub> with piperazine in ethanol according to reported procedures (Tarzia <i>et al.</i> 1988) afforded the piperazinyl derivatives 15<sub>a,b</sub> (Scheme 2). Our final target compounds were readily obtained in good yields and reasonable purities by treating the latter with the appropriate acid chloride.
**Anticancer evaluation:** Anticancer activities of the synthesized compounds were assessed on four cancer cell lines namely; hepatocellular carcinoma (HePG-2), mammary gland breast cancer (MCF-7), human prostate cancer (PC3) and colorectal carcinoma (HCT-116) using MTT assay (Mosmann 1983). Doxorubicin was used as a reference anticancer agent. The results of preliminary anticancer evaluation are shown in *Table 1*. The results of cytotoxicity evaluation showed that the majority of the synthesized compounds displayed moderate cytotoxic activities against the selected cell lines. Compound 23 showed the highest inhibitory effect followed by compound 24 against hepatocellular carcinoma (HePG2) with IC₅₀ values of 15.05 and 17.23 µM respectively. The same two compounds also showed moderate activity against colorectal carcinoma cell line (HCT-116) with IC₅₀ values of 21.93 and 24.06 µM respectively. Compounds with trifluoromethy group attached to C-3 of the triazolophthalazine system (16-19) displayed relatively lower inhibitory potencies than all other compounds.

**Scheme 2:** Synthetic route for preparation of target piperazinyl triazolophthalazines

Reagents and conditions:

a) Piperazine, K₂CO₃/ethanol, rt °C, 6-10 h, 80%.

b) RCOCl, DMF, 80 °C, 4 h, 66-80%.
Table 1: *In vitro* anticancer activity of the new piperazinyl triazolophthalazines

*In vitro* Cytotoxicity IC$_{50}$ (µM)*

<table>
<thead>
<tr>
<th>Cpd.</th>
<th>R</th>
<th>R¹</th>
<th>HePG2</th>
<th>MCF-7</th>
<th>PC3</th>
<th>HCT-116</th>
</tr>
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<tr>
<td>16</td>
<td>CF$_3$</td>
<td>CH$_3$</td>
<td>93.26±5.3</td>
<td>87.10±4.9</td>
<td>&gt;100</td>
<td>94.71±5.6</td>
</tr>
<tr>
<td>17</td>
<td>CF$_3$</td>
<td>C$_6$H$_5$</td>
<td>&gt;100</td>
<td>91.17±5.0</td>
<td>&gt;100</td>
<td>&gt;100</td>
</tr>
<tr>
<td>18</td>
<td>CF$_3$</td>
<td>4-ClC$_6$H$_4$</td>
<td>75.49±3.8</td>
<td>69.11±3.6</td>
<td>81.10±4.5</td>
<td>78.37±4.1</td>
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<tr>
<td>19</td>
<td>CF$_3$</td>
<td>CH=CHC$_6$H$_5$</td>
<td>33.89±2.0</td>
<td>30.49±2.1</td>
<td>40.83±2.3</td>
<td>43.01±2.2</td>
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<td>20</td>
<td>4-CH$_3$C$_6$H$_4$</td>
<td>CH$_3$</td>
<td>55.60±3.3</td>
<td>46.29±2.9</td>
<td>67.27±3.5</td>
<td>61.48±3.4</td>
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<td>4-CH$_3$C$_6$H$_4$</td>
<td>C$_6$H$_5$</td>
<td>29.18±1.9</td>
<td>23.81±1.8</td>
<td>33.37±2.0</td>
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<td>22</td>
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<td>4-ClC$_6$H$_4$</td>
<td>32.75±2.0</td>
<td>29.72±2.1</td>
<td>36.48±2.2</td>
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<td>23</td>
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<td>CH=CHC$_6$H$_5$</td>
<td>15.05±1.2</td>
<td>77.33±4.1</td>
<td>&gt;100</td>
<td>21.93±1.5</td>
</tr>
<tr>
<td>24</td>
<td>4-CH$_3$C$_6$H$_4$</td>
<td>4-CH$_3$C$_6$H$_4$SO$_2$</td>
<td>17.23±1.2</td>
<td>22.39±1.6</td>
<td>25.26±1.8</td>
<td>24.06±1.5</td>
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<tr>
<td></td>
<td>Doxorubicin</td>
<td></td>
<td>4.50±0.2</td>
<td>4.17±0.2</td>
<td>8.87±0.6</td>
<td>5.23±0.3</td>
</tr>
</tbody>
</table>

*IC$_{50}$ (µM): 1 – 10 (very strong). 11 – 20 (strong). 21 – 50 (moderate). 51 – 100 (weak) and above 100 (non-cytotoxic).
Experimental

General:

All melting points were determined using capillary tubes with a Stuart SMP30 apparatus and are uncorrected. ¹H NMR spectra were recorded on Bruker-400-MHz spectrophotometer using DMSO-d₆ as a solvent and TMS as internal reference. ¹³C NMR spectra were recorded on Bruker-100-MHz spectrophotometer using DMSO-d₆ as a solvent and TMS as internal reference. Chemical shifts were recorded in δ ppm downfield the TMS signal. Mass spectra were recorded on Hewlett Packard 5988 spectrometer. Elemental analyses were performed on CHN analyzer. All spectral measurements have been performed at the Regional Center for Mycology & Biotechnology, Al-Azhar University, Cairo, Egypt. Anticancer evaluation was carried out at the Holding Company for Biological Products and Vaccines, Egypt (Vacsera).

General procedure for preparation of (4-(3-substituted-[1,2,4]triazolo[3,4-a]phthalazin-6-y1)piperazin-1-y1)(acyl)methanones (16-24):

Compounds 15 (0.001 mol) was dissolved in dimethyl formamide (20 ml) and acetyl chloride (0.01 mol) or aryl chloride (0.008 mol) was added and the mixture was refluxed at 80°C for 3h. After the end of the reaction (monitored by TLC), the mixture was allowed to cool and poured on crushed ice. On standing, the precipitate was formed and collected by filtration. This solid was recrystallized from ethanol to afford the corresponding compounds.

1-(4-(3-(Trifluoromethyl)-1,2,4]triazolo[3,4-a]phthalazin-6-y1)piperazin-1-y1)ethan-1-one (16):

White solid; Yield: 76%; m.p.255-257°C. IR (KBr) cm⁻¹: 3016 (CH aromatic), 2974 (CH aliphatic), 1643 (C=O), 1589 (C=C aromatic). ¹H NMR (DMSO-d₆) δ ppm: 8.54 (d, 1H, J = 7.8), 8.21 (d, 1H, J = 8.1), 8.06 (t, 1H, J = 7.5), 7.97 (t, 1H, J = 7.6), 3.74 (s, 4H), 2.08 (s, 3H). MS (m/z): 364 (C₁₆H₁₅F₃N₆O, 18.78%, M⁺), 295 (C₁₅H₁₄N₆O, 21.33%), 255 (C₁₃H₁₂N₆O, 16%), 127 (C₆H₁₁N₂O, 100%), 71 (C₆H₅N, 24.3%). ¹³C NMR (DMSO-d₆) δ ppm: 169.10, 158.80, 144.66, 139.26, 138.86, 134.22, 132.15, 127.40, 123.83, 123.48, 120.40, 120.23, 117.55, 51.42, 51.01, 45.47, 40.77 and 21.62. Anal. Calc. for: (C₁₆H₁₅F₃N₆O) (M.W. = 364): C, 52.75; H, 4.15; F, 15.64; N, 23.07%. Found: C, 53.02; H, 54.41; N, 22.89%.

Phenyl-(4-(3-(Trifluoromethyl)-1,2,4]triazolo[3,4-a]phthalazin-6-y1)piperazin-1-y1)methanone (17):

White. Yield: 67%; m.p.263-265°C. IR (KBr) cm⁻¹: 3028 (CH aromatic), 2997 (CH aliphatic), 1624 (C=O), 1589 (C=C aromatic). ¹H NMR (DMSO-d₆) δ ppm: 8.59 (d, 1H, J = 7.76), 8.25 (d, 1H, J = 8.08), 8.08 (t, 1H, J = 7.5), 7.99 (t, 1H, J = 7.6), 7.49 (m, 5H), 3.92 (s, 2H), 3.65 (s, 2H), 3.46 (s, 4H). MS (m/z): 426 (C₂₁H₁₅F₃N₆O, 100%, M⁺), 321 (C₁₄H₁₄F₃N₆, 4.74%), 292 (C₁₃H₉F₃N₅, 2.74%), 104 (C₇H₆N, 1.42%), 77 (C₆H₅, 26.84%). ¹³C NMR (DMSO-d₆) δ ppm: 169.89, 158.83, 144.66, 139.33, 138.94, 136.04, 134.39, 132.29, 130.15, 128.95, 127.5, 123.96, 123.58, 120.5, 117.56, 51.14
and 40.45. Anal. Calc. for: (C\textsubscript{21}H\textsubscript{17}F\textsubscript{3}N\textsubscript{6}O) (M.W. = 426): C, 59.15; H, 4.02; F, 13.37; N, 19.71%; Found: C, 59.38; H, 4.23; N, 19.87%.

(4-Chlorophenyl)(4-(3-( trifluoromethyl)-[1,2,4]triazolo[3,4-a]phthalazin-6-yl)piperazin-1-yl)methanone (18):

White solid; Yield: 77\%; m.p.267-269°C. IR (KBr) cm\textsuperscript{-1}: 3032 (CH aromatic), 2997 (CH aliphatic), 1624 (C=O), 1593 (C=C aromatic). \textsuperscript{1}H NMR (DMSO-\textit{d\textsubscript{6}}) δ ppm: 8.59 (d, 1H, \textit{J} = 7.4), 8.24 (d, 1H, \textit{J} = 8.1), 8.09 (t, 1H, \textit{J} = 7.3), 7.99 (t, 1H, \textit{J} = 8.2), 7.56-7.51 (m, 4H), 3.92 (s, 2H), 3.64 (s, 2H), 3.46 (s, 4H). MS (\textit{m}/\textit{z}): 462 (C\textsubscript{21}H\textsubscript{16}ClF\textsubscript{3}N\textsubscript{6}O, 31.81\%, M\textsuperscript{+}+2), 460 (C\textsubscript{21}H\textsubscript{16}ClF\textsubscript{3}N\textsubscript{6}O, 100\%, M\textsuperscript{+}) 321 (C\textsubscript{14}H\textsubscript{12}F\textsubscript{3}N\textsubscript{6}, 1.69\%), 279 (C\textsubscript{12}H\textsubscript{8}F\textsubscript{3}N\textsubscript{5}, 1.31\%), 139 (C\textsubscript{6}H\textsubscript{4}ClO, 1.8\%), \textsuperscript{13}C NMR (DMSO-\textit{d\textsubscript{6}}) δ ppm: 168.81, 158.84, 144.87, 139.35, 138.95, 134.86, 134.82, 134.43, 132.31, 129.58, 129.02, 127.55, 124.01, 123.66, 120.56, 120.26, 117.58, 51.09 and 40.51. Anal. Calc. for: (C\textsubscript{21}H\textsubscript{16}ClF\textsubscript{3}N\textsubscript{6}O) (M.W. = 460): C, 54.73; H, 3.5; Cl, 7.69; F, 12.37; N, 18.24\%; Found: C, 54.91; H, 3.67; N, 18.07\%.

3-Phenyl-1-(4-(3-( trifluoromethyl)-[1,2,4]triazolo[3,4-a]phthalazin-6-yl)piperazin-1-yl)prop-2-en-1-one (19):

White solid; Yield: 79\%; m.p.261-263°C. IR (KBr) cm\textsuperscript{-1}: 3001 (CH aromatic), 2893 (CH aliphatic), 1647 (C=O), 1608 (C=C aromatic). \textsuperscript{1}H NMR (DMSO-\textit{d\textsubscript{6}}) δ ppm: 8.6 (d, 1H, \textit{J} = 7.8), 8.27 (d, 1H, \textit{J} = 8.1), 8.09 (t, 1H, \textit{J} = 7.1), 8 (t, 1H, \textit{J} = 7.4), 7.74 (d, 2H, \textit{J} = 6.7), 7.55 (d, 1H, \textit{J} = 15.4), 7.44 - 7.34 (m, 4H), 4.03 (s, 2H), 3.89 (s, 2H), 3.47 (s, 4H). MS (\textit{m}/\textit{z}): 452 (C\textsubscript{22}H\textsubscript{19}F\textsubscript{3}N\textsubscript{6}O, 100\%, M\textsuperscript{+}) 375 (C\textsubscript{17}H\textsubscript{13}F\textsubscript{3}N\textsubscript{6}O, 1.96\%), 280 (C\textsubscript{12}H\textsubscript{8}F\textsubscript{3}N\textsubscript{5}, 2.63\%), 131 (C\textsubscript{6}H\textsubscript{5}N\textsubscript{2}, 23.52\%), 77 (C\textsubscript{6}H\textsubscript{5}, 36.23\%). \textsuperscript{13}C NMR (DMSO-\textit{d\textsubscript{6}}) δ ppm: 165.24, 158.84, 144.83, 142.29, 139.33, 138.93, 135.52, 134.87, 134.43, 132.37, 132.05, 129.21, 128.48, 127.54, 123.99, 123.65, 120.56, 120.28, 118.51, 117.6, 51.6 and 41.9. Anal. Calc. for: (C\textsubscript{22}H\textsubscript{19}F\textsubscript{3}N\textsubscript{6}O) (M.W. = 452): C, 61.06; H, 4.23; F, 12.6; N, 18.58\%; Found: C, 60.89; H, 4.42; N, 18.7\%.

1-(4-(3-(p-Toly)-[1,2,4]triazolo[3,4-a]phthalazin-6-yl)piperazin-1-yl)ethan-1-one (20):

White solid; Yield: 69\%; m.p.259-261°C. IR (KBr) cm\textsuperscript{-1}: 3024 (CH aromatic), 2951 (CH aliphatic), 1643 (C=O), 1589 (C=C aromatic). \textsuperscript{1}H NMR (DMSO-\textit{d\textsubscript{6}}) δ ppm: 8.53 (d, 1H, \textit{J} = 7.7), 8.27 (d, 2H, \textit{J} = 7.8), 8.19 (d, 1H, \textit{J} = 8.0), 8.01 (t, 1H, \textit{J} = 7.4), 7.9 (t, 1H, \textit{J} = 7.5), 7.41 (d, 2H, \textit{J} = 7.7), 3.76 (s, 4H), 3.41 (s, 4H), 2.4 (s, 3H, CH\textsubscript{3}), 2.09 (s, 3H, COCH\textsubscript{3}). MS (\textit{m}/\textit{z}): 386 (C\textsubscript{22}H\textsubscript{22}N\textsubscript{6}O, 43.57\%, M\textsuperscript{+}) 330 (C\textsubscript{20}H\textsubscript{20}N\textsubscript{5}, 54.39\%), 261 (C\textsubscript{16}H\textsubscript{13}N\textsubscript{4}, 26.63\%), 214 (C\textsubscript{12}H\textsubscript{14}N\textsubscript{4}, 100\%), 124 (C\textsubscript{6}H\textsubscript{10}N\textsubscript{3}, 15.89\%). \textsuperscript{13}C NMR (DMSO-\textit{d\textsubscript{6}}) δ ppm: 169.06, 157.66, 148.1, 143.18, 140.05, 133.97, 131.15, 129.78, 127.58, 127.19, 124.63, 124.12, 123.49, 119.8, 51.35, 45.74, 21.69 and 21.48. Anal. Calc. for: (C\textsubscript{22}H\textsubscript{22}N\textsubscript{6}O) (M.W. = 386): C, 68.38; H, 5.74; N, 21.75\%; Found: C, 68.59; H, 5.81; N, 21.98\%. 

Phenyl(4-(3-(p-tolyl)-[1,2,4]triazolo[3,4-a]phthalazin-6-yl)piperazin-1-yl)methanone (21):

White solid; Yield: 67%; m.p.261-263°C. IR (KBr) cm⁻¹: 3028 (CH aromatic), 2993 (CH aliphatic), 1635 (C=O), 1589 (C=C aromatic). ¹H NMR (DMSO-d₆) δ ppm: 8.55 (d, 1H, J = 7.9), 8.27 (d, 2H, J = 8.04), 8.2 (d, 1H, J = 8.1), 8.02 (t, 1H, J = 7.6), 7.9 (t, 1H, J = 7.5), 7.49 (m, 5H), 7.42 (d, 2H, J = 7.9), 3.96 (s, 2H), 3.69 (s, 2H), 3.44 (s, 4H), 2.41 (s, 3H). MS (m/z): 484 (C₂₇H₂₄N₆O, 7.06%, M⁺) 301 (C₁₈H₁₅N₄, 12.57%), 259 (C₁₆H₁₁N₄, 6.33%), 105 (C₇H₅O, 100%). ¹³C NMR (DMSO-d₆) δ ppm: 169.79, 157.61, 148.16, 143.21, 140.14, 136.11, 134.02, 131.22, 130.16, 129.83, 128.98, 127.63, 127.51, 127.23, 124.58, 124.03, 123.51, 119.77, 51.27, 40.45 and 21.47. Anal. Calc. for: (C₂₇H₂₄N₆O) (M.W. = 448): C, 72.3; H, 5.39; N, 18.74%; Found: C, 72.52; H, 5.61; N, 18.92%.

(4-Chlorophenyl)(4-(3-(p-tolyl)-[1,2,4]triazolo[3,4-a]phthalazin-6-yl)piperazin-1-yl)methanone (22): White solid; Yield: 74%; m.p.263-265°C. IR (KBr) cm⁻¹: 3082 (CH aromatic), 2993 (CH aliphatic), 1631 (C=O), 1593 (C=C aromatic). ¹H NMR (DMSO-d₆) δ ppm: 8.52 (d, 1H, J = 7.6), 8.25 (d, 2H, J = 7.6), 8.17 (d, 1H, J = 7.9), 8 (t, 1H, J = 7.4), 7.88 (t, 1H, J = 7.2), 7.54 (m, 4H), 7.39 (d, 2H, J = 7.5), 3.94 (s, 2H), 3.66 (s, 2H), 3.43 (s, 4H), 2.39 (s, 3H). MS (m/z): 484 (C₂₇H₂₃ClN₆O, 33.56%, M⁺+2) 482 (C₂₇H₂₃ClN₆O, 64.67%, M⁺) 343 (C₂₀H₁₉N₆, 12.31%), 259 (C₁₆H₁₁N₄, 58.37%), 144 (C₈H₄N₃, 100%). ¹³C NMR (DMSO-d₆) δ ppm: 148.05, 134.18, 130.71, 129.15, 127.76, 124.64, 123.78, 93.79, 51.14, 48.71 and 16.64. Anal. Calc. for: (C₂₇H₂₃ClN₆O) (M.W. = 482): C, 67.15; H, 4.8; Cl, 7.84; N, 17.4%; Found: C, 67.42; H, 4.93; N, 17.28%.

3-Phenyl-1-(4-(3-(p-tolyl)-[1,2,4]triazolo[3,4-a]phthalazin-6-yl)piperazin-1-yl)prop-2-en-1-one (23): White solid; Yield: 71%; m.p.266-268°C. IR (KBr) cm⁻¹: 3020 (CH aromatic), 2978 (CH aliphatic), 1647 (C=O), 1604 (C=C aromatic). ¹H NMR (DMSO-d₆) δ ppm: 8.50 (d, 1H, J = 7.8), 8.28 (d, 2H, J = 7.8), 8.23 (d, 1H, J = 8.1), 8.03 (t, 1H, J = 7.4), 7.92 (t, 1H, J = 7.4), 7.76 (d, 2H, J = 6.7), 7.56 (d, 1H, J = 15.4), 7.41-7.35 (m, 6H), 4.05 (s, 2H), 3.92 (s, 2H), 3.44 (s, 4H), 2.4 (s, 3H). MS (m/z): 474 (C₂₅H₂₆N₆O, 100%, M⁺) 329 (C₂₀H₁₀N₅, 17.15%), 260 (C₁₆H₁₂N₄, 26.66%), 113 (C₈H₄N₂O₂, 32.29%). ¹³C NMR (DMSO-d₆) δ ppm: 165.23, 157.67, 148.17, 143.24, 142.35, 140.13, 135.51, 134.03, 131.23, 130.13, 129.82, 129.27, 128.53, 127.64, 127.25, 124.63, 124.09, 123.54, 119.85, 118.51, 51.56, 45.17, 41.83 and 21.48. Anal. Calc. for: (C₂₅H₂₆N₆O) (M.W. = 474): C, 73.4; H, 5.52; N, 17.71%; Found: C, 73.28; H, 5.68; N, 17.89%.

3-(p-Tolyl)-6-(4-tosylpiperazin-1-yl)-[1,2,4]triazolo[3,4-a]phthalazine (24): White solid; Yield: 71%; m.p.253-255°C. IR (KBr) cm⁻¹: 3028 (CH aromatic), 2981 (CH aliphatic), 1674 (C=O), 1589 (C=C aromatic). ¹H NMR (DMSO-d₆) δ ppm: 8.50 (d, 1H, J = 7.9), 8.24 (d, 2H, J = 7.9), 8.06 (d, 2H, J = 8.1), 7.98 (t, 1H, J = 7.9), 7.82 (t, 1H, J = 8.0 H), 7.72 (d, 1H, J = 7.9), 7.51 (d, 2H, J = 7.8), 7.42 (d, 2H, J = 7.8), 3.47 (s, 4H), 3.24 (s, 4H), 2.43 (s, 3H). MS (m/z): 498 (C₂₇H₂₅N₆O₂S, 13.71%, M⁺) 407 (C₂₅H₁₉N₆O₂S, 57.81%), 381 (C₁₉H₁₉N₂O₂S, 100%), 343 (C₂₆H₁₉N₆, 29.51%), 254 (C₁₅H₁₄N₆, 26.04%), 123 (C₃H₇N₄, 12.66%). ¹³C NMR (DMSO-d₆) δ ppm: 130.46,
129.84, 128.14, 127.61, 50.58, 45.9 and 21.49. Anal. Calc. for: (C_{27}H_{26}N_{6}O_{2}S) (M.W. = 498): C, 65.04; H, 5.26; N, 16.86%; Found: C, 65.31; H, 5.39; N, 16.81; S, 6.57%.

Anticancer activity: All the synthesized compounds were subjected to MTT proliferation assay to investigate their in-vitro cytotoxic activity. Hepatocellular carcinoma (HePG-2), mammary gland breast cancer (MCF-7), Human prostate cancer (PC3) and colorectal carcinoma (HCT-116) cell lines was chosen for investigation.

Conclusion

a series of triazolophthalazine incorporating piperazine derivatives was synthesized and evaluated for their anticancer activity against four human cancer cell lines (Hepatocellular carcinoma (HePG-2), mammary gland breast cancer (MCF-7), Human prostate cancer (PC3) and Colorectal carcinoma (HCT-116)). The results of anticancer evaluation showed that most of the synthesized compounds displayed moderate cytotoxic activities against the selected cell lines. Compound 23 showed the highest inhibitory effect followed by compound 24 against hepatocellular carcinoma and colorectal carcinoma cell lines.

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مشتقات التريازولوفثالازين المتصلة ببيرازين: التشييد ودراسة النشاط المضاد للسرطان

عبد الله السيد تركي، أشرف حسن بومي، عادل حمدي غياني، حمادج انسُذ أتى انخُر

قسم الكيمياء العضوية الصيدلانية، كلية الصيدلة، جامعة الأزهر - القاهرة - مصر

قسم الكيمياء الصيدلانية، كلية الصيدلة، جامعة حورس – دمياط الجديد – مصر

hamadaorganic@azhar.edu.eg

البحث الإلكتروني للباحث الرئيسي:

المختصر:

يُعد السرطان أحد الأسباب الرئيسية للوفاة في جميع أنحاء العالم خلال العقود الماضية. في محاولة لتطوير عامل مضاد للسرطان، تم تشكيل مسلسلة جديدة من مشتقات التريازولوفثالازين المتصلة ببيرازين وتم تقييم نشاطها المضاد للسرطان ضد أربعة أنواع لخلايا السرطان البشرية وهي: سرطان خلايا الكبد وسرطان الثدي وسرطان البروستاتا وسرطان القولون والمستقيم. أظهرت نتائج تقييم السمية الحلوية أن معظم المركبات أنتجت أنماط اشتعال سامة للخلايا متوسطة ضد أربعة أنواع السرطانات المختارة. أظهر المركب 24 أعلى تأثير من حيث نشاط السرطانية بليه المركب 23 ضد كل من سرطان الكبد وسرطان القولون والمستقيم.

الكلمات المفتاحية: المضاد للسرطان، سرطان خلايا الكبد، سرطان الثدي، سرطان البروستاتا، سرطان القولون، والمستقيم