Synthesis and biological activities of some condensed oxazine and pyrimidine derivatives: cyclization, ring transformation and functionalization of oxazine

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2-Amino benzoic acid was acylated using chloroacetyl chloride followed by cycloaddition with benzylidene derivative to yield pyrimidine 3. Benzoxazole 4 reacted with nucleophilic carbon of phenols 5 and 6, active methylene compounds 11 and 12, and enaminic carbons of 16 and 17 to yield compounds 7, 10, 13, 14, 18 and 19 respectively. Also, benzoxazole 6 reacted with hydrazine to yield compounds 5 and 33. Aminoquinazoline 5 underwent a series of reactions using benzaldehyde, NH₂SCN in base/acid medium, chloroacetyl chloride and CS₂ followed by cyclization using ethyl chloroacetate to yield compounds 22, 26, 29, 32, 30 and 31 respectively. Hydrazide 33 underwent a series of cycloaddition and cyclocondensation reactions using compounds like ethyl chloroacetate and/or acetylacetone, maleic anhydride and p-chloromethyl isothiocyanate to yield compounds 34, 36, 37 and 40 respectively. Finally, compound 6 was reacted with ethyl cyanoacetate and/or acetyl acetone to form compounds 43 and 44 respectively.

**Materials and methods**

**Antimicrobial activity**

The antimicrobial activities of some selected compounds were determined using agar diffusion method¹⁶. All samples were assessed in vitro for their antibacterial activity against *Streptococcus pneumoniae* and *Bacillus subtilis* (Gram-positive bacteria) as well as *Escherichia coli* and *Pseudomonas aeruginosa* (Gram-negative bacteria). In addition, antifungal activity was tested in vitro against *Aspergillus fumigatus*¹⁶. Table 1 shows results of the analysis. On the other hand, we obtained good results using a filter paper-sterilized disc saturated with the tested sample plated on solid bacterial medium (nutrient agar broth) or fungal medium (Doxs medium), after incubation¹⁷. The diameter of the clear zone of inhibition was taken as a measure of the inhibitory effect of the tested sample against the particular organism (Table 2).

It is clearly observed that all synthesized compounds exhibited biological activity. From the obtained data, compounds 19, 42, 22, 31 and 30 showed maximum reactivity against both Gram-positive and Gram-negative bacteria, and *Aspergillus fumigatus*, whereas compounds 3, 27, 10, 14 and 24 showed a moderate activity. Compounds 40, 34, 44 and 37 showed no reactivity towards *Candida albicans* or *Aspergillus* fungi.

**Antitumour activity**

The synthesized compounds were screened for their anticancer activity on human cancer cell lines such as HepG-2 cells (human cell line of a well-differentiated hepatocellular carcinoma), MCF-7 cells (breast carcinoma and colon carcinoma isolated from a liver) and HCT-16 cells (colon of a male and female Caucasian aged 15 years). The human cancer cell lines were provided by the National Cancer Institute (NCI), Cairo, Egypt. The cells were propagated in Dulbecco modified Eagle’s medium

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Table 1. 

<table>
<thead>
<tr>
<th>Compound no.</th>
<th>Streptococcus pneumoniae</th>
<th>Bacillus subtilis</th>
<th>Pseudomonas aeruginosa</th>
<th>Escherichia coli</th>
<th>Aspergillus fumigatus</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(G +)</td>
<td>(G –)</td>
<td>(Fungi)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>14.6 ± 1.2</td>
<td>13.7 ± 0.63</td>
<td>13.2 ± 0.72</td>
<td>12.2 ± 1.2</td>
<td>15.2 ± 1.2</td>
</tr>
<tr>
<td>14</td>
<td>12.3 ± 0.58</td>
<td>14.3 ± 0.72</td>
<td>10.3 ± 1.2</td>
<td>15.2 ± 0.63</td>
<td>13.2 ± 0.58</td>
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<tr>
<td>24</td>
<td>12.4 ± 0.58</td>
<td>14.8 ± 0.63</td>
<td>11.2 ± 0.58</td>
<td>12.3 ± 0.63</td>
<td>13 ± 0.72</td>
</tr>
<tr>
<td>27</td>
<td>14.5 ± 1.2</td>
<td>13.7 ± 0.72</td>
<td>15.3 ± 0.72</td>
<td>14.3 ± 0.63</td>
<td>16.8 ± 0.58</td>
</tr>
<tr>
<td>30</td>
<td>14.3 ± 0.58</td>
<td>16.8 ± 0.72</td>
<td>17.5 ± 1.2</td>
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<td>17.6 ± 0.63</td>
</tr>
<tr>
<td>31</td>
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<td>17.1 ± 1.2</td>
<td>12.8 ± 0.53</td>
<td>18.4 ± 0.72</td>
<td>17.2 ± 0.58</td>
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<tr>
<td>Ampicillin</td>
<td>23.8 ± 1.2</td>
<td>32.4 ± 0.63</td>
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<td>–</td>
</tr>
<tr>
<td>Gentamicin</td>
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<td>–</td>
<td>17.3 ± 1.2</td>
<td>19.9 ± 0.72</td>
<td>–</td>
</tr>
<tr>
<td>Amphotericin B</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>23 ± 1.2</td>
</tr>
</tbody>
</table>

(DMEM) supplemented with 10% heat-inactivated foetal bovine serum 1%. All cells were kept at 37°C in a humidified atmosphere with 5% CO2 and were subcultured twice a week10. The obtained results of the biological study of pyrimidine derivatives and their cytotoxic effects showed that the most active quinazoline derivatives were compounds 32, 26 and 29 (Table 3). Accordingly, the newly synthesized quinazoline derivatives 26, 29 and 32 exhibited a potential anticancer activity.

### Experimental

All experiments were performed using drying solvents. Thin-layer chromatography (TLC) was performed. Products were purified by crystallization. Some reagents and solvents were purchased. We measured the melting points using an Electro thermal IA 9100 apparatus with open capillary tubes. The IR spectra (KBr disc) were recorded on a Shimadzu FTIR 8300 PC IR (cm⁻¹). The 1H/13C-NMR spectra were recorded using a Varian Mercury VX-300 NMR (1H, 300 MHz, 13C, 75.4 MHz) spectrometer with DMSO-d6 as a solvent. All chemical shifts were expressed in the δ (ppm) scale using tetramethylsililane (TMS) as an internal standard reference. The coupling constant (J) values were in Hertz. Mass spectrometry was recorded with a Shimadzue QP-2010.

2-(3-Chloro-5-cyano-6-imino-2-oxo-4-phenyl-3,6-dihydropyridine-1(2H)-yl)benzoic acid (3)

A mixture of compound 1 (0.01 mol) and AC2O (10 ml) was refluxed for 2 h. Then benzylidene malononitrile (0.01 mol) in AcOH (10 ml) was added and the reaction mixture was refluxed further for 2 h. The precipitate obtained after concentration and cooling was filtered-off and recrystallized from ethanol to give compound 3; yield 67%; m.p. 149–150°C; IR (KBr) (cm⁻¹) 3433 (OH), 3115 (NH), 1690, 1668 (C=O), 1588 (C=N); 1H NMR (300 MHz, DMSO-d6) δ 11.77 (1H, s, OH), 11.01 (1H, s, NH), 8.53–7.10 (9H, m, 2Ar-H), 4.68 (1H, s, Cl-CH); MS m/z (%): 367.5 (M+ + 2), 365.5 (M+), 90 (100).

N-[2-(1-Hydroxy-2-naphthoyl)phenyl]benzamide (7)

A mixture of compound 4 (0.01 mol) and α- and/or β-naphthol (0.01 mol) in xylene (10 ml) was refluxed for 7 h. The precipitate obtained after concentration and...
Table 3. Inhibitory activity against heptacellular carcinoma, breast carcinoma and colon carcinoma cells detected using viability assay under the present experimental conditions with IC$_{50}$

<table>
<thead>
<tr>
<th>Compound no.</th>
<th>Heptacellular carcinoma</th>
<th>Breast carcinoma</th>
<th>Colon carcinoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>7</td>
<td>28.8</td>
<td>48.9</td>
<td>30.8</td>
</tr>
<tr>
<td>13</td>
<td>30.3</td>
<td>44.7</td>
<td>40.6</td>
</tr>
<tr>
<td>26</td>
<td>108</td>
<td>171</td>
<td>100</td>
</tr>
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<td>29</td>
<td>121</td>
<td>181</td>
<td>109</td>
</tr>
<tr>
<td>32</td>
<td>277</td>
<td>324</td>
<td>389</td>
</tr>
</tbody>
</table>

cooling was filtered-off and recrystallized from ethanol to give two compounds, viz. 7 and 10.

Compound 7; yield 33%; m.p. 157–158°C; IR (KBr) (cm$^{-1}$), 3419 (OH phenolic), 3237 (NH), 1684 (C=O), 1650 (C≡N); $^1$H NMR (300 MHz, DMSO-d$_6$) $\delta$ 12.15 (1H, s, NH), 10.04 (1H, s, OH), 8.72–6.81 (15H, m, 3Ar-H); MS m/z (%): 370 (M$^+$ + 3), 369 (M$^+$ + 2), 105 (100).

$N$-[2-(2-Hydroxy-1-naphthoyl)phenyl]benzamide (10)

Yield 37%; m.p. 180–181°C; IR (KBr) (cm$^{-1}$) 3114 (NH), 1684, 1663 (2C=O), 1650 (C≡N); $^1$H NMR (300 MHz, DMSO-d$_6$) $\delta$ 12.23 (1H, s, OH), 8.72 (2H, s, NH$_2$), 8.21–7.18 (8H, m, 2Ar-H); MS m/z (%): 267 (M$^+$ + 2), 265 (M$^+$), 105, 77 (100).

2-(2-Aminobenzoyl)-3-hydroxy-1H-inden-1-one (13)

A solution of compound 4 (0.01 mol) and 1H-indene-1,3(2H)-dione 11 (0.01 mol) in xylene (15 ml) was refluxed for 7 h. The precipitate obtained upon concentration and cooling was filtered-off and recrystallized from ethanol to give compound 13; yield 55%; m.p. 114–116°C; IR (KBr) (cm$^{-1}$) 3439 (OH), 3239 (NH$_2$), 1684, 1663 (2C=O), 1610 (C≡N); $^1$H NMR (300 MHz, DMSO-d$_6$) $\delta$ 12.23 (1H, s, OH), 8.72–7.06 (15H, m, 3Ar-H); MS m/z (%): 371 (M$^+$ + 2), 370 (M$^+$ + 1), 369 (M$^+$ + 2), 105, 77 (100).

$N$-{2-[(3-Methyl-5-oxo-1-phenyl-4,5-dihydro-1H-pyrazol-4-yl)carbonyl]phenyl}benzamide (14).

A solution of compound 4 (0.01 mol) and pyrazolo derivative 12 (0.01 mol) in xylene (10 ml) was refluxed for 7 h. The precipitate obtained after concentration and cooling was filtered-off and recrystallized from butanol to give compound 14; yield 75%; m.p. 220–222°C. IR (KBr) (cm$^{-1}$) 3445 (NH), 1693 (C=O), 1652 (C≡N); $^1$H NMR (300 MHz, DMSO-d$_6$) $\delta$ 11.03 (1H, s, NH), 8.46–7.10 (9H, m, 2Ar-H), 2.4 (3H, s, COCH$_3$), 3.45 (2H, s, C=CH$_2$); MS m/z (%): 304 (M$^+$).

3-Acetyl-3-(1-aminovinyl)-2-phenylquinolin-4(3H)-one (19)

A mixture of compound 4 (0.01 mol) and enaminone 17 (0.01 mol) in DMF (20 ml) was refluxed for 7 h. The precipitate obtained after concentration and acidification with AcOH (5 ml) was filtered and recrystallized from benzene to give compound 19; yield 77%; m.p. 160–162°C. IR (KBr) (cm$^{-1}$) 3132 (NH$_2$), 1684, 1643 (C=O), 1608 (C≡N); $^1$H NMR (300 MHz, DMSO-d$_6$) $\delta$ 12.1 (2H, s, NH$_2$), 8.7–7.1 (9H, m, 2Ar-H), 2.4 (3H, s, =CH$_2$); MS m/z (%): 304 (M$^+$).

2-Phenyl-2,3-dihydropyrazolo[5,1-b]quinazolin-9(1H)-one (22)

A mixture of compound 5 (0.01 mol) and benzaldehyde (0.01 mol) in AC$_2$O/AcOH (1 : 1) mixture (20 ml) was refluxed for 7 h. The solid obtained after cooling was filtered-off and recrystallized from benzene to give compound 22; yield 77%; m.p. 200–202°C. IR (KBr) (cm$^{-1}$) 3445 (NH), 1693 (C=O), 1652 (C≡N); $^1$H NMR (300 MHz, DMSO-d$_6$) $\delta$ 11.03 (1H, s, NH), 8.46–7.10 (9H, m, 2Ar-H), 2.49 (1H, t, CH$_2$), 2.11 (2H, d, CH$_2$); MS m/z (%): 265 (M$^+$ + 3), 263 (M$^+$), 262 (M$^+$ – 1), 146, 77 (100).
A mixture of quinazoline (0.01 mol) and NH$_4$SCN (0.01 mol) in pyridine (10 ml) was refluxed for 5 h. The precipitate obtained after cooling and acidification with AcOH was filtered-off and recrystallized from ethanol to give compound 24; yield 75%; m.p. 190–192°C; IR (KBr) (cm$^{-1}$) 3373 (NH), 1689, 1670 (C=O), 1265 (C=S); $^1$H NMR (300 MHz, DMSO-d$_6$) $\delta$ 13.38 (1H, s, NH), 12.6 (2H, s, NH$_2$), 12.43 (2H, s, NH$_2$), 8.22–7.28 (4H, m, Ar-H); MS m/z (%): 393 (M$^+$ + 1), 392 (M$^+$), 262 (100).

N,N'-bis(2-Methyl-4-oxoquinazolin-3(4H)-yl) carbamimidothioic acid (26)

A solution of compound 5 (0.01 mol) and NH$_4$SCN (0.01 mol) in acetic acid (10 ml) was refluxed for 5 h. The solid obtained after cooling was filtered-off and recrystallized from ethanol to give compound 26; yield 85%; m.p. 275–277°C; IR (KBr) (cm$^{-1}$) 3386 (NH), 1699, 1667 (C=O), 1254 (C=S); $^1$H NMR (300 MHz, DMSO-d$_6$) $\delta$ 13.38 (1H, s, NH), 12.6 (2H, s, NH$_2$), 12.43 (2H, s, NH$_2$), 8.22–7.28 (4H, m, Ar-H); MS m/z (%): 263 (M$^+$ + 4), 261 (M$^+$ + 2), 259 (M$^+$), 178 (100).

N-[2-(3-Amino-4-oxoquinazolin-2-yl)ethanethioyl] benzamide (27)

A solution of quinazoline (0.01 mol) and benzyol isothiocyanate (prepared by addition of 0.01 mol benzyol chloride and 0.015 mol NH$_4$SCN in dry acetone (25 ml)) was refluxed for 4 h. The precipitate obtained after acidifying and cooling was filtered-off and recrystallized from ethanol to give compound 27; yield 90%; m.p. 190–192°C; IR (KBr) (cm$^{-1}$) 3393 (NH$_2$), 3229 (NH), 1702, 1670 (C=O), 1266 (C=S); $^1$H NMR (300 MHz, DMSO-d$_6$) $\delta$ 12.32 (1H, s, NH), 10.9 (2H, s, NH$_2$), 8.46–6.49 (9H, m, Ar-H), 3.56 (2H, s, CH$_2$); MS m/z (%): 338 (M$^+$ + 1), 392 (M$^+$), 262 (100).

1-Phenyl-3-thioxo-3H,6H-pyrimido[1,6-a][3,1]benzoxazin-6-one (29)

A solution of hydrazide (0.01 mol) and NaOH (0.01 mol) in ethanol (25 ml) was refluxed for 5 h. The precipitate obtained after acidifying and cooling was filtered-off and recrystallized from benzene to give compound 29; yield 95%; m.p. 110–112°C; IR (KBr) (cm$^{-1}$) 1687 (C=O), 1601 (C=N), 1292 (C=S); $^1$H NMR (300 MHz, DMSO-d$_6$) $\delta$ 7.96–7.46 (10H, m, Ar-H + enaminic proton); MS m/z (%): 308 (M$^+$ + 2), 306 (M$^+$), 250, 105, 77 (100).

2-Thioxo-2,3-dihydropyrazolo[5,1-b] quinazolin-9(1H)-one (30)

A mixture of aminooxazinoline (0.01 mol) and carbon disulphide (0.01 mol) in AcOH (20 ml) was refluxed for 10 h. The precipitate obtained after cooling was filtered-off and recrystallized from butanol to give compound 30; yield 95%; m.p. 265–267°C; IR (KBr) (cm$^{-1}$) 3336 (NH), 1650 (C=O), 1614 (C=N), 1296 (C=S); $^1$H NMR (300 MHz, DMSO-d$_6$) $\delta$ 12.49 (1H, s, NH), 8.21–6.52 (4H, m, Ar-H), 2.4(2H, s, CH$_2$); MS m/z (%): 221 (M$^+$ + 4), 220 (M$^+$ + 3), 217 (M$^+$), 217 (100).

2H-Thiazolo[3′,2′,2,3′pyrazolo[5,1-b] quinazoline-2,6(3H)-dione (31)

A mixture of compound (0.01 mol) and ethyl chloroacetate (0.01 mol) and KOH (0.01 mol) in ethanol (25 ml) was refluxed for 10 h. The precipitate obtained after cooling and acidification with AcOH was filtered-off and recrystallized from ethanol to give compound 31; yield 75%; m.p. 305–307°C; IR (KBr) (cm$^{-1}$) 1650 (C=O), 1614 (C=N); $^1$H NMR (300 MHz, DMSO-d$_6$) $\delta$ 8.20–6.49 (5H, m, Ar-H + C=CH), 3.38 (2H, s, CH$_2$); MS m/z (%): 260 (M$^+$ + 3), 259 (M$^+$ + 2), 257 (M$^+$).

2-Chloro-N-{2-[[1Z]-3-chloro-2-hydroxyprop-1-en-1-yl]-4-oxoquinazolin-3(4H)-yl}acetamide (32)

A solution of compound (0.01 mol) and chloroacetyl chloride (0.01 mol) in pyridine (10 ml) was refluxed for 4 h. The precipitate obtained after cooling and acidification with AcOH was filtered-off and recrystallized from ethanol to give compound 32; yield 95%; m.p. 183–185°C; IR (KBr) (cm$^{-1}$) 3450 (OH), 3361 (NH), 1711, 1689 (C=O), 1600 (C=N); $^1$H NMR (300 MHz, DMSO-d$_6$) $\delta$ 15.8 (1H, s, OH), 14.2 (1H, s, NH), 8.21–7.21 (4H, m, Ar-H), 5.9 (1H, s, CH), 4.2 (2H, s, CH$_2$Cl), 3.3 (2H, s, CH$_2$Cl); MS m/z (%): 330 (M$^+$ + 4), 326 (M$^+$ – 2), 119 (100).

2-Methylpyrazolo[5,1-b]quinazolin-9(4H)-one (34)

A solution of hydrazide (0.01 mol)$^{19}$ and ethyl acetoacetate (0.01 mol) in xylene (15 ml) and a few drops of triethylamine (TEA) was heated under reflux for 4 h. The precipitate obtained after acidification with AcOH and cooling was filtered-off and recrystallized from ethanol to give compound 34; yield 75%; m.p. 265°C; IR (KBr) (cm$^{-1}$) 3373 (NH), 1689 (C=O), 1655 (C=N); $^1$H NMR (300 MHz, DMSO-d$_6$) $\delta$ 11.73 (1H, s, NH), 8.47–6.46 (4H, m, Ar-H), 3.1 (1H, s, CH), 2.1 (3H, s, CH$_3$); MS m/z (%): 201 (M$^+$ + 2), 200 (M$^+$ + 1), 119 (100).
A mixture of compound 33 (0.01 mol)\(^{19}\) and acetylacetone (0.01 mol) in xylene (15 ml) and a few drops of TEA was refluxed for 4 h. The precipitate obtained after concentration and cooling was filtered-off and recrystallized from benzene to give compound 36; yield 75%; m.p. 188–190\(^\circ\)C; IR (KBr) (cm\(^{-1}\)) 3179 (NH), 1696 (C=O), 1607 (C=N); \(^1\)H NMR (300 MHz, DMSO-\(d_6\)) \(\delta\) 8.73–7.10 (4H, m, Ar-H), 6.56 (1H, s, NH), 3.2 (2H, s, CH\(_3\)), 2.49 (3H, s, CH\(_3\)), 1.4 (3H, s, CH\(_3\)); MS \(m/z\) (%): 214 (M\(^+\) – 1), 90 (100).

2-(Acetylamino)-N-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)benzamide (37)

A solution of compound 33 (0.01 mol)\(^{19}\) and maleic anhydride (0.01 mol) in AcOH (10 ml) was stirred for 7 h at room temperature. The precipitate obtained after cooling was filtered-off and recrystallized from ethanol to give compound 37; yield 89%; m.p. 1644, 1624 (3C=O), 1599 (O=C=NO); \(^1\)H NMR (300 MHz, DMSO-\(d_6\)) \(\delta\) 11.77, 11.018 and 8.53–9.06 (2H, s, CH=CH), 2.5 (3H, s, CH\(_3\)), 2.5 (3H, s, CH\(_3\)); MS \(m/z\) (%): 275 (M\(^+\) + 2), 273 (M\(^+\)), 89 (100).

3-[6-(4-Chlorophenyl)-4-oxo-2-thioxo-3,4-dihydropyrimidin-1(2H)-yl]-2-methylquinazolin-4(3H)-one (40)

A mixture of hydrazide 33 (0.01 mol)\(^{19}\) and p-chlorocinnamoyl isothiocyanate (0.01 mol) (freshly prepared from p-chlorocinnamoyl chloride (0.01 mol) and NH\(_2\)SCN (0.015)) in acetone (20 ml) was refluxed for 4 h. The precipitate obtained after concentration and cooling was filtered-off and recrystallized from ethanol to give compound 40; yield 88%; m.p. 225–227\(^\circ\)C; IR (KBr) (cm\(^{-1}\)) 3471 (NH, \(\delta\) 3438–3433 cm\(^{-1}\)), 3115 (Ar-H), 1690, 1668, 1588 cm\(^{-1}\); \(^1\)H NMR (300 MHz, DMSO-\(d_6\)) \(\delta\) 9.1 (1H, s, NH), 8.23–6.45 (4H, m, Ar-H), 5.8 (1H, s, CH\(_3\)), 2.5 (3H, s, CH\(_3\)), 2.5 (3H, s, CH\(_3\)); \(^13\)C NMR (75 MHz, DMSO-\(d_6\)) \(\delta\) 134–121 (Ar-C); MS \(m/z\) (%): 203 (M\(^+\) + 4), 199 (M\(^+\)), 92, 77 (100).

1-Acetyl-2-aminoquinolin-4(1H)-one (42)

A solution of benzoazine 6 (0.01 mol) and ethyl cyanoacetate (0.01 mol) in benzene (25 ml) and a few drops of TEA was stirred for 24 h at room temperature. The precipitate obtained after concentration and cooling was filtered-off and recrystallized from ethanol to give compound 42; yield 55%; m.p. 270–272\(^\circ\)C; IR (KBr) (cm\(^{-1}\)) 3321 (NH\(_{\text{stretching}}\)), 1712, 1624 (2C=O), 1600 (C=N); \(^1\)H NMR (300 MHz, DMSO-\(d_6\)) \(\delta\) 9.09–9.06 (2H, s, NH\(_2\)), 8.62–7.22 (4H, m, Ar-H), 5.83 (1H, s, CH\(_3\)), 2.5 (3H, s, CH\(_3\)); \(^13\)C NMR (75 MHz, DMSO-\(d_6\)) \(\delta\) 135, 136 (2C=O), 134–121 (Ar-C); MS \(m/z\) (%): 204 (M\(^+\) + 2), 202 (M\(^+\)), 76 (100).

1-Methyl[1,2,4]triazolo[4,3-a]quinolin-5(3H)-one (43)

A mixture of compound 42 (0.01 mol) and hydrazine hydrate (0.01 mol) in ethanol (25 ml) was refluxed for 4 h. The precipitate obtained after cooling was filtered-off and recrystallized from benzene to give compound 43; yield 75%; m.p. 229–231\(^\circ\)C; IR (KBr) (cm\(^{-1}\)) 3372 (NH), 1711, 1616 (C=N); \(^1\)H NMR (300 MHz, DMSO-\(d_6\)) \(\delta\) 8.54 (1H, s, NH), 8.23–6.45 (4H, m, Ar-H), 5.8 (1H, s, CH\(_3\)), 2.5 (3H, s, CH\(_3\)), 2.5 (3H, s, CH\(_3\)); \(^13\)C NMR (75 MHz, DMSO-\(d_6\)) \(\delta\) 169, 151 (C=O), 133–109 (Ar-C); MS \(m/z\) (%): 203 (M\(^+\) + 4), 199 (M\(^+\)), 92, 77 (100).

3,4-Dimethyl-5H-pyrazolo[4,3-c]quinoline (44)

A solution of benzoazine 6 (0.01 mol) and acetylacetone (0.01 mol) in ethanol (15 ml) and a few drops of TEA was stirred for 24 h at room temperature and then refluxed with hydrazine hydrate (0.01 mol) for 4 h. The precipitate obtained after acidification with AcOH and cooling was filtered-off and recrystallized from ethanol to give compound 44; yield 65%; m.p. 208–210\(^\circ\)C; IR (KBr) (cm\(^{-1}\)) 3264 (NH), 1598 (2C=N); \(^1\)H NMR (300 MHz, DMSO-\(d_6\)) \(\delta\) 9.1 (1H, s, NH), 8.18–7.02 (4H, m, Ar-H), 2.58 (3H, s, CH\(_3\)), 2.5 (3H, s, CH\(_3\)); MS \(m/z\) (%): 197 (M\(^+\)), 130 (100).

Results and discussion

A one-pot three-component anthranilic acid derivative 2, benzylidene malononitrile and triethyl amine resulted in pyridine cyclization followed by 1,3-H shift producing a stable product 3. The IR of compound 3 showed bands around 3433, 3115, 1690, 1658, 1588 cm\(^{-1}\) region, resulting from OH, NH, 2C=O and C=N functions respectively; \(^1\)H NMR showed signals at \(\delta\) 9.177, 11.018 and 8.53–7.10 ppm for OH, NH and ArHs respectively.

Benzoazine derivative 4 was reacted with \(\alpha\)-naphthol and \(\beta\)-naphthol to give the compounds 7 and 10 respectively (Scheme 2). In the \(^1\)H NMR spectrum of compounds 7 and 10, the OH signal resonated at \(\delta\) ~12.1 ppm. The \(\beta\)-naphthol derivative 8 showed bands at \(\delta\) 8.54 (1H, s, NH) and 8.18–7.02 (4H, Ar-H) and the OH signal at \(\delta\) 11.78 (2H, s, CH=CH), 2.5 (3H, s, CH\(_3\)), 2.5 (3H, s, CH\(_3\)); MS \(m/z\) (%): 396.5 (M\(^+\) – 1), 90 (100).
showed signals for OH proton at δ 12.23 ppm; MS spectrum showed m/z = 265 and m/z^2 = 267. The reaction of N-phenyl pyrazolone 12 with benzoazone 4 produced compound 14. Carbonyl groups appeared at 1724, 1684 and 1643 cm\(^{-1}\). In the \(^1\)H NMR spectrum of 14 showed a signal for NH which appeared at δ 11.2 ppm and a multiplet peak for aromatic protons at δ 7.78–7.20 ppm; MS spectrum showed m/z = 397 and m/z^2 = 399.

Benzoazone 4 underwent ring transformation upon treatment with crotonate 16 and/or enammine 17 to give quinoline derivative 18, and/or 19 respectively (Scheme 4). The IR spectrum of compound 18 showed peaks at 3470 and 3185 cm\(^{-1}\) for OH and NH\(_2\) respectively. \(^1\)H NMR spectrum of compound 18 showed signals at δ 13.74 and 12.18 ppm for OH and NH\(_2\) respectively and at δ 1.5 ppm for the CH\(_2\) protons. The structure of compound 19 has been explained in details in the text. Pyrazolopyrimidine derivative 22 was synthesized from condensation of compound 5 with benzaldehyde (Scheme 5). Compound 22 showed absorption bands around 3445, 1693 and 1652 cm\(^{-1}\), corresponding to NH, C=O and C=N functional groups respectively. The \(^1\)H NMR compound 21 revealed signal at δ 11.03 ppm for the NH\(_2\) protons. Base-induced one-pot reaction of compound 5 and ammonium isothiocyanate gave pyrazoloquinazoline 24 (Scheme 5). Its IR spectrum revealed stretching bands for NH, C=O and C=S groups at 3082, 1705 and 1265 cm\(^{-1}\) respectively, while its \(^1\)H NMR showed that NH protons appeared at δ 13.38, 12.67 and 12.43 ppm. MS spectrum showed m/z = 259 and m/z^4 = 263. The 1,3-disubstitute thiourea 26 was obtained by reaction of two equivalents of 5 with ammonium isothiocyanate (Scheme 5). The IR spectrum of 26 exhibited characteristic absorption band for the imino and two carbonyls at 3386, 1699 and 1667 cm\(^{-1}\). The \(^1\)H NMR spectrum displayed signals for proton of mercapto and imino at δ 9.1 and 5.82 ppm respectively. MS spectrum showed m/z = 392. Aminoquinazoline 5 was added to benzoil isothiocyanate to produce thioamide derivative 27 (Scheme 6). The \(^1\)H NMR spectrum of 27 showed two signals at δ 12.32 and 10.9 ppm for S=CNH and NH\(_2\) respectively. The multiplet at δ 8.46–6.49 ppm was for the aromatic protons. MS spectrum showed m/z = 338. Thioamide 27 underwent cyclization using KOH to produce pyrimidobenzoxazine derivative 29 (Scheme 6). The IR spectrum of 29 displayed a strong absorption band at 1687 and 1656 cm\(^{-1}\) for (C=O) and (C=N) respectively. The \(^1\)H NMR of 29 exhibited a multiplet peak at δ = 7.96–7.46 ppm for the aromatic protons. MS spectrum showed m/z = 306, m/z^2 = 308, m/z^3 = 309. Cyclocondensation of amino quinazolinone and carbon disulphide resulted in pyrazole cyclization affording pyrazoloquinazolinone 30 (Scheme 7). In the IR spectrum of 30, there was a band at 3336 cm\(^{-1}\) for NH; while C=O appeared at 1650 cm\(^{-1}\). The NH proton appeared at δ 12.49 ppm and the aromatic protons appeared at 8.21–6.52 ppm. MS showed m/z = 217 and m/z^4 = 221.

Compound 30 underwent heterocyclization upon treatment with ethyl chloroacetate to give compound 31 (Scheme 7). In the IR spectrum of 31, the band at 1650 cm\(^{-1}\) belonged to C=O group. \(^1\)H NMR spectrum exhibited multiplet aromatic protons at δ 8.2–6.49 ppm. MS showed m/z = 257, m/z^2 = 259. Compound 5 underwent acylation using chloroacetyl chloride to give compound 32 (Scheme 7). Stirring benzoazone 6 and hydrazine hydrate at room temperature for 24 h afforded the hydrazide derivative 33 (ref. 19). Upon heating the hydrazide derivative 33 with ethyl acetooacetate, pyrazoloquinazolinone derivative 34 was obtained (Scheme 8). The IR spectrum of condensed quinazolinone 34 indicated the presence of NH group (in the region 3373 cm\(^{-1}\)), C=O (at 1689 cm\(^{-1}\)) and C=N (at 1655 cm\(^{-1}\)). The \(^1\)H NMR showed signal around 11.73 ppm for NH, while the aromatic multiplet appeared at 8.47–6.46 ppm in addition to methyl signals at δ 2.1 ppm. MS spectrum showed m/z^1 = 200, m/z^2 = 201. Compound 33 reacted with acetylacetone to yield pyrazoloquinolinone derivative.
36 (Scheme 8). $^1$H NMR of the same compound showed aromatic protons at 8.73–7.10 ppm, NH at $\delta$ 6.65 ppm and methyl protons at 2.49 ppm. MS spectrum showed $m/z = 214$.

The reaction of maleic anhydride with hydrazide derivative 33 readily generated substituted maleimide derivative 37 (Scheme 8). $^1$H NMR spectrum also showed signals at $\delta$ value 11.78, 9.08–7.25, 5.81 and 2.5 ppm for


NH, aromatic protons, CH=CH and CH₃ protons respectively. MS spectrum showed $m/z = 273, m/z+2 = 275$. The synthesis of quinazolinone with pyrimidine moiety 40 was carried out by intramolecular cycloaddition of hydrazide derivative 33 and cinnamoyl isothiocyanate 38 (Scheme 8). In $^1H$ NMR of pyrimidinethione derivative 40 there are signals at $\delta = 9.2, 8.28–7.36, 6.12$ and $2.44$ ppm were attributed to NH, aromatic protons, pyrimidine and CH₃ protons respectively. MS spectrum showed $m/z = 396$. Reaction of benzoazone 6 and ethyl cyanoacetate yielded pyridine cyclization 42 (Scheme 9). The IR spectrum of 42 showed peaks in the region 3290–3400 cm⁻¹ (NH stretching), 1712 cm⁻¹, 1624 cm⁻¹ (C=O) and 1600 cm⁻¹ (C=N). $^1H$ NMR spectrum of 42 showed
Scheme 7.

Scheme 8.
absorption due to NH$_2$, aromatic protons and enaminic proton at $\delta$ 9.09–9.06, 8.62–7.22 and $\delta$ 5.83 ppm respectively. The MS spectrum showed $m/z = 202$. Quinoline 42 was refluxed with hydrazine hydrate forming triazole derivative 43 after evolution of ammonia gas (Scheme 9). The IR spectrum of 43 showed absorption frequency at 3372, 1671 and 1616 cm$^{-1}$ corresponding to NH, C=O and C=N functions respectively. $^1$H NMR spectrum also showed a signal around $\delta$ 8.54 ppm due to NH, aromatic protons in the region $\delta$ 8.23–6.45 ppm, in addition to aliphatic protons at $\delta$ 2.50 ppm. The MS spectrum showed $m/z = 199$, $m/z^+ = 203$. Also, the structure was proved by $^{13}$C NMR, which led to signals at 169, 151 ppm for SP$^2$ carbonyl, in addition to aromatic SP$^2$ carbons. Benzoxaze 6 underwent ring opening and ketonic hydrolysis upon treatment with acetylacetone in basic medium to yield the ketonic compound C (Scheme 9). Hydrazine was condensed with diketone C followed by intramolecular cyclocondensation to yield the polyheterocyclic compound 44 (Scheme 9). The IR spectrum of compound 44 showed absorption frequency at 3264, 1598 cm$^{-1}$ due to NH and C=N functions respectively.

**Conclusion**

Acylated derivative 2 underwent cycloaddition using benzyldiene to deliver pyridine of type 3. Benzoazone reacted with nucleophilic carbon of phenols to yield derivatives 7 and 10. Cyclic active methylene was also added to compound 4 to yield 13 and 14. Enaminic carbon was added to compound 4 to give 18 and 19. Aminoquinazoline 5 undergoes transformation to 22 and 26 upon treatment with PhHCONCS and/or CS$_2$ to yield condensed system 24 and 31 respectively. Reaction of chloroacetyl chloride and compound 5 yielded acylated product 32. The hydrazide 33 underwent condensation reaction with acetylacetone and/or ethyl acetocetate. Also, 33 condensed with maleic anhydride to yield the maleimide 37. The quinolone derivative 42 was cyclized by hydrazine to give triazoloquinoline 43. Lastly, pyrazoloquinoline 44 was prepared by the reaction of benzoazone 6 with acetylacetone followed by hydrazinolysis.


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