# 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. Benzoxazone 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, benzoxazone 6 reacted with hydrazine to yield compounds 5 and 33. Aminoquinazoline 5 underwent a series of reactions using benzaldhyde, $NH_4SCN$ in base/acid medium, chloroacetyl chloride and $CS_2$ 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 acetyl acetone, maleic anhydride and *p*-chlorocinnamoyl 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.**

**Keywords:** Condensed oxazine, cyclization, functionalization, pyrimidine derivatives, ring transformation.

QUINAZOLINES and quinazolinone derivatives are of special importance owing to their versatile biological and pharmacological activities[1], especially antihistaminic[2,3], analgesic[4], anti-inflammatory[5], antiviral[6], anti HIV[7], antibacterial[7], antifungal[7–9], anticonvulsant[10], antithrombotic,[11] antihypertensive,[12] antitubercular[13], antitumour[14] and insecticidal activities[15]. In this study, we present ring transformation of benzoxazone to acyclic and condensed pyrimidine derivatives using carbon and nitrogen dentates. Moreover, the chemical behaviour of the obtained functionalized quinazolinone towards simple laboratory-available reagents was also studied.

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## Materials and methods

### *Antimicrobial activity*

The antimicrobial activities of some selected compounds were determined using agar diffusion method[16]. 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 incubation[17]. 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

**Table 1.** *In vitro* antimicrobial activity of the synthesized compounds

| | Inhibition zone diameter (mm) | | | | |
|---|---|---|---|---|---|
| | ($G^+$) | | ($G^-$) | | Fungi |
| Compound no. | *Streptococcus pneumoniae* | *Bacillus subtilis* | *Pseudomonas aeruginosa* | *Escherichia coli* | *Aspergillus fumigatus* |
| **10** | 14.6 ± 1.2 | 13.7 ± 0.63 | 13.2 ± 0.72 | 12.2 ± 1.2 | 15.2 ± 1.2 |
| **14** | 12.3 ± 0.58 | 14.3 ± 0.72 | 10.3 ± 1.2 | 15.2 ± 0.63 | 13.2 ± 0.58 |
| **24** | 12.4 ± 0.58 | 14.8 ± 0.63 | 11.2 ± 0.58 | 12.3 ± 0.63 | 13 ± 0.72 |
| **27** | 14.5 ± 1.2 | 13.7 ± 0.72 | 15.3 ± 0.72 | 14.3 ± 0.63 | 16.8 ± 0.58 |
| **30** | 14.3 ± 0.58 | 16.8 ± 0.72 | 17.5 ± 1.2 | 14.2 ± 0.63 | 17.6 ± 0.63 |
| **31** | 15.3 ± 0.63 | 17.1 ± 1.2 | 12.8 ± 0.53 | 18.4 ± 0.72 | 17.2 ± 0.58 |
| Ampicillin | 23.8 ± 1.2 | 32.4 ± 0.63 | – | – | – |
| Gentamicin | – | – | 17.3 ± 1.2 | 19.9 ± 0.72 | – |
| Amphotericin B | – | – | – | – | 23 ± 1.2 |

**Table 2.** Antimicrobial activity of the synthesized compounds

| | Inhibition zone diameter (mm/mg sample) | | | |
|---|---|---|---|---|
| | ($G^+$) | ($G^-$) | Fungi | |
| Compound no. | *Staphylococcus aureus* | *Escherichia coli* | *Candida albicans* | *Aspergillus flavus* |
| **3** | 15 | 20 | 12 | 0.0 |
| **19** | 39 | 35 | 13 | 0.0 |
| **22** | 17 | 32 | 10 | 0.0 |
| **34** | 12 | 10 | 0.0 | 0.0 |
| **37** | 10 | 12 | 0.0 | 0.0 |
| **40** | 12 | 12 | 0.0 | 0.0 |
| **42** | 22 | 18 | 10 | 0.0 |
| **44** | 11 | 11 | 0.0 | 0.0 |

(DMEM) supplemented with 10% heat-inactivated foetal bovine serum 1%. All cells were kept at 37°C in a humidified atmosphere with 5% $CO_2$ and were subcultured twice a week[18]. 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 $^1H/^{13}C$-NMR spectra were recorded using a Varian Mercury VX-300 NMR ($^1H$, 300 MHz, $^{13}C$, 75.4 MHz) spectrometer with DMSO-$d_6$ as a solvent. All chemical shifts were expressed in the $\delta$ (ppm) scale using tetramethylsillane (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 $AC_2O$ (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 (2C=O), 1588 (C=N); $^1H$ NMR (300 MHz, DMSO-$d_6$) $\delta$ 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 $\alpha$- and/or $\beta$-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 $IC_{50}$

| Compound no. | $IC_{50}$ (μg/ml) | | |
|---|---|---|---|
| | Heptacellular carcinoma | Breast carcinoma | Colon carcinoma |
| **7** | 28.8 | 48.9 | 30.8 |
| **13** | 30.3 | 44.7 | 40.6 |
| **26** | 108 | 171 | 100 |
| **29** | 121 | 181 | 109 |
| **32** | 277 | 324 | 389 |

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-$d_6$) $\delta$ 12.15 (2H, s, OH + NH), 8.72–7.06 (15H, m, 3Ar-H); MS *m/z* (%): 371 ($M^+$ + 2), 370 ($M^+$ + 1), 369 ($M^+$ + 2), 105, 77 (100).

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

A solution of compound **4** (0.01 mol) and 1*H*-indene-1,3(2*H*)-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 (2H, s, $NH_2$), 8.21–7.18 (8H, m, 2Ar-H); MS *m/z* (%): 267 ($M^+$ + 2), 265 ($M^+$), 105(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) ($cm^{-1}$) 3057 (NH), 1764, 1684, 1643 (C=O), 1610 (NH…C=O); $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 11.2 (1H, s, NH), 7.78–7.20 (14H, m, Ar-H), 3.3 (1H, s, CH), 2.8 (3H, s, $CH_3$); MS *m/z* (%): 399 ($M^+$ + 2), 397 ($M^+$), 77(100).

### *3-(1-Aminovinyl)-4-oxo-2-phenyl-3,4-dihydroquinoline-3-carboxylic acid (**18**)*

A mixture of compound **4** (0.01 mol) and crotonate **16** (0.01 mol) in DMF (20 ml) was refluxed for 7 h. The precipitate obtained after cooling was filtered-off and recrystallized from ethanol to give compound **18**; yield 75%; m.p. 265–267°C. IR (KBr) ($cm^{-1}$) 3470 (OH), 3185, 3113 ($NH_2$), 1684, 1642 (C=O), 1608 (C=N); $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 13.7 (1H, s, OH), 12.1 (2H, s, $NH_2$), 8.7–7.1 (9H, m, 2Ar-H), 1.4 (2H, s, =$CH_2$); MS *m/z* (%): 306 ($M^+$).

### *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 55%; m.p. 160–162°C. IR (KBr) ($cm^{-1}$) 3185, 3112 ($NH_2$), 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, Ar-H's), 2.4 (3H, s, $COCH_3$), 3.45 (2H, s, C=$CH_2$); 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 $AC_2O$/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), 2.11 (2H, d, $CH_2$); MS *m/z* (%): 265 ($M^+$ + 3), 263 ($M^+$), 262 ($M^+$ – 1), 146, 77 (100).

*2-Amino-9-oxo-1,9-dihydropyrazolo[5,1-b] quinazoline-3-carbothioamide (**24**)*

A mixture of quinazoline **5** (0.01 mol) and $NH_4SCN$ (0.01 mol) in pyridine (10 ml) and a few drops of piperidine was refluxed for 5 h. The obtained precipitate after cooling and acidification with AcOH was filtered-off and recrystallized from ethanol to give compound **24**; yield 75%; m.p. 317–319°C; IR (KBr) ($cm^{-1}$) 3082 (NH), 1705 (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* (%): 263 ($M^+ + 4$), 261 ($M^+ + 2$), 259 ($M^+$), 178(100).

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

A solution of compound **5** (0.01 mol) and $NH_4SCN$ (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 (2NH), 1699, 1667 (C=O), 1254 (C=S); $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 9.1 (1H, s, SH), 5.82 (1H, s, NH), 8.13–7.47 (8H, m, Ar-H), 1.9 (3H, s, $CH_3$), 1.3 (3H, s, $CH_3$); MS *m/z* (%): 393 ($M^+ + 1$), 392 ($M^+$), 262 (100).

*N-[2-(3-Amino-4-oxo-3,4-dihydroquinazolin-2-yl)ethanethioyl]benzamide (**27**)*

A solution of quinazoline **5** (0.01 mol) and benzoyl isothiocyanate (prepared by addition of 0.01 mol benzoyl chloride and 0.015 mol $NH_4SCN$ in dry acetone (25 ml)) was refluxed for 9 h. The precipitate obtained after 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 ($M^+$), 336 ($M^+ - 2$), 77(100).

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

A solution of compound **27** (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 aminoquinazoline **5** (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 **30** (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 **5** (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, $CH_2Cl$), 3.3 (2H, s, $CH_2Cl$); 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 **33** (0.01 mol)[19] and ethyl acetoacetate (0.01 mol) in xylene (15 ml) and a few drops of triethylanine (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).

*2,3a-Dimethyl-3a,4-dihydropyrazolo[5,1-b]quinazolin-9(3H)-one (**36**)*

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 acidification with AcOH and cooling was filtered-off and recrystallized from benzene to give compound **36**; yield 75%; m.p. 188–190°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, $CH_2$), 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. 337–339°C; IR (KBr) ($cm^{-1}$) 3292 (NH), 1711, 1644, 1624 (3C=O), 1599 (O-C=N); $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 11.78 (2H, s, NHs), 9.08–7.25 (4H, m, Ar-H), 5.81, 3.33 (2H, s, CH=CH), 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 $NH_4SCN$ (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°C; IR (KBr) ($cm^{-1}$) 3471 (NH), 1657, 1627 (2C=O), 1594 (C=N), 1248 (C=S); $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 9.2 (1H, s, NH), 8.28–7.36 (8H, m, 2Ar-H), 6.12 (1H, s, CH of pyrimidine ring), 2.44 (3H, s, $CH_3$); MS *m/z* (%): 396.5 ($M^+$), 88(100).

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

A solution of benzoxazine **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 acidification with AcOH and cooling was filtered-off and recrystallized from ethanol to give compound **42**; yield 55%; m.p. 270–272°C; IR (KBr) ($cm^{-1}$) 3321 ($NH_{stretching}$), 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), 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°C; IR (KBr) ($cm^{-1}$) 3372 (NH), 1671 (C=O), 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), 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 benzoxazine **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°C; IR (KBr) ($cm^{-1}$) 3264 (NH), 1598 (2C=N); $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 9.1 (1H, s, NH), $\delta$ 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).

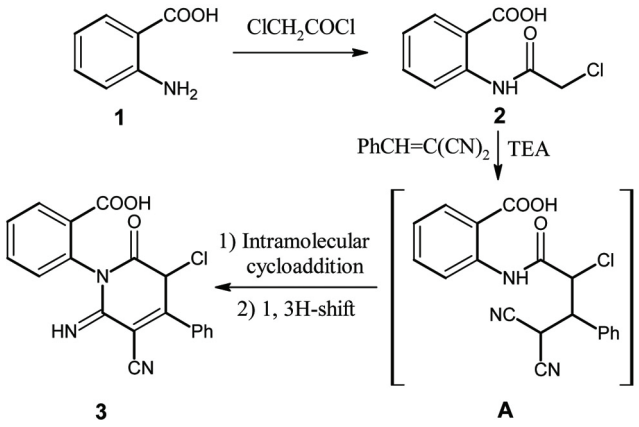
## Results and discussion

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, 1668, 1588 $cm^{-1}$ region, resulting from OH, NH, 2C=O and C=N functions respectively; $^1$H NMR showed signals at $\delta$ 11.77, 11.018 and 8.53–7.10 ppm for OH, NH and ArHs respectively.

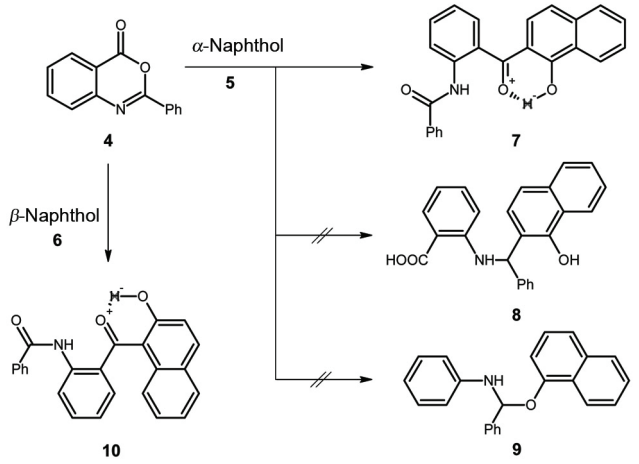
Benzoxazone derivative **4** was reacted with $\alpha$-naphthol and $\beta$-naphthol to give the compounds **7** and **10** respectively (Scheme 2). In the $^1$H NMR spectrum of compounds **7** and **10**, the OH signal resonated at $\delta \sim 12.1$ ppm, NH proton appeared at 10 ppm. MS spectrum showed $m/z = 369$, $m/z^{+1} = 370$ and $m/z^{+2} = 371$. 1,3-Indandione was reacted with benzoxazone **4** to give the diketone derivative **13** (Scheme 3). IR of **13** showed bands at 3439 and 3239 $cm^{-1}$ for OH and $NH_2$ and two C=O bonds at 1684 and 1643 $cm^{-1}$ respectively. The $^1$H NMR of **13**

showed signals for OH proton at $\delta$ 12.23 ppm; MS spectrum showed $m/z$ = 265 and $m/z^{+2}$ = 267. The reaction of *N*-phenyl pyrazolone **12** with benzoxazone **4** produced compound **14**. Carbonyl groups appeared at 1724, 1684 and 1643 $cm^{-1}$. In The $^1$HNMR spectrum of **14** showed a signal for NH which appeared at $\delta$ 11.2 ppm and a multiplet peak for aromatic protons at $\delta$ 7.78–7.20 ppm; MS spectrum showed $m/z$ = 397 and $m/z^{+2}$ = 399.

Benzoxazine **4** underwent ring transformation upon treatment with crotonate **16** and/or enaminone **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 **18** showed signals at $\delta$ 13.74 and 12.18 ppm for OH and $NH_2$ respectively and at $\delta$ 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 functions respectively. The $^1$H NMR compound **21** revealed signal at $\delta$ = 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 $\delta$ 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 $\delta$ 9.1 and 5.82 ppm respectively. MS spectrum showed $m/z$ = 392. Aminoquinazoline **5** was added to benzoyl isothiocyanate to produce thioamide derivative **27** (Scheme 6). The $^1$H NMR spectrum of **27** showed two signals at $\delta$ 12.32 and 10.9 ppm for S=CNH and $NH_2$ respectively. The multiplet at $\delta$ 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 $^1$HNMR of **29** exhibited a multiplet peak at $\delta$ = 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 $\delta$ 12.49 ppm and the aromatic protons appeared at 8.21–6.52 ppm. MS showed $m/z$ = 217 and $m/z^{+4}$ = 221.

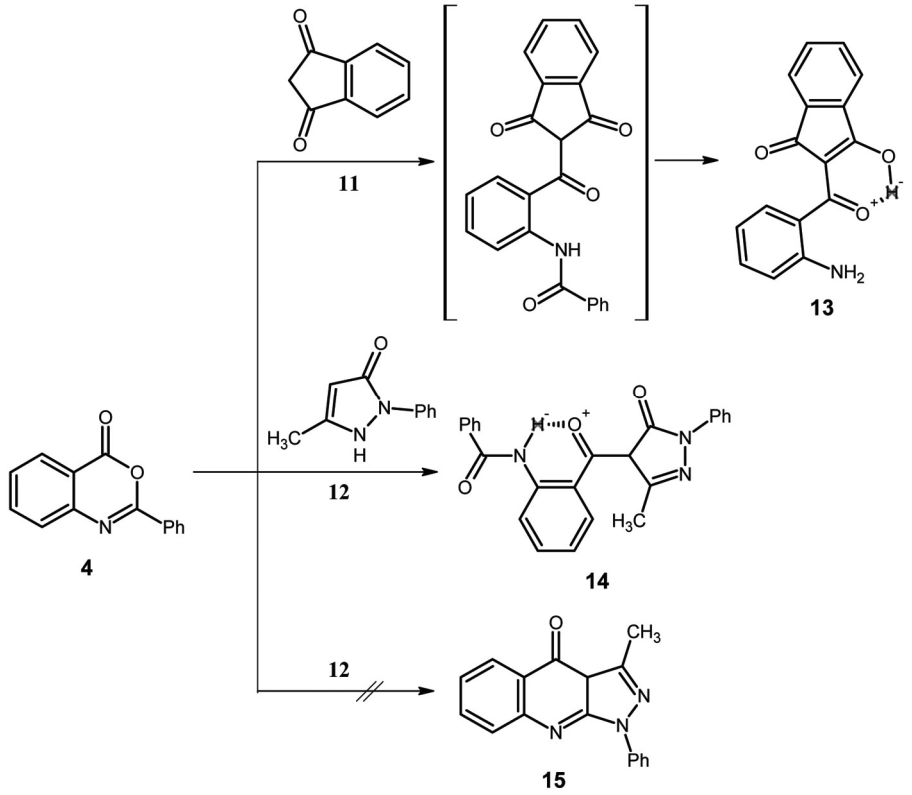



**Scheme 1.**

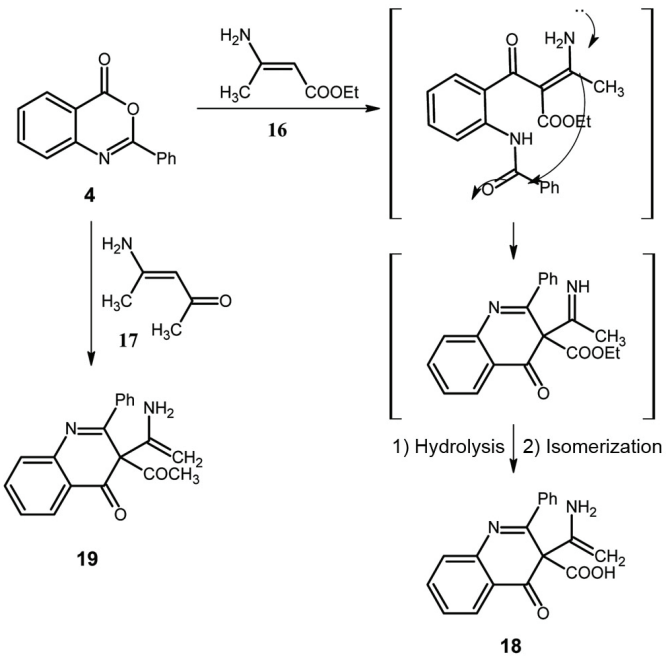



**Scheme 2.**

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 $\delta$ 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 benzoxazone **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 acetoacetate, 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 $\delta$ 2.1 ppm. MS spectrum showed $m/z^{+1}$ = 200, $m/z^{+2}$ = 201. Compound **33** reacted with acetylacetone to yield pyrazoloquinolinone derivative



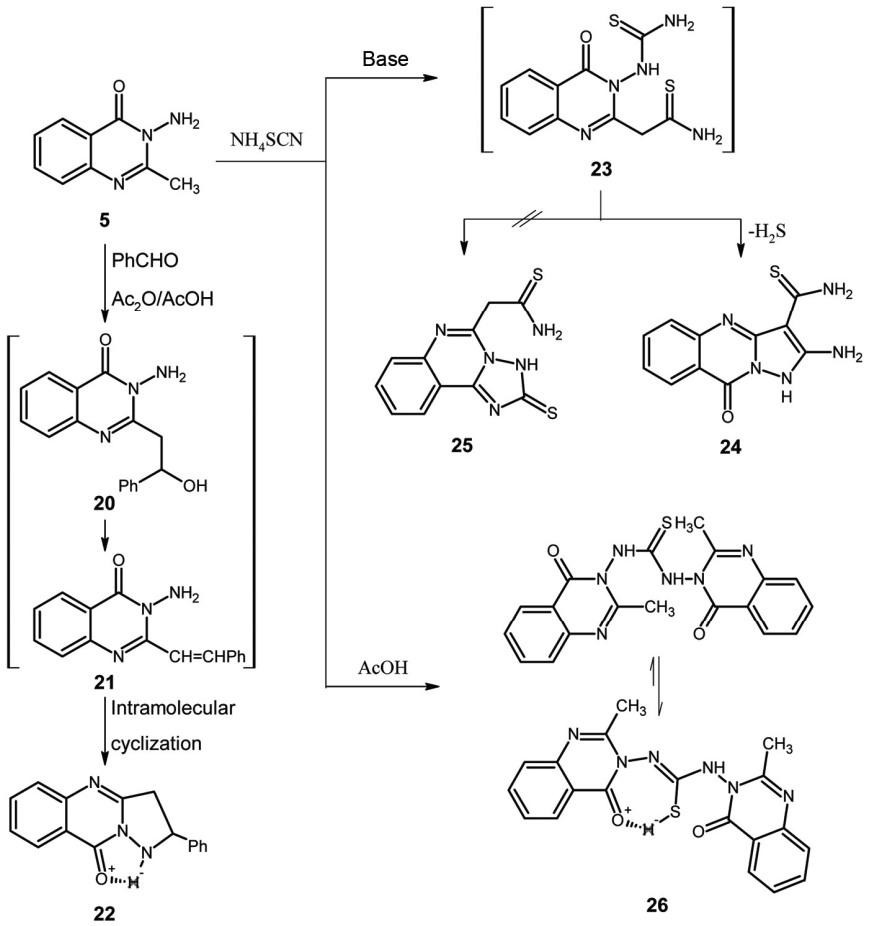

**Scheme 3.**



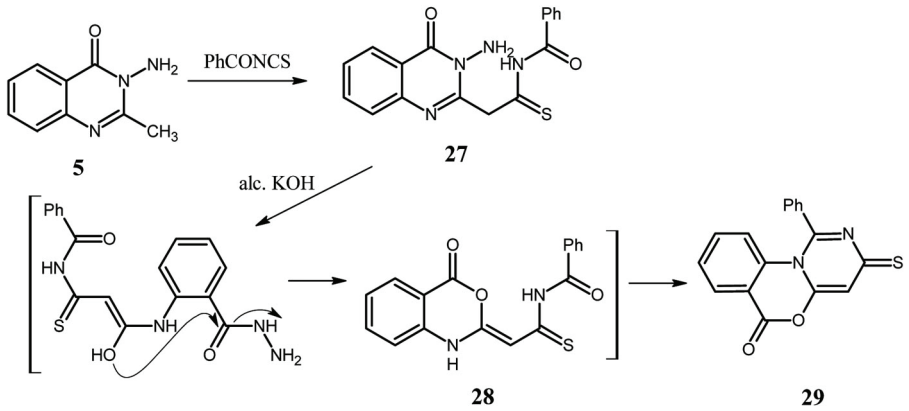

**Scheme 4.**

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 malemide 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

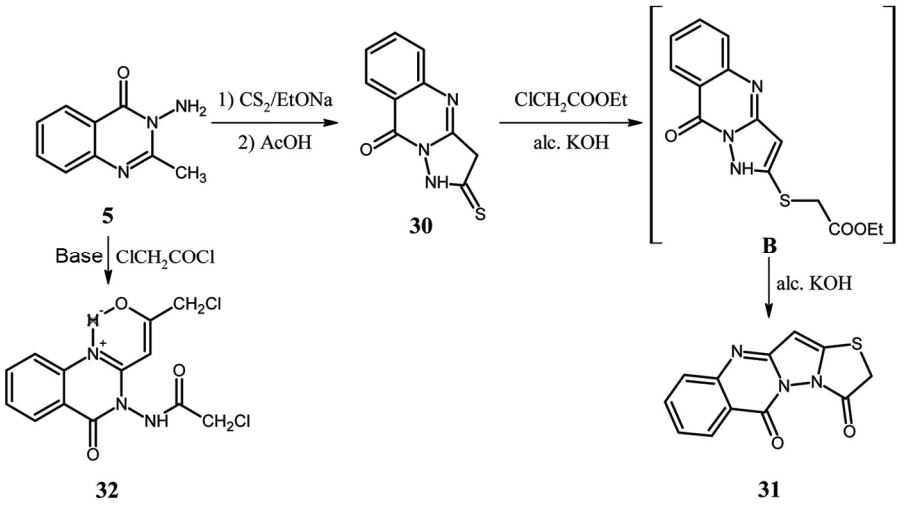



**Scheme 5.**

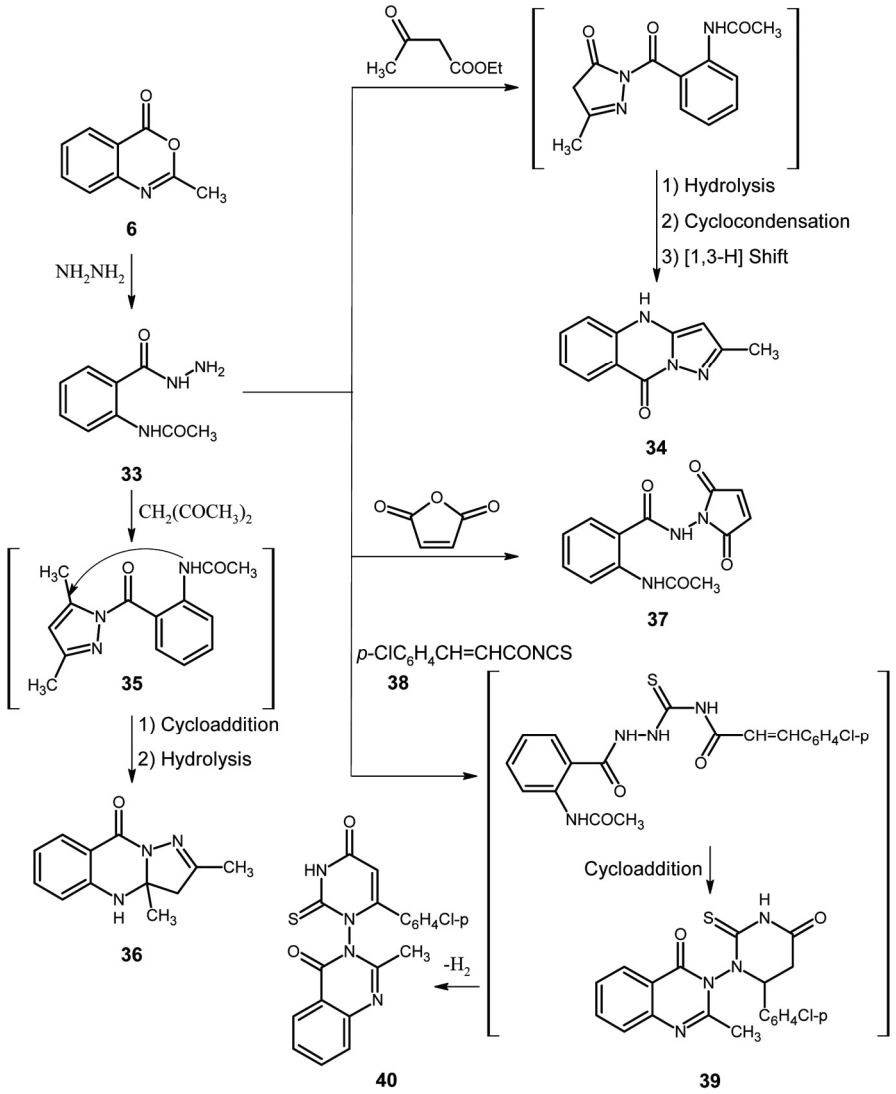



**Scheme 6.**

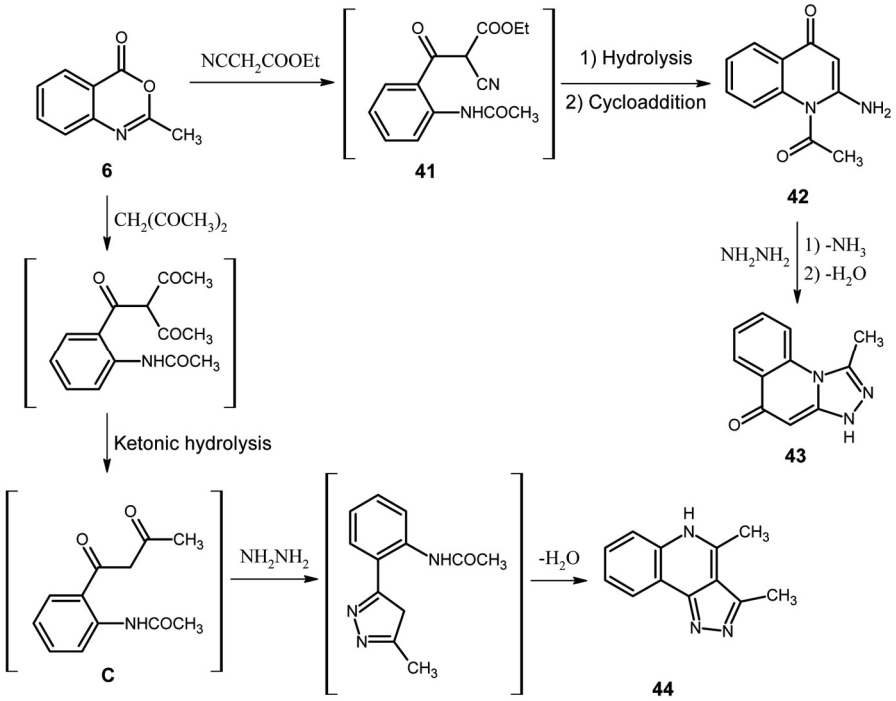
NH, aromatic protons, CH=CH and $CH_3$ protons respectively. MS spectrum showed $m/z = 273$, $m/z^{+2} = 275$. The synthesis of quinazolinone with pyrimidine moiety **40** was carried out by intramolecular cycloaddition of hydrazide derivative **33** and cinnamoyl isothiocyanate **38** (Scheme 8). In $^1$H 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 $CH_3$ protons respectively. MS spectrum showed $m/z = 396$. Reaction of benzoxazone **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). $^1$H NMR spectrum of **42** showed




**Scheme 7.**




**Scheme 8.**




**Scheme 9.**

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. $^1H$ 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, $m/z^{+4}$ = 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. Benzoxazone **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 benzylidene to deliver pyridine of type **3**. Benzoxazone 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 PhHC=O and/or $NH_4SCN$ respectively. Compound **5** reacted with PhCONCS 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 acetoacetate. Also, **33** condensed with maleic anhydride to yield the malemide **37**. The quinolone derivative **42** was cyclized by hydrazine to give triazoloquinoline **43**. Lastly, pyrazoloquinoline **44** was prepared by the reaction of benzoxazone **6** with acetylacetone followed by hydrazinolysis.

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