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PEG mediated synthesis of 6-pyrazinyl-/fused pyrazinyl-quinazolin-4(3H)-ones using Castro-Stephen coupling, oxidation and cyclocondensation reactions

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Abstract: PEG mediated green synthesis of 6-pyrazinyl-/fused pyrazinylquinazolin-4(3H)-ones was developed starting from 6-iodo-3-methyl-2-phenyl-quinazolin-4(3H)-one by means of quinazolinone based internal alkyne/1,2-diketone as intermediates using Castro-Stephen coupling reaction / potassium permanganate mediated oxidation and cyclocondensation reactions.

Keywords: KMnO₄, Bisazaheterocycle; 1,2-diamine; 1,2-diketone

INTRODUCTION

Quinazolin-4(3H)-one either from natural or synthetic origin, is one among the most frequently encountered heterocyclic compound in the field of medicinal chemistry, polymer chemistry and dyes. Particularly, quinazolin-4(3H)-one based C-C linked unsymmetrical bis heterocyclic compounds exhibit wide range of biological activity. For example, 2-hetarylquinazolin-4(3H)-ones exhibit antitubercular⁴, antimicrobial⁵, analgesic⁶, anti inflammatory⁷, antiulcer⁸, anticonvulsant⁹, antihypertensive¹⁰, antiplatelet¹¹, anticancer¹² and antifeedent activities¹³. Also, they have a prominent application in polymer chemistry as heat stable epoxy resins, fiber reactive dyes and polymers¹⁴. The literature survey also revealed the importance of 6-hetaryl-quinazolin-4(3H)-ones in pharmaceutical chemistry as antihypertensive¹⁵, antiviral¹⁶, antitumor¹⁷ and TGFβ type 1 receptor inhibitor to treat many fibrosis¹⁸. Additionally, these act as size expanded nucleoside which in turn useful in the study of steric effects of DNA-protein interactions and also serve as building blocks for a large size genetic system¹⁹.

On the other hand, over many years the pyrazines and fused pyrazines such as quinoxaline and pyridopyrazine compounds have been a source of great interest
to organic, medicinal, and material scientists due to display of diverse biological properties\textsuperscript{16} such as antibacterial, antiviral, antihelmintic, antiinflammatory, anticancer activity.

Poly (ethyleneglycol-400) (PEG-400), most commercially important type of polyether, has drawn a great attention in recent years, due to low toxicity, unique solubility and low cost. It is widely used as a green solvent and also heterogeneous catalyst in organic reactions. PEG, considered as acyclic crown ether analogue, has been developed as green phase transfer catalyst, an alternative to quaternary ammonium salts, crown ethers and also as solvent promoter for various reactions. The literature survey revealed the extensive use of PEG-400 as PTC in nucleophilic substitution reactions\textsuperscript{17}, oxidation\textsuperscript{18} and reduction\textsuperscript{19} reactions. In some instances, the advantage of use of PEG-400 as an alternative to quaternary ammonium salts resulted in higher yields of products and short duration of reaction time in phase transfer reactions.

In view of diverse biological activities of pyrazines / fused pyrazines and quinazolin-4(3H)-one scaffold containing compounds, we are interested in the synthesis of C-C linked unsymmetrical bis heterocyclic compounds wherein, the pyrazine ring linked to 6-position of quinazolin-4(3H)-one. Herein, we report PEG mediated synthesis of 6-pyrazinyl / fused pyrazinylquinazolin-4(3H)-ones, starting from 6-iodo-quinazolin-4(3H)-one in good to high yields. The key intermediates quinazolin-4(3H)-one based alkyne was generated by Castro-Stephen coupling reaction. A one step oxidation and cyclocondensation reactions were carried out in PEG-400 with improved yields.

EXPERIMENTAL

General

IR spectra for all the compounds were recorded in solid KBr on infracold model 337 Perkin-Elmer instrument. Melting points were measured in open capillary tubes and are uncorrected. The \textsuperscript{1}H and \textsuperscript{13}C NMR spectra of the synthesized compounds were recorded at 300 MHz and 75 MHz respectively using Bruker AVANCE 400 MHz NMR spectrometer in CDCl\textsubscript{3} solvent and the chemical shifts were expressed in \( \delta \)/ ppm relative to TMS as internal standard and coupling constants (\( J \)) are in Hz. Spin multiplicities were shown as s (singlet), t (triplet), q (quartet) and m (multiplet). Mass analysis was performed on quadruple-time of flight (Q-Tof) mass spectrometer using electron spray ionization (ESI) in positive mode. TLC is performed using precoated aluminum sheets with silica gel 60 F\textsubscript{254}.

Synthesis

Procedure for the preparation of 3-methyl-2-phenyl-6-(phenylethynyl)quinazolin-4(3H)-one (2). A mixture of 6-iodo-3-methyl-2-phenylquinazolin-4(3H)-one (1 g, 2.76 mmol) and copper(I)phenylacetylide (0.55 g, 3.32 mmol) was refluxed in pyridine (75 mL) under nitrogen atmosphere for 12 h. Then, the reaction mixture was cooled and diluted with water. The resulting solid was filtered off and purified by column chromatography over silica gel using mixture of ethyl acetate and pet-ether (3:7) as an eluent to give light yellow amorphous
solid 3-methyl-2-phenyl-6-(phenylethynyl)quinazolin-4(3H)-one (2). Yield (0.69 g, 75 %), mp 151-153 °C.

Procedure for the preparation of 1-(3-methyl-4-oxo-2-phenyl-3,4-dihydroquinazolin-6-yl)-2-phenylethane-1,2-dione (3). To a solution of alkyn 2 (0.08 g, 0.24 mmol) in 3 mL mixture of PEG, water, dichloromethane (1:1:1) was added potassium permanganate (0.12 g, 0.72 mmol) at portion wise. The resulting solution was stirred at 40 °C for 2.5 h for the completion of the reaction. The precipitated MnO₂ in solution was reduced to soluble Mn²⁺ ions by adding NaNO₂ (0.06 g) and 10 % H₂SO₄ (0.62 mL) in small portion. The combined contents were extracted with ethyl acetate, dried over anhydrous Na₂SO₄ and concentrated under vacuum. The residue was purified over silica gel column chromatography using (1:1) of ethyl acetate and pet-ether as an eluent to give 3 as white powder. Yield (70mg, 80 %); mp 161-163 °C.

Preparation of 3-methyl-2-phenyl-6-pyrazinyl fused pyrazinyl quinazolin-4(3H)-ones (5, 7, 9a-f and 9a′-f).

General procedure I: To a solution of 1,2-diketone 3 (0.20 g, 0.55 mmol) in acetic acid (5 mL) and water (1 mL), the appropriate 1,2-diamine (4, 6 and 8a-f) (0.55 mmol) was added and the resulting solution was stirred at 80 °C. After the completion of reaction (monitored by TLC), the solution was cooled, poured into ice cold water and extracted with ethyl acetate. The organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo. The resulting residue was purified over silica gel column chromatography using mixture of ethyl acetate and pet-ether (4:6) as an eluent to give the corresponding bisaza heterocycles 5, 7, 9a-f and 9a′-f.

General procedure II: To a solution of 1,2-diketone 3 (0.20 g, 0.55 mmol) in PEG-400 : water (3 mL : 1mL) of the appropriate 1,2-diamine (4, 6 and 8a-f) (0.06g, 0.55 mmol) was added and the resulting solution was stirred at 80 °C. After the completion of reaction, the solution was cooled and the solid settled was by filtered, and the solid purified over silica gel column chromatography using mixture of ethyl acetate and pet-ether (4:6) as an eluent to give the corresponding bisaza heterocycles 5, 7, 9a-f and 9a′-f. The recovered PEG-400 / water solution was reused for further four cycles for compound 7.

RESULTS AND DISCUSSION

6-Iodo-3-methyl-2-phenylquinazolin-4(3H)-one (1) was prepared using reported procedure²⁰ and which is the key material for quinazolin-4(3H)-one based internal alkyn (Scheme 1). At the outset, only a few reports are available for the preparation of quinazolin-4(3H)-one based internal alkynes²¹-²³.
In particular, earlier the synthesis of 2-benzoyl-6-(phenylethynyl) quinazolin-4(3H)-one was achieved employing Sonogashira coupling reaction. Alternatively, we considered to utilize Castro–Stephens coupling reaction for the synthesis of 3-methyl-2-phenyl-6-(phenylethynyl)quinazolin-4(3H)-one (2) due to its straightforward and efficiency. Remarkably, this process avoids use of palladium salts. To this end, the compound 1 was treated with copper (I) phenylacetylide in pyridine under reflux for 12 h to give an alkyne 2.

To the best of our knowledge, this is a new compound. The alkyne 2 was characterized by IR, HRMS, 1H and 13C NMR spectral data. The peaks at $\nu_{\text{max}}$ 2200 cm$^{-1}$ in IR and at $\delta$ 90.9, 88.4 ppm in 13C NMR spectra of 2 indicate the presence of acetylenic group. Furthermore, in 1H NMR, the upfield shift of signals are observed for C-5H and C-7H of quinazolin-4(3H)-one (δ 8.49, and 7.85 ppm) in comparison with the corresponding signals in 1 (δ 8.65 and 8.01 ppm). This upfield shift is rationalized on the basis of diamagnetic anisotropic effect of acetylene moiety. 2-Phenyl-3-methyl 6-iodoquinazolin-4(3H)-one showed the [M+H]$^+$ ion peak at m/z 337.1327 in high resolution mass spectrum, corresponding to the molecular chemical formula of C$_{23}$H$_{16}$N$_2$O.

Various oxidizing agents were reported to oxidize the internal alkyne to 1,2-diketone. Among them, potassium permanganate at neutral pH conditions was used under different conditions as an efficient oxidizing agent due to low cost, easy availability and simple work-up procedure. Initially, we choose KMnO$_4$ oxidation in the presence of NaHCO$_3$ / MgSO$_4$ in acetone-water solvent mixture and carried out the transformation of internal alkyne 2 to 1,2-diketone 3 at room temperature for 4 h. The desired product 3 was obtained in 60% yield. In order to increase the yield of 3, we intended to use KMnO$_4$ oxidation in PEG-400 owing to its crown ether and PTC property.

Although, potassium permanganate oxidation of alkyne to $\alpha$-diketone under various reaction conditions including PTC condition were reported, but in combination with PEG-400 is not explored till date. These observations prompted us to use PEG-400 as phase transfer catalyst in the potassium permanganate oxidation of quinazolin-4(3H)-one based alkyne 2 to the 1,2-diketone 3. The reaction of alkyne 2 with KMnO$_4$ in aqueous dichloromethane (DCM : H$_2$O [1:1]) using PEG-400 as phase transfer catalyst at pH ~7-7.5 for 2.5 h at 40 °C led to the desired compound 1,2-diketone 3 in 80% isolated yield (Scheme 2). To the best of our knowledge, the compound 3 is a new compound and hence, its structure was established by IR, HRMS, 1H and 13C NMR spectral data. The appearance of three peaks (1677, 1709, 1774 cm$^{-1}$) in IR and also in 13C NMR spectra (δ 193.6, 192.7, 161.8) designate the presence of three carbonyl groups in 3. In 1H NMR spectrum, the downfield shift of C-5H and C-7H in quinazolinoine moiety (δ 8.84, d, $J = 1.18$ Hz, 1H; δ 8.4, dd, $J = 1.98$ Hz, 8.50 Hz, 1H) and ortho protons of phenyl ring (δ 8.01, dd, $J = 1.06$ Hz, 8.24 Hz, 2H) is due to
paramagnetic anisotropic effect of C=O groups. N-Methyl protons are resonating at δ 3.51 as singlet and the remaining nine aromatic protons are accounted in the range δ 7.85-7.52. The high resolution mass spectrum showed the [M+H]^+ ion peak at m/z 369.1235 indicates the molecular weight of 3 as 368.1163. This oxidation method provides a very simple procedure that results the 1,2-diketone in good yield and high purity. The advantage of this method over the other KMnO4 oxidation reactions are i) PEG-400 act as PTC as well as reaction medium ii) shorter duration of time and iii) avoiding the use of salts such as MgSO4 and NaHCO3. 1,2-Diketone 3 was in hand, then we proceeded for the preparation of 6-pyrazinyl/fused pyrazinylquinazolin-4(3H)-ones.

Previously, the synthesis of pyrazines and fusedpyrazines was reported from the condensation of 1,2-dicarbonyl compound and 1,2-diamine in acetic acid or aqueous acetic acid. The condensation of diketone 3 independently with symmetrical 1,2-diamines 4 and 6 in aqueous acetic acid for 12 h at 80 °C. The expected cyclo-condensed and oxidative cyclo-condensed products, 6-pyrazinyl/fusedpyrazinylquinazolin-4(3H)-ones 5 (68 % yield) and 7 (70 % yield) were obtained respectively. We intended to use neutral solvent that can expect to perform function of aqueous acetic acid in the condensation of 1,2-dicarbonyl compound and symmetrical 1,2-diamines 4 and 6. Alternatively, the same reaction was carried out in PEG-400/water (3:1) at 80 °C for 12 h. After work-up, the desired cyclo-condensed and oxidative cyclo-condensed products 5 (75 % yield) and 7 (78 % yield) were isolated respectively. These two compounds were characterized by IR, HRMS, 1HNMR and 13C NMR spectral data.

![Scheme 2. Synthesis of 3-methyl-2-phenyl-6-pyrazinyl/fused pyrazinylquinazolin-4(3H)-ones (5 and 7)](image)

To generalize the scope of the reaction, experiments were performed with various unsymmetrical 1,2-diamines 8a-f which would afford inseparable mixture regiosomeric products 9a-f and 9a'-f. The isomers 9 were not separable by column chromatography using a mixture of different solvent mixtures (Scheme 3).

The hydroxyl groups of PEG-400 via hydrogen bonding with oxygen atoms of carbonyl groups might increase the electrophilic character of dicarbonyl carbons, thereby accelerating the rate of addition of 1,2-diamines on carbonyl groups. These factors might be responsible for acceleration of the cyclocondensation reaction for quinoxaline and pyrazine ring formation. The solvent PEG was recycled and reused in cyclocondensation of 3 with compound 6 to get 7 and
the corresponding data was presented in Table 1. The solvent was reused for 4 cycles without loss of activity and observed yield of the product 78 – 61 % from 1st to 4th run of PEG-400.

![Scheme 4. Synthesis of 3-methyl-2-phenyl-6-fused pyrazinylquinazolin-4(3H)-one regioisomers (9a-f and 9a'-f).](image)

Table 1: Recycling of PEG-400:H2O solvent in cyclocondensation of 3 with 7.

<table>
<thead>
<tr>
<th>Product 10</th>
<th>Fresh</th>
<th>2nd run</th>
<th>3rd run</th>
<th>4th run</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yield, %</td>
<td>78</td>
<td>75</td>
<td>70</td>
<td>61</td>
</tr>
</tbody>
</table>

An array of 6-quinazoxylinyl or 6-pyridopyrazinylquinazolinones 5, 7, and 9 were obtained in high yields (70-78%) from PEG mediated cyclo-condensation of 3 with various corresponding 1, 2-diamines 4, 6, and 8a-g.

**CONCLUSION**

In conclusion, a novel PEG mediated protocol for the synthesis of 6-hetarylquinazolin-4(3H)-ones have been achieved. The Castro–Stephen coupling reaction and PEG mediated KMnO₄ oxidation provided key intermediates internal alkyne 2 and 1,2-diketone 3 in high yields. The PEG mediated KMnO₄ oxidation of 3 has been reported for the first time to get 1,2-diketone 3. Interestingly, the KMnO₄ oxidation in PEG-400 medium is an efficient, simple, and more economical with amplified reaction rate, when compared to the previous protocols has been found. Further, the novel 6-pyrazinyl/fusedpyrazinylquinazolin-4(3H)-ones were synthesized in high yields from PEG mediated cyclocondensation reaction of 3 with 1,2-diamines 4, 6, and 8a-g that appears to good substitute to aqueous acetic acid medium. Therefore, the overall procedure is an efficient and high yielding synthesis to get 6-hetarylquinazolin-4(3H)-ones. Employing the same strategy, work is under progress for the synthesis of new heterocyclic compounds.

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ИЗВОД

СИНТЕЗА 6-ПИРАЗИНИЛ-/КОНДЕНЗОВАНИХ ПИРАЗИНИЛКИНАЗОЛИН-4(3Н)-ОНА ПРИМЕНОМ CASTRO-STEPHEN КУПЛОВАЊА, РЕАКЦИЈАМА ИКСИДАЦИЈЕ И ЦИКЛОКОНДЕНЗАЦИЈЕ УЗ РЕАКЦИЈУ КАБИЈУ МЕДИЈУМ

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Развијен је еколошки поступак за синтезу пиразинилкиназолин-4(3Н)-она полазећи од 6-јод-3-метил-2-фенилкиназолин-4(3Н)-она у присуству киназолин алкина / 1,2-дивалентног као интермедијера, примењом Castro-Stephen купловања и оксидацијом калијума-перманганата и реакције циклокондензације, уз PEG као реакциони медијум.

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SUPPLEMENTARY MATERIAL TO
PEG mediated synthesis of 6-pyrazinyl-/fused pyrazinyl-quinazolin-4(3H)-ones using Castro-Stephen coupling, oxidation and cyclocondensation reactions

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ANALYTICAL AND SPECTRAL DATA OF THE SYNTHESIZED COMPOUNDS

3-Methyl-2-phenyl-6-(phenylethynyl)quinazolin-4(3H)-one (5): Yield (0.69 g, 75 %), mp 151-153 °C. ¹H NMR (300 MHz, CDCl₃) δ 8.49 (d, J = 1.80 Hz, 1H, Ar-H), 7.85 (dd, J = 2.44 Hz, 8.24 Hz, 1H, Ar-H), 7.70-7.71 (m, 1H, Ar-H), 7.53-7.57 (m, 7H, Ar-H), 7.35-7.38 (m, 3H, N-CH₃); ¹³C NMR (75 MHz, CDCl₃) δ 161.9, 156.5, 146.7, 136.8, 135.1, 131.6, 130.1, 129.9, 128.5, 128.3, 127.9, 127.6, 122.7, 122.0, 120.4, 90.9, 88.4, 34.3; IR (KBr) 2200, 1666 cm⁻¹; ESI-HRMS: [M+H]⁺ m/z 337.1327.

1-(3-Methyl-4-oxo-2-phenyl-3,4-dihydroquinazolin-6-yl)-2-phenylethane-1,2-dione (6): Yield (70 mg, 80 %); mp 161-163 °C. ¹H NMR (300 MHz, CDCl₃) δ 8.84 (d, 1H, J = 1.18 Hz, Ar-H), 8.40 (dd, J = 1.98 Hz, 8.5Hz, 1H, Ar-H), 8.01 (dd, J = 1.06 Hz, 8.24 Hz, 2H, Ar-H), 7.85(d, 1H, J = 8.54 Hz, Ar-H), 7.66-7.68 (m, 1H, Ar-H), 7.52-7.60 (m, 7H, Ar-H), 3.51 (s, 3H, N-CH₃); ¹³C NMR (75 MHz, CDCl₃) δ 193.6, 192.7, 161.8, 158.9, 151.3, 134.9, 136.4, 132.6, 130.8, 130.5, 129.8, 128.9, 128.8, 128.5, 127.8, 120.2, 34.4; IR (KBr) 1774, 1709, 1666 cm⁻¹; ESI-HRMS: [M+H]⁺ m/z 369.1235.

3-Methyl-2-phenyl-6-(3-phenylquinoxalin-2-yl)quinazolin-4(3H)-one (8): White powder, mp 219-220 °C. ¹H NMR (300 MHz, CDCl₃) δ 8.61 (s, 1H, Ar-H), 8.19-8.21 (m, 2H, Ar-H), 7.79-7.84 (m, 3H, Ar-H), 7.54 - 7.65 (m, 8H, Ar-H), 7.34 -7.39 (m, 3H, Ar-H), 3.49 (s, 3H, N-CH₃); ¹³C NMR (75 MHz, CDCl₃) δ 162.3, 156.9, 153.3, 151.2, 147.3, 141.2, 138.7, 137.8, 135.5, 130.2, 130.1, 129.8, 129.2, 129.1, 128.8, 128.5, 128.1, 127.3, 120.3, 34.3; IR (KBr) 3062, 1674 cm⁻¹. ESI-HRMS: [M+H]⁺ calculated for C₂₀H₂₁N₄O: m/z 441.1715; found at m/z 441.1706.
3-Methyl-2-phenyl-6-(3-phenylpyrazin-2-yl)quinazolin-4(3H)-one (10):
White powder, mp 180-181 °C. ¹H NMR (300 MHz, CDCl₃) δ 8.66 (s, 2H, Ar-H), 8.50 (d, J = 2.3 Hz, 1H, Ar-H), 7.78 (dd, J = 2.6 Hz, 8.30 Hz, 1H, Ar-H), 7.45-7.64 (m, 8H, Ar-H), 7.31-7.34 (m, 3H, Ar-H), 3.48 (s, 3H, N-CH₃); ¹³C NMR (75 MHz, CDCl₃) δ 162.2, 156.9, 152.9, 151.4, 147.3, 142.5, 142.2, 138.1, 137.4, 135.3, 130.2, 129.6, 128.9, 128.5, 128.2, 127.9, 127.3, 120.5, 34.3; IR (KBr) 3057, 2924, 1680 cm⁻¹; ESI-HRMS: [M+H]⁺ calculated for C₁₉H₁₅N₄O; m/z 391.1558; found at m/z 391.1548.

6-(6-Bromo-3-phenylquinazolin-2-yl)-3-methyl-2-phenylquinazolin-4(3H)-one (12a or 12a') White powder, mp 240-242 °C. ¹H NMR (300 MHz, CDCl₃) δ 9.18 (d, J = 2.5 Hz, 1H, Ar-H), 8.71 (d, J = 2.5 Hz, 1H, Ar-H), 8.67 (d, J = 1.9 Hz, 1H, Ar-H), 7.84 (dd, J = 2.07 Hz, 8.5 Hz , 1H, Ar-H), 7.56 - 7.67 (m, 9H, Ar-H), 7.39 - 7.30 (m, 3H, Ar-H), 3.51 (s, 3H, N-CH₃); ¹³C NMR (75 MHz, CDCl₃) δ 162.3, 157.5, 153.7, 152.7, 147.7, 141.9, 140.0, 138.4, 137.3, 135.5, 135.2, 133.9, 131.5, 130.5, 130.3, 129.8, 129.3, 128.9, 128.6, 127.9, 127.5, 121.1, 120.5, 34.4; IR (KBr) 3060, 1682 cm⁻¹; ESI-HRMS: [M+H]⁺ calculated for C₁₉H₁₃N₄BrO; m/z 519.0820; found at m/z 519.0822.

6-(6-Chloro-3-phenylquinazolin-2-yl)-3-methyl-2-phenylquinazolin-4(3H)-one (12b or 12b') White powder, mp 215-217 °C. ¹H NMR (300 MHz, CDCl₃) δ 8.58 (d, J = 8.4 Hz, 1H, Ar-H), 8.20 (d, J = 2.29 Hz, 1H, Ar-H), 8.14 (d, J = 9.1 Hz, 1H, Ar-H), 7.82 (dd, J = 2.1 Hz, 9.0 Hz, 1H, Ar-H), 7.73 (dd, J = 2.28 Hz, 8.85 Hz, 1H, Ar-H), 7.64-7.65 (m, 1H, Ar-H), 7.53 - 7.59 (m, 7H, Ar-H), 7.35 - 7.40 (m, 3H, Ar-H), 3.50 (s, 3H, N-CH₃); ¹³C NMR (75 MHz, CDCl₃) δ 162.2, 157.0, 153.7, 152.7, 147.5, 141.7, 140.2, 138.3, 137.2, 135.3, 135.4, 133.8, 131.5, 130.5, 130.2, 129.8, 129.7, 129.3, 128.9, 128.6, 127.9, 127.4, 124.0, 120.4, 34.4; IR(KBr) 3060, 2923, 1682 cm⁻¹; ESI-HRMS: [M+H]⁺ calculated for C₁₉H₁₃N₄ClO; m/z 475.1325; found at m/z 475.1332.

3-Methyl-6-(5-nitro-3-phenylquinazolin-2-yl)-2-phenylquinazolin-4(3H)-one (12c or 12c') Yellow powder, mp 247-249 °C. ¹H NMR (300 MHz, CDCl₃) δ 8.64 (d, J = 2 Hz, 1H, Ar-H), 8.41 (dd, J = 1.06 Hz, 8.5 Hz, 1H, Ar-H), 8.20 (dd, J = 1.22 Hz, 7.6 Hz, 1H, Ar-H), 8.10 (dd, J = 2.13 Hz, 8.5 Hz, 1H, Ar-H), 7.83-7.86 (m, 1H, Ar-H), 7.73 (d, J = 8.39 Hz, 1H, Ar-H), 7.54-7.61 (m, 7H, Ar-H), 7.39-7.46 (m, 3H, Ar-H), 3.47 (s, 3H, N-CH₃); ¹³C NMR (75 MHz, CDCl₃) δ 162.1, 157.3, 154.9, 153.5, 148.1, 147.1, 140.9, 137.9, 136.2, 135.7, 135.2, 133.8, 133.2, 130.3, 129.9, 129.7, 129.1, 128.9, 128.7, 128.4, 128.0, 127.8, 124.6, 120.2, 34.5; IR(KBr) 3056, 2923, 1673 cm⁻¹; ESI-HRMS: [M+H]⁺ calculated for C₁₉H₁₃N₄O₃; m/z 486.1566; found at m/z 486.1552.

3-Methyl-6-(6-nitro-3-phenylquinazolin-2-yl)-2-phenylquinazolin-4(3H)-one (12d or 12d') Yellow powder, mp 252-254 °C. ¹H NMR (300 MHz, CDCl₃) δ 9.10 (d, J = 2.3 Hz, 1H, Ar-H), 8.61 (d, J = 1.2 Hz, 1H, Ar-H), 8.56 (dd, J = 2.44 Hz, 9.15 Hz, 1H, Ar-H), 8.31-8.32 (m, 1H, Ar-H), 7.88 (dd,
\[ J = 2.13 \text{ Hz}, 8.7 \text{ Hz}, 1\text{H, Ar-H}, 7.54-7.60 \text{ (m, 1H, Ar-H)}, 7.54-7.55 \text{ (m, 7H, Ar-H)} \]

\[ 3.51(s, 3H, N-CH}_3 \]

1H NMR (300 MHz, CDCl$_3$) \( \delta 9.21 \text{ (d, } J = 2.3 \text{ Hz, 1H, Ar-H)}, 8.71 \text{ (d, } J = 7.13 \text{ Hz, 1H, Ar-H}), 8.56-8.69 \text{ (m, 3H, Ar-H)}, 7.55-7.67 \text{ (m, 8H, Ar-H)}, 7.33 - 7.41 \text{ (m, 3H, Ar-H)} \]

13C NMR (125 MHz, CDCl$_3$) \( \delta 162.1, 157.3, 156.3, 155.4, 154.0, 148.1, 147.8, 139.4, 137.4, 136.7, 136.4, 148.2, 150.1, 135.0, 130.3, 130.1, 129.0, 12.7, 128.4, 128.0, 127.4, 121.1, 120.5, 34.4; \]

IR (KBr) 3060, 2924, 1682 cm$^{-1}$; ESI-HRMS: [M+H]$^+$ calculated for C$_{28}$H$_{20}$N$_5$O: m/z 442.1667; found at m/z 442.1650.

6-(7-Bromo-2-phenylpyrido[2,3-b]pyrazin-3-yl)-3-methyl-2-phenylquinazolin-4(3H)-one (12f or 12f'): White powder, mp 148-149 °C. 1H NMR (300 MHz, CDCl$_3$) \( \delta 8.58 \text{ (d, } J = 1.91 \text{ Hz, 1H, Ar-H}), 8.38 \text{ (d, } J = 2.1 \text{ Hz, 1H, Ar-H}), 8.05 \text{ (d, 1H, Ar-H)}, 7.81-7.89 \text{ (m, 2H, Ar-H)}, 7.53-7.67 \text{ (m, 7H, Ar-H)}, 7.33 - 7.41 \text{ (m, 3H, Ar-H)}, 3.50(s, 3H, N-CH}_3 \]

13C NMR (75 MHz, CDCl$_3$) \( \delta 162.1, 157.3, 156.3, 155.4, 154.0, 148.1, 147.8, 139.4, 137.4, 136.7, 136.4, 135.3, 135.0, 130.3, 130.1, 129.0, 12.7, 128.4, 128.0, 127.4, 121.1, 120.5, 34.4; \]

IR (KBr) 3060, 2924, 1682 cm$^{-1}$; ESI-HRMS: [M+H]$^+$ calculated for C$_{28}$H$_{19}$N$_5$OBr: m/z 520.0772; found at m/z 520.0795.