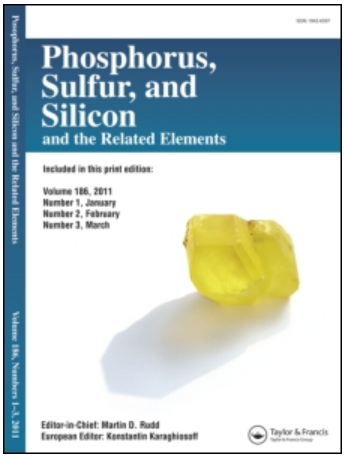

Phosphorus, Sulfur, and Silicon and the Related Elements

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Synthesis of Quinoline-Based Thieno-Seleno-Phenylquinazolinones

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Synthesis of Quinoline-Based Thieno-Seleno-Phenylquinazolinones

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The synthesis of quinoline-substituted phenylquinazolinones containing sulfur and selenium is described. These molecules were isolated from a series of reactions of 2-phenyl-4H-3,1-benzoxazin-4-one with 2-chloro, 2-thieno, and 2-selenoquinoline-3-carbaldehyde hydrazones. The structure of the isolated compounds has been elucidated on the basis of IR, ^{1}H NMR, mass spectral, and elemental analysis data.

Keywords Phenylquinazolinone; quinoline; selenium; sulfur

INTRODUCTION

It has been more than a century since the initial studies on 4(3*H*)-quinazolinones[**1**],[1] and they are well known as biologically active compounds.[2] Several 2-styrylquinazolin-4(3*H*)-ones have been prepared since 1910[3] and are active against certain types of cancers.[4] Perydylvinyl-4(3*H*)-quinazolinones[**2**] showed anticonvulsant, hypnotic, tranquilizing, and muscle relaxant activity.[5] The atropisomers, 2-(2-heteroarylvinyl)-3-aryl-6-fluro-4(3*H*)-quinazolinone[**3**], known as AMPA (α-amino-3hydroxy-5-methyl-4-isoxazolepropanoic acid) receptor antagonists,[6] 2,6-disubstituted 4(3*H*)-quinazolinones[**4**] are known as trace membrane receptor antagonists and their activity, has been subjected to extensive molecular modeling.[7] Various 2- and 3-disubstituted quinazolines (C-2, N-3) have been studied

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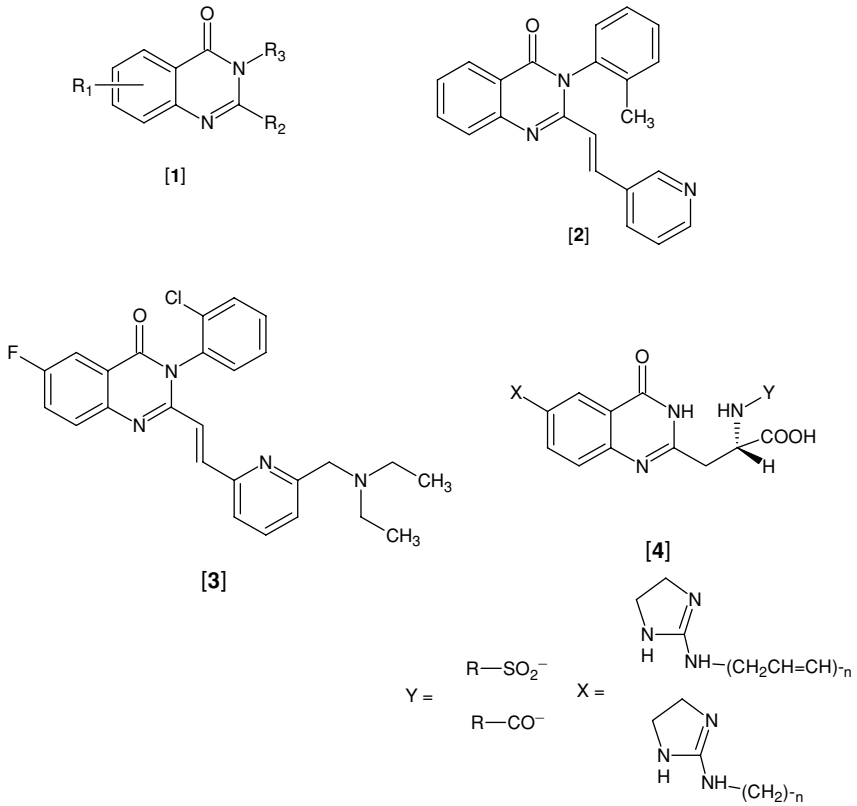
their interesting pharmacological activities such as analgesic, anti-inflammatory,[8] antibacterial,[9] anticonvulsant,[10] antihypertensive,[11] and antimalarial activities,[12] etc. Treatments of diabetic complications such as cataracts, nephropathy, and neuropathy,[13] and significant anti-Parkinsonian activity against tremor, rigidity, hypokinesia, and catatonia has been evaluated in vivo in rats and mice of quinazolinylthiazolidinone[14] and anticancer[15] activities. Recent modeling and quantitative structure-activity relationships (QSAR) studies include quinazolinone inhibitors of poly (ADP-ribose) polymerase,[16] indicating that quinazolinone drug design is approaching the preclinical stage (Scheme 1).



SCHEME 1 Various structures of standard drugs possessing quinazoline moiety.

Further, it is well known that number of heterocyclic compounds containing S and Se exhibit a wide variety of biological activities. Even

though sulfur and selenium are considered to be isosteric as defined by Longmuir[17] and Erlenmeyer,[18] the reports about selenium-containing heterocycles are few.[19–21] However, the medicinal application of isosterism has been reviewed by Klayman and Gunther.[22] The antioxidant and anticancer activity of selenium-containing compounds have been reported[23–25] recently. Selenium plays an important role in decreasing oxidative stress in HIV-affected cells and possibly suppresses the rate of HIV replication.[26,27] Recent research proposes that HIV may be capable of incorporating host selenium into viral selenoproteins that have glutathione-peroxide activity. Though the significance of these findings requires further clarification, they suggest that both the human immune system and the activity of the virus are affected by selenium nutritional status.[28,29] In recent years, the number of publications devoted to various aspects of fused heterocycles containing sulfur and selenium has sharply increased.

Due to great pharmacological importance and with the above facts, we carried out the synthesis of some new heterocycles such as sulfur- and selenium-containing phenylquinazolinones through a nitrogen bridge in order to enhance the biological activity.

RESULTS AND DISCUSSION

Numerous condensed quinolines and quinazolines offer valuable pharmacological activities as mentioned earlier, and, therefore, they are useful materials in drug research. Hence, in continuation of our study in developing condensed quinoline derivatives, it appeared expedient to synthesize a series of systematically condensed and appropriately functionalized quinoline-substituted phenylquinazolines.

In the present work, an attempt has been made to undertake the synthesis of (**6b–d**), (**7b–d**), and (**8b–d**) derivatives through a multistep processes. The required starting compounds **2a–d** and **3a–d** were synthesized according to the reported methods.[30] To achieve these targeted molecules, the required compounds, 2-phenyl-4-3,1-benzoxazin-4-ones (**5a–d**), were prepared by a cyclization reaction between anthranilic acid and benzoyl chloride using pyridine as a solvent and also as a base. The formation of (**5a–d**) was confirmed by a sharp band at 1715 cm^{-1} for C=O group along with a peak at 1178 cm^{-1} for C–O stretching in IR spectra. Then **5a–d** was converted to (**6a**), (**7a**), and (**8a**) through its nucleophilic substitution reaction with **4a–d**. The insertion of nitrogen in the ring of **5a** was characterized by the disappearance of an absorption band at 1178 cm^{-1} of C–O and shift of carbonyl (C=O) absorption bands from 1710, 1716, and 1720 cm^{-1}

in the series of chlorine, sulfur, and selenium containing **4a–d**. The accession of targeted compound (**6a**), (**7a**), and (**8a**) were confirmed by the disappearance of singlets in ^{1}H NMR at δ 5.54, 5.42, and 5.45 of the NH_2 group. This shows the formation of desired compounds (**6a**), (**7a**), and (**8a**) from **4a–d**. Finally the formation of the desired series (**6a**), (**7a**), and (**8a**) were confirmed by means of obtained molecular ion peaks at 410$[M]^+$, 408$[M]^+$, and 455$[M]^+$ in mass spectra. Similarly other compounds in the (**6b–d**), (**7b–d**), and (**8b–d**) series are also elucidated on the basis of IR, ^{1}H NMR, mass spectral data, and elemental analysis (Scheme 2).

CONCLUSION

In conclusion, we developed a versatile and useful new access to a different scaffold of biologically important quinoline-based sulfur- and selenium-containing phenylquinazolinones (**6a–d**), (**7a–d**), and (**8a–d**) using an efficient and simple methodology based on a cyclization, condensation technique. However, the availability and simplicity of the starting materials and the experimental procedure itself make this path more flexible to obtain a high yield of phenylquinazolines. Further research is underway to use this procedure to synthesize other derivatives.

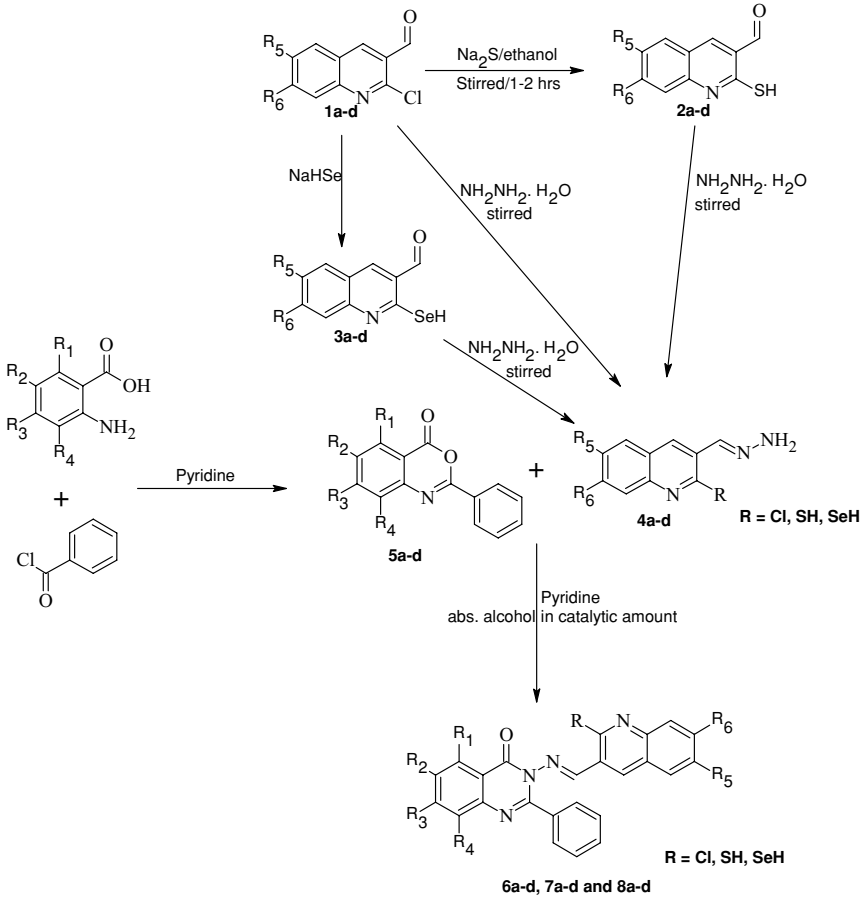
MATERIALS AND METHODS

General Procedure

The purity of the compounds was checked by thin layer chromatography (TLC) on silica gel plates using petroleum ether: ethyl acetate solvent. Melting points were determined in open capillary tubes and are uncorrected. IR spectra were recorded in KBr pellets on a Perkin-Elmer 157 IR spectrophotometer. ^{1}H NMR spectra were recorded in DMSO-d_6 on an EM-390(300 MHz) NMR spectrometer, and mass spectra were recorded on a MASPEC low resolution instrument operating at 70 eV.

2-Mercaptoquinoline-3-carbaldehyde (2a)

Yield 70%, m.p. 160°C; IR (KBr) cm^{-1}; 3020 (C—H, Ar-H); 1710 (C=O), 1583 (C=N), 2593 (S—H); ^{1}H NMR (DMSO d_6), δ 10.1 (s, 1H, CHO), 8.8 (s, 1H, H-4), 8.1 (d, 1H, H-5), 8.0 (d, 1H, H-8), 7.9 (dt, 1H, H-6), 7.7 (dt, 1H, H-7); MS: m/z 189 $[M]^+$; Anal. Calcd. For ($C_{10}H_7NOS$) %: C, 63.47; H, 3.73; N, 7.40. Found: C, 63.44; H, 3.69; N, 7.42.



(6a), (7a) and **(8a)** : R_1=R_2=R_3=R_4= H. R_5=R_6= H.

(6b), (7b) and **(8b)** : R_1= R_2= R_4= H, R_3= CH_3. R_5=H, R_6=OCH_3.

(6c), (7c) and **(8c)** : R_1= R_2= R_4= H, R_3=NO_2. R_5=H, R_6=OCH_3.

(6d), (7d) and **(8d)** : R_1= R_2= R_4= H, R_3=Cl. R_5=H, R_6= Cl

SCHEME 2 Synthetic route for the synthesis of phenylquinazolines (**6a–d**), (**7a–d**), and (**8a–d**).

2-Selenoquinoline-3-carbaldehyde (3a)

Yield 70%, m.p. 185°C; IR (KBr) cm^{-1}; 3020 (C—H, Ar-H); 1710 (C=O), 1583 (C=N), 2598 (Se-H); ^1H NMR (DMSO d_6), δ 10.1 (s, 1H, CHO), 8.7 (s, 1H, H-4), 8.3 (d, 1H, H-5), 8.0 (d, 1H, H-8), 7.8 (dt, 1H, H-6), 7.5 (dt, 1H, H-7); MS: m/z 236 $[M]^+$; Anal. Calcd. For ($C_{10}H_7NOSe$) %: C, 63.47; H, 3.73; N, 7.40. Found: C, 63.44; H, 3.69; N, 7.42.

General Procedure for the Synthesis of 2-Chloro, 2-Mercapto, 2-Selenoquinoline-3-carbaldehyde hydrazone (4a–c)

A hydrazine hydrate solution (80%, 0.02 mol) was added dropwise at room temperature and with stirring over 1–2 h to an ethanolic solution containing 1.91 g, 1.89 g, and 2.36 g of 2-chloro, 2-mercapto, and 2-seleno quinoline-3-carbaldehydes (0.01 mol). The resulting yellow and brown colored solid was washed with diethyl ether, filtered, and dried under vacuum and recrystallized from methanol.

2-Chloro-3-(hydrazinomethyl)quinoline (4a)

Yield 80%, m.p. 135°C; IR (KBr) cm^{-1}; 3015 (C—H, Ar-H); 1590 (C=N), 830 (C-Cl); ^1H NMR (DMSO d_6), δ 8.0 (s, 1H, H-4), 7.5 (s, 1H), 8.7 (s, 1H, CHN), 5.54 (s, 2H, NH_2); MS: m/z 205 $[M]^+$; Anal. Calcd. For ($C_{10}H_8Cl\ N_3$) %: C, 58.41; H, 3.92; N, 20.43. Found: C, 58.44; H, 3.89; N, 20.45.

2-Mercaptoquinoline-3-carbaldehyde hydrazone (4b)

Yield 75%, m.p. 145°C; IR (KBr) cm^{-1}; 3018 (C—H, Ar-H); 1598 (C=N), 2585 (S-H); ^1H NMR (DMSO d_6), δ 7.9 (s, 1H, H-4), 7.5 (s, 1H, C-4), 8.9 (s, 1H, CHN), 5.42 (s, 2H, NH_2), 10.5 (s, 1H, SH); MS: m/z 203 $[M]^+$; Anal. Calcd. For ($C_{10}H_9N_3S$) %: C, 59.09; H, 4.46; N, 20.67. Found: C, 59.03; H, 4.53; N, 20.69.

2-Selenoquinoline-3-carbaldehyde hydrazone (4c)

Yield 75%, m.p. 173°C ; IR (KBr) cm^{-1}; 3016 (C—H, Ar-H); 1591 (C=N), 2583 (S-H); ^1H NMR (DMSO d_6), δ 7.8 (s, 1H, H-4), 7.6 (s, 1H, C-4), 8.9 (s, 1H, CHN), 5.45 (s, 2H, NH_2), 11.3 (s, 1H, SeH); MS: m/z 250 $[M]^+$; Anal. Calcd. For ($C_{10}H_9N_3Se$) %: C, 59.09; H, 4.46; N, 20.67. Found: C, 59.03; H, 4.53; N, 20.69.

2-Phenyl-4*H*-3,1-benzoxazin-4-one (5a)

Yield 63%, m.p. 115°C; IR (KBr) cm^{-1}; 3028 (C—H, Ar-H); 1715 (C=O), 1590 (C=N), 1178 (C-O); ^1H NMR (DMSO d_6), δ 7.6 (m, 9H, Ar-H); MS:

m/z 223 $[M]^+$; Anal. Calcd. For ($C_{14}H_9NO_2$) %: C, 75.33; H, 4.03; N, 60.27. Found: C, 75.29; H, 4.01; N, 60.25.

General Procedure for the Synthesis of 3-{[(1)-(2-Chloroquinolin-3-yl)methylene]amino}-2-phenylquinazolin-4(3*H*)-one (6a–d), (7a–d), and (8a–d)

A mixture containing 2.23 g of 2-phenyl-4*H*-3,1-benzoxazin-4-one (0.01 mol) and 2.05 g, 2.03 g, and 2.50 g of 2-chloro, 2-mercapto, 2-selenoquinoline-3-carbaldehyde hydrazone (0.01 mol) was dissolved in ethanol, and to this was added a catalytic amount of pyridine. The reaction mass was refluxed for 4–5 h. Then the cooled reaction mixture was poured on crushed ice, and the obtained yellow-, brown-, and dark brown-colored precipitate was filtered and recrystallized from ethanol.

3-{[(2-Chloroquinolin-3-yl)methylidene]amino}-2-phenylquinazolin-4(3H)-one (6a)

Yield 75%, m.p. 165°C; IR (KBr) cm^{-1}; 3015 (C—H, Ar-H); 1588 (C=N), 1710 (C=O), 1360 (C—N); ^1H NMR (DMSO d_6), δ 7.1–8.0 (m, 14H, Ar-H), 8.7 (s, 1H, CHN); MS: m/z 410 $[M]^+$; Anal. Calcd. For ($C_{24}H_{15}Cl\,N_4O$) %: C, 70.16; H, 3.68; N, 13.64. Found: C, 70.14; H, 3.61; N, 13.69.

3-{[(2-Chloro-7-methoxyquinolin-3-yl)methylene]amino}-7-methyl-2-phenylquinazolin-4(3H)-one (6b)

Yield 75%, m.p. 185°C; IR (KBr) cm^{-1}; 3029(C—H, Ar-H); 1620 (C=N), 1681 (C=O), 1318 (C-N), 1182 (C-O-C), 2975 (C—H, CH_3); ^1H NMR (DMSO d_6), δ 7.5 (m, 12H, Ar-H), 3.93 (s, 3H, OCH_3), 2.4 (s, 3H, CH_3), 8.3 (s, 1H, CHN); MS: m/z 454 $[M]^+$; Anal. Calcd. for ($C_{26}H_{19}Cl\,N_4O_2$) %: C, 68.65; H, 4.21; N, 12.32. Found: C, 68.63; H, 4.25; N, 12.35.

3-{[(2-Chloro-7-methoxyquinolin-3-yl)methylene]amino}-7-nitro-2-phenylquinazolin-4(3H)-one (6c)

Yield 75%, m.p. 169°C; IR (KBr) cm^{-1}; 3021(C—H, Ar-H); 1615 (C=N), 1675 (C=O), 1331 (C-N),1185 (C-O-C), 1390 (NO_2), 2975 (C—H, CH_3); ^1H NMR (DMSO d_6), δ 7.5 (m, 10H, Ar-H), 8.6 (s, 2H), 3.89 (s, 3H, OCH_3), 8.5 (s, 1H, CHN); MS: m/z 485 $[M]^+$; Anal. Calcd. For ($C_{25}H_{16}Cl\,N_5O_4$) %: C, 61.80; H, 3.32; N, 14.41. Found: C, 61.78; H, 3.35; N, 14.40.

7-Chloro-3-{[(2,7-dichloroquinolin-3-yl)methylene]amino}-2-phenylquinazolin-4(3H)-one (6d)

Yield 75%, m.p. 161°C; IR (KBr) cm^{-1}; 3013(C—H, Ar-H); 1590 (C=N), 748 (C-Cl), 1710 (C=O), 1370 (C-N); ^1H NMR (DMSO d_6), δ 7.4 (m, 8H, Ar-H), 6.9 (s, 4H, H-4), 8.5 (s, 1H, CHN); MS: m/z 479 $[M]^+$; Anal. Calcd.

For ($C_{24}H_{13}Cl_3N_4O$) %: C, 60.09; H, 2.73; N, 11.68. Found: C, 60.11; H, 2.76; N, 11.64.

3-{[(2-Mercaptoquinolin-3-yl)methylene]amino}-2-phenyl quinazolin-4(3H)-one (7a)

Yield 68%, m.p. 171°C; IR (KBr) cm^{-1}; 3019 (C—H, Ar-H); 1602 (C=N), 1716 (C=O), 1345 (C-N); ^1H NMR (DMSO d_6) δ 7.0–7.9 (m, 14H, Ar-H), 10.1 (s, 1H, SH), 8.7 (s, 1H, CHN); MS: m/z 408 $[M]^+$; Anal. Calcd. For ($C_{24}H_{16}N_4OS$) %: C, 70.57; H, 3.95; N, 13.72. Found: C, 70.52; H, 3.90; N, 13.68.

3-{[(2-Mercapto-7-methoxyquinolin-3-yl)methylene]amino}-7-methyl-2-phenylquinazolin-4(3H)-one (7b)

Yield 68%, m.p. 176°C; IR (KBr) cm^{-1}; 3018(C—H, Ar-H); 1625 (C=N), 1679 (C=O), 1300 (C-N), 1395 (NO_2); ^1H NMR (DMSO d_6), δ 7.1–8.0 (m, 12H, Ar-H), 3.81 (s, 3H, OCH_3), 10.3 (s, 1H, SH), 2.2 (s, 3H, CH_3), 8.5 (s, 1H, CHN); MS: m/z 452 $[M]^+$; Anal. Calcd. For ($C_{26}H_{20}N_4O_2S$) %: C, 69.01; H, 4.45; N, 12.38. Found: C, 69.05; H, 4.41; N, 12.41.

3-{[(2-Mercapto-7-methoxyquinolin-3-yl)methylene]amino}-7-nitro-2-phenylquinazolin-4(3H)-one (7c)

Yield 68%, m.p. 183°C; IR (KBr) cm^{-1}; 3025(C—H, Ar-H); 1611 (C=N), 1695 (C=O), 1321 (C-N), 1395 (NO_2); ^1H NMR (DMSO d_6), δ 7.1–7.9 (m, 10H, Ar-H), 8.5 (s, 2H), 10.7 (s, 1H, SH), 3.9(s, 3H, OCH_3), 8.6 (s, 1H, CHN); MS: m/z 483 $[M]^+$; Anal. Calcd. For ($C_{25}H_{17}N_5O_4S$) %: C, 62.10; H, 3.54; N, 14.48. Found: C, 62.12; H, 3.58; N, 14.44.

7-Chloro-3-{[(7-chloro-2-mercaptoquinolin-3-yl)methylene]amino}-2-phenylquinazolin-4(3H)-one (7d)

Yield 68%, m.p. 168°C; IR (KBr) cm^{-1}; 3015(C—H, Ar-H); 1625 (C=N), 1730 (C=O), 700 (C-Cl), 1300 (C=S), 1361(C-N); ^1H NMR (DMSO d_6), δ 7.1–7.9 (m, 8H, Ar-H), 6.9 (s, 4H, H-4),10.2 (s, 1H, SH), 8.5 (s, 1H, CHN); MS: m/z 477 $[M]^+$; Anal. Calcd. For ($C_{24}H_{14}Cl_2N_4OS$) %: C, 60.38; H, 2.96; N, 11.74. Found: C, 60.39; H, 2.91; N, 11.75.

3-{[(2-Selenooquinolin-3-yl)methylene]amino}-2-phenylquinazolin-4(3H)-one (8a)

Yield 68%, m.p. 171°C; IR (KBr) cm^{-1} ; 3019 (C—H, Ar-H); 1602 (C=N), 1720 (C=O), 1345 (C-N); ^1H NMR (DMSO d_6) δ 7.0–8.1 (m, 14H, Ar-H), 11.1 (s, 1H, SeH), 8.7 (s, 1H, CHN); MS: m/z 455 $[M]^+$; Anal. Calcd. For ($C_{24}H_{16}N_4OSe$) %: C, 63.30; H, 3.54; N, 12.30. Found: C, 63.33; H, 3.51; N, 12.35.

3-{[(2-Seleno-7-methoxyquinolin-3-yl)methylene]amino}-7-methyl-2-phenylquinazolin-4(3H)-one (8b)

Yield 55%, m.p. 197°C; IR (KBr) cm^{-1}; 3018(C—H, Ar-H); 1625 (C=N), 1679 (C=O), 1300 (C-N); ^{1}H NMR (DMSO d_6), δ 7.–8.0 (m, 12H, Ar-H), 3.81 (s, 3H, OCH_3), 11.4 (s, 1H, SeH), 2.2 (s, 3H, CH_3), 8.5 (s, 1H, CHN); MS: m/z 499 $[M]^+$; Anal. Calcd. For ($C_{26}H_{20}N_4O_2Se$) %: C, 62.53; H, 4.04; N, 11.22. Found: C, 62.49; H, 4.10; N, 11.29.

3-{[(2-Seleno-7-methoxyquinolin-3-yl)methylene]amino}-7-nitro-2-phenylquinazolin-4(3H)-one (8c)

Yield 58%, m.p. 191°C; IR (KBr) cm^{-1}; 3023(C—H, Ar-H); 1615 (C=N), 1699 (C=O), 1325 (C-N), 1391 (NO_2); ^{1}H NMR (DMSO d_6), δ 7.0–8.1 (m, 10H, Ar-H), 8.4 (s, 2H), 11.7 (s, 1H, SeH), 3.9(s, 3H, OCH_3), 8.8 (s, 1H, CHN); MS: m/z 530 $[M]^+$; Anal. Calcd. For ($C_{25}H_{17}N_5O_4Se$) %: C, 56.61; H, 3.23; N, 13.20. Found: C, 56.57; H, 3.29; N,13.25.

7-Chloro-3-{[(7-chloro-2-seleenoquinolin-3-yl)methylene]amino}-2-phenylquinazolin-4(3H)-one (8d)

Yield 58%, m.p. 183°C; IR (KBr) cm^{-1}; 3011(C—H, Ar-H); 1621 (C=N), 1733 (C=O), 709 (C-Cl), 1308 (C=S), 1368(C-N); ^{1}H NMR (DMSO d_6), δ 7.2–8.0 (m, 8H, Ar-H), 6.9 (s, 4H, H-4),11.2 (s, 1H, SeH),8.5 (s, 1H, CHN); MS: m/z 524 $[M]^+$; Anal. Calcd. For ($C_{24}H_{14}Cl_2N_4OSe$) %: C, 54.98; H, 2.69; N, 10.69. Found: C, 54.91; H, 2.73; N, 10.61.

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