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SYNTHESIS AND BIOLOGICAL ACTIVITIES OF SELENIUM/THIOETHER QUINAZOLINE COMPOUNDS

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Abstract – In view of the important role of quinazoline skeletons in anti-cancer drugs like Gefitinib® and the vital importance of organoselenium compounds in biomedicine field, in this protocol, twenty quinazoline selenium derivatives were designed and synthesized with the aim to develop new anti-cancer drugs by utilizing the synergistic effects of quinazoline skeleton and selenium. In addition, the synthetic method of thioether substituted quinazolines was improved. The biological activities of title compounds were determined against A549 cancer cells *in vitro* by using MTT assay at 1 μM and 10 μM concentrations. The results showed that most of the title compounds had good anticancer activities. Of note, 6-chloro-4-benzylselenoquinazoline (**G5**) exhibited better inhibitory activity (67.8% inhibition ratio) than the positive control drug Gefitinib® (62.9% inhibition ratio) at the concentration of 10 μM. These findings will provide some clues for further research of anticancer drugs.

INTRODUCTION

As important aza-heterocyclic compounds, quinazoline has unique biological activities.[1] Quinazolines containing pharmacophore groups have attracted attention for decades and continue to be the focus of biological and pharmaceutical scientific studies today, showing excellent biological activity in anticancer,[2] anti-oxidation,[3] increasing tolerance,[4] anti-influenza virus,[5] and inhibition of plant bacteria.[6] Especially, thioether-containing quinazolines were synthesized by the reaction of 2-aminobenzoic acid with isothiocyanate followed by the addition of 1-chloromethyl-4-methoxybenzene, and they showed wider anticancer activity than 5-FU as reported by El-Messery.[7] Quinazoline-2-thiones showed significant inhibitory effect on Caco-2 and MCF-7 by El-Gazzar.[8] A series of 2,4-disubstituted

quinazolines were synthesized by Li[9] and Buggana,[10] which have excellent antitumor activities against five tumor cells (MDA-MB-231, MCF-7, PC-3, HGC-27 and MGC-803). Selenides and diselenides containing imidazole or pyridine moieties, synthesized by Matsumura,[11] showed good anticancer activities and low toxicity of non-target cells. In recent years, the biological activities of 4-aminoquinazoline derivatives[12] and 4-thioquinazoline derivatives[13] have been extensively studied. But little attention has been paid to the anticancer activities of 4-selenoquinazoline derivatives.[14] In our previous work, biquinazoline diselenides compounds and sodium quinazoline-4-diselenide compounds were found to exhibit good anticancer activities, but the solubility and stability were not satisfactory.[15] In continuation of our work on selenoquinazoline derivatives, herein, a series of 4-selenium substituted quinazoline derivatives were designed and synthesized (**Figure 1**), and their biological activities against cancer cell lines were evaluated *in vitro* through MTT assay by using Gefitinib® as a positive control. Besides, similar quinazoline thioether derivatives were designed and synthesized as contrast.

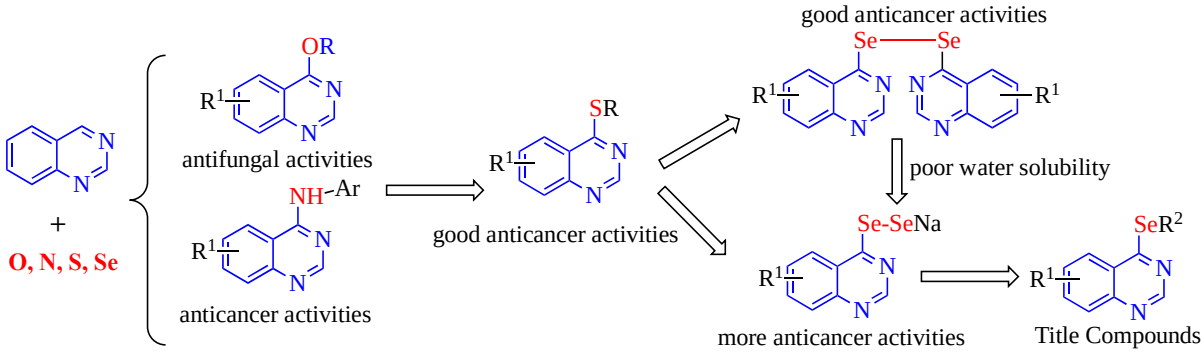
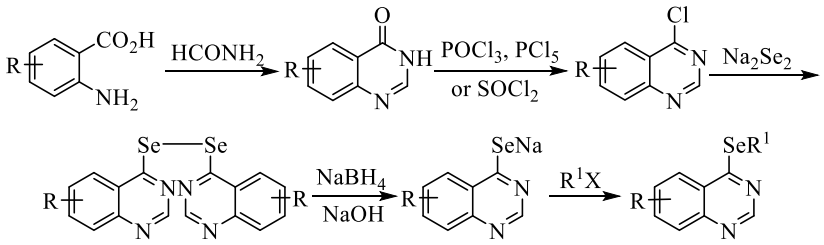


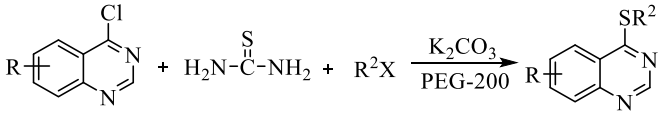
Figure 1

RESULTS AND DISCUSSION

Synthesis of title compounds: Treatment of 2-aminobenzoic acid with formamide gave quinazolin-4-one compounds by cyclization, chlorination of which under refluxing conditions then afforded 4-chloroquinazoline compounds. After that, 4-chloroquinazoline compounds reacted with sodium diselenide to generate biquinazoline selenide compounds, reduction of which by using $NaBH_4$ led to sodium quinazoline selenide. Finally, 4-selenoquinazoline compounds (**G_1-G_{12}**) were synthesized *via* the reaction of sodium quinazoline selenide with halohydrocarbons. Besides, 4-sulfenylquinazoline compounds (**G_{13}-G_{20}**) were synthesized through one-pot reaction of 4-chloroquinazolines, thioureas and halohydrocarbons in the presence of K_2CO_3 in green solvent PEG-200. All the synthesized compounds were characterized by ^{1}H NMR, ^{13}C NMR and IR (**Figure 2**).



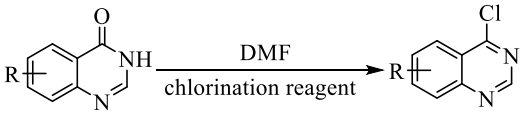
G_1: R = H; R^1 = -CH_2Ph; G_2: R = H; R^1 = -$CH_2CH{=}CH_2$; G_3: R = H; R^1 = -CH_2Me; G_4: R = H; R^1 = -$(CH_2)_3$Me;
G_5: R = 6-Cl; R^1 = -CH_2Ph; G_6: R = 6-Cl; R^1 = -$CH_2CH{=}CH_2$; G_7: R = 6-Cl; R^1 = -CH_2Me;
G_8: R = 6-Cl; R^1 = -$(CH_2)_3$Me; G_9: R = 6,8-diCl; R^1 = -CH_2Ph; G_{10}: R = 6,8-diCl; R^1 = -$CH_2CH{=}CH_2$;
G_{11}: R = 6,8-diCl; R^1 = -CH_2Me; G_{12}: R = 6,8-diCl; R^1 = -$(CH_2)_3$Me.



G_{13}: R = H; R^2 = -CH_2Ph; G_{14}: R = H; R^2 = -$CH_2CH{=}CH_2$; G_{15}: R = H; R^2 = -CH_2Me;
G_{16}: R = H; R^2 = -$(CH_2)_3$Me; G_{17}: R = 6,8-diCl; R^2 = -CH_2Ph; G_{18}: R = 6,8-diCl; R^2 = -$CH_2CH{=}CH_2$;
G_{19}: R = 6,8-diCl; R^2 = -CH_2Me; G_{20}: R = 6,8-diCl; R^2 = -$(CH_2)_3$Me.

Figure 2

Optimization of reaction conditions for the chlorination step: Common chlorinating reagents are $SOCl_2$、$POCl_3$ and PCl_5, and their chlorinating ability is gradually enhanced. Interestingly, we found that the chlorination of quinazolin-4-ones bearing different substituents required chlorinating reagents with different chlorinating ability. Specifically, a gradually stronger chlorinating reagents were needed for the chlorination of non-substituted, single-substituted and disubstituted quinazolin-4-ones (**Figure3**). Besides, the chlorination efficiency was affected by the reaction time because the chlorination reaction could not be finished in too short reaction time, whereas too long reaction time would lead to side reactions. Therefore, the chlorinating reagents and reaction time for the synthesis of 4-chloroquinazoline compounds were screened. The results are shown in **Table 1**.



R = H; 6-Cl; 6,8-diCl

Figure 3

Table 1. Effects of chlorinating reagents

Entry	R	Reagent for Chlorination	Time (h)	Yield (%)[a]
1	H	$SOCl_2$	4	48.2
2	H	$SOCl_2$	6	60.4
3	H	$POCl_3$	6	78.5
4	H	$POCl_3$	8	81.2
5	6-Cl	$SOCl_2$	8	60.3

6	6-Cl	$POCl_3$	8	73.4
7	6-Cl	$POCl_3$	10	75.8
8	6, 8-diCl	$POCl_3$	10	45.6
9	6, 8-diCl	$POCl_3/PCl_5$	10	62.2
10	6, 8-diCl	$POCl_3/PCl_5$	12	50.8

[a]Isolated yields.

As shown in **Table 1**, in the chlorination reaction of quinazolin-4-one compounds, using chlorinating reagents with relatively strong chlorination ability and appropriately extending the reaction time could increase the yield of the chlorination products. In summary, $POCl_3$ should be selected as the chlorinating reagent for the synthesis of 4-chloroquinazoline and 4, 6-dichloroquinazoline in 8-10 h. For the synthesis of 4, 6, 8-trichloroquinazoline, mixtures of $POCl_3$ and PCl_5, and reaction time of 10 h should be applied to the reaction. The chlorination reaction also clearly reflected the electronic effect of chloro-substituent on the chlorination reaction of quinazoline.

Optimization of the reaction conditions for the synthesis of 4-selenoquinazoline compounds (**Method 1**):[16] The general method for the synthesis of 4-substituted selenoquinazoline compounds is using 4-chloroquinazoline as an electrophilic reagent (**Figure 4**). Specifically, 4-chloroquinazoline or substituted 4-chloroquinazoline was added to an ethanolic sodium diselenide solution in 1 h. Then the solution was heated to reflux for 8-24 h, and reaction completion was monitored by thin-layer chromatography (TLC). After cooling, the solvents were removed *in vacuo* and recrystallized from DMF–EtOH. In this work, **Method 2** is designed to synthesize selenoquinazoline compounds. Firstly, 4-chloroquinazolines reacted with Na_2Se_2 to give biquinazoline diselenides, which were then reduced by $NaBH_4$ in the presence of NaOH leading to sodium quinazoline-4-selenolates. Finally, the organoselenium quinazoline compounds were synthesized *via* nucleophilic substitution reaction of sodium quinazoline-4-selenolates with halogenated hydrocarbons (**Figure 4**).

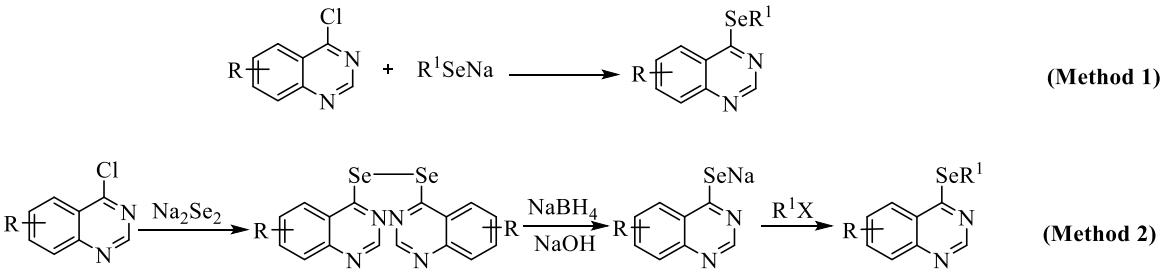


Figure 4

Table 2. Yields of 4-selenoquinazoline compounds in methods 1 and 2

Compounds	R	R^1	Yield (%)[a]	
			Method 1	Method 2
G_1	H	$-CH_2Ph$	25.1	43.3
G_2	H	$-CH_2CH{=}CH_2$	22.3	36.0
G_3	H	$-CH_2Me$	38.9	59.6
G_4	H	$-(CH_2)_3Me$	42.6	60.4
G_7	6-Cl	$-CH_2Me$	21.4	33.3
G_{11}	6,8-diCl	$-CH_2Me$	20.3	24.6

[a]Isolated yields.

Table 2 showed that **Method 2** was more efficient than **Method 1**. The main reason was that sodium (alkyl)selenolates in **Method 1** were less stable than sodium quinazoline-4-selenolate in **Method 2**. In addition, the nucleophilic substitution of 4-chloroquinazolines were adversely affected by the large steric hindrance. In **Method 2**, the conjugation of selenium anion with quinazoline made it more stable, thereby enabling an easier nucleophilic substitution reaction with halogenated hydrocarbons.

Optimization of the reaction conditions for the synthesis of 4-thioquinazoline compounds: Substituted 4-thioquinazoline compounds were generally synthesized by using **Method A**[17](**Figure 5**). Specifically, quinazolin-4-one reacted with P_4S_{10} in pyridine to give quinazoline-4-thiol intermediates, which then reacted with halogenated hydrocarbons, affording 4-thioquinazoline compounds. The classical **Method A** requires the use of toxic and harmful reagents such as P_4S_{10} and pyridine. In order to develop a green synthesis strategy, classical **Method A** was improved (**Method B**): using PEG-200 instead of pyridine as solvent, using thiourea instead of P_4S_{10} as vulcanization reagent. Additionally, the step-by-step reaction of **Method A** was improved to a one-pot reaction in **Method B**. The results of **Method A** and **B** are shown in **Table 3**. Pleasantly, the yield of **Method B** is superior to the yield of **Method A**.

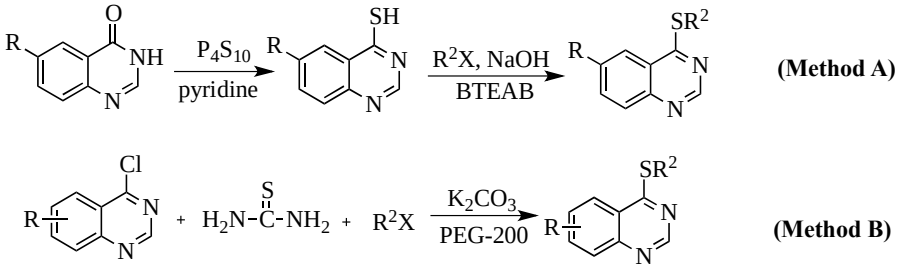


Figure 5

Table 3. Yields of 4-thioquinazoline compounds in method **A** and **B**

Compounds	R	R^2	Yield (%)[a]	
			Method A	Method B
G13	H	$-CH_2Ph$	42.1	70.0
G14	H	$-CH_2CH=CH_2$	26.9	40.3
G15	H	$-CH_2Me$	33.2	57.9
G16	H	$-CH_2(CH_2)_2Me$	44.7	61.4
G19	6,8-diCl	$-CH_2Me$	36.2	57.7

[a]Isolated yields.

Bioactivity assay of title compounds: Inhibitory activity of title compounds against A549 tumor cells was tested *in vitro* by using Gefitinib® as the positive control drug and DMSO as negative control. The results are summarized in **Table 4**. As shown in **Table 4**, **G1**-**G20** had inhibitory activities against A549. The inhibition ratio at the concentration of 10 μM were higher than those at the concentration of 1 μM. Therefore, the tested compounds were concentration-dependent inhibitors. Notably, the inhibitory activity of 4-selenoquinazoline compounds and 4-sulfenylquinazoline compounds at the concentration of 1 μM was similar to that of the positive control drug Gefitinib®. Exultantly, the inhibitory activity of **G4**, **G5** and **G7** was better than the positive control drug Gefitinib® at the concentration of 1 μM. With regard to the structure-activity relationships, it was found that the inhibitory activity of 6-chloro-substituted selenoquinazolines was significantly better than that of non-substituted or 6,8-dichloro-substituted selenoquinazolines at the concentration of 1 μM. Similar structure-activity relationship was also observed at the concentration of 10 μM. Especially, **G5** showed excellent inhibitory activity against A549 cells. **G4** and **G15** were also worth further study and discussion.

Table 4. Inhibition ratio of A549 cells treated with different drug concentrations after 48 h *in vitro*

Compouds	Name	Inhibition ratio (%)	
		1 μM	10 μM
G1	4-benzylselenoquinazoline	21.54±1.28*	29.17±0.91*
G2	4-allylselenoquinazoline	25.78±2.00*	36.63±1.84*
G3	4-ethylselenoquinazoline	21.51±2.10*	24.35±6.77*
G4	4-butylselenoquinazoline	32.76±3.76*	48.95±1.65*
G5	6-chloro-4-benzylselenoquinazoline	43.83±4.84*	67.76±0.79*
G6	6-chloro-4-allylselenoquinazoline	26.47±1.65*	37.89±2.10*
G7	6-chloro-4-ethylselenoquinazoline	31.80±1.65*	39.16±3.01*
G8	6-chloro-4-butylselenoquinazoline	24.84±1.21*	30.65±0.45*
G9	6,8-dichloro-4-benzylselenoquinazoline	14.20±3.76*	27.15±2.56*
G10	6,8-dichloro-4-allylselenoquinazoline	19.23±0.46*	23.28±2.10*
G11	6,8-dichloro-4-ethylselenoquinazoline	22.00±2.29*	26.50±0.80*
G12	6,8-dichloro-4-butylselenoquinazoline	20.48±2.20*	26.36±1.52*
G13	4-benzylsulfenylquinazoline	19.88±1.66*	34.16±1.66*
G14	4-allylsulfenylquinazoline	15.10±1.13*	28.2 ± 1.68*
G15	4-ethylsulfenylquinazoline	20.55±5.22*	56.37±3.92*

G_{16}	4-butylsulfenylquinazoline	18.45±5.12*	32.33±2.10*
G_{17}	6,8-dichloro-4-benzylsulfenylquinazoline	21.61±1.65*	31.81±3.76*
G_{18}	6,8-dichloro-4-allylsulfenylquinazoline	17.55±0.80*	23.67±3.76*
G_{19}	6,8-dichloro-4-ethylsulfenylquinazoline	18.15±2.11*	26.61±2.00*
G_{20}	6,8-dichloro-4-butylsulfenylquinazoline	21.48±2.00*	33.31±0.92*
	Gefitinib®	25.00±1.83*	62.86±1.83*

*Compared with DMSO control, compound **G_1-G_{20}**, Gefitinib® treatment of 48 h showed statistically significant inhibition ($P<0.05$) against cell growth.

CONCLUSION

A series of 4-selenoquinazoline compounds and 4-thioquinazoline compounds were synthesized by using anthranilic acids as starting materials, and their anticancer activities against A549 cell lines were tested through MTT method. The results showed that all the title compounds could inhibit A549 cell lines, especially **G_4**, **G_5** and **G_{15}**. The organoselenium quinazoline compounds exhibited stronger anticancer activities than organosulfur quinazoline compounds. Importantly, 6-substituted-4-selenoquinazoline compound **G_5** had an inhibitory ratio of 67.8%, which was better than the positive control (anticancer drug Gefitinib®). Detailed and in-depth studies of the anticancer activities of **G_5** are carried out in our laboratory, and we will report the results in the near future.

EXPERIMENTAL

***Instruments*.** All melting points of the products were determined on a MP120 digital melting point tester (Jinan Haineng Instruments, Ltd. Co., China) and are not corrected. The infrared spectra were recorded on a MAGANA-IR550 FTIR spectrometer in KBr disks. ^{1}H and ^{13}C NMR spectra were recorded on a spectrometer BRUKER-II 500 MHz (500 and 125 MHz respectively) at room temperature in $CDCl_3$ using TMS as internal standard. All of chemicals were analytical reagent and used without further purification.

***Synthesis of 4-selenoquinazoline compounds*:** 6.0 mmol selenium powder and 4.0 mmol $NaBH_4$ were added in the reaction bottle in turn, and 10.0 mL anhydrous EtOH was added slowly under ice bath. The reaction system gradually showed reddish brown from black. The reaction system continued to be stirred for 10-15 min under ice bath, and then changed to reflux for 30-45 min to prepare Na_2Se_2 alcohol solution. 4.0 mmol 4-chloroquinazoline derivatives were added in batches, refluxed for 2 h, filtered, and the mother liquor was transferred into another reaction flask. 0.4 mmol NaOH was added to make the reaction system alkaline. Then 4.0 mmol $NaBH_4$ was added, and the reaction gradually became orange-yellow solution, refluxed for 2-3 h. Finally, 4.0 mmol various halogenated hydrocarbons were added in batches, refluxed for 1-3 h, and the reaction was detected by TLC. After the reaction was completed, the crude product was obtained by cooling, separating, desolventizing and drying. The crude product was separated and purified by EtOAc-petroleum ether mixed eluent in column chromatography, and the yield was

calculated to obtain compound **G_1-G_{12}**.

***Synthesis of 4-thioquinazoline compounds*:** 2.0 mmol 4-chloroquinazoline derivatives, 5.0 mmol thiourea, 4.0 mmol halohydrocarbon and 8.0 mmol K_2CO_3 were successively added into the reaction flask, and then the mixed solvent of polyethylene glycol-200 and water was added. The reaction was carried out at room temperature for 24 h, TLC was used to detect the reaction. After the reaction was completed, the crude product was obtained by cooling, separating, drying and desolventizing. The crude product was separated and purified by EtOAc-petroleum ether mixed eluent in column chromatography, and the yield was calculated to obtain compound **G_{13}-G_{20}**.

4-Benzylselenoquinazoline (G_1): Orange-yellow solid, yield 43.3%, R_f = 0.36 (EA: PE=1:4, v:v), mp 98.0-100.0 °C. ^{1}H NMR spectrum (500 MHz, $CDCl_3$), δ, ppm (J, Hz): 9.03 (1H, s), 7.97 (1H, d, J = 8.5), 7.91 (1H, d, J = 8.0), 7.83-7.86 (1H, m), 7.55-7.58 (1H, m), 7.45 (2H, d, J = 7.0), 7.30 (2H, t, J = 7.0), 7.24-7.26 (1H, m), 4.70 (2H, s). ^{13}C NMR spectrum (125 MHz, $CDCl_3$), δ, ppm: 171.7, 153.6, 148.0, 138.3, 133.8, 129.2, 128.9, 128.6, 127.6, 127.2, 126.2, 125.1, 29.4. IR spectrum (thin layer), ν, cm^{-1}: 3069, 3036 ($\nu_{Ar\text{-}H}$), 2917 ($\nu_{as}CH_2$), 2849 (ν_sCH_2), 1667-1453 (Ar skeleton vibration), 772, 748 ($\delta_{Ar\text{-}H}$).

4-Allylselenoquinazoline (G_2): Brownish yellow needle crystal, yield 36.0%, R_f = 0.30 (EA: PE=1:3, v:v), mp 51.9-52.0 °C. ^{1}H NMR spectrum (500 MHz, $CDCl_3$), δ, ppm (J, Hz): 8.29 (1H, d, J = 8.0), 8.07 (1H, s), 7.69-7.75 (2H, m), 7.49 (1H, t, J = 7.0), 5.97-6.03 (1H, m), 5.28 (2H, t, J = 10.0), 4.64 (2H, d, J = 5.5). ^{13}C NMR (125 MHz, $CDCl_3$), δ, ppm: 173.9, 160.7, 147.8, 146.4, 134.3, 131.9, 127.3, 127.2, 126.7, 118.8, 48.3. IR spectrum (thin layer), ν, cm^{-1}: 3018-3084 ($\nu_{=CH}$ + $\nu_{Ar\text{-}H}$), 2917 ($\nu_{as}CH_2$), 2849 (ν_sCH_2), 1667-1477 (Ar skeleton vibration). 766, 692 ($\delta_{Ar\text{-}H}$).

4-Ethylselenoquinazoline (G_3): Pale yellow solid, yield 59.6%, R_f = 0.27 (EA: PE=1:3, v:v), mp 78.0-78.5 °C. ^{1}H NMR spectrum (500 MHz, $CDCl_3$), δ, ppm (J, Hz): 8.32 (1H, d, J= 8.0), 8.07 (1H, s), 7.70-7.77 (2H, m), 7.50 (1H, t, J = 8.0), 4.08 (2H, q, J = 7.5), 1.43 (3H, t, J = 7.5). ^{13}C NMR (125 MHz, $CDCl_3$), δ, ppm: 160.9, 148.2, 146.3, 134.1, 127.4, 127.2, 126.7, 122.2, 42.1, 14.9. IR spectrum (thin layer), ν, cm^{-1}: 3051 ($\nu_{Ar\text{-}H}$), 2968 ($\nu_{as}CH_3$), 2917 ($\nu_{as}CH_2$), 2869 (ν_sCH_3), 2852 (ν_sCH_2), 1664-1474 (Ar skeleton vibration). 760, 692 ($\delta_{Ar\text{-}H}$).

4-Butylselenoquinazoline (G_4): Dark yellow solid, yield 60.4%, R_f = 0.34 (EA: PE=1:3, v:v), mp 139.0-141.0 °C. ^{1}H NMR spectrum (500 MHz, $CDCl_3$), δ, ppm (J, Hz): 8.31 (d, J = 8.0, 1H), 8.04 (1H, s), 7.70-7.76 (2H, m), 7.48-7.51 (1H, m), 4.01 (2H, t, J = 7.5), 1.75-1.82 (2H, m), 1.38-1.44 (2H, m), 0.97 (3H, t, J = 7.5). ^{13}C NMR (125 MHz, $CDCl_3$), δ, ppm: 161.0, 148.0, 146.6, 134.1, 127.4, 127.2, 126.7, 122.2, 46.8, 31.4, 19.9, 13.6. IR spectrum (thin layer), ν, cm^{-1}: 3060 ($\nu_{Ar\text{-}H}$), 2953 ($\nu_{as}CH_3$), 2926 ($\nu_{as}CH_2$), 2866 (ν_sCH_3), 1658-1450 (Ar skeleton vibration). 763, 689 ($\delta_{Ar\text{-}H}$).

6-Chloro-4-benzylselenoquinazoline (G_5): White solid, yield 30.9%, R_f = 0.35 (EA: PE=1:3, v:v), mp

102.0-104.0 °C. ^{1}H NMR spectrum (500 MHz, $CDCl_3$), δ, ppm (J, Hz): 8.29 (1H, d, J = 2.0), 8.10 (1H, s), 7.64-7.70 (2H, m), 7.26-7.35 (5H, m), 5.20 (2H, s). ^{13}C NMR (125 MHz, $CDCl_3$), δ, ppm: 160.0, 146.5, 135.4, 134.8, 133.3, 129.2, 128.5, 128.1, 126.3, 123.2, 49.8. IR spectrum (thin layer), ν, cm^{-1}: 3054 ($\nu_{Ar\text{-}H}$), 2914 ($\nu_{as}CH_2$), 2855 (ν_sCH_2), 1664-1444 (Ar skeleton vibration). 834, 695 ($\delta_{Ar\text{-}H}$).

6-Chloro-4-allylselenoquinazoline (G$_6$): Orange-yellow needle crystal, yield 21.4%, R_f = 0.29 (EA: PE=1:3, v:v), mp 109.0-110 °C; ^{1}H NMR spectrum (500 MHz, $CDCl_3$), δ, ppm (J, Hz): 8.28 (1H, d, J = 2.0), 8.01 (1H, s), 7.65-7.71 (2H, m), 5.98 (2H, t, J = 10.0), 5.26-5.33 (2H, m), 4.64 (1H, d, J = 6.0). ^{13}C NMR (125 MHz, $CDCl_3$), δ, ppm: 159.8, 146.6, 146.4, 134.8, 133.2, 131.5, 129.2, 126.2, 123.2, 119.2, 48.5. IR spectrum (thin layer), ν, cm^{-1}: 3018-3066 ($\nu_{Ar\text{-}H}$+$\nu_{=CH}$), 2914 ($\nu_{as}CH_2$), 2846 (ν_sCH_2), 1664-1462 (Ar skeleton vibration). 834, 802 ($\delta_{Ar\text{-}H}$).

6-Chloro-4-ethylselenoquinazoline (G$_7$): Orange solid, yield 33.3%, R_f = 0.36 (EA: PE=1:2, v:v), mp 100.0-102.0 °C. ^{1}H NMR spectrum (500 MHz, $CDCl_3$), δ, ppm (J, Hz): 8.28 (1H, d, J = 1.5), 8.05 (1H, s), 7.64-7.70 (2H, m), 4.07 (2H, q, J = 7.0), 1.43 (3H, t, J = 7.0). ^{13}C NMR (125 MHz, $CDCl_3$), δ, ppm: 159.9, 146.6, 146.5, 134.6, 133.1, 129.1, 126.1, 123.2, 42.3, 14.8. IR spectrum (thin layer), ν, cm^{-1}: 3053 ($\nu_{Ar\text{-}H}$), 1664-1444 (Ar skeleton vibration).

6-Chloro-4-butylselenoquinazoline (G$_8$): Beige solid, yield 46.7%, R_f = 0.32 (EA: PE=1:2, v:v), mp 98.0-99.5 °C. ^{1}H NMR spectrum (500 MHz, $CDCl_3$), δ, ppm (J, Hz): 8.27 (1H, s), 8.02 (1H, s), 7.64-7.69 (2H, m), 4.00 (2H, t, J = 7.0), 1.75-1.81 (2H, m), 1.38-1.44 (2H, m), 0.98 (3H, t, J = 7.5). ^{13}C NMR (125 MHz, $CDCl_3$), δ, ppm: 160.0, 146.8, 146.6, 134.6, 133.1, 129.1, 126.1, 123.2, 47.0, 31.4, 19.9, 13.6; IR spectrum (thin layer), ν, cm^{-1}: 3069 ($\nu_{Ar\text{-}H}$), 2959 ($\nu_{as}CH_3$), 2926 ($\nu_{as}CH_2$), 2867 (ν_sCH_3), 2855 (ν_sCH_2), 1652-1462 (Ar skeleton vibration). 832, 793 ($\delta_{Ar\text{-}H}$).

6,8-Dichloro-4-benzylselenoquinazoline (G$_9$): Orange-red solid, yield 27%, R_f = 0.28 (EA: PE=1:2, v:v), mp 129.0-131.0 °C. ^{1}H NMR spectrum (500 MHz, $CDCl_3$), δ, ppm (J, Hz): 8.21 (1H, d, J = 2.5), 8.19 (1H, s), 7.81 (1H, d, J = 2.0), 7.33-7.38 (5H, m), 5.19 (2H, s). ^{13}C NMR (125 MHz, $CDCl_3$), δ, ppm: 159.5, 147.0, 143.4, 134.9, 134.6, 133.0, 132.9, 129.2, 128.7, 128.1, 125.3, 124.3, 50.0. IR spectrum (thin layer), ν, cm^{-1}: 3063 ($\nu_{Ar\text{-}H}$), 2923 ($\nu_{as}CH_2$), 2849 (ν_sCH_2), 1679-1450 (Ar skeleton vibration). 796, 724 ($\delta_{Ar\text{-}H}$).

6,8-Dichloro-4-allylselenoquinazoline (G$_{10}$): Pale yellow solid, yield 53.1%, R_f = 0.31 (EA: PE=1:2, v:v), mp 105.0-106.0 °C. ^{1}H NMR spectrum (500 MHz, $CDCl_3$), δ, ppm (J, Hz): 8.21 (1H, s), 8.12(1H, s), 7.82 (1H, s), 5.96-5.98 (1H, m), 5.27-5.35 (1H, m), 4.64 (2H, d, J = 5.5). ^{13}C NMR (125 MHz, $CDCl_3$), δ, ppm: 159.2, 147.0, 143.5, 134.7, 133.0, 132.9, 131.2, 125.2, 124.2, 119.6, 48.7. IR spectrum (thin layer), ν, cm^{-1}: 3080-3021 ($\nu_{Ar\text{-}H}$+$\nu_{=CH}$), 2920 ($\nu_{as}CH_2$), 2846 (ν_sCH_2), 1673-1459 (Ar skeleton vibration). 842, 776 ($\delta_{Ar\text{-}H}$).

6,8-Dichloro-4-ethylselenoquinazoline (G11): Dark yellow solid, yield 24.6%, R_f = 0.33 (EA: PE=1:1, v:v), mp 186.0-188.0 °C. ^{1}H NMR spectrum (500 MHz, $CDCl_3$), δ, ppm (J, Hz): 8.21 (1H, d, J = 2.5), 8.15 (1H, s), 7.81 (1H, d, J = 2.5), 4.08 (2H, q, J = 7.0), 1.43 (3H, t, J = 7.5). ^{13}C NMR (125 MHz, $CDCl_3$), δ, ppm: 159.3, 147.0, 143.6, 134.5, 132.9, 132.8, 125.1, 124.3, 42.6, 14.8. IR spectrum (thin layer), ν, cm^{-1}: 3075 ($\nu_{Ar\text{-}H}$), 2955 ($\nu_{as}CH_3$), 2923 ($\nu_{as}CH_2$), 2869 (ν_sCH_3), 2855 (ν_sCH_2), 1670-1453 (Ar skeleton vibration). 843, 790 ($\delta_{Ar\text{-}H}$).

6,8-Dichloro-4-butylselenoquinazoline (G12): Yellow-green solid, yield 46.3%, R_f = 0.26 (EA: PE=1:1, v:v), mp 94.5-96.0 °C. ^{1}H NMR spectrum (500 MHz, $CDCl_3$), δ, ppm (J, Hz): 8.20 (1H, d, J = 2.5), 8.12 (1H, s), 7.81 (1H, d, J = 2.0), 4.01 (2H, t, J = 7.5), 1.75-1.80 (2H, m), 1.39-1.43 (1H, m), 0.98 (3H, t, J = 7.5). ^{13}C NMR (125 MHz, $CDCl_3$), δ, ppm: 159.5, 147.3, 143.6, 134.5, 132.9, 132.8, 125.1, 124.3, 47.2, 31.2, 19.8, 13.6. IR spectrum (thin layer), ν, cm^{-1}: 3068 ($\nu_{Ar\text{-}H}$), 1679-1450 (Ar skeleton vibration).

4-Benzylsulfenylquinazoline (G13): White solid, yield 70.0%, R_f = 0.34 (EA: PE=1:3, v:v), mp 97.8-99.0 °C. ^{1}H NMR spectrum (500 MHz, $CDCl_3$), δ, ppm (J, Hz): 9.02 (1H, s), 8.05 (d, J = 9.0, 1H), 7.97 (1H, d, J = 8.5), 7.82-7.86 (1H, m), 7.53-7.57 (1H, m), 7.47 (2H, d, J = 7.5), 7.30-7.36 (3H, m), 4.65 (2H, s). ^{13}C NMR (125 MHz, $CDCl_3$), δ, ppm: 171.0, 153.4, 147.8, 136.8, 133.7, 129.2, 128.7, 127.5, 123.8, 123.6, 123.3, 33.8. IR spectrum (thin layer), ν, cm^{-1}: 3076 ($\nu_{Ar\text{-}H}$), 1548-1448 (Ar skeleton vibration).

4-Allylsulfenylquinazoline (G14): Yellow liquid, yield 40.3%, R_f = 0.29 (EA: PE=1:2, v:v). ^{1}H NMR spectrum (500 MHz, $CDCl_3$), δ, ppm (J, Hz): 8.33 (1H, d, J = 8.0), 7.71-7.75 (2H, m), 7.52 (1H, t, J = 7.5), 5.98-6.02 (1H, m), 5.28-5.32 (2H, m), 4.65 (2H, d, J = 5.5). ^{13}C NMR (125 MHz, $CDCl_3$), δ, ppm: 160.8, 148.0, 146.2, 134.3, 131.8, 127.4, 127.3, 126.8, 122.1, 118.9, 48.3. IR spectrum (thin layer), ν, cm^{-1}: 3066 ($\nu_{Ar\text{-}H}$), 1463-1538 (Ar skeleton vibration).

4-Ethylsulfenylquinazoline (G15): Maize-yellow solid, yield 57.9%, R_f = 0.30 (EA: PE=1:2, v:v), mp 32.0-33.0 °C. ^{1}H NMR spectrum (500 MHz, $CDCl_3$), δ, ppm (J, Hz): 8.98 (1H, s), 8.08 (1H, d, J = 9.0), 7.96 (1H, d, J = 8.5), 7.84 (1H, t, J = 7.0), 7.57 (1H, t, J = 7.0), 3.39 (2H, q, J = 7.0), 1.47 (3H, t, J = 7.0). ^{13}C NMR (125 MHz, $CDCl_3$), δ, ppm: 171.7, 153.5, 147.7, 133.6, 128.6, 127.2, 124.0, 123.8, 24.0, 14.2. IR spectrum (thin layer), ν, cm^{-1}: 3066 ($\nu_{Ar\text{-}H}$), 1463-1538 (Ar skeleton vibration).

4-Butylsulfenylquinazoline (G16): Pale yellow solid, yield 61.4%, R_f = 0.34 (EA: PE=1:2, v:v), mp 72.0-73.0 °C. ^{1}H NMR spectrum (500 MHz, $CDCl_3$), δ, ppm (J, Hz): 8.32 (1H, d, J = 8.0), 8.03 (1H, s), 7.69-7.73 (2H, m), 7.50 (1H, t, J = 7.0), 4.00 (2H, t, J = 7.0), 1.79 (2H, t, J = 6.5), 1.40-1.45 (2H, m), 0.98 (3H, t, J = 7.0). ^{13}C NMR (125 MHz, $CDCl_3$), δ, ppm: 161.0, 148.1, 146.6, 134.1, 127.1, 127.2, 126.7, 122.2, 46.8, 31.4, 19.9, 13.6. IR spectrum (thin layer), ν, cm^{-1}: 3056 ($\nu_{Ar\text{-}H}$), 2958 ($\nu_{as}CH_3$), 2922 ($\nu_{as}CH_2$), 2863 (ν_sCH_3), 1405 -1658 (Ar skeleton vibration).

6,8-Dichloro-4-benzylsulfenylquinazoline (G17): White solid, yield 59.4%, R_f = 0.26 (EA: PE=1:1, v:v),

mp 119.6-121.0 °C. ^{1}H NMR spectrum (500 MHz, $CDCl_3$), δ, ppm (J, Hz): 9.10 (1H, s), 7.96 (2H, d, J = 2.0), 7.89 (1H, d, J = 2.0), 7.45 (1H, d, J = 7.5), 7.30-7.36 (3H, m), 4.64 (2H, s). ^{13}C NMR (125 MHz, $CDCl_3$), δ, ppm: 170.9, 153.9, 143.7, 136.1, 134.4, 134.1, 132.5, 129.2, 128.7, 127.7, 124.8, 121.9, 34.4; IR spectrum (thin layer), ν, cm^{-1}: 3065 (ν_{Ar-H}), 2976 ($\nu_{as}CH_2$), 2920 (ν_sCH_2), 1405-1596 (Ar skeleton vibration).

6,8-Dichloro-4-allylsulfenylquinazoline (G$_{18}$): Yellow solid, yield 64.8%, R_f = 0.30 (EA: PE=1:1, v:v), mp 90.0-91.0 °C. ^{1}H NMR spectrum (500 MHz, $CDCl_3$), δ, ppm (J, Hz): 9.07 (1H, s), 7.98 (1H, d, J = 2.0), 7.91 (1H, d, J = 2.0), 5.98-6.03 (1H, m), 5.41(1H, d, J = 17.0), 5.22 (1H, d, J = 10.0), 4.06 (2H, d, J = 7.0). ^{13}C NMR (125 MHz, $CDCl_3$), δ, ppm: 170.8, 153.9, 143.6, 134.4, 134.1, 132.5, 132.0, 125.0, 121.9, 119.1, 32.8. IR spectrum (thin layer), ν, cm^{-1}: 3010-3079 (ν_{Ar-H}+$\nu_{=CH}$), 2926 ($\nu_{as}CH_2$), 2848 (ν_sCH_2), 1462-1676 (Ar skeleton vibration).

6,8-Dichloro-4-ethylsulfenylquinazoline (G$_{19}$): Pale yellow solid, yield 57.7%, R_f = 0.27 (EA: PE=2:1, v:v), mp 84.0-85.0 °C. ^{1}H NMR spectrum (500 MHz, $CDCl_3$), δ, ppm (J, Hz): 8.20 (1H, s), 8.15 (1H, s), 7.81 (1H, s), 4.09 (2H, q, J = 7.5), 1.43 (3H, t, J = 7.0). ^{13}C NMR (125 MHz, $CDCl_3$), δ, ppm: 159.3, 147.0, 143.6, 134.4, 132.9, 132.8, 125.0, 124.2, 42.5, 14.7. IR spectrum (thin layer), ν, cm^{-1}: 3075 (ν_{Ar-H}), 2958 ($\nu_{as}CH_3$), 2926 ($\nu_{as}CH_2$), 2864 (ν_sCH_3), 2855 (ν_sCH_2), 1455-1672 (Ar skeleton vibration).

6,8-Dichloro-4-butylsulfenylquinazoline (G$_{20}$): White solid, yield 65.1%, R_f = 0.33 (EA: PE=2:1, v:v), mp 109.8-110.5 °C. ^{1}H NMR spectrum (500 MHz, $CDCl_3$), δ, ppm (J, Hz): 8.20 (1H, d, J = 2.5), 8.12 (1H, s), 7.81 (1H, d, J = 2.5), 4.01 (2H, t, J = 7.0), 1.75-1.79 (2H, m), 1.39-1.43 (2H, m), 0.98 (3H, t, J = 7.5). ^{13}C NMR (125 MHz, $CDCl_3$), δ, ppm: 159.4, 147.3, 143.5, 134.8. 132.8, 132.7, 125.1, 124.2, 47.2, 31.2, 19.8, 13.5. IR spectrum (thin layer), ν, cm^{-1}: 3080 (ν_{Ar-H}), 2958 ($\nu_{as}CH_3$), 2917 ($\nu_{as}CH_2$), 2872 (ν_sCH_3), 2857 (ν_sCH_2), 1459 -1670 (Ar skeleton vibration).

***Cell culture and drug action*:** A549 were cultured in DMEM high sugar medium containing 10% FBS (Fetal Bovine Serum) at 37 °C and 5% CO_2 concentration. The medium was replaced for 2 days. The passage period was 3-4 days. The drugs were dissolved in DMSO and prepared into 1 mM and 10 mM storage solution, respectively, which were diluted into 1 μM and 10 μM drug concentrations in the culture solution. Cells in the logarithmic growth phase were divided into two parts. One was treated with DMSO alone as negative control, and the other was treated with drug Gefitinib®.

***MTT assay*:** All kinds of mentioned above cell lines were cultured under 96-well plates (3,000 cells per well) condition. Those cells were further stored at 37 °C for 24 h in 10% FBS/RPMI 1640 medium. After cells prepared, those tested cells were divided into two parts. One was treated with DMSO alone as negative control, and another one was treated with varied tested drug concentrations. All concentrations of tested drug were tested inhibitor activity in 48 h. The results of target compounds antitumor activity

were produced by an ELISA plate reader (BioTek-synergy HT). The test was done three times separately. Accordingly, the following formula was used to calculate the inhibition rates of all compounds against tested tumor cells.

$$\text{Inhibition ratio (\%)} = (1 - \text{experiment value/negative control value}) \times 100\%$$

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