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ARTICLE

Synthesis and Transformation of 4-(1-Chloro-1-nitroethyl)-6,7-dimethoxy-2-methylquinazoline: Spectral Characterization and Anti-cancer Properties of some Novel Quinazoline Derivatives

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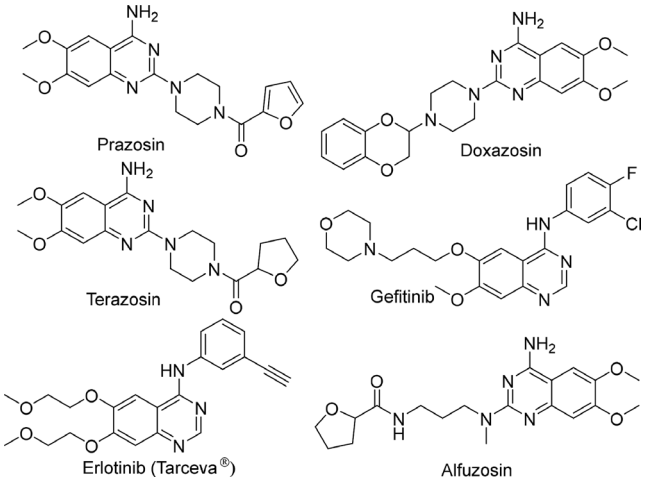
Abstract

An efficient and simple method has been reported for the synthesis of 4-(1-Chloro-1-nitroethyl)-6,7-dimethoxy-2-methylquinazoline (**2**) as a key compound for further transformation to other novel 6,7-dimethoxy-2-methyl-4-substituted quinazolines. The structure of the synthesized compounds was characterized by spectroscopic methods. The pathway of some unprecedented reactions was proposed. (*E*)-1-(6,7-dimethoxy-2-methylquinazolin-4-yl)-3-(4-nitrophenyl)prop-2-en-1-one **(11)** exhibits high in vitro cytotoxicity on three cell lines, *Hepatocellular carcinoma* (Hep-G2), *Human lung carcinoma* (LU-1), and *Human breast carcinoma* (MCF-7) with IC_{50} of 2.1, 11.6 and 2.2 μM, respectively.

1 | INTRODUCTION

Quinazolines, an important class of fused heterocyclic compounds have attracted high attention in organic and medicinal chemistry due to their significant and wide range of biological activities. Quinazolines is considered as an important starting material for the synthesis of various physiological significance and pharmacological utilized molecules. During the past several decades, interest in synthesis and expanding the biological effects of quinazoline and quinazolinone derivatives grew exponentially, as indicated by the large number of publications reporting the syntheses and isolations of these compounds from natural as well as their biological applications[1–7] It could be seen from the reviews[1–6] that: i) Traditional synthetic methods for quinazoline derivatives still in general use; ii) Quinazoline derivatives with substituent groups at 2-, 4- and 6-position could promote the anti-cancer and antimicrobial activities; iii) Many of approved drugs with quinazoline structure in commercial availability are 4-aminoquinazoline derivatives with two alkoxy, mainly two methoxy groups at 6- and 7-position such as: Prazosin is a sympatholytic medication that is used to treat high blood pressure, anxiety, and posttraumatic stress disorder; Doxazosin is a non-selective alpha-1 adrenergic antagonist (alpha-blocker) used in the therapy of hypertension and benign prostatic hypertrophy; Terazosin is a selective alpha-1 antagonist used for treatment of symptoms of an enlarged prostate; Gefitinib is a drug used for certain breast, lung and other cancers; Erlotinib (Tarceva) is a drug used to treat non-small cell lung cancer, pancreatic cancer and several other types of cancer; Alfuzosin is used to improve urination in men with benign prostatic hyperplasia.[6]



Some time ago, we focused our attention to several natural arylolefins (eugenol, methyleugenol, safrole, anethole) from vegetable essential oils that could act as good substrates in order to prepare heterocyclic compounds. For example, many poly-functionalized quinolines were synthesized from eugenol with a convenient route;[8,9] 4,5-dimethoxy-2-(3-methylfuroxan-4-yl) phenylamine (**Am**), which was synthesized from methyleugenol, acted as a key compound for preparation of some series of imines, azo, 1,3-thiazolidin-4-ones and indoles incorporating furoxan moiety.[10,11]

Considering above mentions, we have decided to design and synthesize a series of 6,7-dimethoxy-2-methyl-4-substituted quinazolines and to investigate whether the resulting compounds have useful anti-cancer activities.

2 | RESULTS AND DISCUSSION

As mentioned above and in literature,[12] our quinazoline derivatives were designed on purpose in which substituents at 2,4,6 positions were set up to improve anti-cancer activity; 6,7-dimethoxy-quinazoline was derived from methyleugenol-a natural source; R substituent was a changeable group to expand our research as presented in Scheme 1 (The numeration on presented structures is specifically used for NMR analysis).

First of all, 4,5-dimethoxy-2-(3-methylfuroxan-4-yl) phenylamine (**Am**) was prepared from methyleugenol according to our manner.[10] Then, amide **1** was obtained in 80% yield when a mixture of **Am**, Ac_2O in ethanol was refluxed for 3 hoursours. Next, in the reaction *b*, DMF/$POCl_3$ was used in order to convert amide **1** into quinazoline **2** in 64% yield.

The IR, ^1H, ^{13}C and MS spectra of **1** and **2** (see Experimental) are associated with their structures. For example, In the ESI MS of **2**, there is a pseudomolecular ion peak at m/z 311.9/52% ($M + H^+$) accompanied by a isotope peak at m/z 314.0/20% (^{37}Cl), and the base peak at m/z 265.9/100% ($M + H^+$-NO_2) accompanied by an isotope peak at m/z 267.9/20% (^{37}Cl). These correspond with the presence of one Cl atom in molecule $C_{13}H_{14}ClN_3O_4$ of **2**. The proton and carbon signals of **2** were assigned by using NOESY, HSQC and HMBC spectra. For example, six singlets in ^1H NMR spectrum of **2** were distinguished using NOESY spectrum as in Figure 1.

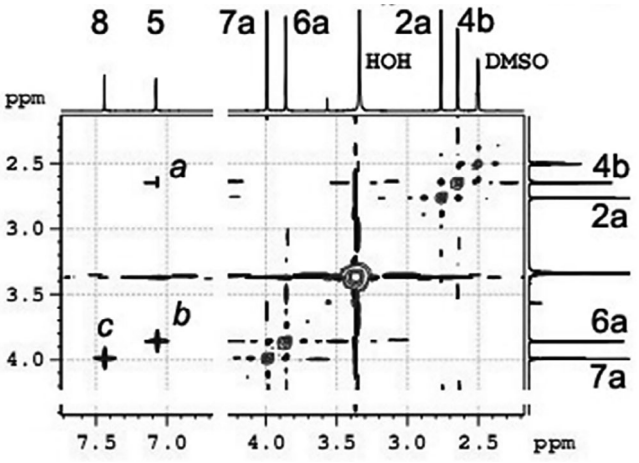
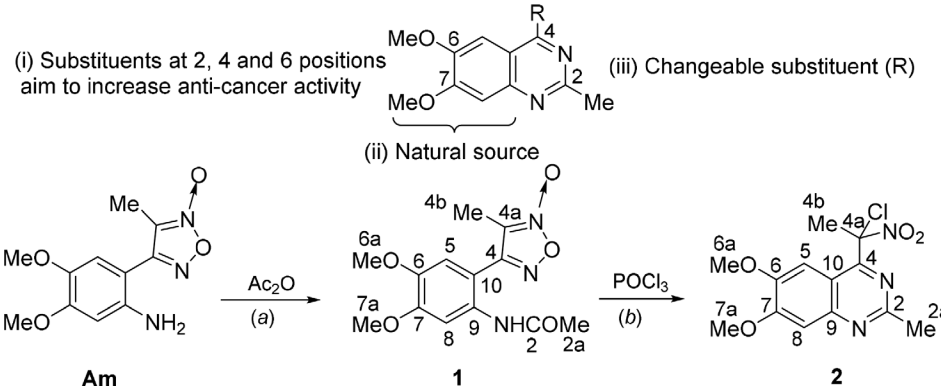


FIGURE 1 NOESY spectrum of **2**



SCHEME 1 Synthesis of quinazoline **2**

Singlet at 7.08 ppm gives rise to two cross peaks *a* and *b* with two singlets of methyl protons at 2.64 ppm and 3.86 ppm, while singlet at 7.44 ppm has only one cross peak *c* with singlet of methyl protons at 3.99 ppm. Thus, singlet at 7.08 ppm is assigned to aromatic H5, singlet at 7.44 ppm - to aromatic H8; two methyl groups at 2.64 ppm and 3.86 ppm are assigned to H4b and H6a, respectively; methyl group at 3.99 ppm is assigned to H7a. Singlet of methyl group at 2.76 ppm does not have any cross peak, so it belongs to H2a.

Because compound **2** is the product of unprecedented reaction (*b* in Scheme 1), its single crystal X-ray diffraction was analyzed. The results (Figure 2) shown that **2** crystallized in triclinic system and each unit cell is occupied with a pair of enantiomers of **2** with *S*-configuration C4a and *R*-configuration C′4a.

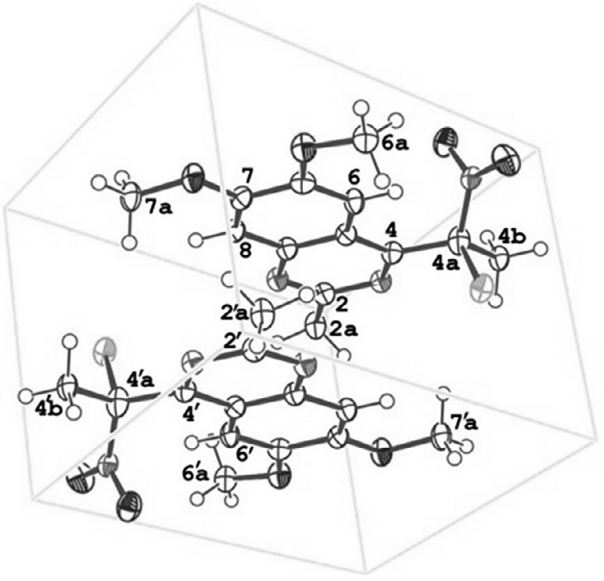


FIGURE 2 Crystal packing of **2**, showing a pair of enantiomers

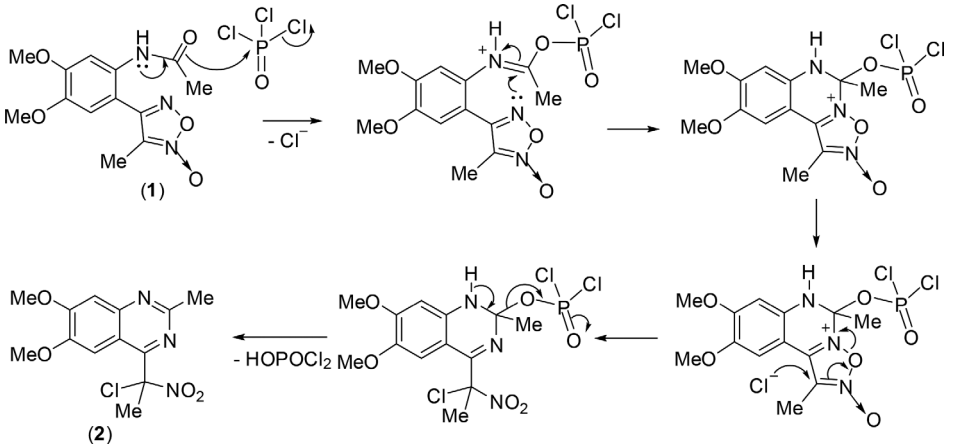
It is known that DMF and $POCl_3$ are ready to form in situ formylating agent (Wilsmeier-Haack reagent), which allows the formylation of electron-rich arenes.[13] This brings up the question: how was the compound **1** converted into the quinazoline **2**? In order to answer this question, the reaction of **1** with $POCl_3$ was also carried out in two other manners than that described in the Experimental to evaluate the role of DMF and HCl. In the first manner, a mixture of **1** and $POCl_3$ (without DMF) was heated at 60°C for 4 hoursours. In the second manner, a mixture of **1**, DMF and concentrated hydrochloric acid (without $POCl_3$) was heated at 60°C for 4 hours. The first try gave compound **2** in 62% yield only, meanwhile, the **Am** was obtained in 72% yield due to hydrolysis in the second manner. These results allow us to explain the formation of **2** from **1** ignoring DMF and HCl as Scheme 2.

The activation exerted by the nitro, chloro and hetaryl groups renders an availability of the ethyl side chain of **2** for various chemical transformations as presented in Scheme 3.

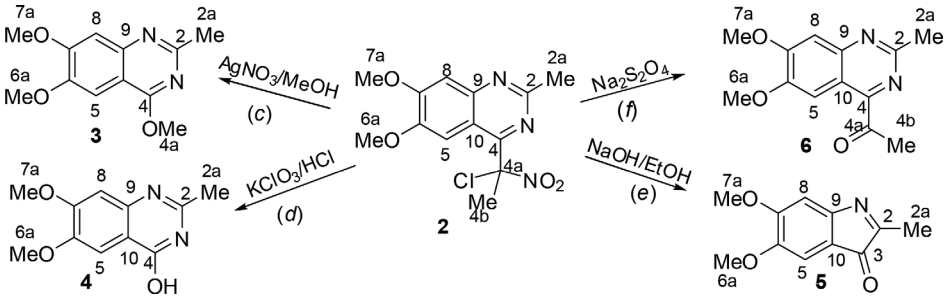
When compound **2** was reacted with $AgNO_3$ in MeOH (reaction *c*, Scheme 3), instead of substitution or elimination products, compound **3** was obtained with the yield of 52%. The IR absorption and MS data (see Experimental) correspond with the formula of **3** in which six proton singlets and twelve carbon signals of **3** were assigned using NOESY and HMBC spectra. The formation of **3** can be explained as in Scheme 4.

Upon the treating **2** with $KClO_3$/HCl solution, it was oxidized to form compound **4** (reaction *d*, Scheme 3). All obtained data from IR, MS, ^1H, ^{13}C and HMBC spectra of **4** (see Experimental, Table 2) are associated with its structure.

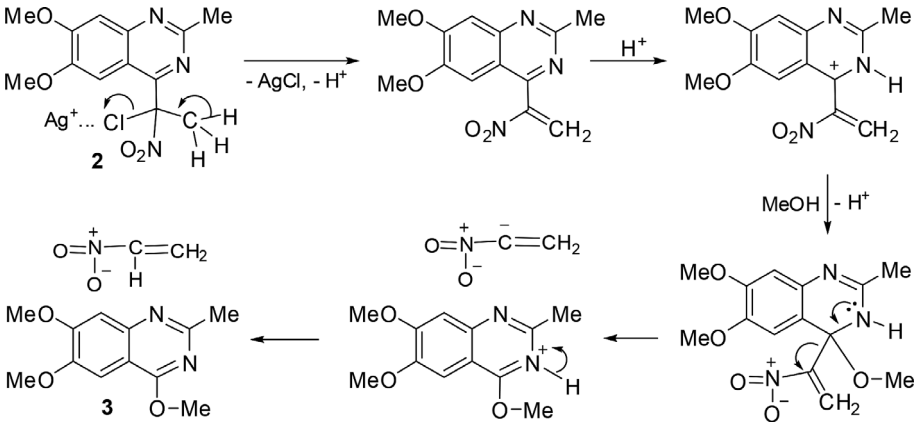
Interestingly, upon refluxing quinazoline **2** and NaOH in 95% ethanol (v/v) we obtained an indole derivative, compound **5** (reaction *e*, Scheme 3). Strong absorption band at 1671 cm^{-1} and weak absorption band at



SCHEME 2 Explanation of the formation of **2**



SCHEME 3 Chemical transformation of **2**



SCHEME 4 Proposed explanation of the formation of **3**

TABLE 1 Cancer cytotoxicity evaluation on four cell lines, IC_{50} (μM)

Compd.	KB	Hep-G2	Lu	MCF-7
2	78.0	–	–	–
4	109.1	–	–	–
5	8.00	41.79	94.95	12.0
7	1.23	1.25	1.84	3.57
10	8.6	11.6	–	–
11	> 337	2.1	11.6	2.2
Ellipticine	1.14	1.14	1.71	1.70

TABLE 2 ^{1}H and ^{13}C NMR signals of compounds **1–6**, δ (ppm)

Comp.	1	2	3	4	5	6
H2a/H4b	2.00 s / 1.94 s	2.76 s / 2.64 s	2.60 s / 4.10 s	2.62 s / –	2.30 s / –	2.76 s / 2.74 s
H6a/H7a	3.76 s / 3.79 s	3.86 s / 3.99 s	3.89 s / 3.93 s	3.90 s / 3.93s	3.84 s / 3.87 s	3.90 s / 3.98 s
H5/H8	7.06 s / 7.24 s	7.08 s / 7.44 s	7.29 s / 7.21s	7.46 s / 7.35s	7.39 s / 7.04 s	7.95 s / 7.34 s
C2/C2a/C4b	168.9/23.6/8.7	160.4/29.7/25.5	161.2/25.1/54.4	156.6/18.2/–	152.8/21.3/–	161.0/25.6/27.9
C4/C4a	157.1 / 114.4	157.3 / 103.9	165.4 / –	158.6 / –	– / –	155.4 / 202.5
C5/C8	113.1 / 109.6	100.3 / 107.3	101.1 / 104.8	105.9 / 102.3	104.9 / 107.4	106.1 / 102.8
C6/C7	146.6 / 151.1	150.0 / 156.0	149.3 / 155.6	149.1 / 155.2	147.9 / 154.4	150.7 / 156.0
C6a/C7a	56.1 / 56.4	55.7 / 56.4	56.1 / 55.9	55.8 / 56.0	55.6 / 55.8	55.7 / 56.2
C9/C10	130.8 / 112.1	150.1 / 113.2	146.4 / 107.6	136.5 / 112.4	145.1 / 113.4	150.9 / 113.9

1637 cm^{-1} in IR spectrum of **5** indicate the presence of conjugated N=C-C=O group. The remarkable difference in NMR spectra of **5** in comparison with spectrum of **2** is the decrease of one proton signal of methyl group, one methyl carbon signal and one other carbon signal. Furthermore, all signals in HMBC of **5** (Figure 3) are associated with its structure.

In Figure 3 the cross peak *r* of methyl protons H2a indicates that signal at 152.8 ppm belongs to C2. The cross peaks *m, p* of two methoxy group (H6a, H7a) show signal of C6 and C7, consequently the largest chemical shift signal at 161.3 ppm should be assigned to carbonyl carbon C3. The signal of C3 has stronger cross peaks *s* with aromatic proton at 7.39 and weaker cross peak *t* with aromatic proton at 7.03 ppm. Because three-bond correlations are stronger than four-bond one, therefore the signal at 7.39 ppm is assigned to H5 and the signal at 7.03 ppm is assigned to H8. Similarly, proton and carbon signals of **5** were assigned.

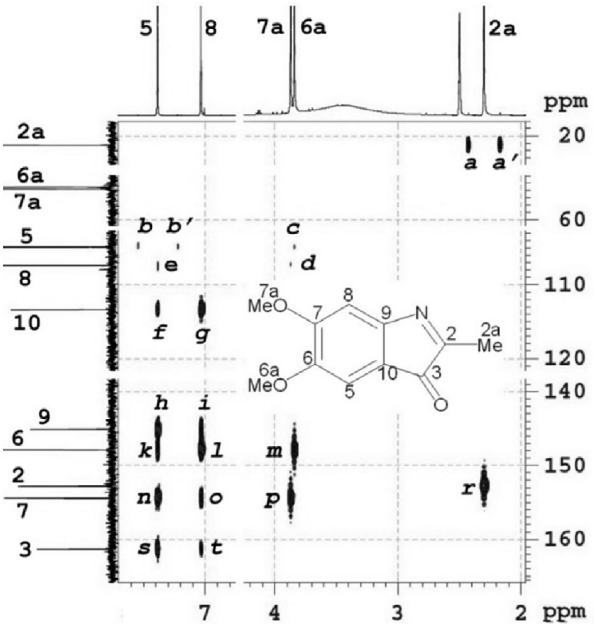
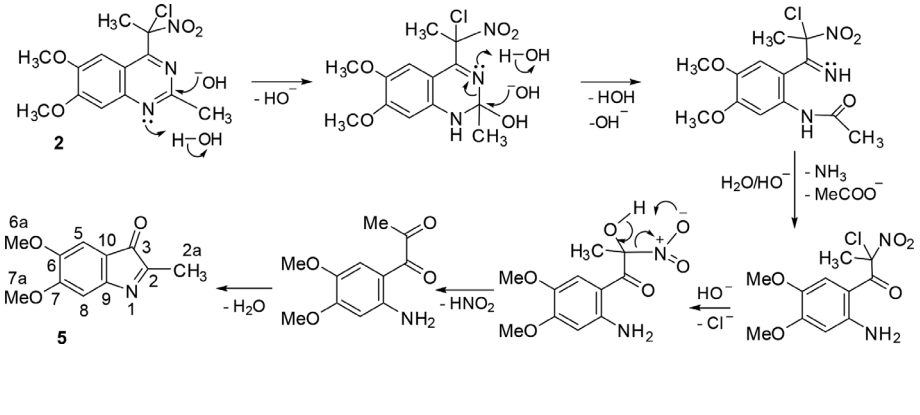


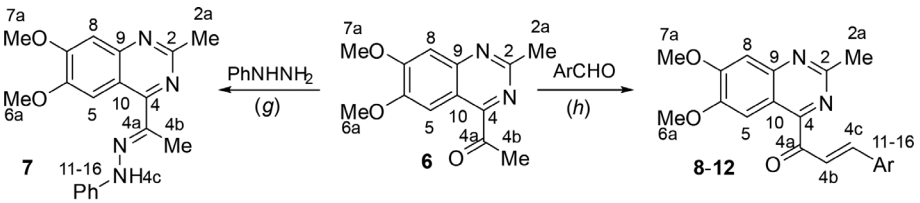
FIGURE 3 A part of HMBC spectrum of **5**

It is known that quinazolines is destroyed when its alkaline or acidic solution boiled. *o*-Aminobenzaldehyde, ammonia, and formic acid are formed when quinazoline is boiled with hydrochloric acid.[5] The formation of **5** from **2** can be explained as in Scheme 5.

When the compound **2** was reacted with $Na_2S_2O_4$ in alkaline medium (reaction *f* in Scheme 3) the nitro group was reduced to an amino group, atom Cl was replaced by OH group followed by the releasing NH_3 to afford methyl ketone **6**. The IR spectrum of **6** showed strong absorption band at 1691 cm^{-1} attributed to C=O group. The ESI + MS spectrum of **6** displayed an intensive peak at m/z 246.9 (100%, $[M + H]^+$) corresponding to the expected molecular formula $C_{13}H_{14}N_2O_3$ (M = 246 au). Six proton singlets and thirteen carbon signals of **6** (Table 2) were assigned using its HMBC spectrum. The remarkable difference in ^{13}C NMR spectrum of **6** in comparison with spectrum of **2** is the absence of signal at 103.9 ppm (C4a of **2**) and the appearance of the signal at 202.5 ppm assigned to carbonyl carbon (C4a of ketone **6**). The condensation of **6** and phenylhydrazine to form phenylhydrazone **7** (reaction *g* in Scheme 6) was a final characterization for ketone **6**.



SCHEME 5 Explanation of the formation of **5**



SCHEME 6 Condensation reactions of ketone **6**

Ar: Ph (**8**), 4-MeOPh (**9**), 4-Me_2NPh (**10**), 4-O_2NPh (**11**), 2-O_2NPh (**12**).

TABLE 3 ^{1}H and ^{13}C NMR signals of compounds **7–12**, δ (ppm), *J* (Hz)

Comp.	7	8	9	10	11	12
H2a	2.72 s	2.81 s	2.93 s	2.87 s	2.82 s	2.81 s
H4b	–	7.81 d, *J* 16	7.85 d, *J* 16	7.50 d, *J* 15	7.90 d, *J* 16	7.92 d, *J* 16
H4c	–	7.90 d, *J* 16	7.87 d, *J* 16	7.67 d, *J* 15	8.07 d, *J* 16	8.09 d, *J* 16
H6a/H7a	3.89 s / 3.97 s	3.91 s / 4.00 s	4.04 s / 4.06 s	3.88 s / 3.98 s	3.92 s / 3.99 s	3.94 s / 4.01 s
H5/H8	7.29 s / 8.54 s	7.84 s / 7.39 s	8.09 s / 7.31 s	7.74 s / 7.35 s	7.89 s / 7.39 s	7.95 s / 7.41 s
H12/H16	7.39/7.39 d, *J* 8	7.48/7.48 d*J* 8	7.66/7.66 d, *J* 9	7.61/7.61 d, *J* 7	8.08/8.08 d, *J* 9	– / 8.05 d, *J* 8
H13/H15	7.29/7.29 t, *J* 8	7.80/7.80 t, *J* 8	6.95/6.95 d, *J* 9	6.74/6.74 d, *J* 7	8.28/8.28 d, *J* 9	8.13 d/7.85 t, *J* 8
H14/H14a	6.90 t, *J* 8 / –	7.48 t, *J* 8/ –	–/ 3.87 s (MeO)	–/ 3.01 s (Me_2N)	– / –	7.74 t, *J* 8 / –
C2/C2a	160.0 / 24.6	161.0 / 25.6	161.9 / 26.1	159.8 / 24.4	161.1 / 25.6	161.0 / 25.5
C4/C4a	144.7 / 151.0	156.1 / 191.7	157.5 / 192.1	154.5 / 185.6	156.2 / 191.5	155.9 / 191.3
C4b/C4c	13.3 / –	123.6/145.8	121.1 / 146.1	121.5 / 144.5	142.6 / 127.3	140.2 / 127.6
C5/C8	106.1 / 102.7	106.2 / 102.6	106.2 / 103.5	107.6 / 102.8	106.3 / 102.6	106.2 / 102.5
C6/C7	155.6 / 159.4	150.7 / 157.1	151.0 / 156.3	151.0 / 156.3	150.9 / 156.3	150.9 / 156.3
C6a/C7a	55.6 / 56.1	55.7 / 56.1	56.3 / 56.4	55.5 / 56.0	55.8 / 56.2	55.7 / 56.2
C9/C10	149.9 / 114.8	150.3 / 114.6	149.8 / 115.8	146.8 / 115.7	150.5 / 114.7	150.5 / 114.7
C11/14/14a	141.6/120.9/–	134.2 / 131.1/–	127.6/162.1/55.5	124.0/148.1/40.1	140.7/148.4 / –	129.6/131.3 / –
C12/C16	129.1 / 129.1	129.1 / 129.1	130.8 / 130.8	130.8 / 130.8	129.9 / 129.9	148.6 / 129.2
C13/C15	113.6 / 113.6	128.9 / 128.9	114.5 / 114.5	110.9 / 110.9	124.1 / 124.1	124.8 / 134.0

Next, ketone **6** was subject for the crotonic condensation reaction to promote the side chain. Quinazolines are stable in cold dilute acid and alkaline solutions, but it is destroyed when these solutions are boiled,[5] therefore the reaction of **6** with aromatic aldehydes (reaction *h* in Scheme 6) was carried out in ethanol with 10% hydrochloric acid as catalyst at room temperature. The obtained products (**8**-**12**) are yellow solids melting at about 200°C (see Experimental).

Two IR absorption bands at 1656-1691 and 1611-1615 cm^{-1} of **8**-**12** are associated with conjugated α,β-unsaturated carbonyl system of Hr-CO-CH=CH-Ar. Two doublets at 7.51-7.92 and 7.67-8.10 ppm with $J = 16$ Hz (Table 3) confirm the presence of *trans* -CH=CH- group in molecules of **8**-**12**. By using HMBC spectra all ^{1}H NMR and ^{13}C NMR signals of **8**-**12** were assigned as listed in Table 3.

Compounds **2**, **4**, **5**, **7**, **10** and **11** were tested for cell in vitro cytotoxicity on four cell lines *Human epidermic carcinoma* (KB), *Hepatocellular carcinoma* (Hep-G2), *Human lung carcinoma* (Lu), and *Human breast carcinoma* (MCF-7). The cell in vitro cytotoxicity of examined compounds, IC_{50} (μM), are listed in Table 1. The potency of the anticancer effect of the tested compounds was compared with ellipticine which was used as a standard drug. All selected compounds exhibited quite good anticancer activity with selectivity of one or some cancer cell lines. Especially, compounds **7** and **11** performed IC_{50} values close to that of the standard drug on Hep-G2 and MCF-7, ccompound **7** also inhibited well KB cell line, Table 1.

3 | CONCLUSIONS

4-(1-Chloro-1-nitroethyl)-6,7-dimethoxy-2-methylquinazoline (**2**) was synthesized and used as a key compound for further transformation to 4,6,7-trimethoxy-2-methylquinazoline (**3**), 6,7-dimethoxy-2-methylquinazolin-4-ol (**4**), 5,6-dimethoxy-2-methyl-3H-indol-3-one (**5**), 1-(6,7-dimethoxy-2-methyl-quinazolin-4-yl)ethanone (**6**), 6,7-dimethoxy-2-methyl-4-(1-[2-phenylhydrazono]ethyl)quinazoline (**7**), (E)-1-(6,7-dimethoxy-2-methylquinazolin-4-yl)-3-phenylprop-2-en-1-one (**8**), (E)-1-(6,7-dimethoxy-2-methylquinazolin-4-yl)-3-(4-methoxyphenyl)prop-2-en-1-one (**9**), (E)-1-(6,7-dimethoxy-2-methyl-quinazolin-4-yl)-3-(4-[dimethylamino] phenyl)prop-2-en-1-one (**10**), (E)-1-(6,7-dimethoxy-2-methyl-quinazolin-4-yl)-3-(4-nitrophenyl)prop-2-en-1-one (**11**) and (E)-1-(6,7-dimethoxy-2-methylquinazolin-4-yl)-3(2-nitrophenyl)prop-2-en-1-one (**12**). Detailed NMR spectroscopic investigations with all prepared compounds were performed. The pathway of some unprecedented reactions was proposed. Compound **11** exhibits high in vitro cytotoxicity on three cell lines, *Hepatocellular carcinoma* (Hep-G2), *Human lung carcinoma* (LU-1), and *Human breast carcinoma* (MCF-7) with IC_{50} is 2.1, 11.6 and 2.2 μM respectively.

3.1 | Experimental Section

3.1.1 | General

IR spectra were recorded on an IMPACK-410 NICOLET spectrometer in KBr discs at 400-4000 cm^{-1}. ESI mass

spectra were recorded using Agilent LC-MSD-Trap-SL series 1100 spectrometer. NMR spectra were recorded on a Bruker AVANCE 500 MHz spectrometer, in DMSOd_6 with TMS as the internal standard, at 298-300 K. C, H, and N were analyzed on a LECO CHNS model 932 elemental analyser. The anticancer activities were tested at the Experimental Biological Laboratory - Institute of Chemistry of Natural Compounds (in Hanoi), according to the described method;[14] IC_{50} values were calculated based on OD values taken on an Elisa instrument at 515-540 nm.

3.1.2 | Preparation

4-(2-acetamido-4,5-dimethoxyphenyl)-3-methyl-1,2,5-oxadiazole-2-oxide (1)

A solution of 4,5-dimethoxy-2-(3-methylfuroxan-4-yl) phenylamine (**Am**, previously prepared in reference [10], 2.51 g, 10 mmol) in ethanol (200 mL) and acetic anhydride (1 mL, 10.5 mmol) was refluxed for 3 hours. After cooling down to room temperature, the precipitate was filtered out and recrystallized from EtOH to give white crystals (**1)** in 2.34 g and 80% yield, mp 171-172°C. IR (cm^{-1}): 3261 (NH); 3044, 2952, 2836 (C-H); 1672 (C=O); 1618, 1531, 1487 (ring). ^{1}H NMR and ^{13}C NMR see Tables 2. ESI, +MS, *m/z* (au)/relative intensity (%): 316/100 ($M + Na^+$). *Anal*. Calcd for $C_{13}H_{15}N_3O_5$ (M 293.28): C, 53.24; H, 5.16; N, 14.33. Found: C, 52.98; H, 5.35; N, 14.65.

4-(1-Chloro-1-nitroethyl)-6,7-dimethoxy-2-methylquinazoline (2)

To a solution of $POCl_3$ (8 mL) and DMF (4 mL) at 0-5°C, **2** (1.85 g, 7 mmol) was slowly added and stirred. The reaction mixture was heated at 60°C and stirred for 4 h. After cooling down to room temperature, 30 mL cool water (0-5°C) was added. The obtained mixture was neutralised with 5 M NaOH solution. The precipitate was filtered out and recrystallized from EtOH-H_2O 1:1 by volume to give dark yellow needles (**2)** in 1.396 g (64% yield), mp 167-168°C. IR (cm^{-1}): 3080, 2991, 2935 (C-H); 1613, 1565, 1500 (ring). ^{1}H NMR and ^{13}C NMR see Table 2. ESI, +MS, *m/z* (au)/relative intensity (%): [311.9/52, 314.0/20 ($M + H^+$)]; [265.9/100, 267.9/38 ($M + H^+$-NO_2]. *Anal*. Calcd for $C_{13}H_{14}ClN_3O_4$ (M 311.07): C, 50.09; H, 4.53; N, 13.48. Found: C, 49.81; H, 4.75; N, 13.20.

4,6,7-Trimethoxy-2-methylquinazoline (3)

A solution of $AgNO_3$ (170 mg, 1 mmol) and **2** (312 mg, 1 mmol) in ethanol (25 mL) was refluxed for 3 h. The grey precipitate was filtered out and the filtrate was left at room temperature to give white crystals (**3)** in 122 mg and 52% yield, mp 164-166°C. IR (cm^{-1}): 3045, 2976 (C-H); 1611, 1560, 1512 (ring). ^{1}H NMR and ^{13}C NMR see Table 2. ESI, +MS, *m/z* (au)/relative intensity (%): 235/100 ($M + H^+$). *Anal*. Calcd for $C_{12}H_{14}N_2O_3$ (M 234.25): C, 61.53; H, 6.02; N, 11.96. Found: C, 61.23; H, 6.31; N, 12.14.

6,7-Dimethoxy-2-methylquinazolin-4-ol (4)

A solution of **2** (312 mg, 1 mmol) in hydrochloric acid 1:1 (5 mL) was heated at 50°C and a solution of $KClO_3$ (367 mg in 5 mL water) was slowly added during 30 minutes under stirring. The reaction mixture was stirred for 1 hour at 50°C. The precipitate was filtered out, washed with water and recrystallized from 95% EtOH to give white crystals (**4)** in 180 mg and 59% yield, mp 173-175°C. IR (cm^{-1}): 3452 (OH); 2985, 2922(C-H); 1611, 1468 (ring). ^{1}H NMR and ^{13}C NMR see Table 2. ESI, MS, *m/z* (au)/relative intensity (%): +MS, 220.9/100 ($M + H^+$); -MS, 218.8/30 ($M-H^+$), 203.8/100 ($M-H^+$-Me). *Anal*. Calcd for $C_{11}H_{12}N_2O_3$ (M 220.22): C, 59.99; H, 5.49; N, 12.72. Found: C, 59.68; H, 5.24; N, 12.89.

5,6-Dimethoxy-2-methyl-3H-indol-3-one (5)

A mixture of **2** (312 mg, 1 mmol) in NaOH solution (1 g in 10 mL of water) was refluxed for 6 hours. After cooling down to room temperature, the precipitate was filtered out and recrystallized from EtOH-H_2O 1:1 by volume to give yellow needle crystals (**5)** in 168 mg and 82% yield, decomposed at 253-255°C. IR (cm^{-1}): 3021, 2999, 2896 (C-H); 1671 (C=O); 1637, 1613, 1505 (ring). ^{1}H NMR and ^{13}C NMR see Tables 2. *Anal*. Calcd for $C_{11}H_{11}NO_3$ (M 205.21**):** C, 64.38; H, 5.40; N, 6.83. Found: C, 64.69; H, 5.15; N, 6.55.

1-(6,7-Dimethoxy-2-methylquinazolin-4-yl)ethanone (6)

$Na_2S_2O_4$ (5.32 g) was dissolved in 0.75 M NaOH solution (40 mL) to form first solution. A solution of **2** (1.56 g, 5 mmol) in ethanol (30 mL) was heated at 70°C and the first solution was slowly added during 1 hour under stirring. The reaction mixture was stirred for additional 2 hours at 70°C, and then ethanol was evaporated. After cooling, ice (20 g) was added. The precipitate was filtered out, washed with water and recrystallized from 95% EtOH to give yellow crystals (**6)** in 763 mg and 62% yield, mp 185-186°C. IR (cm^{-1}): 3130, 3020, 2924, 2830(C-H); 1691 (C=O); 1615, 1555, 1450 (ring). ^{1}H NMR and ^{13}C NMR see Table 2. ESI, +MS, *m/z* (au)/relative intensity (%): 246.9/100 ($M + H^+$). *Anal*. Calcd for $C_{13}H_{14}N_2O_3$ (M 246.10): C, 63.40; H, 5.73; N, 11.38. Found: C, 63.09; H, 5.95; N, 11.57.

6,7-dimethoxy-2-methyl-4-(1-[2-phenylhydrazono]ethyl) quinazoline (7)

To a solution of **6** (246 mg, 1 mmol) in EtOH (15 mL) at 60°C, a solution of $C_6H_5NHNH_2$.HCl (145 mg, 1 mmol), CH_3COONa (82 mg, 1 mmol) in EtOH (10 mL) was slowly added under stirring. The reaction mixture was stirred for 5 hours at 60°C and left at room temperature to give an orange precipitate. The precipitate was filtered out and recrystallized from 95% EtOH to afford orange needles (**7**) in 235 mg (70% yield), mp 151-153°C. IR (cm^{-1}): 3443, 3250 (NH); 2922, 2852 (C-H); 1601, 1543, 1451 (ring). ^1H NMR and ^{13}C NMR see Table 3. *Anal.* Calcd for $C_{19}H_{20}N_4O_2$ (M 336.39): C, 67.84; H, 5.99; N, 16.66. Found: C, 67.52; H, 6.21; N, 16.35.

(E)-1-(6,7-dimethoxy-2-methylquinazolin-4-yl)-3-phenylprop-2-en-1-one (8)

To a solution of **6** (246 mg, 1 mmol) in concentrated hydrochloric acid (5 mL) and water (4 mL), a solution of PhCHO (106 mg, 1 mmol) in EtOH (5 mL) was slowly added under stirring. The reaction mixture was stirred for 24 hours at room temperature. The obtained mixture was neutralized with 10% NaOH solution. The precipitate was filtered out and recrystallized from 95% EtOH to afford yellow needles (**8**) in 248 mg (71% yield), mp 183-184°C. IR (cm^{-1}): 3093, 2922, 2852 (C-H); 1665/1615 (-CO-CH=CH-); 1593, 1551, 1521 (ring). ^1H NMR and ^{13}C NMR see Table 3. *Anal.* Calcd for $C_{20}H_{18}N_2O_3$ (M 334.37): C, 71.84; H, 5.43; N, 8.38. Found: C, 72.04; H, 5.18; N, 8.06.

(E)-1-(6,7-dimethoxy-2-methylquinazolin-4-yl)-3-(4-methoxyphenyl)prop-2-en-1-one (9)

The compound was prepared starting from **2** (246 mg, 1 mmol) and 4-MeOPh-CHO (136 mg, 1 mmol) according to the procedure for the preparation of **8**. The yield was 237 mg (65%), yellow needles (**9**) mp 187-189°C. IR (cm^{-1}): 2966, 2923, 2850 (C-H); 1664/1617 (-CO-CH=CH-); 1597, 1547, 1499 (ring). ^1H NMR and ^{13}C NMR see Table 3. ESI, MS, *m/z* (au)/relative intensity (%): +MS, 396.9/70 ($M + MeOH+H^+$); -MS, 394.8/100 ($M + MeOH-H^+$). *Anal.* Calcd for $C_{21}H_{20}N_2O_4$ (M 364.39): C, 69.22; H, 5.53; N, 7.69. Found: C, 69.54; H, 5.28; N, 7.86.

(E)-1-(6,7-dimethoxy-2-methylquinazolin-4-yl)-3-(4-[dimethylamino]phenyl)prop-2-en-1-one (10)

This compound was prepared starting from **2** (246 mg, 1 mmol) and 4-Me_2NPh-CHO (149 mg, 1 mmol) according to the procedure for the preparation of **8**. The yield was 215 mg (57%), yellow needles (**10**) mp 178-180°C. IR (cm^{-1}): 3095, 2926, 2860 (C-H); 1658/1615 (-CO-CH=CH-); 1580, 1548, 1527 (ring). ^1H NMR and ^{13}C NMR see Table 3. *Anal.* Calcd for $C_{22}H_{23}N_3O_3$ (M 377.44): C, 70.01; H, 6.14; N, 11.13. Found: C, 69.72; H, 5.94; N, 11.41.

(E)-1-(6,7-dimethoxy-2-methylquinazolin-4-yl)-3-(4-nitrophenyl)prop-2-en-1-one (11)

This compound was prepared starting from **2** (246 mg, 1 mmol) and 4-O_2NPh-CHO (151 mg, 1 mmol) according to the procedure for the preparation of **8**. The yield was 258 mg (68%), yellow needles (**11**) mp 195-196°C. IR (cm^{-1}): 3090, 2980, 2848 (C-H); 1674/1610 (-CO-CH=CH-); 1599, 1552, 1523 (ring). ^1H NMR and ^{13}C NMR see Table 3. *Anal.* Calcd for $C_{20}H_{17}N_3O_5$ (M 379.37): C, 63.32; H, 4.52; N, 11.08. Found: C, 63.61; H, 4.24; N, 11.31.

(E)-1-(6,7-dimethoxy-2-methylquinazolin-4-yl)-3-(2-nitrophenyl)prop-2-en-1-one (12)

This compound was prepared starting from **2** (246 mg, 1 mmol) and 2-O_2NPh-CHO (151 mg, 1 mmol) according to the procedure for the preparation of **8**. The yield was 216 mg (57%), yellow needles (**12**) mp 172-193°C. IR (cm^{-1}): 3070, 2923, 2851 (C-H); 1681/1615 (-CO-CH=CH-); 1555, 1506, 1450 (ring). ^1H NMR and ^{13}C NMR see Table 3. *Anal.* Calcd for $C_{20}H_{17}N_3O_5$ (M 379.37): C, 63.32; H, 4.52; N, 11.08. Found: C, 63.59; H, 4.26; N, 11.37.

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