Bioorganic & Medicinal Chemistry 19 (2011) 4399–4404

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry

journal homepage: www.elsevier.com/locate/bmc

Design and synthesis of 4-amino-2-phenylquinazolines as novel topoisomerase I inhibitors with molecular modeling

Thanh Nguyen Le [a], Su Hui Yang [a], Daulat Bikram Khadka [a], Hue Thi My Van [a], Suk Hee Cho [a], Youngjoo Kwon [b], Eung-Seok Lee [c], Kyung-Tae Lee [d], Won-Jea Cho [a,*]

[a] College of Pharmacy and Research Institute of Drug Development, Chonnam National University, Gwangju 500-757, Republic of Korea
[b] College of Pharmacy, Ewha Womans University, Seoul 120-750, Republic of Korea
[c] College of Pharmacy, Yeungnam University, Kyongsan 712-749, Republic of Korea
[d] College of Pharmacy, Kyung-Hee University, Seoul 130-701, Republic of Korea

ARTICLE INFO

Article history:
Received 4 April 2011
Revised 6 May 2011
Accepted 7 May 2011
Available online 20 May 2011

Keywords:
4-Amino-2-phenylquinazolines
Topoisomerase I
Cytotoxicity
Docking study
DNA intercalation

ABSTRACT

4-Amino-2-phenylquinazolines **7** were designed as bioisosteres of 3-arylisoquinolinamines **6** that were energy minimized to provide stable conformers. Interestingly, the 2-phenyl ring of 4-amino-2-phenylquinazolines was parallel to the quinazoline ring and improved their DNA intercalation ability in the DNA–topo I complex. Among the synthesized 4-amino group-substituted analogs, 4-cyclohexylamino-2-phenylquinazoline **7h** exhibited potent topo I inhibitory activity and strong cytotoxicity. Interestingly, consistency was observed between the cytotoxicities and topo I activities in these quinazoline analogs, suggesting that the target of 4-amino-2-phenylquinazolines is limited to topo I. Molecular docking studies were performed with the Surflex–Dock program to afford the ideal interaction mode of the compound into the binding site of the DNA–topo I complex in order to clarify the topo I activity of **7h**.

1. Introduction

Eukaryotic DNA topoisomerase I (topo I) is a crucial enzyme that works to relax supercoiled DNA during replication, transcription, and mitosis.[1] In a number of human solid tumors, the intracellular level of topo I is higher than that in normal tissues, signifying that controlling the topo I level is essential in treating cancers.[2] By stabilizing the cleavable topo I–DNA ternary complex with drug, topo I inhibitors exhibit their antitumor activities. Therefore, topo I enzyme has been considered a promising target for the development of novel cancer chemotherapeutics.[3]

Representative topo I inhibitors, such as topotecan and irinotecan as analogs of camptothecin (CPT), have been launched as clinically used drugs. However, severe drawbacks of these drugs, such as unstable chemical structure and rapid efflux from the cell by membrane pumps, prompted us to develop non-camptothecin topo I inhibitors.[4]

The non-CPT topo I inhibitors include indenoisoquinolines,[5] indolocarbazones,[6] saintopin,[7] benzophenazines,[8] terpyridines,[9] and 3-arylisoquinolines.[10] The X-ray crystal structures of topo I–DNA complex bound to topotecan, indenoisoquinoline, and indolocarbazone have been solved.[11]

We investigated the structure–activity relationships of 3-arylisoquinolinones **1** against human tumor cell lines with molecular modeling study and conducted a diverse modification study of 3-arylisoquinoline skeleton to furnish indeno[1,2-*c*]isoquinolines **2**,[12] isoindolo[2,1-*b*]isoquinolinones **3**,[13] 12-oxobenzo[*c*]phenanthridinones **4**,[14] and benz[*b*]oxepines **5**[15] as the constrained forms of the 3-aryl rings as shown in Figure 1. Most of these 3-arylisoquinoline analogs showed micromolar cytotoxicities against several tumor cell lines as topo I inhibitors.

In this investigation, we observed that the amide carbonyl group of 3-arylisoquinolinone played an important role in the cytotoxicities, and the transformation of the amides to amines increased water solubility while retaining the biological potency. Among the 3-arylisoquinolinamines, **6a** was subjected to in vivo assay using BDF1 mice (P388 leukemia) and afforded 160 *T*/*C*% with low toxicity.[16] The high oral bioavailability and promising pharmacokinetic data of **6a** provided valuable information for studying related compounds.

In general, the binding mode of a drug to its receptor site is influenced by subtle electronic or steric factors, and these two functions play an important role in the bioactive conformation of the drug molecule. Rigid structures are commonly considered to have little conformational entropy compared to flexible molecules and can be more efficiently fitted into the binding site of a receptor.[17] However, additional methylene unit or heteroatoms in a constrained structure affect the physicochemical and/or biological

* Corresponding author. Tel.: +82 62 530 2933; fax: +82 62 530 2911.
E-mail address: wjcho@jnu.ac.kr (W.-J. Cho).

0968-0896/$ - see front matter © 2011 Elsevier Ltd. All rights reserved.
doi:10.1016/j.bmc.2011.05.012

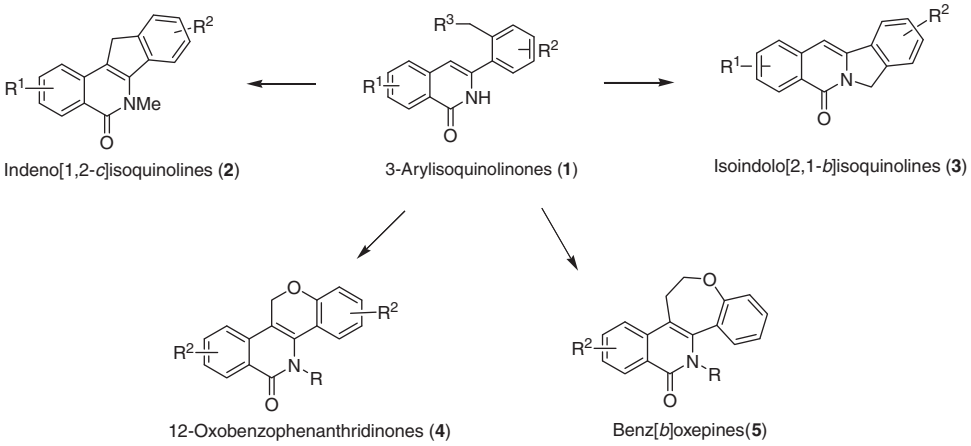


Figure 1. Chemical modification of 3-arylisoquinolinones (**1**) to indeno[1,2-*c*]isoquinolines (**2**), isoindolo[2,1-*b*]isoquinolines (**3**), 12-oxobenzophenanthridinones (**4**) and benz[*b*]oxepines (**5**).

effects, too. We have also observed that the flatness of the compounds provides an advantage for positioning in the topo I–DNA ternary complex due to its DNA intercalating ability.

The X-ray crystallographic structure of 3-arylisoquinoline showed that the torsion angle of the 3-phenyl ring with the isoquinoline plate was 30° and it was not suitable for intercalation into the DNA base pairs.[18]

In the above investigation, we designed the 4-amino-2-phenylquinazolines as the bioisosteres of 3-arylisoquinolines. When 4-amino-2-phenylquinazoline was minimized in Sybyl, the torsion angle of the 2-phenyl ring with the quinazoline ring was only 8.2°, meaning that all pi electrons of the 2-phenyl ring could conjugate with those in the quinazoline template. Moreover, we assumed that the stable conformer of 4-amino-2-phenylquinazolines could be effective as a DNA intercalator in the DNA–topo I complex because they do not contain an extra methylene unit or heteroatoms.

2. Chemistry

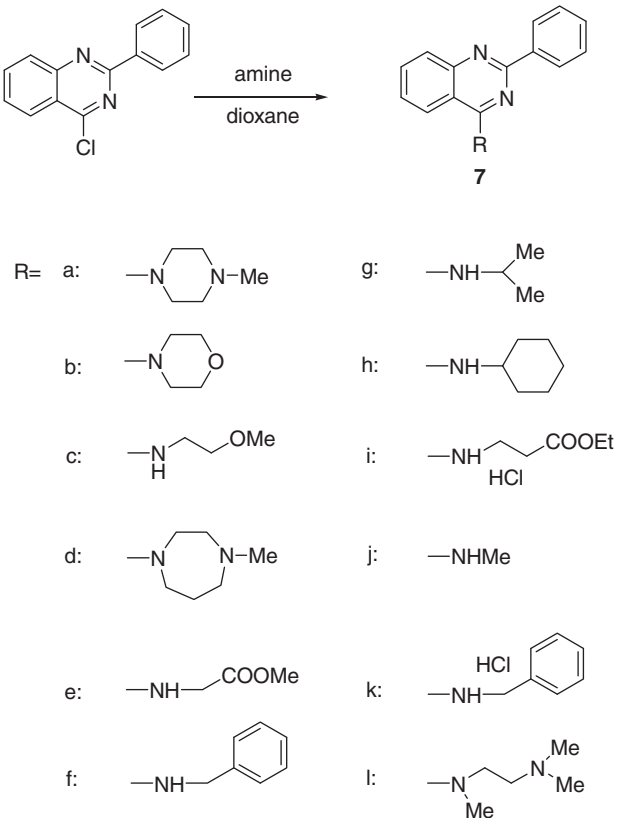
Diverse substitution on C4 was accomplished by the reaction of 4-chloro-2-phenylquinazoline with various amines in dioxane to furnish the desired products in good yield as shown in Scheme 1.

3. Results and discussion

3.1. Biological evaluation

The in vitro cytotoxicity experiments of the synthesized compounds were conducted against four human tumor cell lines including A 549 (lung), SKOV-3 (ovarian), SK-MEL-2 (melanoma), and HCT 15 (colon) cells using sulforhodamine B (SRB) assays.[19]

The topo I inhibitory activity assay was performed using the supercoiled DNA unwinding method.[20] The compounds were dissolved in DMSO at 20 mM as stock solutions. The DNA topo I potency was determined by assessing the relaxation of supercoiled DNA pBR322. A mixture of 200 ng of pBR322 plasmid DNA and 2 units of calf thymus DNA topo I (Fermentas, USA) was incubated without and with the prepared compounds at 37 °C for 30 min in relaxation buffer (35 mM Tris–HCl (pH 8.0), 72 mM KCl, 5 mM $MgCl_2$, 5 mM dithiothreitol, 2 mM spermidine, 0.01% bovine serum albumin). The reaction (final volume: 20 μL) was terminated by adding 5 μL of stop solution containing 10% SDS, 0.2% bromophenol blue, 0.2% xylene cyanol and 30% glycerol. DNA samples were then electrophoresed on 1% agarose gels at 15 V for 6 h in TAE running buffer. Gels were stained for 30 min in an aqueous solution of ethidium bromide (0.5 μg/ml). DNA bands were visualized by transillumination with UV light and were quantitated using Alpha-Imager™ (Alpha Innotech Corporation).



Scheme 1. Synthesis of 4-amino-2-phenylquinazolines (**7a–l**).

In Table 1, the IC_{50} cytotoxicity values obtained with cell lines and the relative topo I activities of the compounds are expressed semi-quantitatively as follows: – no activity, + very weak activity, ++ weak activity, +++ lower activity than CPT, ++++ similar or greater activity than CPT.

As expected, 4-amino-2-phenylquinazolines showed excellent topo I inhibitory activity compared to 3-arylisoquinolinamines as depicted in Figures 2 and 3 and Table 1. In particular, isopropylamino- or cyclohexyl-substituted quinazolines **7g** and **7h** exhibited potent topo I poison (++++) comparable to the representative topo I

Table 1
Synthetic yield, IC_{50} cytotoxicity (μg/mL) and topo I inhibitory activity of the compounds

No.	Compd	Yield	A549	HCT15	OV-3	MEL-2	Topo I[a]
1	**7a**	88	26.88	22.37	26.84	37.04	++
2	**7b**	94	52.76	51.84	56.98	65.23	+++
3	**7c**	90	27.45	26.84	22.90	27.64	+
4	**7d**	88	24.10	20.10	26.10	36.55	+++
5	**7e**	85	36.26	37.46	35.50	37.63	+
6	**7f**	84	15.13	13.91	31.73	31.21	++
7	**7g**	89	7.53	4.11	16.90	16.47	++++
8	**7h**	84	7.23	2.76	9.82	9.63	++++
9	**7i**	88	>100	>100	>100	>100	–
10	**7j**	88	29.32	21.17	33.62	24.36	–
11	**7k**	84	9.79	6.13	9.50	15.78	–
12	**7l**	91	28.13	26.47	25.53	28.92	++
13	Doxorubicin		0.01	0.05	0.08	0.09	
14	Camptothecin		0.072	0.096	1.54	6.88	++++

[a] Activity is expressed semi-quantitatively as follows: – no activity, + very weak activity, ++ weak activity, +++ lower activity than CPT, ++++ similar or greater activity than CPT.

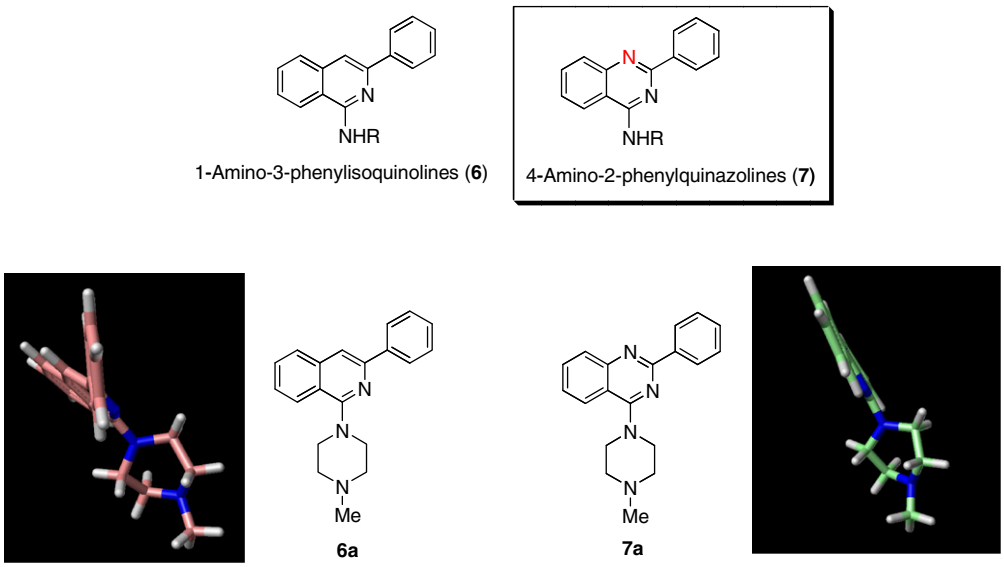


Figure 2. The structures of 1-amino-3-phenylisoquinolines (**6**) and 4-amino-2-phenylquinazolines (**7**). Energy minimized conformers and comparison of torsion angles between *N*-methylpiperazinyl-3-arylisoquinoline (**6a**) and 2-phenyl-4-*N*-methylpiperazinylquinazoline (**7a**).

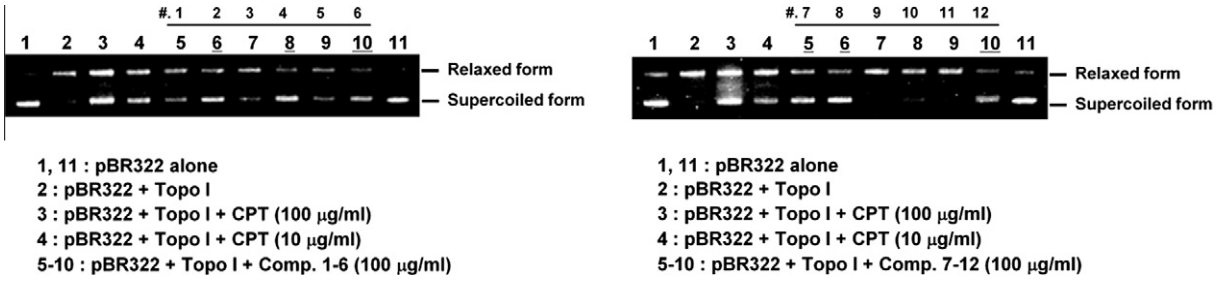


Figure 3. Topo I inhibitory activities of the synthesized quinazolines. Lanes # 1–12 correspond to the synthesized compounds: 1 (**7a**), 2 (**7b**), 3 (**7c**), 4 (**7d**), 5 (**7e**), 6 (**7f**), 7 (**7g**), 8 (**7h**), 9 (**7i**), 10 (**7j**), 11 (**7k**), 12 (**7l**).

inhibitor CPT. Moderate topo I inhibitory activity (+++) was observed in morpholine- or *N*-methylhomopiperazinyl-substituted compounds **7b** and **7d**. Overall, the topo I activities of the heteroatom containing amines such as *N*-methylpiperidine **7a**, methoxyethylamine **7c**, methylacetateamine **7e**, and ethylpropionateamine **7i** were poor. In many cases a discrepancy between the cytotoxicity and topo I poison was reported.[21] This was also observed in indenoisoquinoline and benzazepine derivatives, and it could be explained by problems in drug penetration, cell membrane distribution, and different targets. However, compounds **7g** and **7h** displayed potent cytotoxicities (2.76–16.47 μg/ml) as well as topo I inhibitory activity (++++). Consistency between cytotoxicities and topo I activities was also observed in other poorly active compounds. Based on the observation, we can exclude the possibility of other targets for explaining the cytotoxicities of these 4-amino-2-phenylquinazolines.

3.2. Docking study

The docking study was conducted using Surflex–Dock in Sybyl version 8.1.1 by Tripos Associates, operating under Red Hat Linux 4.0 with an IBM computer (Intel Pentium 4, 2.8 GHz CPU, 1 GB memory).

With the X-ray crystallographic structure of topo I–DNA complex with indenoisoquinoline, docking studies of indenoisoquinolines in the active site have been more realistic than those of molecules at non-clarified binding sites. The structure of the inhibitor **7h** was drawn into the Sybyl package with standard bond lengths and angles, and was minimized using the conjugate gradient method. The Gasteiger–Huckel charge, with a distance-dependent dielectric function, was applied for the minimization of the molecule. We chose the 1SC7 (PDB code) structure from the Protein Data Bank and the structure was modified. The phosphoester bond of G12 in 1SC7 was constructed and the SH of G11 on the scissile strand was changed to OH.

After performing Surflex–Dock, the scores of 10 docked conformers were ranked in a molecular spread sheet. We chose the best total scoring conformer (7.80) and speculated regarding the detailed binding modes in the cavity. The resulting docking model exposed a binding pattern similar to the indenoisoquinoline model.

In this model, the isoquinoline ring intercalated between the −1 and +1 bases, parallel to the plane of the base pairs, and the C-1 nitrogen of 4-amino-2-phenyl-cyclohexylaminoquinazoline **7h** had a H-bond to Arg 364, which is considered an important amino acid that interacts with the ligand in the DNA–topo I active site. In this model, the isoquinoline ring worked as a DNA intercalator. The 4-cyclohexyl amino group of **7h** showed hydrophobic interaction with T 10 methyl group and Ala 351 side chain and seemed to increase the topo I activity of **7h**. Moreover, the 2-phenyl group is positioned to DNA base pairs as the parallel form to the isoquinoline ring of **7h**. Thus, the importance of the DNA intercalation of **7h** and the hydrogen bond was clarified through the molecular docking study. Docking and space filling models of **7h** are shown in Figure 4.

4. Conclusion

In conclusion, we designed the 4-amino-2-phenylquinazolines as bioisosteres of 3-arylisoquinolinamines. The conformers of the energy minimized quinazolines and 3-arylisoquinolines are quite different. Interestingly, the 2-phenyl ring of the 4-amino-2-phenylquinazolines was parallel to the quinazoline ring and improved the DNA intercalation ability in the DNA–topo I complex. Among the synthesized 4-amino group-substituted analogs, 4-cyclohexylamino-2-phenylquinazoline **7h** exhibited potent topo I inhibitory activity as well as strong cytotoxicity. As expected, molecules containing the 4-amino-2-phenylquinazolines exhibited potent topo I inhibitory activities with relatively strong cytotoxicities against four different tumor cell lines. On the other hand, the heteroatom containing amines such as *N*-methylpiperidine **7a**, methoxyethylamine **7c**, methylacetateamine **7e**, and ethylpropionateamine **7i** showed poor topo I poison, even though some of them exhibited strong cytotoxicity. Consistency between cytotoxicities and topo I activities was observed in these series, suggesting that the target of 4-amino-2-phenylquinazolines is limited to topo I enzyme.

Molecular docking studies were performed with the Surflex–Dock program in order to clarify the topo I activity of **7h** and to afford the ideal interaction mode of the compound in the binding site of the DNA–topo I complex.

We found the bioisosteres of 3-arylisoquinolines by inserting nitrogen atom at C-4 and obtained topo I inhibitory activities similar to those of the constrained structures such as indenoisoquinolines, isoindolo[2,1-*b*]isoquinolines, and ben[*b*]oxepines. In further studies of other rigidified structures of 3-arylisoquinolines, structural modifications such as 3,4-diarylation of 3-arylisoquinolines are currently being performed and will be reported in due course.

5. Experimental section

5.1. Chemistry

Melting points were determined by the capillary method on an Electrothermal IA9200 digital melting point apparatus and were uncorrected. Nuclear magnetic resonance (NMR) data for ^{1}H NMR were collected on a Varian 300 FT spectrometer at the Korea Basic Science Institute and were reported in ppm, downfield from the peak of the internal standard, tetramethylsilane. The data are reported as follows: chemical shift, number of protons, multiplicity (s: singlet, d: doublet, t: triplet, q: quartet, m: multiplet, br: broadened). IR spectra were recorded on JASCO-FT IR spectrometer using $CHCl_3$ or KBr pellets. Mass spectra were obtained on JEOL JNS-DX 303 using the electron-impact (EI) method. Column chromatography was performed on Merck silica gel 60 (70–230 mesh). TLC was performed using plates coated with silica gel 60 F254 that were purchased from Merck.

5.2. General procedure for the synthesis of 4-amino-2-phenylquinazolines

A suspension of 4-chloro-2-phenylquinazoline (200 mg, 0.83 mmol) and amine (17 mmol) in dioxane (10 mL) was refluxed

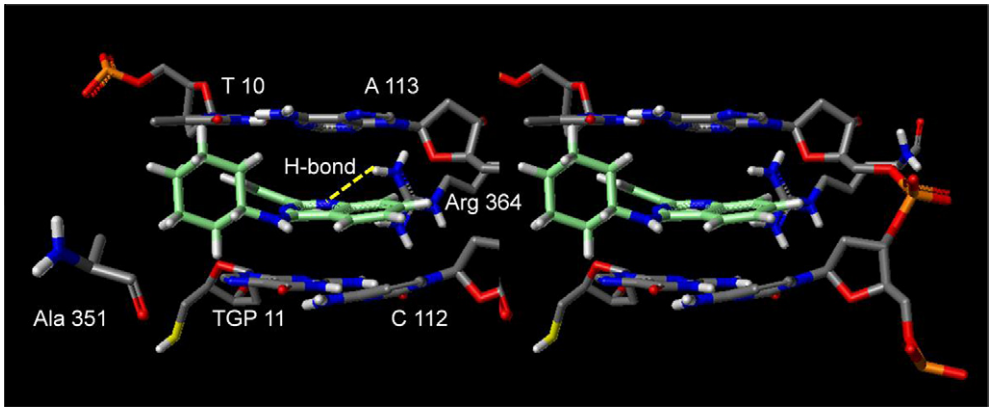


Figure 4. Stereo viewing docked models of **7h** in the active site of DNA–topo I complex.

for 24 h. The reaction was quenched with water and extracted with methylene chloride. The methylene chloride solution was sequentially washed with 5% aqueous NaOH, water, and brine and dried over anhydrous sodium sulfate. After removing the solvent, the residue was separated by column chromatography on silica gel with methylene chloride–methanol (20:1) to give the desired compound. Treatment of the free amine compound with *c*HCl in acetone gave the hydrochloride salt form of the amines as precipitates.

5.2.1. 4-(4-Methylpiperazin-1-yl)-2-phenylquinazoline (7a)

White solid (88%). mp: 92.5–93.5 °C, 270–272 °C (HCl salt). IR (cm^{-1}): 2963, 1557, 1500. ^1H NMR (300 MHz, $CDCl_3$) δ: 8.55 (m, 2H), 7.97 (m, 1H), 7.95 (m, 1H), 7.72 (m, 1H), 7.49–7.40 (m, 4H), 3.90 (t, J = 5 Hz, 4H), 2.67 (t, J = 5 Hz, 4H), 2.39 (s, 3H). Anal. ($C_{19}H_{20}N_4$) C, H, N. EIMS *m/z* (%): 304 (M^+, 3).

5.2.2. 4-Morpholin-4-yl-2-phenylquinazoline (7b)

White solid (94%), IR (cm^{-1}): 2968, 1560, 1500. mp: 124–125 °C, 291–293 °C (HCl salt). ^1H NMR (300 MHz, $CDCl_3$) δ: 8.57–8.54 (m, 2H), 7.98 (m, 1H), 7.88 (m, 1H), 7.73 (m, 1H), 7.50–7.42 (m, 4H), 3.96–3.93 (m, 4H), 3.87–3.83 (m, 4H). Anal. ($C_{18}H_{17}N_3O$) C, H, N. EIMS *m/z* (%): 291 (M^+, 39).

5.2.3. (2-Methoxyethyl)-(2-phenylquinazolin-4-yl)amine (7c)

Yellow solid (90%). mp: 130.5–131.5 °C, 228–230 °C (HCl salt). IR (cm^{-1}): 3355, 2978, 1570, 1533. ^1H NMR (300 MHz, $CDCl_3$) δ: 8.57–8.53 (m, 2H), 7.92 (m, 1H), 7.73–7.68 (m, 2H), 7.50–7.37 (m, 4H), 6.14 (t, J = 4.7 Hz, 1H), 4.01 (q, J = 5.1 Hz, 2H), 3.73 (t, J = 5.1 Hz, 2H), 3.44 (s, 3H). Anal. ($C_{17}H_{17}N_3O$) C, H, N. EIMS *m/z* (%): 279 (M^+, 85).

5.2.4. 4-(4-Methyl-[1,4]diazepan-1-yl)-2-phenylquinazoline (7d)

White solid (88%). mp: 81–83 °C. IR (cm^{-1}): 2962, 1557, 1500. ^1H NMR (300 MHz, $CDCl_3$) δ: 8.57–8.52 (m, 2H), 7.97–7.91 (m, 2H), 7.68 (m, 2H), 7.50–7.38 (m, 4H), 4.19 (m, 2H), 4.09 (t, J = 5 Hz, 2H), 3.00 (m, 2H), 2.68 (m, 2H), 2.42 (s, 3H), 2.23 (m, 2H). Anal. ($C_{20}H_{22}N_4$) C, H, N. EIMS *m/z* (%): 318 (M^+, 40).

5.2.5. (2-Phenylquinazolin-4-ylamino)acetic acid methyl ester (7e)

White solid (85%). mp: 140–141 °C, 235–237 °C (HCl salt). IR (cm^{-1}): 1342, 1728, 1571, 1531. ^1H NMR (300 MHz, $CDCl_3$) δ: 8.57–8.54 (m, 2H), 7.92 (m, 1H), 7.81–7.70 (m, 2H), 7.49–7.40 (m, 4H), 6.49 (t, J = 4.8 Hz, 1H), 4.52 (d, J = 4.8 Hz, 2H), 3.84 (s, 3H). EIMS *m/z* (%): 293 (M^+, 44).

5.2.6. Benzyl(2-phenylquinazolin-4-yl)amine (7f)

White solid (84%). mp: 121.5–123.5 °C, 272–274 °C (HCl). IR (cm^{-1}): 3300, 1561, 1530. ^1H NMR (300 MHz, $CDCl_3$) δ: 8.59–8.55 (m, 2H), 7.93 (m, 1H), 7.73–7.70 (m, 2H), 7.48–7.37 (m, 9H), 5.96 (t, 1H), 5.02 (t, J = 5.4 Hz, 2H). Anal. ($C_{21}H_{17}N_3$) C, H, N. EIMS *m/z* (%): 311 (M^+, 78).

5.2.7. Isopropyl(2-phenylquinazolin-4-yl)amine (7g)

Yellow solid (89%). mp: 147–148 °C, 280–282 °C (HCl salt). IR (cm^{-1}): 3285, 2964, 1566, 1524. ^1H NMR (300 MHz, $CDCl_3$) δ: 8.58–8.55 (m, 2H), 7.90 (m, 1H), 7.73–7.66 (m, 2H), 7.49–7.42 (m, 4H), 5.48 (d, 1H), 4.73 (m, 1H), 1.41 (d, J = 5 Hz, 6H). Anal. ($C_{17}H_{17}N_3$) C, H, N. EIMS *m/z* (%): 263 (M^+, 36).

5.2.8. Cyclohexyl(2-phenylquinazolin-4-yl)amine (7h)

White solid (84%). mp: 154–155 °C, 262–264 °C. IR (cm^{-1}): 3300, 1561, 1530. ^1H NMR (300 MHz, $CDCl_3$) δ: 8.56–8.53 (m, 2H), 7.90 (m, 1H), 7.72–7.65 (m, 2H), 7.49–7.39 (m, 4H), 5.54 (d, 1H), 4.41 (m, 1H), 2.25 (m, 2H), 1.87–1.31 (m, 8H). Anal. ($C_{20}H_{21}N$) C, H, N. EIMS *m/z* (%): 303 (M^+, 10).

5.2.9. 3-(2-Phenylquinazolin-4-ylamino)propionic acid ethyl ester (7i)

Oil (88%). mp: 268–270 °C (HCl salt). IR (cm^{-1}): 3402, 1728, 1571, 1531. ^1H NMR (300 MHz, $CDCl_3$) δ: 8.57–8.53 (m, 2H); 7.91 (m, 1H); 7.73–7.68 (m, 2H); 7.49–7.39 (m, 4H); 6.51 (t, J = 5.7 Hz, 1H); 4.15 (q, J = 6 Hz, 2H); 4.09 (q, J = 7.2 Hz, 2H); 2.81 (t, J = 6 Hz, 2H); 1.25 (t, J = 7.2 Hz, 3H). HRMS-EI (Calcd for C_{18} H_{17} N_3O_2): 307.3551. Found: 307.3556. EIMS *m/z* (%): 307 (M^+, 65).

5.2.10. Methyl(2-phenylquinazolin-4-yl)amine (7j)

White solid (81%). mp: 94–96 °C, 297–299 °C (HCl salt). IR (cm^{-1}): 3340, 2956, 1570, 1527. ^1H NMR (300 MHz, $CDCl_3$) δ: 8.60–8.56 (m, 2H), 7.90 (m, 2H), 7.69–7.63 (m, 1H), 7.49–7.34 (m, 4H), 5.83 (d, J = 4.2 Hz, 1H), 3.28 (d, J = 4.2 Hz, 2H). Anal. ($C_{15}H_{13}N_3$) C, H, N. EIMS *m/z* (%): 235 (M^+, 48).

5.2.11. *N,N,N′*-Trimethyl-*N′*-(2-phenylquinazolin-4-yl)ethane-1,2-diamine (7l)

Oil (91%). mp: 286–288 °C (HCl salt). IR (cm^{-1}): 2963, 1557, 1500. ^1H NMR (300 MHz, $CDCl_3$) δ: 8.56–8.52 (m, 2H), 8.01 (m, 1H), 7.92 (m, 1H), 7.68 (m, 1H), 7.48–7.34 (m, 4H), 3.94 (t, J = 8 Hz, 2H), 3.46 (s, 3H), 2.79 (d, J = 8 Hz, 2H), 2.34 (s, 6H). HRMS-EI (Calcd for C_{19} H_{22} N_4): 306.4139. Found: 306.4135. EIMS m/*z* (%): 306 (M^+, 28).

Acknowledgment

This work was supported by Korea Research Foundation grant (KRF-2009-0071379).

References and notes

1. (a) Wang, J. C. *Annu. Rev. Biochem.* **1996**, *65*, 635; (b) Liu, L. F. *Annu. Rev. Biochem.* **1989**, *58*, 351.
2. Liew, S. T.; Yang, L. X. *Curr. Pharm. Des.* **2008**, *14*, 1078.
3. (a) Takagi, K.; Dexheimer, T. S.; Redon, C.; Sordet, O.; Agama, K.; Lavielle, G.; Pierre, A.; Bates, S. E.; Pommier, Y. *Mol. Cancer Ther.* **2007**, *6*, 3229; (b) Bjornsti, M. A.; Benedetti, P.; Viglianti, G. A.; Wang, J. C. *Cancer Res.* **1989**, *49*, 6318; (c) Hsiang, Y. H.; Liu, L. F. *Cancer Res.* **1988**, *48*, 1722.
4. Gounder, M. K.; Nazar, A. S.; Saleem, A.; Pungaliya, P.; Kulkarni, D.; Versace, R.; Rubin, E. H. *Invest. New Drugs* **2008**, *26*, 205.
5. (a) Meng, L. H.; Liao, Z. Y.; Pommier, Y. *Curr. Top. Med. Chem.* **2003**, *3*, 305; (b) Morrell, A.; Antony, S.; Kohlhagen, G.; Pommier, Y.; Cushman, M. *J. Med. Chem.* **2006**, *49*, 7740; (c) Nagarajan, M.; Morrell, A.; Ioanoviciu, A.; Antony, S.; Kohlhagen, G.; Agama, K.; Hollingshead, M.; Pommier, Y.; Cushman, M. *J. Med. Chem.* **2006**, *49*, 6283.
6. Yamashita, Y.; Fujii, N.; Murakaya, C.; Ashizawa, T.; Okabe, M.; Nakano, H. *Biochemistry* **1992**, *31*, 12069.
7. Yamashita, Y.; Kawada, S.; Fujii, N.; Nakano, H. *Biochemistry* **1991**, *30*, 5838.
8. Vicker, N.; Burgess, L.; Chuckowree, I. S.; Dodd, R.; Fokes, A. J.; Hardick, D.; Hancox, T. C.; Miller, W.; Milton, J.; Sohal, S.; Wang, S.; Wren, S. P.; Charlton, P. A.; Dangerfield, W.; Liddle, C.; Mistry, P.; Stewart, A. J.; Denny, W. A. *J. Med. Chem.* **2002**, *45*, 721.
9. Thapa, P.; Karki, R.; Thapa, U.; Jahng, Y.; Jung, M. J.; Nam, J. M.; Na, Y.; Kwon, Y.; Lee, E.-S. *Bioorg. Med. Chem.* **2010**, *18*, 377.
10. Cho, W. J.; Min, S. Y.; Le, T. N.; Kim, T. S. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 4451.
11. Staker, B. L.; Feese, M. D.; Cushman, M.; Pommier, Y.; Zembower, D.; Stewart, L.; Burgin, A. B. *J. Med. Chem.* **2005**, *48*, 2336.
12. (a) Van, H. T. M.; Le, Q. M.; Lee, K. Y.; Lee, E. S.; Kwon, Y.; Kim, T. S.; Le, T. N.; Lee, S. H.; Cho, W. J. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 5763; (b) Cho, W. J.; Le, Q. M.; Van, H. T. M.; Lee, K. Y.; Kang, B. Y.; Lee, E. S.; Lee, S. K.; Kwon, Y. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 3531.
13. Van, H. T. M.; Cho, W. J. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 2551.
14. Lee, S. H.; Van, H. T. M.; Yang, S. H.; Lee, K. T.; Kwon, Y.; Cho, W. J. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 2444.
15. Khadka, B. K.; Cho, W. J. *Bioorg. Med. Chem.* **2011**, *19*, 724.
16. Kim, K. E.; Cho, W.-J.; Chang, S. J.; Yong, C. S.; Lee, C. H.; Kim, D. D. *Int. J. Pharm.* **2001**, *217*, 101.
17. Merabet, N.; Dumond, J.; Collinet, B.; Van Baelinghem, L.; Boggetto, N.; Ongeri, S.; Ressad, F.; Reboud-Ravaux, M.; Sicsic, S. *J. Med. Chem.* **2004**, *47*, 6392.
18. Cho, W. J.; Kim, E. K.; Park, I. Y.; Jeong, E. Y.; Kim, T. S.; Le, T. N.; Kim, D. D.; Lee, E. S. *Bioorg. Med. Chem.* **2002**, *10*, 2953.

19. Rubinstein, L. V.; Shoemaker, R. H.; Paull, K. D.; Simon, R. M.; Tosini, S.; Skehan, P.; Scudiero, D. A.; Monks, A.; Boyd, M. R. *J. Natl. Cancer Inst.* **1990**, *82*, 1113.
20. Zhao, L. X.; Moon, Y. S.; Basnet, A.; Kim, E. K.; Jahng, Y.; Park, J. G.; Jeong, T. C.; Cho, W. J.; Choi, S. U.; Lee, C. O.; Lee, S. Y.; Lee, C. S.; Lee, E. S. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 1333.
21. (a) Fox, B. M.; Xiao, X.; Antony, S.; Kohlhagen, G.; Pommier, Y.; Staker, B. L.; Stewart, L.; Cushman, M. *J. Med. Chem.* **2003**, *46*, 3275; (b) Morrell, A.; Antony, S.; Kohlhagen, G.; Pommier, Y.; Cushman, M. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 1846.