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ARTICLE *in* BIOORGANIC & MEDICINAL CHEMISTRY LETTERS · APRIL 2013

Impact Factor: 2.42 · DOI: 10.1016/j.bmcl.2013.03.107 · Source: PubMed

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Synthesis, single crystal and antitumor activities of benzimidazole–quinazoline hybrids

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ARTICLE INFO

Article history:
Received 11 February 2013
Revised 16 March 2013
Accepted 26 March 2013
Available online 3 April 2013

Keywords:
Cancer
Quinazoline
Benzimidazole
Regioisomers
Antitumor activity
Docking

ABSTRACT

A series of novel regioisomeric hybrids of quinazoline/benzimidazole viz. (3-allyl-2-methyl-3*H*-benzimidazol-5-yl)-(2-substituted-quinazolin-4-yl)-amine and (1-allyl-2-methyl-1*H*-benzimidazol-5-yl)-(2-substituted-quinazolin-4-yl)-amine of biological interest were synthesized. All the synthesized compounds were well characterized by ^{1}H and ^{13}C NMR as well as mass spectroscopy. The newly synthesized compounds were screened for in vitro antitumor activities against 60 tumor cell lines panel assay. A significant inhibition for cancer cells were observed with compound **9** and also more active against known drug 5-fluorouracil (5-FU) in some tumor cell lines. Compound **9** displayed appreciable anticancer activity against leukemia, colon, melanoma, renal and breast cancer cell lines.

The development of new anti-cancer therapeutic tools has advanced greatly in the past decade; thus approaches for the treatment of cancer have moved towards targeting the specific molecular alterations that occur in tumor cells. This approach has been concentrated on the development of both small molecules and biological agents that have shown remarkable clinical activity without toxicity associated with conventional chemotherapy.[1] Many of chemotherapeutics currently used in cancer therapy are agents which inhibit tumor growth by inhibiting the replication and transcription of DNA. The practice of chemotherapy of cancer suffers from various drawbacks viz. the participation of a number of enzymes like ribonucletides reductase (RNR), topoisomerase I (Topo I) and topoisomerase II (Topo II) etc. at different stages of development of cancer,[2] survival of cancer cells even under anaerobic conditions,[3] and ultimately the problem of multidrug resistance[4] developed in the cancerous cells towards chemotherapeutic agents. The wide occurrence of the heterocycles in bioactive natural products made them important synthetic targets. Fused pyrimidines have drawn the attention of medicinal chemists as chemotherapeutic agents, where several member of this class has earned valued places in chemotherapy as effective agents.[5] Quinazoline derivatives have attracted attention due to their broad range of pharmacological activities, which include antifungal,[6] antimalarial,[7] anti-inflammatory,[8] anticonvulsant,[9] antibacterial,[10] antihypertensive[11] and anticancer.[12,13] Several of these compounds exhibited dihydrofolate reductase and tyrosine kinase[14] inhibitors such as erlotinib, gefitinib, caneratinib, vandetanib and lapatinib (Chart 1). Some quinazoline derivatives interact with tubulin[15] and interfere with its polymerization, others act by modulating aurora kinase activity[16] or have an effect in critical phases in the cell cycle[17] or act as apoptosis inducers.[18] The reported significance of such synthons generated the interest to exploit this valuable structure in the designing and synthesis of new quinazoline analogue as antitumor agents.

Benzimidazole, a heteroaromatic organic compound also created an interest in medicinal and biological properties such as antitumor,[19] antibacterial,[20] antihypertensive,[21] anti-inflammatory,[22] vasodilator[23] and antiviral[24] agents. Benzimidazole derivatives are known inhibitors of cyclin dependent kinase or tyrosine kinase and are useful for inhibiting cell proliferation for the treatment of cancer.[25] Due to structural similarity of benzimidazole nuclei with some naturally occurring compounds such as purine, they can easily interact with biomolecules of the living systems.

In the present investigation, we have combined the structural artifacts of benzimidazole and quinazoline moieties as hybrid and substituted them with secondary amines in order to observe the effect of electron-donor and acceptor nitrogen groups within the moieties. Introduction of alkyl or allyl groups on benzimidazole and aryl groups of quinazoline moiety are also known to increase lipid solubility of polar compounds, a character very much needed for the activity (Fig. 1).

To achieve the targets, we have synthesized a new series of regioisomeric hybrids, (3-allyl-2-methyl-3*H*-benzimidazol-5-yl)-

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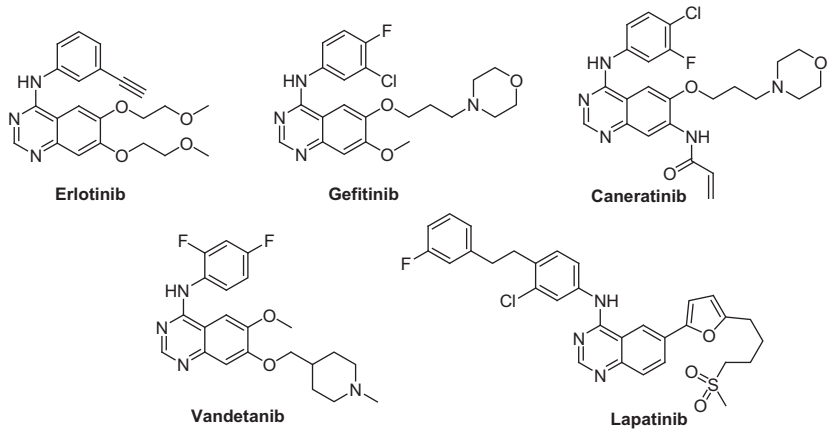


Chart 1.

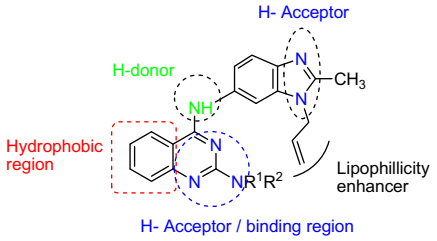


Figure 1. Proposed hypothetic model for hybrid compounds.

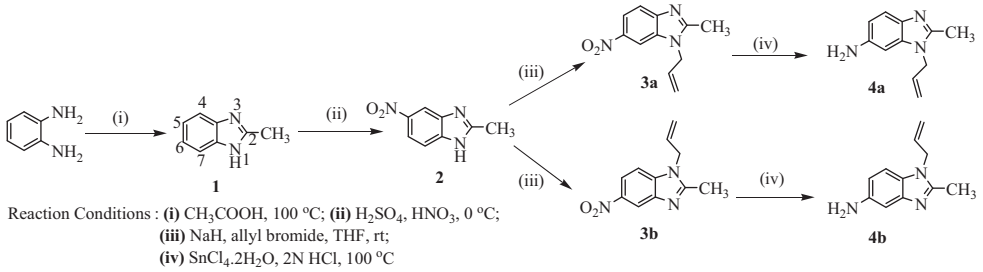
(2-substituted-quinazolin-4-yl)-amine and (1-allyl-2-methyl-1*H*-benzimidazol-5-yl)-(2-substituted-quinazolin-4-yl)-amine and evaluated for their anticancer activity against 60 tumor cell lines. The thrust of efforts in the derivatization of such type of compounds focused mainly on the secondary amines at 2-position of quinazoline to find out an active antitumor agent with potentiated activity and selectivity toward cancerous cells.

Schemes 1 and 2 outlines the synthetic pathways to obtain compounds **4a**–**b** and **8**–**13** respectively. Treatment of *o*-phenylenediamine with acetic acid at 100 °C for 24 h followed by nitration with equal amounts nitric acid and sulfuric acid at 0 °C for 5 h to obtain 2-methyl-5-nitro-1*H*-benzimidazole (**2**)[26] with 80% yield. Treatment of compound **2** with allyl bromide in the presence of sodium hydride and THF at room temperature for 8 h got a mixture of 1-allyl-2-methyl-5-nitro-1*H*-benzimidazole (**3a**) and 1-allyl-2-methyl-6-nitro-1*H*-benzimidazole (**3b**). Reduction of **3a** and **3b** with stannous chloride and 2 N HCl at 110 °C for 7 h afforded regioisomeric 3-allyl-2-methyl-3*H*-benzimidazol-5-ylamine (**4a**) with 65% yield (mp = 137–139 °C) and 1-allyl-2-methyl-1*H*-benzimidazole-5-ylamine (**4b**) with 25% yield (mp = 137–139 °C) (Scheme 1). Appearance of 2*H* broad singlet at δ 3.56 and 3.74 (exchangeable with D_2O) in ^{1}H NMR spectra and two NH_2 stretchings at 3380, 3270 and 3380, 3272 cm^{-1} in IR spectra confirmed the structures of **4a** and **4b** respectively.

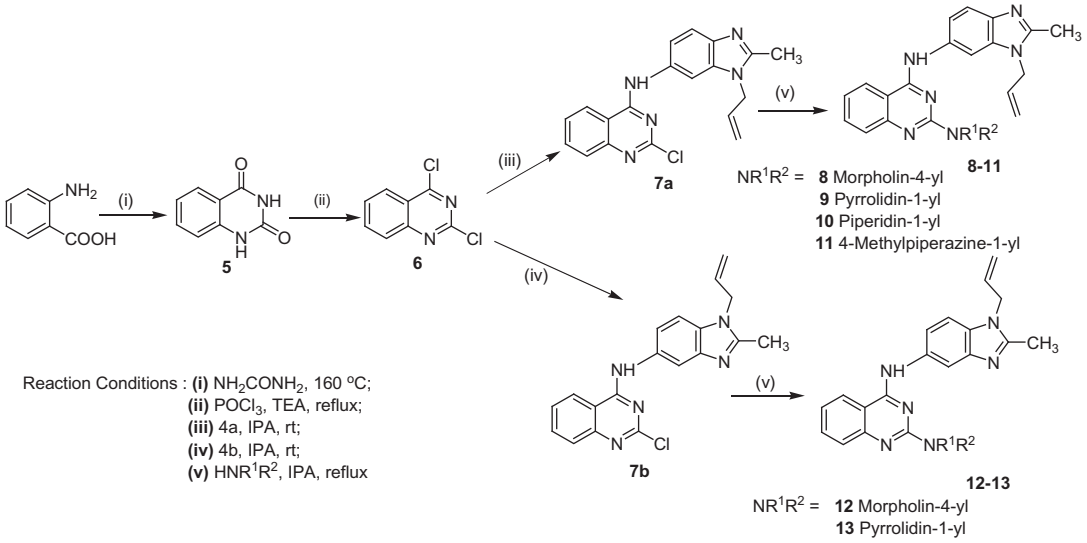
For target compounds **8**–**13**, 2,4-dichloroquinazoline (**6**)[27] was treated separately with **4a** and **4b** in isopropyl alcohol (IPA) at room temperature for 8–12 h afforded (3-allyl-2-methyl-3*H*-benzimidazol-5-yl)-(2-chloro-quinazolin-4-yl)-amine (**7a**) with 92% yield (mp = 210–215 °C) and (1-allyl-2-methyl-1*H*-benzimidazol-5-yl)-(2-chloro-quinazolin-4-yl)-amine (**7b**) with 82% yield (mp = 217–220 °C) respectively. IR spectra of these compounds showed NH stretching at 3258 and 3252 cm^{-1}, respectively. Compounds **7a** was refluxed with 1.2 equiv. of morpholine-4-yl in IPA for 7–8 h and after column chromatography gave solid pure compound **8** (Scheme 2). The presence of 4*H* singlet at δ 3.88 (O-morCH$_2$), 4*H* triplet at δ 3.76 (N-morCH$_2$) in ^{1}H NMR spectrum and signals at δ 65.7 (O-morCH$_2$), 46.5 (N-morCH$_2$) in ^{13}C NMR spectrum confirmed the synthesis of **8**.

Similarly, compounds **7a** and **7b** were further reacted with secondary amines at the same reaction conditions gave pure compounds **9**–**11** and **12**–**13** respectively.

Structures of all novel compounds were similarly confirmed by NMR and mass spectroscopic techniques (Supplementary data). Complete and unambiguous assignments for all ^{1}H and ^{13}C resonances could be achieved on the basis of chemical shift considerations, coupling information and NOE difference spectra. Discrimination between **8**–**11** and **12**–**13** were achieved by considering 2D NOE difference experiments (positive NOEs on signals of N-CH$_2$ protons due to the allyl chain and singlet of aromatic ring of benzimidazole with compounds **8**–**11**, and positive NOE's on signal of N-CH$_2$ protons due to the allyl chain and doublet of aromatic ring of benzimidazole and negative NOE with singlet of compounds **12**–**13** as shown in Fig. 2) and energy minimized structures (allyl group approaching towards the singlet of aromatic ring of



Scheme 1. Synthetic route for the preparation of compounds **4a** and **4b**.



Scheme 2. Synthetic route for the preparation of target compounds (**8**–**13**).

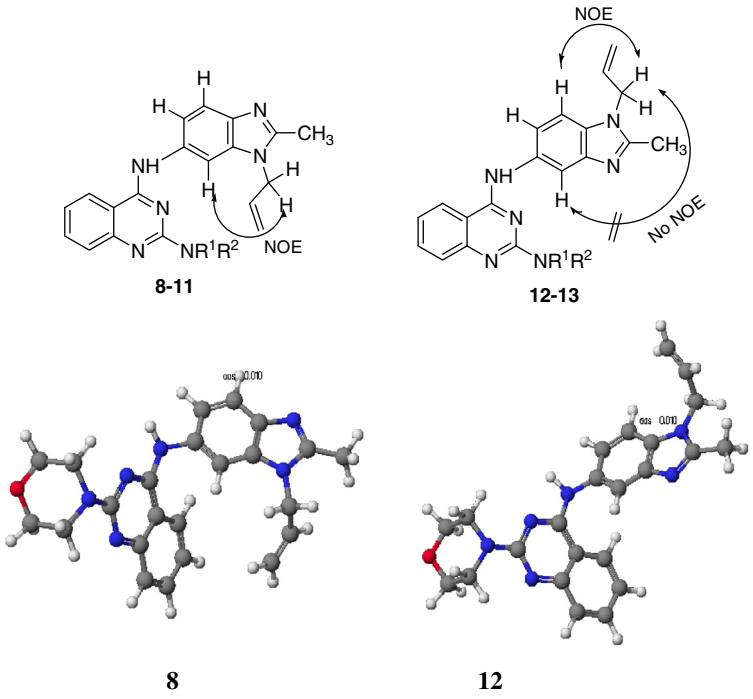


Figure 2. 2D NOEs ^{1}H, ^{1}H correlations used for structural assignment of compounds **8**–**11**, **12**–**13** (upper), energy minimization of **8** and **12** (lower).

benzimidazole in **8** and allyl group is near to doublet of aromatic ring of benzimidazole in **12**).

Moreover, the structure of compound **12** was confirmed by measuring X-ray crystallography.[28] In the crystal structure of the compound, it crystallizes with $Z = 4$ in the space group $P2_1/c$ (Table 1). The molecular solid state structure and numbering system is indicated in Figure 3. Molecule presents certain disorder in the terminal allyl group. Thus there is some ambiguity in the atomic positions of the allyl group. These disorders are expected due to the conformational flexibility of the allyl fragment. The six-membered morpholine ring is positioned planar to the quinazoline ring that exists in chair conformation. Atom system C13–O1–C12 is in regular tetrahedron sp^3 angle of 109.5°. Atom system C14–N6–C11 having some angle strain, deviated by 4.1° from the ideal value (angle strain is calculated as the difference between internal angle and the ideal sp^3 angle of 109.5°). The structure of the compound **12** shown in Fig. 3 is more likely on the basis of standard bond distances and angles.

The benzimidazole ring is deviated from the planar quinazoline by 19.9°. The bond length of two C–N bonds linking between benzimidazole and quinazoline are differ, with the short C16–N3 [1.359 (4) Å] bond having a double-bond character compared with the longer N3–C8 [1.419 (4) Å] on benzimidazole side. It is indicated that the two carbon atom (C16 and C8) in the molecule occupy anti-positions relative to the mean plane of the ring system. This anti-position of both carbon atoms in each molecule is one of the reason which makes the two rings are non planar. The crystal structure revealed that conformation morpholine was approaching

Table 1
Summary of crystal data, data collection and structure refinement for compound **12**

A. Crystal data	
Empirical formula	$C_{23}H_{24}N_6O$
Formula weight	400.48
Crystal color, habit	Colorless, Crystals
Crystal dimensions	0.23 × 0.18 × 0.13 mm
Crystal system	Monoclinic
Lattice parameters	a = 6.3175 (2) Å b = 23.8231 (6) Å c = 14.1809 (4) Å α = 90.0° β = 98.004 (3)° γ = 90.0°, V = 2113.47 (10) Å^3
Space group	$P2_1/c$
Z value	4
D_{calcd}	1.259 Mg/m^3
F (000)	848
μ (Mo K_a)	0.081 mm^{-1}
Mo K_a radiation, λ	0.7107 cm^{-1}
T	150 (2) K
B. Data collection and refinement	
Diffractometer	Crystalispro, Agilent Technology CCD
Structure solution	Direct methods
Radiation	MoK_α (λ = 0.7107 Å) Graphite monochromated
Radiation source	Fine-focus sealed tube
$2\theta_{max}$	32.267°
No. of reflections measured	Total: 16020 Unique: 3720 (R_{int} = 0.0278)
Absorption corrections	Semi-emipirical from equivalents
Max. and min. transmission	0.9895 and 0.9815
Refinement method	Full-matrix least-square on F 2
Data/restraints/parameters	3720/29/292
Final R indices [I > 2sigma(I)]	R_1 = 0.0530, wR_2 = 0.1472
R indices (all data)	R_1 = 0.0635, wR_2 = 0.1577
Goodness of fit on F2	1.026
Extinction coefficient	0.011 (3)
Largest diff. peak and hole	0.302 and −0.345 eA^{-3}

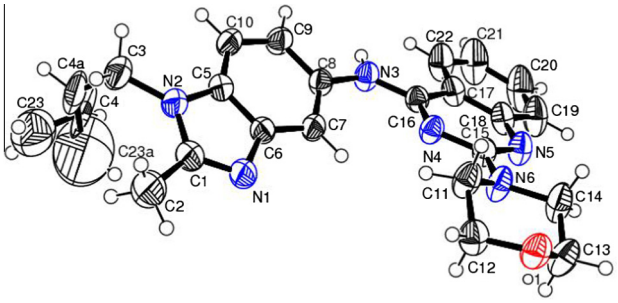


Figure 3. ORTEP diagram of compound **12** (CCDC 928250).

to the benzimidazole moiety. The bond length of N1–C1 [1.314 (5)] of benzimidazole ring is shorter having double bond character than that longer bond length of C1–N2 [1.369 (5)] indicate the presence of allyl group at N2 position and quinazoline attached at the 5-position of benzimidazole (C8).

Seven out of eight synthesized compounds (**7a–b**, **8–9**, **11–13**) (Table 2) were subjected to the National Cancer Institute (NCI), Bethesda, Maryland, USA on the basis of degree of structure variation and computer modeling techniques for disease-oriented human cell lines screening assay for their in vitro antitumor activities.[29–31] A single dose (10 μM) of the test compounds were used in the full NCI 60 cell lines panel assay which includes nine tumor subpanels namely; leukemia, non-small cell lung, colon, CNS, melanoma, ovarian, renal, prostate and breast cancer cells. The data reported as mean-graph of the percent growth of the treated cells and presented as percentage growth inhibition (GI%).

Preliminary in vitro antitumor screening revealed that only compounds **8** and **9** showed significant growth inhibition (more than 60%) for most of the cancer cell lines. On the contrary the percentage inhibition of compounds **7a–b** and **11–13** did not reach 50%. This shows that the presence of secondary amine (morpholine or pyrrolidine) is essential in place of chloro at 2-position of quinazoline for activity of compounds.

Regarding the activity toward individual cell lines; all compounds showed selective potency toward renal cancer cells A498 with GI values of 44.5%, 31.5%, 41.1%, 28.5%, 20.7%, and 27.6% of respective compounds **7a**, **7b**, **8**, **9**, **12** and **13**. Leukemia cancer cells HL-60 (TB) proved to be selective sensitive to **8** with GI value of 61.9%. Compound **9** showed selectivity toward leukemia cancer cells K-562, MOLT-4, RPMI-8226 and SR with GI values of 98.0%, 50.0%, 45.0% and 94.2% respectively, colon cancer cells COLO 205, HCC-2998 and HT29 with GI values of 76.6%, 80.3% and 94.3% respectively, melanoma cancer cell LOX IMVI with GI value of 97.5% and breast cancer cell MDA-MB-231/ATCC with GI value of 58.0%. Compound **9** showed higher activity than 5-fluorouracil in leukemia cancer cells (K-562, MOLT-4, RPMI-8226 and SR), colon cancer cells (HCC-2998, HCT-116 and HT-29) and melanoma (LOX IMVI and SK-MEL-5). In addition compound **11** showed sensitivity to leukemia cancer cell MOLT-4, non-small cell lung cancer cell HOP-92 and colon cancer cell HT29 having GI values of 43.1%, 42.4% and 42.6% respectively. From Table 2, it is revealed that compound **9** is more active towards numerous cancer cell lines belonging to different tumor subpanels.

On the basis of these activities, it has been proved that (3-allyl-2-methyl-3*H*-benzimidazol-5-yl)-(2-amino-quinazolin-4-yl)-amine (**8–9**, **11**) are more active antitumor agents than their regioisomeric analogue (1-allyl-2-methyl-1*H*-benzimidazol-5-yl)-(2-amino-quinazolin-4-yl)-amine (**12–13**). Substitution of chloro (**7a**) with secondary amines such as morpholin-4-yl (**8**) and 4-methylpiperzin-1-yl (**11**) did not improve their activity much. But substitution of chloro (**7a**) with pyrrolidin-1-yl (**9**) proved the remarkably activity as antitumor agents. Similarly compound **7b** showed activity in some of the tumor cell lines but substitution at 2-position of quinazoline with morpholin-4-yl (**12**) and pyrrolidin-1-yl (**13**) decreased its potency. Thus, allyl group of benzimidazole approached towards the secondary amine at 2-position of quinazoline (**9**) showed higher activity than on the opposite side (**13**).

We have observed the compliance of compounds by determining the lipophilicity via 'Shake Flask' method[32] (Supplementary data). Within the series of two chloro isomers, **7a** showed higher log*P* value than **7b**. Introduction of secondary substituted amines at 2-position of quinazoline moiety resulted in increase of log*P* value (lipophilicity). From Table 3, it is clear that lipophilicity is a crucial factor for the activity amongst the synthesized compounds in this series as compound **9** has higher log*P* value which corresponds to higher antitumor activity.

In vitro evaluation of compound **9** exhibited remarkable anticancer activity towards leukemia cancer cell lines as shown in Table 2. So we have performed docking experiments with ribonucleotide reductase (RNR), topoisomerase I (Topo I) and topoisomerase II (Topo II) that possesses potent chemotherapeutic efficacy against leukemia.[33] We have carried out docking[34] of most active compound **9** in the active site ribonucleotide reductase (enzyme responsible for DNA replication, pdb ID 4R1R), topoisomerase I (pdb ID 1A36) and topoisomerase II (pdb ID 1BJT). Docking of compound **9** in the active site of RNR showed H-bond interactions between N atom of quinazoline moiety with F1023 amino acid residue of active site, N atom of pyrrolidine moiety with F1023 and T1025 amino acid residue and NH group with Q294 amino acid residue (Fig. 4). Similarly compound **9** was also docked with active site of topoisomerase I and II (another enzyme involved in the propagation of cancer, synthesis of raw material for replication of

Table 2
The percentage growth inhibition (GI%) of the selected compounds over the full panel of tumor cell lines

Cell line type	Cell line name	**7a**	**7b**	**8**	**9**	**11**	**12**	**13**	5-FU
Leukemia	CCRF-CEM	Nt	Nt	Nt	Nt	31.5	Nt	Nt	57.1
	HL-60(TB)	15.9	–	61.9	11.5	–	13.5	–	47.9
	K-562	25.2	21.3	35.6	98.0	37.8	–	14.9	42.3
	MOLT-4	21.3	–	nt	50.0	43.1	–	–	43.1
	RPMI-8226	24.7	22.3	nt	45.0	28.5	13.4	12.2	41.4
	SR	–	–	–	94.2	nt	–	11.0	24.8
Non-small cell lung cancer	A549/ATCC	18.5	–	11.8	25.4	–	–	10.1	34.2
	EKVX	–	17.2	–	–	nt	–	–	58.4
	HOP-62	–	–	–	–	11.3	–	–	47.8
	HOP-92	–	–	–	18.6	42.4	-	15.5	50.6
	NCI-H226	–	17.8	–	–	13.6	–	22.0	69.5
	NCI-H23	–	–	–	11.3	19.2	–	–	39.0
	NCI-H322M	–	–	–	–	–	–	–	59.5
	NCI-H460	–	–	–	18.7	–	–	–	13.0
	NCI-H522	–	–	–	–	–	–	–	58.0
Colon cancer	COLO 205	–	–	–	–	23.6	–	Nt	40.2
	HCC-2998	–	–	–	76.6	–	–	–	L
	HCT-116	–	–	–	80.3	33.0	–	–	17.8
	HCT-15	–	–	–	20.6	10.1	–	–	26.5
	HT29	–	–	34.7	94.3	42.6	–	–	27.1
	KM12	–	–	11.9	29.9	20.5	–	–	40.7
	SW-620	–	–	–	24.9	–	–	–	50.1
CNS cancer	SF-268	10.1	–	–	13.1	–	–	–	59.0
	SF-295	15.2	10.3	–	16.3	–	–	–	69.1
	SF-539	–	–	–	–	23.5	–	–	L
	SNB-19	–	–	–	–	–	–	–	65.9
	SNB-75	–	–	12.6	16.3	17.6	–	–	65.9
	U251	–	–	–	–	10.2	–	–	50.3
Melanoma	LOX IMVI	–	–	–	97.5	18.0	–	–	30.4
	MALME-3M	–	Nt	–	–	–	Nt	–	58.2
	M14	–	–	–	10.3	–	–	–	Nt
	MDA-MB-435	–	–	–	–	–	–	–	36.6
	SK-MEL-2	–	–	–	–	–	–	–	95.5
	SK-MEL-28	–	–	–	19.8	–	–	–	Nt
	SK-MEL-5	–	–	–	37.6	18.3	–	–	33.7
	UACC-257	–	–	–	–	–	–	–	19.5
	UACC-62	–	10.2	–	–	–	–	–	39.7
Ovarian cancer	IGROV1	–	–	–	–	–	–	–	51.2
	OVCAR-3	–	–	–	–	–	–	–	47.4
	OVCAR-4	–	–	–	–	20.7	–	–	59.4
	OVCAR-5	–	–	–	–	16.5	–	–	44.3
	OVCAR-8	–	–	20.1	15.9	23.4	–	–	Nt
	NCI/ADR-RES	–	10.5	23.6	16.7	–	–	–	47.6
	SK-OV-3	–	–	–	–	–	–	–	77.5
Renal cancer	786-0	12.2	–	–	24.0	–	–	11.1	48.7
	A498	44.5	31.5	41.2	28.5	–	20.7	27.6	L
	ACHN	–	–	–	–	–	–	–	39.3
	CAKI-1	12.8	16.9	11.5	15.0	14.4	–	10.2	39.4
	RXF 393	12.5	–	–	47.6	–	–	–	34.3
	SN12C	–	–	–	–	–	–	–	54.0
	TK-10	–	–	–	–	–	–	–	66.9
	UO-31	–	10.3	14.7	31.9	34.2	–	10.1	41.3
Prostate cancer	PC-3	18.0	19.5	11.4	–	25.9	11.9	18.2	58.2
	DU-145	–	–	–	26.2	–	–	–	35.5
Breast cancer	MCF7	–	–	–	38.1	14.4	–	–	11.5
	MDA-MB-231/ATCC	10.1	14.5	–	58.0	22.8	–	–	78.1
									Nt
	HS 578T	–	–	–	13.1	23.3	–	–	L
	BT-549	–	–	–	13.1	20.7	–	–	37.8
	T-47D	18.5	21.3	11.2	–	20.6	–	22.6	56.7
	MDA-MB-468	16.3	19.1	–	–	–	–	13.3	Nt

–, GI <10%; nt, not tested; L, lethal; The showed inhibition percentage are measured at a single concentration of 10 μM.

DNA). Here also this compound interacted with the active site of amino acids through number of H-bonds (Supplementary data).

Therefore, docking of compound **9** in the active site of these enzymes indicated the probable mode of action of this compound for anticancer activities. Remarkable, such correlations between the experimental data, lipophilicity and docking studies are useful for refining the structure of the molecules and improving their efficacies.

In conclusion, we have reported the synthesis of novel antitumor molecules. Here, we have separated two regioisomers, identified by various spectroscopic techniques and evaluated for 60 tumor cell lines for anticancer activity. Some of these compounds have shown remarkable antitumor activity. Compound **9** showed broad spectrum antitumor agents showing effectiveness toward numerous cell lines belonging to different tumor subpanels. Thus, the introduction of pyrrolidine moiety is preferred over chloro and other secondary amines at 2-position of quinazoline.

Table 3
Experimental determined lipophilicity

Compounds	*P*	log *P*
7a	125.9	2.10
7b	14.72	1.17
8	648.45	2.81
9	797.24	2.90
10	524.8	2.72
11	10.82	1.03
12	309.35	2.49
13	324.50	2.51

P—partition coefficient; log *P*—logarithm of the partition coefficient.

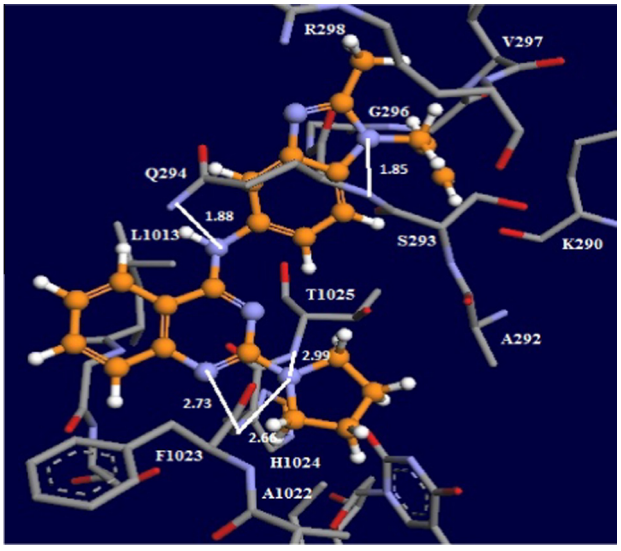


Figure 4. Compound **9** docked in the active site of RNR. Hs' are omitted for clarity. Carbon atoms of compound **9** are given different color.

Molecular docking also showed H-bonding interaction in the active site of RNR, Topo I and Topo II that also supported its activity. These hybrids of benzimidazole and quinazoline analogue could be further used as potent antitumor agents. Further optimizations of antitumor profiling of these series are currently ongoing in lab.

Acknowledgment

We thank to Council of Scientific and Industrial Research (02(0034)/11/EMR-II) for the research Grant. We also thank Punjab University, Chandigarh for recording NMR and mass spectra and Dr. Shaikh M. Mobin IIT Indore for X-ray crystallography, NCI, USA is gratefully acknowledged for investigating antitumor activities.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bmcl.2013.03.107.

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