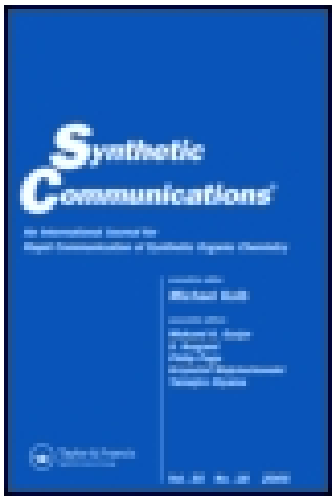


Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

A Convenient and Scalable Synthesis of 2,3-Dihydroquinazolin-4(1H)-one Derivatives and Their Anticancer Activity

Lingayya Rajaka[a], Nageshwar Rao Penumati[a], K. Nagaiah[a], Poornachandra Y[b] & Ganesh Kumar C[b]

[a] Organic and Biomolecular Chemistry Division, CSIR - Indian Institute of Chemical Technology, Hyderabad, India

[b] Medicinal Chemistry and Pharmacology Division, CSIR -Indian Institute of Chemical Technology, Hyderabad, India

Accepted author version posted online: 08 Jun 2015.

To cite this article: Lingayya Rajaka, Nageshwar Rao Penumati, K. Nagaiah, Poornachandra Y & Ganesh Kumar C (2015): A Convenient and Scalable Synthesis of 2,3-Dihydroquinazolin-4(1H)-one Derivatives and Their Anticancer Activity, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry

To link to this article: http://dx.doi.org/10.1080/00397911.2015.1046555

A Convenient and Scalable Synthesis of 2,3-Dihydroquinazolin-4(1*H*)-one Derivatives and their Anticancer Activity

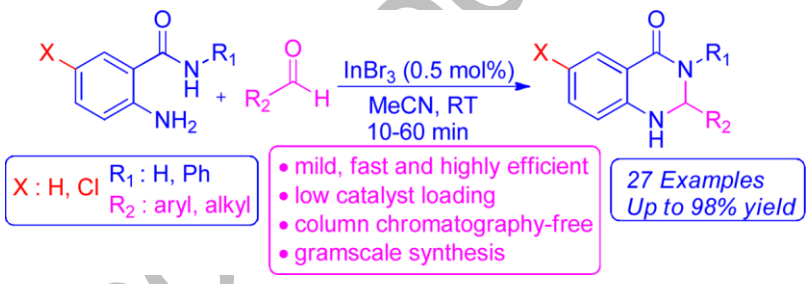
Lingayya Rajaka[1], Nageshwar Rao Penumati[1], K. Nagaiah[1], Poornachandra Y[2], Ganesh Kumar C[2]

[1]Organic and Biomolecular Chemistry Division, CSIR - Indian Institute of Chemical Technology, Hyderabad, India, [2]Medicinal Chemistry and Pharmacology Division, CSIR -Indian Institute of Chemical Technology, Hyderabad, India

Corresponding author: E-mail: nagaiah@iict.res.in, nagasaisrikari@gmail.com

Abstract

An efficient and mild $InBr_3$ – catalyzed approach to synthesize 2,3-dihydroquinazolin-4(1*H*)-one derivatives (**3a-3aa**) has been developed. Notably, all the products were isolated by recrystallization and the reaction is accessible on a gram scale. Moreover, the reactions only require 10-60 min. All the synthesized compounds were evaluated for their *in vitro* anticancer activity against four human cancer cell lines.



KEYWORDS: Aromatic aldehydes, Cyclocondensation, Indium(III) bromide, 2,3-dihydroquinazolin-4(1*H*)-ones, Anticancer activity

INTRODUCTION

Cancer is a systemic disease characterized by uncontrolled growth of abnormal cells and a leading cause of fatality worldwide. It continues to be a major threat to human health [1]. In 2012, cancer caused death lead to 8.2 million people worldwide [2]. In the past few decades many efforts have been made for the treatment of cancer, but the success towards the treatment of cancer remains a challenge. Therefore, there is an increasing demand for the discovery of new antitumor agents, which should be highly potent, selective and less toxic.

2,3-Dihydroquinazolin-4(1*H*)-one derivatives are an important class of fused N-containing heterocycles with various biological, medicinal, and pharmacological activities such as antitumor[3], antibiotic[4], antifungal[5], analgesic[6], diuretic[7], antifertility[8], antidepressant[9], antihistaminic[10], vasodilating[11], and antifibrillatory agent[12]. In addition, these compounds can act as potent tubulin inhibitors with promising anti-proliferative activity against several human cancer cell lines[13]. Additionally, they can act analogous to the antimitotic agent colchicine[14]. On the other hand, dihydroquinazolinones can easily be oxidized to their quinazolin-4(3*H*)-one analogues[15], which are themselves more important and bioactive N-based heterocyclic compounds[16], occuring in several natural products such as rutaecarpine and lutonin A[17]. As a consequence of this biological significance, the 2,3-dihydroquinazolin-4(1*H*)-one frame work is described as a privileged scaffold for drug design. Some examples of diverse commercial pharmaceuticals and natural products with quinazolinone core skeleton are shown in the Figure 1 [18].

Several methods have been reported in literature for the synthesis of 2,3-dihydroquinazolin-4(1*H*)-one derivatives, some of them suffer from harsh reaction conditions, excess catalyst loading, prolonged time, hazardous and expensive catalyst[19]. Therefore, there is still a demand for simple, efficient and easy work-up method.

Over the past few years, indium(III) salts have emerged as an efficient, mild Lewis acid catalysts for various organic transformations, due to its advantages such as relatively low toxicity, higher stability in H_2O, operational simplicity, strong tolerance towards functional groups and substances containing N- and O-atoms[20]. Herein, we describe the synthesis of 2,3- dihydroquinazolin-4(1*H*)-one derivatives using 0.5 mol % $InBr_3$ as catalyst under mild conditions in ≤60 min.

RESULTS AND DISCUSSION

Chemistry

At the outset, we carried out the cyclocondensation reaction between 2-aminobenzanilide (**1a**) and benzaldehyde (**2a**) in MeCN at room temperature with altered catalyst loading and their results are summarized in Table 1. Without any catalyst, the yield was poor even after longer time, but at reflux temperature moderate yields were obtained (Table 1, entries 1, 2 and 3). Under low catalyst loading conditions the reaction time was increased (Table 1, entries 4-6). It was found that 0.5 mol % of $InBr_3$ efficiently catalyzed the reaction, which was completed in 60 min with excellent yield (Table 1, entry 7) and upon increasing catalyst loading did not show any significant change in the reaction (Table 1, entries 8 and 9). Further investigation of the In(III) catalyst precursors

revealed that the best result was achieved with $InBr_3$ (Table 1, entries 10 and 11). With other catalysts, such as $FeBr_3$ (74 %), $CuBr_2$ (67 %), and $ZnCl_2$ (77 %) less satisfactory results were obtained (Table 1, entries 12-14).

To determine the effect of solvents, we carried out our reaction in different solvent systems as depicted in Table 1. In all the solvents screened, it was found that MeCN was the most suitable one for this reaction. In H_2O, the reaction does not proceed at room temperature, whereas at reflux, it proceeds well but requires a long reaction time, due to the poor solubility of the starting materials in H_2O.

With these optimized conditions in hand, we extended the scope of our method by synthesizing an array of 2,3-dihydroquinazolin-4(1*H*)-one derivatives bearing either electron-donating or electron-withdrawing groups on the aromatic ring (Table 2). The cyclization of 2-aminobenzanilide (**1a**) with aromatic aldehyde having no substituent such as benzaldehyde, and 1-naphthaldehyde afforded **3a** and **3l**, respectively, with excellent yield (Table 2, entries 1 and 12). The presence of an electron-withdrawing CN group, as well as Me, *iPr*, MeO, F, Br, and Ph in *para*-posititon of aryl ring, is well tolerated in synthesizing dihydroquinazolinones with excellent yields. We further elaborate the scope of our method to study 2,4-; 3,4-disubstituted and 3,4,5-trisubstituted benzaldehydes. It is evident from Table 2 that disubstituted and trisubstituted benzaldehydes are well tolerated substrates under the optimized reaction conditions.

Following the results we proceeded to highlight the efficiency of our catalytic system in synthesizing 2,3-dihydroquinazolinone derivates by reacting 5-chloro substituted 2-aminobenzamide with aromatic aldehydes bearing electron-donating and electron-withdrawing substituents to form a corresponding products **3m-3y** (Table 2) with excellent yields. The electronic effects have no significant impact on the reaction rate and time. Further, aliphatic aldehydes were tested in the reaction, corresponding products were isolated in good yields (Table 2, entries 26 and 27). Finally, the reaction is accessible on a high scale (10 mmol of 2-aminobenzanilide and benzaldehyde) requiring only 60 min to achieve excellent conversion (92%).

Thus we have synthesized a series of 2,3-dihydroquinazolin-4(1*H*)-one derivates (**3a-3aa**) in excellent yields. The structures of all the products were confirmed by ^{1}H-NMR, ^{13}C-NMR, IR, *Ms* and HRMS. The data of the known products were found to be in good agreement with those reported in the literature. The HRMS analysis of **3a** shows a $(M+H)^{+}$ peak at *m/z* = 301.13271 as $C_{20}H_{17}ON_2$, and $(M+Na)^{+}$ peak at *m/z* = 323.11462 as $C_{20}H_{16}ON_2Na$, which matches the expected 2,3-diphenyl-2,3-dihydroquinazolin-4(1*H*)-one. Spectral data of ^{1}H- and ^{13}C-NMR of the molecule are in good accord with its structure.

Based on the relevant literature,[19c] a plausible mechanism was proposed to account for the $InBr_3$ catalyzed reaction (Figure 2). First, condensation of **I** with aldehyde promoted by $InBr_3$, affords an imine intermediate **II** [15]. The part of amide in intermediate **II** could be converted into tautomer in the presence of $InBr_3$. Meanwhile, the part of imine in

intermediate **III** could be activated by $InBr_3$. Thus, intermediate **III** could be converted to intermediate **IV** by intramoleculer nucleophilic attack of the amide nitrogen on activated imine carbon. Finally, 2,3-dihydroquinazolin-4(1*H*)-ones (**V**) could be formed by a 1,5-proton transfer of **IV**.

BIOLOGICAL EVALUATION

Anticancer Activity

Synthesized compounds were evaluated for their *in vitro* cytotoxicity against four different human cancer cell lines, *i.e.*, lung cancer (A549), breast cancer (MCF7), cervical cancer (HeLa), and prostate cancer (DU145) by previously reported MTT assay [21] performed in a 96 well plate. Doxorubicin is one of the most effective antitumor agent and used as a reference drug in this study. Results of *in vitro* anticancer activity were compared with that of reference drug and the results are reported in *Table 3*. Compounds **3x**, **3o**, **3u** and **3n** exhibited promising cytotoxicity against all the four tested cancer cell lines. It was observed that the presence of different substituents like 1-naphthyl, and isopropyl, bromo, methyl on phenyl ring in the 2,3-dihydroquinazolin-4(1*H*)-one moiety contributed towards cytotoxicity against tested cell lines. Further, the compounds **3p**, **3q**, **3v**, **3w**, **3y** and **3k** containing both electron-donating as well as electron-withdrawing groups on phenyl ring of the 2,3-dihydroquinazolin-4(1*H*)-one moiety exhibited good cytotoxicity against the human breast cancer cell line, MCF7 and prostate cancer cell line, DU145, while the compound **3m** showed good cytotoxicity towards A549 and HeLa cancer cell lines. Moreover, the other compounds showed moderate cytotoxicity against the tested cell lines. The parameter expressed in terms of IC_{50} which corresponds to the

concentration required for 50% inhibition of cell viability. The IC_{50} values (in µM) were expressed as the means ± SD of three independent experiments.

CONCLUSIONS

In summary, a series of 2,3-dihydroquinazolin-4(1*H*)-one derivatives (**3a-3aa**) were synthesized by using 0.5 mol % $InBr_3$ as catalyst. The protocol demonstrated a concise, efficient, mild and facile condition favouring short reaction time, safe experimental procedures, and practically free of chromatographic separation. Synthesized compounds was assessed for their *in vitro* cytotoxicity against lung cancer (A549), breast cancer (MCF7), cervical cancer (HeLa) and prostate cancer (DU145) cell lines. The *in vitro* assay results showed that the compounds **3x**, **3o**, **3u** and **3n** exhibited promising cytotoxicity against all the four human cancer cell lines. Further the compounds **3p**, **3q**, **3v**, **3w, 3y** and **3k** showed good activity against MCF7 and DU145 cancer cell lines, while compound **3m** showed good cytotoxicity towards A549 and HeLa cancer cell lines. Based on these preliminary results, further mechanism of action of compounds and SAR studies under progress will be reported in due course.

EXPERIMENTAL

General Procedure For Synthesis Of 2,3-Dihydroquinazolin-4(1*H*)-Ones (3a-3aa)

Indiumtribromde (0.5 mol %) was added to a solution of 2-amino benzanilide or 2-amino-5-chloro benzamide (1 mmol) and desired aldehydes (1 mmol) in acetonitrile (3mL). The mixture was stirred at room temperature for the specified period of time. The progress of the reaction was monitored by TLC. After completion of reaction, solvent

was evaporated at reduced pressure, and solid was partitioned between ethyl acetate (15.0 mL) and water (15.0 mL), and transferred to a separatory funnel. The organic layer was washed with water, and brine, dried over anhydrous Na_2SO_4 (s) and concentrated *in vacuo*. The residue was purified by recrystallization from CH_2Cl_2/Hexane to afford the corresponding pure 2,3-dihydroquinazolin-4(1*H*)-ones (**3a-3aa**) as solids with excellent yields.

SUPPLEMENTAL MATERIAL

Supplemental data for this article can be accessed on the publisher's website.

ACKNOWLEDGMENTS

We thank the Director of CSIR-Indian Institute of Chemical Technology for the generous support and CSIR, New Delhi for funding through the programme ORIGIN XII FYP (CSC-0108). R. L. thanks CSIR, New Delhi for the Research Fellowship.

REFERENCES

[1] Donna, S. S.; Robert, D. K. *Chem. Rev.* **2009**, *109*, 2859-2861.

[2] *WHO* Website: http://www.who.int/cancer/en and World cancer report 2014.

[3] Hour, M. J.; Huang, L. J.; Kuo, S. C.; Xia, Y.; Bastow, K.; Nakanishi, Y.; Hamel, E.; Lee, K. H. *J. Med. Chem*. **2000**, 43, 4479-4487.

[4] Russell, H. E.; Alaimo, R.J. *J. Med. Chem.* **1972**, *15*, 335-336.

[5] Xu, Z.; Zhang, Y.; Fu, H.; Zhong, H.; Hong, K.; Zhu, W. *Bioorg. Med. Chem. Lett*. **2011**, 21, 4005-4007.

[6] Okumura, K.; Oine, T.; Yamada, Y.; Hayashi, G.; Nakama, M. *J. Med. Chem*. **1968**, 11, 348-352.

[7] Cohen, E.; Klarberg, B.; Vaughan, J. R. *J. Am. Chem. Soc*. **1959**, 81, 5508-5509.

[8] Cooper, E. R. A.; Jackson, H. *J. Reprod. Fert*. **1973**, 34, 445-449.

[9] Rexall Drug Co., U.S. Patent 3,257,397, **1966** (*Chem. Abstr*. **1966**, *65*, 8933b).

[10] Alagarsamy, V.; Solomon, V. R.; Murugan, M. *Bioorg. Med. Chem.* **2007**, 15, 4009-4015.

[11] Levin, J. I.; Chan, P. S.; Bailey, T.; Katocs, A. S.; Venkatesan, A. M. *Bioorg. Med. Chem. Lett*. **1994**, 4, 1141-1146.

[12] Bonola, G.; Da Re, P.; Magistretti, M. J.; Massarani, E.; Setnikar, I. *J. Med. Chem.* **1968**, 11, 1136-1139.

[13] Chinigo, G. M.; Paige, M.; Grindrod, S.; Hamel, E.; Dakshanamurthy, S.; Chruszcz, M.; Minor, W.; Brown, M. L. *J. Med. Chem*. **2008**, 51, 4620-4631.

[14] Graening, T.; Schmalz, H. G. *Angew. Chem. Int. Ed*. **2004**, 43, 3230-3256.

[15] Abdel-Jalil, R. J.; Voelter, W.; Saeed, M. *Tetrahedron Lett*. **2004**, 45, 3475-3476.

[16] (a) Neil, G. L.; Li, L. H.; Buskirk, H. H.; Moxley, T. E. *Cancer Chemother. Rep.* **1972**, *56*, 163-173. (b) Horton, D. A.; Bourne, G. T.; Smythe, M. L. *Chem. Rev*. **2003**, 103, 893-930.

[17] (a) Michael, J. P. *Nat. Prod. Rep*. **2004**, 21, 650-668. (b) Ma, Z. Z.; Hano, Y.; Nomura, T.; Chen, Y. J. *Heterocycles*, **1997**, 46,541-546.

[18] (a) Christina, F.; Foy, J. M.; Pratt, C. N. F. W.; Purvis, J. R. *J. Pharm. Pharmacol*. **1981**, 33, 219-222. (b) Verdel, B. M.; Souverein, P. C.; Egberts, A. C. G.; Leufkens, H. G. *Ann. Pharm.* **2006**, 40, 1040-1046, and references therein. (c) Kobayashi, Y.; Nakano,

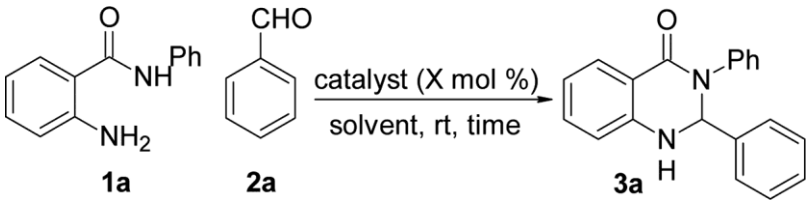
Y.; Kizaki, M.; Hoshikuma, K.; Yokoo, Y.; Kamiya, T. *Planta Med*. **2001**, 67, 628-633. (d) Mhaske, S. B.; Argade, N. P. *Tetrahedron* **2006**, 62, 9787-9826.

[19] For selected examples, see: (a) Moore, J. A.; Sutherland, G. J.; Sowerby, R.; Kelly, E. G.; Palermo, S.; Webster, W. *J. Org. Chem.* **1969**, 34, 887-892. (b) Sharma, S. D.; Kaur, V. *Synthesis* **1989**, 677-680. (c) Chen, J.; Wu, D.; He, F.; Liu, M.; Wu, H.; Ding, J.; Su, W. *Tetrahedron Lett.* **2008**, 49, 3814-3818. (d) Ding, Q.-S.; Zhang, J.-L.; Chen, J.-X.; Liu, M.-C.; Ding, J.-C.; Wu, H.-Y. *J. Heterocycl. Chem.* **2012**, 49, 375-380. (e) Prakash, M.; Kesavan, V. *Org. Lett.* **2012**, 14, 1896-1899. (f) Safari, J.; Gandomi-Ravandi, S. *J. Mol. Catal. A: Chem.* **2013**, 371, 135-140. (g) Dabiri, M.; Salehi, P.; Baghbanzadeh, M.; Zolfigol, M. A.; Agheb, M.; Heydari, S. *Catal. Commun*. **2008**, 9, 785-788. (h) Yoo, C. L.; Fettinger, J. C.; Kurth, M. J. *J. Org. Chem*. **2005**, 70, 6941-6943. (i) Dabiri, M.; Salehi, P.; Otokesh, S.; Baghbanzadeh, M.; Kozehgary, G.; Mohammadi, A. A. *Tetrahedron Lett*. **2005**, 46, 6123-6126. (j) Chen, J.; Su, W.; Wu, H.; Liu, M.; Jin, C. *Green Chem*. **2007**, 9, 972-975.

[20] (a) Cintas, P. *Synlett*, **1995**, 1087-1096. (b) C.-J., Li.; T.-H., Chan. *Tetrahedron.* **1999**, 55, 11149-11176. (b) Shen, Z.-L.; Wang, S.-Y.; Chok, Y.-K.; Xu, Y.-H.; Loh, T.-P. *Chem. Rev.* **2013**, 113, 271-401.

[21] Mosmann, T. *J. Immunol. Methods*. **1983**, *65*, 55-63.

Table 1. Cyclocondensation reaction of 2-aminobenzanilide with benzaldehyde under different reaction conditions[a]



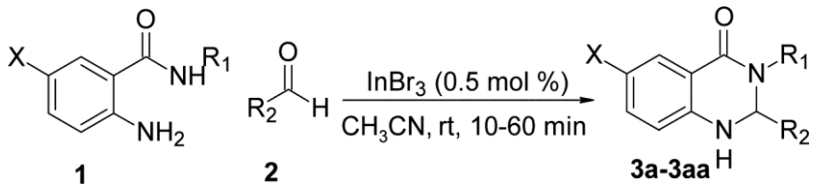
1a 2a 3a

Entry	Catalyst (mol %)	Solvent	Time	Yield[b] (%)
1	None	MeCN	24 h	12
2[c]	None	MeCN	12 h	23
3[d]	None	MeCN	12 h	32
4	$InBr_3$ (0.05)	MeCN	12 h	58
5	$InBr_3$ (0.1)	MeCN	7 h	66
6	$InBr_3$ (0.25)	MeCN	3 h	78
7	**$InBr_3$ (0.5)**	**MeCN**	**1 h**	**94**
8	$InBr_3$ (1)	MeCN	1 h	95
9	$InBr_3$ (2)	MeCN	1 h	95
10	$InCl_3$ (0.5)	MeCN	1 h	86
11	$In(OTf)_3$ (0.5)	MeCN	1 h	89
12	$FeBr_3$ (0.5)	MeCN	4 h	74
13	$CuBr_2$ (0.5)	MeCN	6 h	67
14	$ZnCl_2$ (0.5)	MeCN	5 h	77
15	$InBr_3$ (0.5)	MeCN/H_2o(1:1)	2 h	88
16	$InBr_3$ (0.5)	H_2O	12 h	0

17[d]	$InBr_3$ (0.5)	H_2O	12 h	58
18	$InBr_3$ (0.5)	DCM	2 h	80
19	$InBr_3$ (0.5)	DMF	4 h	78
20	$InBr_3$ (0.5)	DCE	3 h	81
21	$InBr_3$ (0.5)	DMSO	2 h	83
22	$InBr_3$ (0.5)	THF	4 h	82
23	$InBr_3$ (0.5)	MeOH	5 h	81

[a]Reaction conditions: **1a** (1.0 mmol), **2a** (1.0 mmol), Catalyst (0.5 mol %), in a solvent (3.0 mL). [b]Yield of isolated products (average of two runs). [c]The reaction was run at 50 °C. [d]The reaction was run at 100 °C

Table 2. Synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones in the presence of $InBr_3$[a]



Entry	X	R_1	R_2	Time (min)	Product	Yield[b] (%)
1	H	Ph	C_6H_5	60	**3a**	94
2	H	Ph	4-MeC_6H_4	40	**3b**	96
3	H	Ph	4- IsopropylC_6H_4	50	**3c**	97
4	H	Ph	4- $MeOC_6H_4$	10	**3d**	98
5	H	Ph	3,4-$(MeO)_2C_6H_3$	30	**3e**	95
6	H	Ph	3,4,5-$(MeO)_3C_6H_2$	30	**3f**	96
7	H	Ph	4 – FC_6H_4	45	**3g**	96
8	H	Ph	2,4- diClC_6H_3	60	**3h**	94
9	H	Ph	4 – BrC_6H_4	60	**3i**	97
10	H	Ph	4 – PhC_6H_4	60	**3j**	96
11	H	Ph	4 – CNC_6H_4	60	**3k**	93
12	H	Ph	1 - Naphthyl	60	**3l**	94
13	Cl	H	C_6H_5	60	**3m**	97
14	Cl	H	4 – MeC_6H_4	30	**3n**	95
15	Cl	H	4- IsopropylC_6H_4	40	**3o**	96
16	Cl	H	4- $MeOC_6H_4$	10	**3p**	98
17	Cl	H	3,4-$(MeO)_2C_6H_3$	20	**3q**	96
18	Cl	H	3,4,5-$(MeO)_3C_6H_2$	30	**3r**	95

19	Cl	H	4 - FC_6H_4	50	**3s**	94
20	Cl	H	2,4- diClC_6H_3	60	**3t**	93
21	Cl	H	4 – BrC_6H_4	50	**3u**	96
22	Cl	H	4 – PhC_6H_4	40	**3v**	95
23	Cl	H	4 – CNC_6H_4	60	**3w**	93
24	Cl	H	1 - Naphthyl	60	**3x**	95
25	Cl	H	4 – $NO_2C_6H_4$	60	**3y**	94
26	H	Ph	Butyl	60	**3z**	75
27	H	Ph	Pentyl	60	**3aá**	79

[a]Reaction conditions: **1 (** 1.0 mmol), **2** (1.0 mmol), $InBr_3$ (0.5 mol%), in MeCN (3.0 mL).

[b]Yield of isolated products.

Table 3. *In vitro* cytotoxicity evaluation of compounds **3a-3y**

Compounds ($\mu g\ mL^{-1}$)	IC_{50} values (in μM)[a]			
	A549 (Lung cancer)	MCF7 (Breast cancer)	HeLa (Cervical cancer)	DU145 (Prostate cancer)
3a	21.5 ± 0.22	-[b]	22.4 ± 0.32	-[b]
3b	25.2 ± 0.32	-[b]	22.4 ± 0.26	-[b]
3c	-[b]	-[b]	-[b]	-[b]
3d	-[b]	82.4 ± 0.52	-[b]	80.4 ± 0.48
3e	-[b]	-[b]	-[b]	-[b]
3f	19.7 ± 0.18	-[b]	18.7 ± 0.19	-[b]
3g	-[b]	-[b]	-[b]	-[b]
3h	20.6 ± 0.21	50.1 ± 0.48	18.3 ± 0.32	60.2 ± 0.12
3i	-[b]	-[b]	-[b]	-[b]
3j	38.6 ± 0.42	-[b]	34.8 ± 0.43	-[b]
3k	28.9 ± 0.32	15.0 ± 0.24	25.8 ± 0.25	12.1 ± 0.21
3l	38.5 ± 0.24	24.3 ± 0.18	34.8 ± 0.34	21.3 ± 0.13
3m	12.5 ± 0.18	44.2 ± 0.42	10.7 ± 0.26	61.8 ± 0.52
3n	13.9 ± 0.12	12.7 ± 0.26	11.2 ± 0.18	11.4 ± 0.24
3o	10.5 ± 0.08	6.0 ± 0.16	8.8 ± 0.15	4.1 ± 0.11
3p	-[b]	12.0 ± 0.14	-[b]	9.6 ± 0.22
3q	22.5 ± 0.22	9.9 ± 0.26	20.1 ± 0.17	7.2 ± 0.08
3r	32.9 ± 0.18	14.5 ± 0.32	31.2 ± 0.27	11.7 ± 0.16
3s	46.9 ± 0.26	17.4 ± 0.33	44.6 ± 0.21	14.3 ± 0.40

3t	20.9 ± 0.24	12.9 ± 0.15	19.1 ± 0.25	10.4 ± 0.21
3u	8.9 ± 0.18	11.9 ± 0.21	7.8 ± 0.14	9.8 ± 0.16
3v	-[b]	9.6 ± 0.09	-[b]	8.1 ± 0.27
3w	41.3 ± 0.32	8.8 ± 0.12	39.2 ± 0.29	7.9 ± 0.20
3x	7.9 ± 0.15	8.2 ± 0.22	6.3 ± 0.09	5.1 ± 0.19
3y	14.1 ± 0.21	10.4 ± 0.36	14.05 ± 0.42	9.1 ± 0.13
Doxorubicin (Standard)	0.1 ± 0.04	0.1 ± 0.08	0.09 ± 0.02	0.06 ± 0.04

[a]Results are expressed as the means ± SD of three independent experiments. [b]No activity

Figure 1. Some marketed drugs and natural products with dihydroquinazolinone and quinazolinone core skeleton.

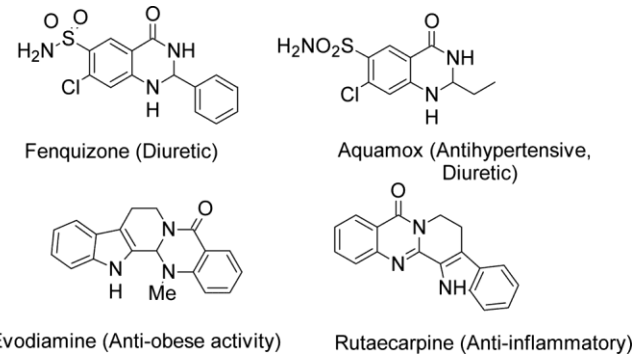


Figure 2. A plausible mechanism.