Bioorganic & Medicinal Chemistry Letters 26 (2016) 3014–3018

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

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

Quinazolinones–Phenylquinoxaline hybrids with unsaturation/saturation linkers as novel anti-proliferative agents

Jyothsna Devi Palem [a], Gopi Reddy Alugubelli [a], Rajashaker Bantu [a], Lingaiah Nagarapu [a,*], Sowjanya Polepalli [b], S. Nishanth Jain [b], Raju Bathini [c], Vijjulatha Manga [c]

[a] Organic Chemistry Division II (CPC), CSIR-Indian Institute of Chemical Technology, Tarnaka, Hyderabad 500007, India
[b] Center for Chemical Biology, CSIR-Indian Institute of Chemical Technology, Tarnaka, Hyderabad 500007, India
[c] Molecular Modeling and Medicinal Chemistry Group, Department of Chemistry, Osmania University, Tarnaka, Hyderabad 500007, India

ARTICLE INFO

Article history:
Received 3 February 2016
Revised 6 April 2016
Accepted 7 May 2016
Available online 11 May 2016

Keywords:
Quinazolinones
Allylphenyl quinoxaline
Heck-cross coupling
Anti-proliferative activity
Cancer cell lines
DNA intercalates

ABSTRACT

A new series of novel quinazolinones with allylphenyl quinoxaline hybrids **9a**–**n** were efficiently synthesized in good yields by the reaction of 3-allyl-2-methylquinazolin-4(3*H*)-one (**5a**–**n**) with bromophenyl) quinoxaline (**8**) utilizing Pd catalyzed Heck-cross coupling and evaluated for anti-proliferative activity against four cancer cell lines such as HeLa (cervical), MIAPACA (pancreatic), MDA-MB-231 (breast) and IMR32 (neuroblastoma). Compounds **9a**, **9e**, **9g** and **9h** exhibited promising anti-proliferative activity with GI_{50} values ranging from **0.06** to **0.2** μM against four cell lines, while compounds **9e** and **9k** showed significant activity against HeLa and MIAPACA cell lines and compounds **9b**, **9d**, **9h** and **9j** showed selective potency against IMR32 and MDA-MB-231 cell lines. This is the first report on the synthesis and in vitro anti-proliferative evaluation of *E*-2-(4-substituted)-3-(3-(4-(quinoxalin-2-yl)phenyl)allyl) quinazolin-4(3*H*)-ones (**9a**–**n**). Docking results indicate a sign of good correlation between experimental activity and calculated binding affinity (dock score), suggesting that these compounds could act as promising DNA intercalates.

The quinazolinone moiety containing natural products (Luotonin, Rutaecarpine, Tryptanthrin, Chloroqualone, Alloqualone, etc.) represent the medicinally and pharmaceutically important class of compounds,[1,2] because of their diverse range of biological activities such as anti-cancer, diuretic, anti-inflammatory, anti-convulsant and anti-hypertensive[3–6] activity. In recent years, quinazolinone embedded numerous natural products have been identified.[7–15] The cytotoxic alkaloid Luotonin A and its derivatives infused with quinazolinone moiety are clinically proven as anti-cancer agents (Fig. 1).[16–24] Previous studies have clearly demonstrated that Luo functions as DNA topoisomerase-I poison.[25] Considering the potent bioactivities of the compounds possessing Luo pharmacophore, we were interested to synthesize novel Luo analogues and evaluated their anti-cancer activities such as cytotoxicity, cell cycle regulation and mechanistic aspects.

A hybrid anti-cancer agent, which combines different heterocyclic compounds in one, which increases the cytotoxicity and enhances specificity was recently demonstrated.[26] The initial study proved that pyrroloquinoline nucleus leads to the selective inhibition of tumor growth.[27–32] Recently, as part of our on-going programme to discover and develop tumor growth inhibitors and apoptosis inducers as a potential new anti-cancer agents, we have identified several classes of molecules that includes 1*H*-pyrazole-5-carboxylic acid, 1*H*-pyrrolo[3,4-*b*]quinolin-3(2*H*)-one, analogues of (+)-varitriol, novel derivatives of benzosuberones with thiazolidine-2,4-diones and fused coumarin moieties.[33] In the present investigation, we have discovered a novel quinazolinones bearing allylphenyl quinoxaline hybrids, by employing Heck-cross methodology to elicit combined anti-tumour efficacy/cytotoxicity against different cancer cell lines in vitro (HeLa, MIAPACA, MDA-MB-231and IMR32). Significantly, the compounds **9k**, **9h** have shown promising cytotoxicity against the HeLa cancer cell lines with GI_{50} values of 0.06 and 0.2 μM, respectively and the compounds **9a**, **9g**, **9k** and **9h** displayed the most potent selectivity against HeLa and MDA-MB-231 cell lines with GI_{50} values of 0.08 and 0.4 μM, respectively. Quinazolinone derivatives are reported as anti-cancer agents and many of them showed good DNA intercalation.[34,35] To assess the possible intercalating potency of the synthesized compounds a molecular docking studies were performed using DNA structure obtain from PDB. The protein structure bound to respinomycin D was downloaded, as it belongs to anthracycline family of antitumor antibiotics. Since doxorubicin also belongs to the same family it has been taken as standard.

* Corresponding author. Tel.: +91 40 27191509; fax: + 91 40 27193382.
E-mail addresses: lnagarapuiict@yahoo.com, nagarapu@iict.res.in (L. Nagarapu).

http://dx.doi.org/10.1016/j.bmcl.2016.05.021
0960-894X/

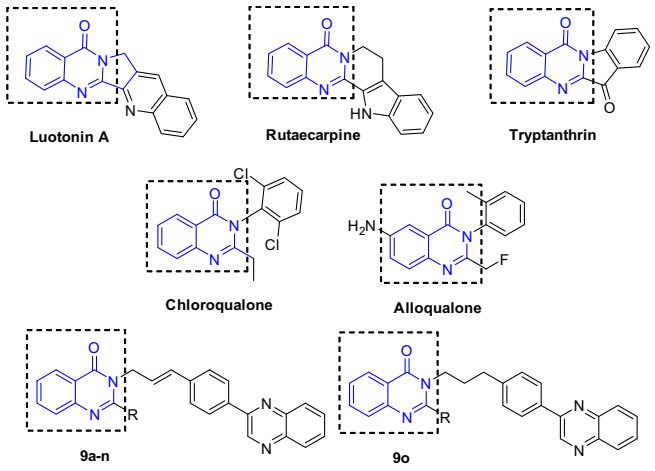


Figure 1. Quinazolinone scaffold containing natural products and its designed conjugates (**9a**–**n**, **9o**).

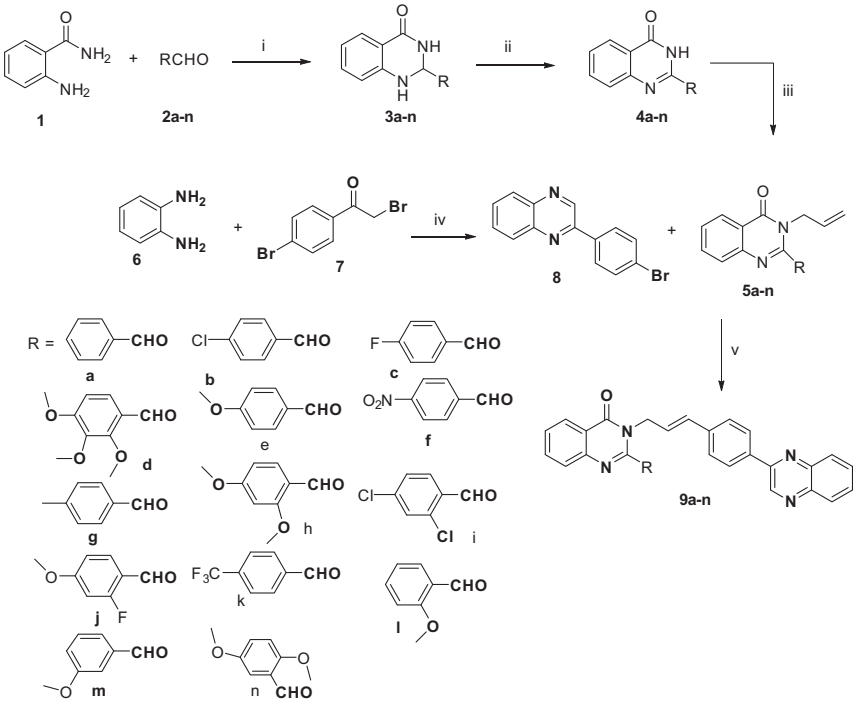
The clinical agent doxorubicin is well-studied of this class but has a relatively simple molecular architecture in which the pendant daunosamine sugar residue is in the DNA minor groove. The compounds **9a**–**9o** were evaluated in silico (docking) to identify their hypothetical binding mode using the NMR structure of the respinomycin D intercalation complex with a double stranded DNA molecule (AGACGTCT)2 complex in solution[36] derived from NOE restraints and molecular dynamics simulations.

Synthesis of targeted (*E*)-2-(4-substituted)-3-(3-(4-(quinoxalin-2-yl)phenyl)allyl)quinazolin-4(3*H*)-ones (**9a**–**n**) were achieved by Pd catalyzed Heck-cross coupling reaction [$Pd(OAc)_2$, PPh_3, K_2CO_3, DMF/H_2O (8:2), at 120 °C for 4 h] of halo-qunaxolines with substituted 3-allylquinazolinones. The 2-(4-bromophenyl)quinoxaline (**8**) was readily prepared by the reaction of *ortho*-phenylene diamine (**6**) with various phenacyl bromides (**7**) in presence of catalytic amounts of Zr/WO_3 at 80 °C. It was further coupled with 3-allylquinazolinone derivatives **5a**–**n**; which were obtained by the reaction of various benzaldehydes (**2a**–**n**) with anthranilamide (**1**) in presence of phase transfer catalyst TBAHS in methanol, followed by oxidation of 2-phenyl-2,3-dihydro qunazolinones (**3a**–**n**) and allylation with allylbromide in presence of K_2CO_3 at room temperature for 2-phenyl quinazolin-4(3*H*)-ones (**4a**–**n**) (Scheme 1).

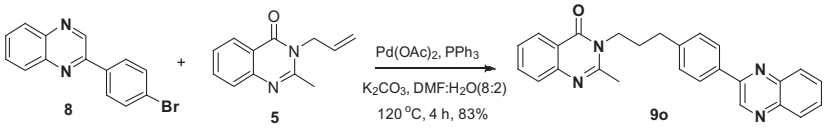
Under similar Heck-coupling conditions [$Pd(OAc)_2$, PPh_3, K_2CO_3, DMF/H_2O (8:2), 120 °C for 4 h] when 2-(4-bromophenyl)quinoxaline (**8**) was reacted with 3-allyl-2-methylquinazolin-4(*H*)-one (**5**) saturated 2-methyl-3-(3-(4-(quinoxalin-2-yl)phenyl)propyl) quinazolin-4(3*H*)-one (**9o**) was obtained with an yield of 67% (Scheme 2).

All the newly synthesized compounds were characterized by using ^{1}H NMR, ^{13}C NMR, IR and mass spectrometry. Spectral data of all synthesized compounds were in good agreement with the proposed structures. IR spectrum revealed the presence of C=O bond (1680–1700 cm^{-1}) and CH (2928–2934 cm^{-1}) functional groups of compounds **9a**–**n**, which were further confirmed by ^{1}H NMR. The characteristic proton of quinoxaline displayed at δ 9.0–9.3 ppm and double bond protons appeared as a multiplet at δ 6.50–6.30 ppm with coupling constant between 17 and 16 Hz. Compound **9o** indicating the reduction of double bond showed two additional triplets and one multiplet, one triplet at δ 4.16–4.01 ppm, another triplet at δ 2.8–2.6 ppm and one proton appeared as a multiplet at δ 2.2–2.1 ppm. The molecular formula of all the synthesized compounds was confirmed by HRMS data analysis. For instance, **9a** displayed a molecular ion peak at *m*/*z* 467.18664 $[M+H]^+$ suggesting the molecular formula of $C_{31}H_{23}ON_4$.

Effects of the compounds on the viability of human cancer cells: The in vitro anti-proliferative activity of the designed compounds **9a**–**n** was evaluated against four different human cancer cell lines, HeLa (cervical), MIAPACA (pancreatic), MDA-MB-231 (breast) and IMR32 (neuroblastoma) summarized in Table 1. The compounds were picked up for an advanced assay against these four human



Scheme 1. Synthesis of (*E*)-2-(4-substituted)-3-(3-(4-(quinoxalin-2-yl)phenyl)allyl)quinazolin-4(3*H*)-ones (**9a**–**n**). *Reagents and conditions:* (i) MeOH, reflux, 2 h; (ii) $KMnO_4$, acetone, reflux, 1 h; (iii) allyl bromide, K_2CO_3, DMF, rt, 8 h; (iv) Zr/WO_3, 80 °C, 30 min; (v) $Pd(OAc)_2$, PPh_3, K_2CO_3, DMF/H_2O (8:2), 120 °C, 4 h.



Scheme 2. Synthesis of 2-methyl-3-(3-(4-(quinoxalin-2-yl)phenyl)propyl)quinazolin-4(3*H*)-one (**9o**).

Table 1
(GI_{50}/μM)[a] values of the tested compounds against four human cancer cell lines

Compound	HeLa		MIAPACA		MDA-MB-231		IMR32		XP Dockscore (kcal/mol)
	GI_{50} (μM)	PGI_{50}	GI_{50} (μM)	PGI_{50}	GI_{50} (μM)	PGI_{50}	GI_{50} (μM)	PGI_{50}	
9a	5.1 ± 0.3	5.292	2.8 ± 0.4	5.552	6.4 ± 0.9	5.193	1.01 ± 0.06	5.995	−3.326
9b	69.5 ± 0.19	4.158	6.4 ± 0.06	5.193	0.57 ± 0.06	6.244	<0.01	—	−4.405
9c	16.1 ± 0.2	4.793	<0.01	—	1.7 ± 0.07	5.769	65 ± 0.9	4.187	−4.272
9d	2.5 ± 0.6	5.602	2.2 ± 0.3	5.657	<0.01	—	0.77 ± 0.09	6.113	−3.506
9e	1.2 ± 0.62	5.920	2.1 ± 0.05	5.677	0.64 ± 0.04	6.193	2.8 ± 0.2	5.552	−2.286
9f	0.9 ± 0.4	6.045	6.1 ± 0.5	5.214	0.14 ± 0.08	6.853	<0.01	—	−3.490
9g	9.2 ± 0.6	5.036	11.4 ± 0.6	4.943	1.24 ± 0.08	5.906	2.2 ± 0.05	5.657	−1.370
9h	31.6 ± 0.2	4.500	13.6 ± 0.8	4.866	<0.01	—	6.3 ± 0.9	5.200	−2.488
9i	>100	—	4.4 ± 0.2	5.356	0.4 ± 0.01	6.397	2.6 ± 0.05	5.585	−3.64
9j	0.9 ± 0.02	6.045	28.6 ± 0.1	4.543	<0.01	—	1.2 ± 0.07	5.920	−3.054
9k	17.7 ± 0.8	4.752	10 ± 0.3	5	1.8 ± 0.03	5.744	5.3 ± 0.6	5.275	−3.004
9l	>100	—	2.2 ± 0.4	5.657	>100	—	0.47 ± 0.05	6.327	−3.360
9m	0.12 ± 0.52	6.920	2 ± 0.2	5.698	1.25 ± 0.09	5.903	0.32 ± 0.04	6.494	−2.982
9n	0.038 ± 0.021	7.420	1.8 ± 0.01	5.744	1.36 ± 0.01	5.866	0.28 ± 0.02	6.55	−3.501
9o	0.032 ± 0.022	7.494	1.2 ± 0.001	5.920	0.62 ± 0.001	6.207	0.22 ± 0.001	6.657	−4.956
Doxo-rubicin	0.073 ± 0.001	7.136	0.097 ± 0.002	7.013	0.085 ± 0.001	7.070	0.023 ± 0.002	7.638	−10.925
Paclitaxel	0.025 ± 0.001	7.602	0.056 ± 0.002	7.251	0.091 ± 0.005	7.040	0.075 ± 0.003	7.124	−5.597

[a] GI_{50}: 50% growth inhibition, concentration of drug resulting in a 50% reduction in net protein increase compared with control cells.

cancer cell lines at five concentrations (0.01, 0.1, 1, 10, 100 μM). GI_{50} (growth inhibitory activity) was calculated and these values corresponded to the concentration of the compound causing 50% decrease in the net cell growth as compared to that of the standard drugs, Doxorubicin and Paclitaxel. Results were calculated for each of these parameters if the level of activity was reached; however, if the effect was not achieved, the value was expressed as greater or less than the maximum or minimum concentration tested.

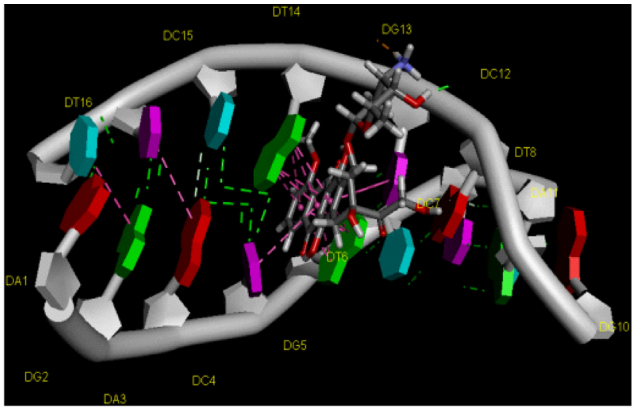
Based on Table 1, the synthesized series of quinazolinones bearing allylphenyl quinoxaline hybrids **9a**–**n** showed significant to moderate cancer cell growth inhibition with GI_{50} values (0.08–0.2 μM). The effect of various substituents on phenyl ring was examined. The structure–activity relationship (SAR) study revealed that the functional group change on phenyl ring is crucial for inducing anti-proliferative activity against particular cancer cell lines. Specifically, series of the compounds **9g**, **9h**, **9f**, **9k**, **9c**, **9b** and **9a** exhibited promising anti-proliferative activity with GI_{50} values less than 0.01 μM, in particular against MIAPACA, MDA-MB-231and IMR32 human cancer cell lines. Introduction of substituent (*p*-Me, *p*-OCH_3, 2,4-di-OCH_3, *p*-Cl, *p*-NO_2 and *p*-CF_3) on phenyl ring was associated with a significant increase in the growth inhibitory effect against MIAPACA, MDA-MB-231and IMR32 human cancer cell lines. In comparison, electron donating groups present on phenyl ring shows effect on HeLa, MDA-MB-231and IMR32 human cancer cell lines. Finally, we observed that the series of the compounds **9a**–**n** exhibited good growth inhibitory activity and electron donating groups present on phenyl ring in **9e**, **9d**, **9m** derivatives played an important role in the anti-proliferative activity.

Studies of molecular docking: To gain more insight into the interactions of novel quinazolinone derivatives **9a**–**o**, molecular docking studies were performed. NMR structure of double stranded DNA molecule (AGACGTCT)2 complex in solution (PDB id: 1N37) was downloaded from protein data bank (www.rcsb.org). Interactions of the docked DNA with ligands were analyzed to identify their hypothetical binding mode.

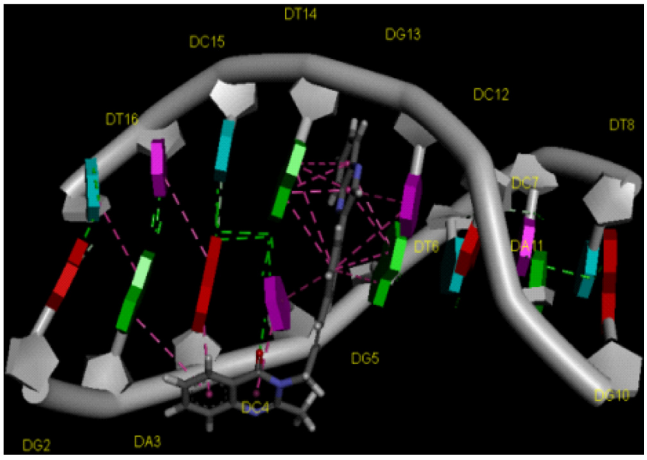
Molecules were built using Maestro build panel and prepared by LigPrep OPLS_2005 force field. The DNA was prepared using protein preparation module applying the default parameters. Grid was generated around the active site of the DNA by selecting the co-crystallized ligand. Receptor Van der Waals scaling for the non-polar atoms was kept 0.9.[37] GLIDE 5.6[38] was used for molecular docking. Low energy conformation of the ligands was selected and docked into the grid using extra precision (XP) docking mode[39–41]. The docking calculation of all the compounds are depicted in Table 1.

Conformation occupying the position between the base pairs indicates a sign of good intercalation. Hydrogen bonding is an important factor to understand the binding with hetero atoms, docking interactions of the doxorubicin with DNA showed three H-bond interactions. One with DG13 nucleotide and remaining two H-bonds with DC12 (H), DC12(O), dockscore for doxorubicin was found to be −10.92 (kcal/mol). The compound **9o** and **9c** showed one H-bond interaction with DC4 and DC12, with a dock-score of −4.95 and −4.27 (kcal/mol) respectively. A regression analysis between dock score (binding affinity) and pGI_{50} values of the synthesised molecules were carried out. It gave a correlation coefficient *r* of 0.73 representing significant correlation between DNA binding (dock score) and anti-proliferative activity. Figure 3 shows the scatter plot of dock score versus pGI_{50}. DNA intercalation with H-bond interactions is illustrated in Figure 2A for doxorubicin, Figure 2B for **9o** and Figure 2C for **9c** compounds respectively.

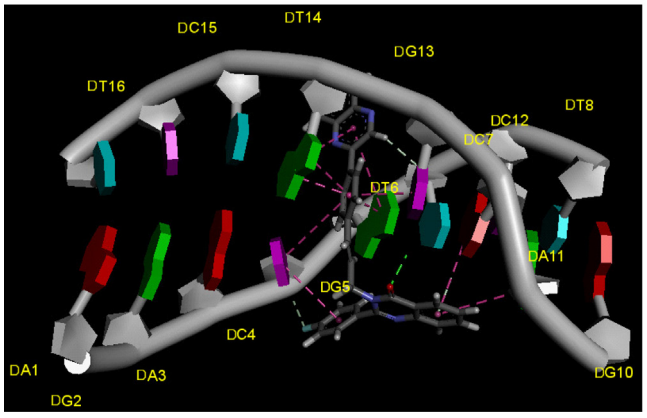
Taken together, we have synthesized a series of novel quinazolinone derivatives **9a**–**o** by using Heck cross-coupling reaction of allylquinazolinones with bromo quinaxolines and evaluated their in vitro cytotoxicity against HeLa, MDA-MB-23, MIAPACA and IMR32 cell lines. Among the tested cancer cell lines, compounds **9a**, **9e**, **9g** and **9h** exhibited potent activity against four tested human cancer cell lines, while compounds **9e** and **9k** were more potent against HeLa and MIAPACA cell lines and compounds **9b**,



A



B



C

Figure 2. Superimposition in DNA-intercalation site of (A) doxorubicin, (B) compound **9o**, (C) compound **9c**.

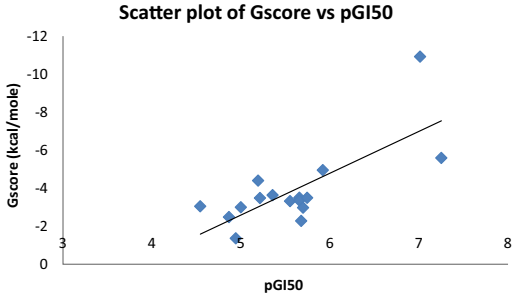


Figure 3. Scatter plot of dock score versus pGI50.

9d, **9h** and **9j** were selectively potent against IMR32 and MDA-MB-231 cell lines. Carrying out the substitution on quinazolinone was associated with a distinct tendency to increase the in vitro cytotoxic potential. The molecule **9o** can act as good intercalating agent. The synthesized molecules can be considered as lead molecules, and further optimization will result in a good intercalating agent. This study provides valuable information for further drug design and in developing more promising anticancer agents.

Acknowledgements

The authors gratefully acknowledge the financial support through the project: DST-SERB/EMEQ-078/2013 and the University Grant Commission (UGC), New Delhi for the award of fellowship to JS.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bmcl.2016.05.021.

References and notes

1. Bonola, G.; Da Re, P.; Magistretti, M. J.; Massarani, E.; Setnikar, I. *J. Med. Chem.* **1968**, *11*, 1136.
2. Okumura, K.; Oine, T.; Yamada, Y.; Hayashi, G.; Nakama, M. *J. Med. Chem.* **1968**, *11*, 348.
3. Chan, J. H.; Hong, J. S.; Kuyper, L. F.; Jones, M. L.; Baccanari, D. P.; Tansik, R. L.; Boytos, C. M.; Rudolph, S. K.; Brown, A. D. *J. Heterocycl. Chem.* **1997**, *34*, 145.
4. Gackenheimer, S. L.; Schaus, J. M.; Gehlert, D. R. *J. Pharmacol. Exp. Ther.* **1996**, *732*, 113.
5. Dempcy, R. O.; Skibo, E. B. *Biochemistry* **1991**, *30*, 8480.
6. Nordisk-Droge, N. A. 18113, Patent, Ed. Nordisk Drogeand Kemi-Kalieforretning AIS: Luchthaven Schiphol. The Netherlands, 1965.
7. Michael, J. P. *Nat. Prod. Rep.* **2005**, *22*, 627.
8. Michael, J. P. *Nat. Prod. Rep.* **2004**, *21*, 650.
9. Michael, J. P. *Nat. Prod. Rep.* **2003**, *20*, 476.
10. Michael, J. P. *Nat. Prod. Rep.* **2002**, *19*, 742.
11. Michael, J. P. *Nat. Prod. Rep.* **2001**, *18*, 543.
12. Michael, J. P. *Nat. Prod. Rep.* **2000**, *17*, 603.
13. Zhang, Ying; Huang, Yin-Jiu; Xiang, Hong-Mei; Wang, Pei-Yi; De-Yu, Hu; Xue, Wei; Song, Bao-An; Yang, Song *Eur. J. Med. Chem.* **2014**, *78*, 23.
14. Barbosa, M. L. C.; Lima, L. M.; Tesch, R.; Mauricio, C.; Sant'Anna, R.; Totzke, F.; Kubbutat, M. H. G.; Schachtele, C.; Laufer, S. A.; Barreirot, E. J. *Eur. J. Med. Chem.* **2014**, *71*, 1.
15. Khan, Imtiaz; Ibrar, Aliya; Abbas, Naeem; Saeed, Aamer *Eur. J. Med. Chem.* **2014**, *76*, 193.
16. Ma, Z. Z.; Hano, Y.; Nomura, T.; Chen, Y. J. *Heterocycles* **1997**, *46*, 541.
17. Wall, M. E.; Wani, M. C.; Cook, C. E.; Palmer, K. H.; Mcphail, A. T.; Sim, G. A. *J. Am. Chem. Soc.* **1966**, *88*, 3888.
18. Takimoto, C. H.; Wright, J.; Arbuck, S. G. *Biochim. Biophys. Acta* **1998**, *1400*, 107.
19. Leary, O. J.; Muggia, F. M. *Eur. J. Cancer* **1998**, *34*, 1500.
20. Saltz, L. B.; Cox, J. V.; Blanke, C.; Rosen, L. S.; Fehrenbacher, L.; Moore, M. J.; Maroun, J. A.; Ackland, S. P.; Locker, P. K.; Pirotta, N.; Elfring, G. L.; Miller, L. L. *N. Eng. J. Med.* **2000**, *343*, 905.
21. Ozols, R. F. *Int. J. Gynecol. Cancer* **2000**, *10*, 33.
22. Vanhoefer, U.; Harstrick, A.; Achterrath, W.; Cao, S.; Seeber, S.; Rustum, Y. M. *J. Clin. Oncol.* **2001**, *19*, 1501.
23. Ulukan, H.; Swaan, P. W. *Drugs* **2002**, *62*, 2039.
24. Garcia-Carbonero, R.; Supko, J. G. *Clin. Cancer Res.* **2002**, *8*, 641.
25. Cagir, A.; Jones, S. H.; Gao, R.; Eisenhauer, B. M.; Hecht, S. M. *J. Am. Chem. Soc.* **2003**, *125*, 13628.
26. Trafalis, D. T. P.; Geromichalos, G. D.; Koukoulitsa, C.; Papageorgiou, A.; Karamanakos, P.; Camoutsis, C. *Breast Cancer Res. Treat.* **2006**, *97*, 17.
27. Ferlin, M. G.; Bortolozzi, R.; Brun, P.; Castagliuolo, I.; Hamel, E.; Basso, G.; Viola, G. *ChemMedChem* **2010**, *5*, 1373.
28. Nieman, J. A.; Nair, S. K.; Heasley, S. E.; Schultz, B. L.; Zerth, H. M.; Nugent, R. A.; Chen, K.; Stephanski, K. J.; Hopkins, T. A.; Knechtel, M. L.; Oien, N. L.; Wieber, J. L.; Wathen, M. W. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 3039.
29. Dalla Via, L.; Gia, O.; Gasparotto, V.; Ferlin, M. *Eur. J. Med. Chem.* **2008**, *43*, 429.
30. Ferlin, M. G.; Marzano, C.; Dalla Via, L.; Chilin, A.; Zagotto, G.; Guiotto, A.; Moro, S. *Bioorg. Med. Chem.* **2005**, *13*, 4733.
31. Preobrazhenskaya, M. N. *Chem. Heterocycl. Compd.* **1985**, *21*, 13.
32. Kidwai, M.; Venkataramanan, R.; Mohan, R.; Sapra, P. *Curr. Med. Chem.* **2002**, *9*, 1209.
33. (a) Nagarapu, L.; Gaikwad, H. K.; Sarikonda, K.; Mateti, J.; Rajashaker, B.; Mahduri, K. M.; Kalvendi, S. *Eur. J. Med. Chem.* **2010**, *45*, 4720; (b) Nagarapu, L.;

Gaikwad, H. K.; Bantu, R. *Eur. J. Med. Chem.* **2011**, *46*, 2152; (c) Nagarapu, L.; Paparaju, V.; Satyender, A. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 2351; (d) Nagarapu, L.; Yadagiri, B.; Bantu, R. *Eur. J. Med. Chem.* **2014**, *71*, 91; (e) Nagarapu, L.; Yadagiri, B.; Bantu, R. *Eur. J. Med. Chem.* **2014**, *79*, 260.
34. Marvania, Bhavin; Lee, Pei-Chih; Chaniyara, Ravi; Dong, Huajin; Suman, Sharda; Kakadiya, Rajesh; Chou, Ting-Chao; Lee, Te-Chang; Shah, Anamik; Su, Tsann-Long *Bioorg. Med. Chem.* **2011**, *19*, 1987.
35. Garofalo, Antonio; Goossens, Laurence; Baldeyrou, Brigitte; Lemoine, Amelie; Ravez, Severine; Six, Perrine; David-Cordonnier, Marie-Helene; Bonte, Jean-Paul; Depreux, Patrick; Lansiaux, Amelie; Goossens, Jean-Francois *J. Med. Chem.* **2010**, *53*, 8089.
36. Searle, M. S.; Maynard, A. J.; Williams, H. E. *Org. Biomol. Chem.* **2003**, *7*, 60.
37. Friesner, R. A.; Banks, J. L.; Murphy, R. B.; Glide *J. Med. Chem.* **2004**, *47*, 1739.
38. *Glide Version 5.6.* Schrödinger, LLC: New York, 2010.
39. Bharate, S. B.; Nagaraju, M.; Sudhakar, M.; Bharate, J. B.; Ramesh, M.; Yadav, R. M.; Vishwakarma, R. A. *Arkivoc* **2012**, *viii*, 308–318.
40. Alafeefy, Ahmed Mahmoud *J. Saudi Chem. Soc.* **2011**, *15*, 337.
41. Omar Al-Deeb, A. *World Appl. Sci. J.* **2008**, *5*, 94.