Research Article

SHetA2 — A Mini Review of a Promising Anticancer Drug

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REVIEW ARTICLE

Heteroarotinoids (Hets) are a novel class of heterocycles which contain an aryl ring and a heterocylic ring and which show potential as anticancer drugs [1]. These heteroarotinoids control cell growth, differentiation, and apoptosis of the cancer cells. Heteroarotinoids were originally derived from an arotinoid class related to retinoids by strategically placing a heteroatom (O,N,S) in the molecular framework of a saturated six-membered ring [2-7]. This modification in the cyclohexyl ring reduced the toxicity of analogs of several the natural retinoids, including all-trans retinoic acid, by 1000-fold and thus showed promising activity against a variety of cancer cells [2-10]. Based on structure-activity relationships (SAR), various Hets have been synthesized with several displaying significant anticancer activity [4-10].Further structural modifications led to a related class of compounds known as Flexible Heteroarotinoids (Flex-Hets) in which certain linking groups situated between a saturated heterocyclic ring and an aryl group were altered. It was discovered that by including more flexible urea and thiourea linkers the anticancer activity increased markedly.¹ Consequently, the introduction of a thiourea linker not only provided flexibility between the ring systems, but also increased the scope of activity of the drug against a series of cancer cells lines including breast, head-neck, kidneys, lung and certain ovarian cancers [1,3-6,8,9].

Ultimate structural refinement in the Flex-Hets series led to SHetA2 (1, NSC 726289) [the official name is N-(3,4dihydro-2,2,4,4,-tetramethyl-2H-1-benzothiopyran-6-yl)-N'(4nitrophenyl)thiourea] which was developed in our laboratory [1]. The structure is comprised of a sulfur-containing heterocylic ring, a thiourea linker, and a 4-nitrophenyl substituent. SHetA2 (1) showed the greatest level of efficacy and potency in the inhibition of various cancer cells lines while retaining a low level or no activity in normal cell cultures [1,10,11]. The differential effect exhibited by SHetA2 on cancer versus normal cells appears to be by direct targeting of the mitochondria and reducing the Bcl-2 and Bcl-xl proteins of cancer cells while causing a minimal effect on normal cells [11].Due to this promising anticancer activity in an organotypic model, the National Cancer Institute (NCI) was prompted to accept the drug into the RAPID (Rapid Access to Preventive Intervention Development, NSC 72689) program for preclinical studies as a therapeutic and chemopreventive agent for cancer [12]. The corresponding ester analog 2 has exhibited good activity but is not the subject of this review.

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Chemistry synthesis

To date, there have been only two synthetic strategies for the synthesis of SHetA2 (1). The initial method involved a 6-step sequence starting from thiophenol (3) as shown in Scheme 1 [1]. The thiol 3 underwent a Michael addition with mesityl oxide (4) to give ketone 5. Treatment of ketone 5 with excess CH_3MgBr generated the tertiary alcohol 6. Dehydration-cyclization of 6 was accomplished by $AlCl_3$ in CS_2 to afford thiochroman 7. Nitration of thiochroman 7 was achieved using HNO_3/Ac_2O to afford the 6-isomer 8 in a modest yield (26%), with several byproducts being formed, including some via oxidation of the sulfur atom. Reduction of the nitro group in 8 occurred with Fe/AcOH in refluxing EtOH to yield amine 9, a key intermediate in the synthesis of several Flex-Hets. Finally, amine 9 was further reacted with 4-nitroisothiocyanate to produce SHetA2 (1) in a quantitative yield.

Seltzman and coworkers [13], developed an alternative route to overcome the low yield in the nitration step previously cited



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in the synthesis of SHetA2 (1). 4-Acetamidothiophenol (10) was used as the starting material, instead of thiophenol (3) (Scheme II). Compound 10 underwent 1,4-addition to mesityl oxide (4) to give 11. Treatment of 11 with methyllithium afforded the carbinol 12 in high yield. Cyclization of 12 afforded the intermediate 13 in the presence of AlCl₃ in chlorobenzene as solvent. Hydrolysis of the 13 with conc. HCl and basification gave the key intermediate amine 9, which then treated with 4-nitroisothiocyanate offered 1. This synthetic strategy provided two benefits. Primarily it resulted in a five-fold improvement in the yield of the SHetA2 family of anticancer compounds. Secondly, the procedure also demonstrated an approach to overcome the limitation of the Grignard chemistry in the conversion of 5 to 6, which resulted from poor solubility, and the reduced reactivity of the Grignard reagent as compared to its replacement by methyllithium.

Biological Activity of SHetA2

SHetA2 [1, NSC 726189] has displayed strong activity against head and neck cell carcinoma (UMSCC38 human cell lines) [9] ovarian (OVCAR-3 and Caov-3 cultures) [14,15] and kidney cell lines (Caki-1) [9,14,15] via an induction of apoptosis. Moreover, 1 has exhibited very low toxicity and excellent discrimination between malignant and benign cells [1,11]. The genotoxicity battery (bacterial-Ames test), in vitro chromosomal aberration, and in vivo chromosomal aberration (mouse micronucleus) indicated that SHetA2 was not genotoxic [16]. A subchronic 14day study in rats and dogs did not reveal significant toxicity up to the highest doses examined [16].A 28-day subchronic toxicity study in dogs resulted in no apparent toxicity with a value of 1500 mg/kg/day with No Adverse Event Level (NOAEL) [16]. Oral administration of SHetA2 (1) reduced the growth of ovarian and kidney cancerous xenograft tumors at 10 mg/kg/day and tumors at 10 mg/kg/day and 60/mg/kg/day, respectively [15,11,17]. Consequently, the therapeutic window for administrative safety with SHetA2 (1) can be 25-150 fold above in vivo effective doses. Ovarian cancer is the most deadly of all gynecologic malignancies which is often diagnosed at a late stage [18]. Following surgery, a combination treatment with cis-platin and taxane has often been



applied [19]. Thus **1** might improve therapy for ovarian cancer without significant toxicity.

With renal cancer cell lines (Caki-1 and 786-0), along with an immortalized normal kidney cell line and primary cultures of kidney cells (RTC 91696), SHetA2 (1), exhibited the following inhibitory data [15]. The maximum inhibition for growth observed in terms of efficacy was 84.40% ± 3.86% for the Caki-1, 72.00% ± 5.06% for the 786-0, 51.05% ± 7.07% for HK-2 normal, and 36.84% ± 6.80% for RTC 91696 normal cell lines. The corresponding potency values [IC50-concentration required to induce half maximal efficacy] were 4.93 $\pm \mu$ mol/L, 7.55% ± 0.38 μ mol/L, 4.50 ± 0.28 μ mol/L, and 4.57 ± 0.49 μ mol/L, respectively [15]. A lack of DNA mutagenicity was also observed with 1 with controls which included SHetA3 (2) and DMSO (solvent). The positive controls caused revertant mutations, which allowed bacteria TA1535, TA 1537, TA 98, TA 100, and WP2 uvrA to grow in histidine-deficient media. Neither SHetA2 (1) or SHetA3 (2) induced a major increase in revertant colony counts in any of the bacterial strains [15].

Pharmacokinetic studies in mice have been performed on 1 as well as the development of an HPLC/UV method to determine the presence of the agent in plasma [20]. Mouse plasma binding protein was found to be 99.3-99.5% at low molar concentrations. Using a two-compartment deconvolution model, oral bioavailability values were found to be 15% at 20 mg/kg and 19% at 60 mg/kg. An internal standard of XK469 (MeXK469) and SHetA2 (1) were isolated from mouse plasma by solid phase extraction. Separation of the analytes was achieved on a C18 column using a mobile phase of acetonitrile and water. Detection by UV was at 341 nm. Dosage via i.v. bolus at 20 mg/kg and oral administration at 20 mg/kg and 60 mg/kg led to linear standard curves between 25 nM and 2500 nM. Coefficients of variation on the data ranged from 11.1% to 1.5%. Recovery was 85.8% for SHetA2 (1) and 80.6% for the standard. Plasma concentrations of ~ 10 mM were achieved in about 5 min in mice, following an i.v. bolus dose. A mean initial $t_{1/2}$ of 40 min and a terminal $t_{1/2}$ of 11.4 h were obtained. Total body clearance was about 1.81 $\mu L/h/kg.$ At steady state, the volume of distribution (V_{disss}) was 20.8 μ L/kg. Thus, the data suggest that SHetA2 (1) is a reasonable candidate for further development as a potential anticancer agent. It was noteworthy that the corresponding urea analog of **1** binds plasma proteins [14] even more efficiently than 1 and has yet to be investigated for activity on a broad scale.

The resistance of normal cells to SHetA2 (1) has been attributed to induction of cell cycle arrest and survival pathways that prevent apoptosis in healthy cells. Specific abnormalities in cancer cells set the integration of these survival pathways to default into apoptosis. Data to support this hypothesis comes from the observation that 1 induces G1 cell cycle arrests in cancer and healthy cell cultures through degradation of cyclin D1 and down-stream signaling consequences involving cyclin E, p21, and Rb [21].

Effect of SHetA2 on Renal and Ovarian Cancer

Kidney cancer constitutes approximately $\sim 3\%$ of all human malignancies with a detection rate of 30,000 new cases per year in US and about 20,000/year in the EU [22]. SHetA2 (1) was

chosen as a lead compound for kidney cancer due to its high growth inhibition across a series of 60 human tumor cell lines at micromolar concentrations [3,15,16]. It was shown that SHetA2 (1) induced apoptosis in the Caki-1 kidney cancer lines through reduction of Bc1-2 protein and induction of PARP-1 and caspase 3 cleavages, whereas normal kidney epithelial cells exhibited resistance [15]. SHetA2 (1) regulated kidney cancer cell growth, differentiation and apoptosis through multiple molecular events by downstream of nuclear factor- κ B repression and independent of cellular redox regulation.

Ovarian and renal cancers are two of the most lethal cancers due to their poor response to chemotherapy and their ability to develop resistance [3]. According to a statistical study, ovarian cancer is the leading cause of gynecologic cancer leading to mortality in women in the United States [23]. A study of 1 on renal and ovarian cancer cells revealed altered secretion of thrombospondin-4 (TSP-4), vascular endothelial growth factor A (VEGF), and fibroblast growth factor (bFGF) proteins from normal and cancerous ovarian and renal cultures [3]. Thymidine phosphorylase (TP) expression was inhibited in cancer, but not normal cultures. Endothelial tube formations were stimulated by 1 on cancer cells, but not on normal cells, and 1 reduced secretion of this angiogenic activity [24]. SHetA2 (1) directly inhibited endothelial cell tube formation and proliferation through G1 cell cycle arrest, but not apoptosis. Recombinant TP reversed SHetA2 anti-angiogenic activity. Moreover, 1 inhibition of in vivo angiogenesis was observed in Caki-1 renal cancer xenografts. The data suggest that 1 inhibits angiogenesis through alteration of angiogenic factor secretion by cancer cells and through direct effects on endothelial cells.

Effect of SHetA2 on Lung Cancer

Recent studies also evaluated the use of SHetA2 (1) as a possible drug to treat lung cancer. SHetA2 (1) effectively inhibits the growth of NSCLC cells both *in vitro* and *in vivo*. The data suggest that 1 triggers ER stress and induces CHOP-dependent DR5 expression, leading to caspase 8-dependant apoptosis [25]. SHetA2 (1) is also believed to activate both the intrinsic and extrinsic pathways of the apoptosis by stress initiation or by cross-talk between the extrinsic and intrinsic apoptosis pathway. Further studies revealed the SHetA2 (1) down regulates c-FLIP in human NSCLC cells which in turn causes induction of apoptosis and enhancement of TRAIL induced apoptosis. This result also complemented the finding of Benbrook and coworkers that the DR5-mediated extrinsic apoptotic pathway played a critical role in SHetA2-induced apoptosis in human NSCLC cells [26].

Synthesis of Metabolite of SHetA2

It is significant that the most useful drugs often require an improvement in hydrophilicity which can increase the aqueous solubility. Higher hydrophilicity sometimes correlates with reduce lipid tissue uptake, which typically results in higher levels of drug availability both in blood or plasma concentrations available for delivery to target tumor cells. It is conceivable that major polar metabolites could result in animals. Consequently, it was imperative to determine the nature of the metabolites from SHetA2 (1). The metabolites are illustrated in (Figure 1) as **14-21**. The objectives were to study the *in vitro* metabolism



tandem mass spectrometry.

of SHetA2 (1) in rat and human liver microsomes and in vivo metabolism in the mouse [17]. The mass spectral fragmentation of 1 was determined, and the metabolism of 1 in human and rat liver microsomes was investigated using multi-stage LC-MS (MSⁿ) on an ion-trap mass spectrometer coupled with a photo diode array (PDA) UV detector set at 340 nm. Incubating 1 in human and rat liver microsomes was done with and without the addition of glutathione (GSH) [17]. Separation of 1 and its metabolites was accomplished on a narrow-bore C18 column with a gradient of two eluents: A, 5% acetonitrile, 0.01% TFA and B, 95% acetonitrile, 0.01% TFA. Monitoring of the disappearance of SHetA2 (1) and the formation of its metabolites was performed at various times in human and rat liver microsomes over 1 hour. Following i.v. and p.o. administration of **1** in the mouse at 20 mg/ kg and 40 mg/kg, respectively, both plasma and metabolite levels of SHetA2 (1) were monitored for 18 hour by HPLC-UV. The in vitro studies in the absence of GSH revealed oxidation of the four methyl groups of 1 which were labeled as one mono-, two di-, and one tri-hydroxylated metabolite. In the presence of GSH, the same primary metabolites were detected along with four GSH adducts of 1. In vivo monohydroxylated metabolites were also found in mouse and rat plasma. Two GSH adducts ${\bf 20}$ and ${\bf 21}$ of ${\bf 1}$ were observed in rat liver following bolus i.v. administration of ${\bf 1}$ at 40 mg/kg. It is clear that compounds with increased polarity are the major metabolites from SHetA2 (1) in rats and human liver microsomes.

As described above, 7 metabolites were identified from SHetA2 (1) [17]. The preparation of metabolite **15** has been accomplished in a multi-step synthesis along with a potential prodrug **22**. Initial screening by the National Cancer Institute indicated that both **15** and the prodrug **22** possessed low activity in all of the tests. Since the oxidative pathway for SHetA2 primarily involves the sulfur-containing ring, especially the attached methyl groups, the activity of SHetA2 (**1**) may require the hydrophobic germinal dimethyl groups on the ring for maximum utility. Efforts are

underway to grow crystals suitable for X-ray analysis of SHetA2 (1) and of one or more metabolites. In addition, searches are being conducted to determine if a specific enzyme is inactivated by 1 and if a crystal can be grown with the agent docked in its binding site. Such structural information will be instructive regarding preferred conformation of the molecule(s) in the solid state and for an improved design for chemotherapeutic agents related to 1.

Synthesis of Metabolite 15 and Prodrug 22 of SHetA2



The metabolite **15** and the prodrug **22** were synthesized in a 14-step linear sequence starting with thiophenol (**3**) (Scheme III) [27]. Michael addition of **3** with 3-methyl-2-butenoic acid (**23**) using piperdine as the base gave 3-(phenylthio)-3-butenoic acid (**24**), which was then subjected to ring closure using polyphosphoric acid to afford 2,2-dimethylthiochroman-4-one (**25**). Conversion of **25** to the trimethylsilyl cyanohydrin **26**, followed by treatment with phosphorus oxychloride in benzene/ pyridine, provided the unsaturated carbonitrile **27**. Saturation of the double bond in **27** with sodium borohydride generated **28**, which was alkylated with CH_3I and NaH to give **29**. Hydrolysis of the nitrile group gave acid **30**, which on reduction, afforded the key intermediate alcohol **31**.

Acylation of 31 with acetic anhydride and DMAP in methylene



JSM Chem 1(1): 1005 (2013)

chloride gave the corresponding acetate intermediate **32**. The reaction of **32** using an $\text{HNO}_3/\text{Ac}_2\text{O}$ produced the nitro ester **33** in a low yield (~20%). Most reactions prior to nitration and after nitration all gave good to excellent yields. The nitration step proceeded poorly since the required conditions oxidized the sulfur and also led to increased yields of the product nitrated at C-8. Reduction of the nitro group in **33** using iron and acetic acid at 115 °C afforded the amine **34**. Saponification of **34** was accomplished to give amino alcohol **35**. Treatment of **34** and **35** with 4-nitrophenylisothiocyanate in dry THF generated the products **15** and **22**, respectively, in high yields.

Preliminary Docking Studies

A experimental study was conducted with **1** and **15** at Ambit Biosciences Corporation [4215 Sorrento Valley Blvd, San Diego, C 92121] for activity against B-Raf Kinase [27,28].The technique employed was an active-site dependent competition binding assay with an immobilized, active site directed ligand. In the competitive studies, the percent control for **1** was 87% with B-Raf while that of its mutant [B-Raf-V600E] was 77%. Interestingly, **1** with KIT kinase gave Kd values of 820 nM for KIT and 1300 nM for KIT-V559D.

The corresponding K_d values for **15** were 1200 nM and 4100 nM [27]. Although the activity is less for **1** with the kinases examined, compared to standards cited, additional work is needed to ascertain if other kinases will respond to the action of **1**.

To assess the activity of **15**, molecular docking experiments employed using Glide (version 5.6, Schrodinger suite 2010) [27] and crystal structures of B-Raf (IUWJ.pdb) and KIT (IT46.pdb) were downloaded from the PDB [27,29-31]. Using the crystal structure of KIT (Figure 2) and by comparing the docking ability of the well-known anticancer agent, Imatinib, it was possible to evaluate the interactions of **15** versus Imatinib in the binding pocket. The H-bonding of **15** with two amino acids in the binding pocket of KIT were identical to that involving Imatinib as was true for hydrophobic contacts. Glide docking scores were -11.97 for Imatinib and -8.70 for **15**, with a lower score indicating greater binding affinity. Thus, **15** is suggested to have potential as a possible chemotherapeutic agent for select malignancies.

In summary, SHetA2 (1) has exhibited useful pharmaceutical properties, has low toxicity as determined in mice and dogs, can be quantitatively detected in plasma, has a mean $t_{1/2}$ of about 40 min as observed in mice, and has displayed a significant differential for inducing apoptosis in cancer cells compared to healthy cells [10,11]. Moreover, the agent has shown strong activity against head/neck cancer cells [5,9] ovarian cancer cells [8,14] and kidney cancer cells [15] as discussed. Mechanistic studies to date have revealed that 1 induces an intrinsic apoptosis pathway through induction of mitochondrial swelling and release of cytochrome c, reduction of Bc1-2 levels, exposure to phosphatidyl serine on the cell surface, and activation of caspase 9 and caspase 3 [8,10,11,15]. Normal cells are resistant to these mitochondrial effects and to apoptosis [10]. It is speculated that the overall influence of SHetA2 (1) may be the result of changes in the membrane of cancer cells compared to normal cells. This remains to be defined by experiment. Nevertheless, based on



Figure 2 Plausible binding mode of 15 with the crystal structure of KIT by molecular docking. Agent 15 is in green stick and ball representation, and the magneta dashed lines represent the hydrogen bond interactions. Permission was granted by the Copyright Clearance Center Inc. of Taylor and Frances for this Figure [http://www.informaworld.com.].

the information gathered to date on agent **1**, the chemistry and the biology strongly suggest that SHetA2 (**1**) should proceed to clinical trials.

REFERENCES

- Liu S, Brown CW, Berlin KD, Dhar A, Guruswamy S, Brown D, et al. Synthesis of flexible sulfur-containing heteroarotinoids that induce apoptosis and reactive oxygen species with discrimination between malignant and benign cells. J Med Chem. 2004; 47: 999-1007.
- Brown CW, Liu S, Klucik J, Berlin KD, Brennan PJ, Kaur D, et al. Novel heteroarotinoids as potential antagonists of Mycobacterium bovis BCG. J Med Chem. 2004; 47: 1008-1017.
- 3. Myers T, Chengedza S, Lightfoot S, Pan Y, Dedmond D, Cole L, et al. Flexible heteroarotinoid (Flex-Het) SHetA2 inhibits angiogenesis in vitro and in vivo. Invest New Drugs. 2009; 27: 304-318.
- Benbrook DM, Madler MM, Spruce LW, Birckbichler PJ, Nelson EC, Subramanian S, et al. Biologically active heteroarotinoids exhibiting anticancer activity and decreased toxicity. J Med Chem. 1997; 40: 3567-3583.
- Zacheis D, Dhar A, Lu S, Madler MM, Klucik J, Brown CW, et al. Heteroarotinoids inhibit head and neck cancer cell lines in vitro and in vivo through both RAR and RXR retinoic acid receptors. J Med Chem. 1999; 42: 4434-4445.
- 6. Dhar A, Liu S, Klucik J, Berlin KD, Madler MM, Lu S, et al. Synthesis, structure-activity relationships, and RARgamma-ligand interactions of nitrogen heteroarotinoids. J Med Chem. 2000; 43; 303.
- Benbrook DM, Subramanian S, Gale JB, Liu S, Brown CW, Boehm MF, et al. Synthesis and characterization of heteroarotinoids demonstrate structure specificity relationships. J Med Chem. 1998; 41: 3753-3757.
- Guruswamy S, Lightfoot S, Gold MA, Hassan R, Berlin KD, Ivey RT, et al. Effects of retinoids on cancerous phenotype and apoptosis in organotypic cultures of ovarian carcinoma. J Natl Cancer Inst. 2001; 93: 516-525.
- 9. Chun KH, Benbrook DM, Berlin KD, Hong WK, Lotan R. The synthetic heteroarotinoid SHetA2 induces apoptosis in squamous carcinoma cells through a receptor-independent and mitochondria-dependent pathway. Cancer Res. 2003; 63: 3826-3832.

- 10. Liu T, Hannafon B, Gill L, Kelly W, Benbrook D. Flex-Hets differentially induce apoptosis in cancer over normal cells by directly targeting mitochondria. Mol Cancer Ther. 2007; 6: 1814-1822.
- 11. Benbrook DM, Kamelle SA, Guruswamy SB, Lightfoot SA, Rutledge TL, Gould NS, et al. Flexible heteroarotinoids (Flex-Hets) exhibit improved therapeutic ratios as anti-cancer agents over retinoic acid receptor agonists. Invest New Drugs. 2005; 23: 417-428.
- 12.Benbrook DM, Lightfoot S, Ranger-Moore J, Liu T, Chengedza S, Berry WL, et al. Gene expression analysis of biological systems driving an organotypic model of endometrial carcinogenesis and chemoprevention. Gene Regul Syst Bio. 2008; 2: 21-42.
- 13. Tallent CR, Twine Jr. CE, Risbood P, Seltzmann HH. An improved preparation of 2,2,4,4-tetramethyl-6-aminothiochroman, a key intermediate to urea and thiourea heteroarotinoids for anticancer studies. Org. Prep. Proced. Int. 2007; 39: 96-101.
- 14. Le TC, Berlin KD, Benson SD, Eastman MA, Bell-Eunice G, Nelson AC, et al. Heteroarotinoids with anti-cancer activity against ovarian cancer cells. Open Med Chem J. 2007; 1: 11-23.
- 15. Liu T, Masamha CP, Chengedza S, Berlin KD, Lightfoot S, He F, et al. Development of flexible-heteroarotinoids for kidney cancer. Mol Cancer Ther. 2009; 8: 1227-1238.
- 16. Kabirov KK, Kapetanovic IM, Benbrook DM, Dinger N, Mankovskaya I, Zakharov A, et al. Oral toxicity and pharmacokinetic studies of SHetA2, a new chemopreventive agent, in rats and dogs. Drug Chem Toxicol. 2013; 36: 284-295.
- 17.Liu Z, Zhang Y, Hua YF, Covey JM, Benbrook DM, Chan KK, et al. Metabolism of a sulfur-containing heteroarotionoid antitumor agent, SHetA2, using liquid chromatography/tandem mass spectrometry. Rapid Commun Mass Spectrom. 2008; 22: 3371-3381.
- Hennessy BT, Coleman RL, Markman M. Ovarian cancer. Lancet. 2009; 374: 1371-1382.
- 19. Kim A, Ueda Y, Naka T, Enomoto T. Therapeutic strategies in epithelial ovarian cancer. J Exp Clin Cancer Res. 2012; 31: 14.
- 20.Zhang Y, Hua Y, Benbrook DM, Covey JM, Dai G, Liu Z, et al. High performance liquid chromatographic analysis and preclinical pharmacokinetics of the heteroarotinoid antitumor agent, SHetA2. Cancer Chemother Pharmacol. 2006; 58: 561-569.
- 21. Masamha CP, Benbrook DM. Cyclin D1 degradation is sufficient to induce G1 cell cycle arrest despite constitutive expression of cyclin E2 in ovarian cancer cells. Cancer Res. 2009; 69: 6565-6572.
- 22. Kirkali Z, Tuzel E, Mungan MU. Recent advances in kidney cancer and metastatic disease. BJU Int. 2001; 88: 818-824.
- 23.Greenlee RT, Murray T, Bolden S, Wingo PA. Cancer statistics, 2000. CA Cancer J Clin. 2000; 50: 7-33.
- 24. Chengedza S, Benbrook DM. NF-kappaB is involved in SHetA2 circumvention of TNF-alpha resistance, but not induction of intrinsic apoptosis. Anticancer Drugs. 2010; 21: 297-305.
- 25. Lin Y, Liu X, Yue P, Benbrook DM, Berlin KD, Khuri FR, et al. Involvement of c-FLIP and survivin down-regulation in flexible heteroarotinoidinduced apoptosis and enhancement of TRAIL-initiated apoptosis in lung cancer cells. Mol Cancer Ther. 2008; 7: 3556-3565.
- 26. Lin YD, Chen S, Yue P, Zou W, Benbrook DM, Liu S, et al. CAAT/enhancer binding protein homologous protein-dependent death receptor 5 induction is a major component of SHetA2-induced apoptosis in lung cancer cells. Cancer Res. 2008; 68: 5335-5344.
- 27. Nammalwar B, Bunce RA, Benbrook DM, Lu T, Li H-F, Chen Y-D, et al. Synthesis of N-[3,4-dihydro-4-(hydroxymethyl)-2,2,4-trimethyl-2H-1-

benzothiopyran-6-yl]-N'-(4-nitrophenyl)thiourea, a major metabolite of N-{3,4-dihydro-2,2,4,4-tetramethyl-2H-1-benzothiopyran-6-yl}-N'-(4-nitrophenyl)-thiourea. Phosphorus, Sulfur, and Silicon and The Related Elements. 2011; 186: 189-204. Figure 2 is reprinted by permission of the publisher [Taylor & Frances Ltd. http://www.tandf. co.uk/journals].

- 28.Bamborough P, Drewry D, Harper G, Smith GK, Schneider K. Assessment of chemical coverage of kinome space and its implications for kinase drug discovery. J Med Chem. 2008; 51: 7898-7914.
- 29. Wilhelm S, Carter C, Lynch M, Lowinger T, Dumas J, Smith RA, et al. Discovery and development of sorafenib: a multikinase inhibitor for treating cancer. Nat Rev Drug Discov. 2006; 5:835-844.
- 30. Mol CD, Dougan DR, Schneider TR, Skene RJ, Kraus ML, Scheibe DN, et al. Structural basis for the autoinhibition and STI-571 inhibition of c-Kit tyrosine kinase. J Biol Chem. 2004; 279: 31655-31663.
- 31. Wan PT, Garnett MJ, Roe SM, Lee S, Niculescu-Duvaz D, Good VM, et al. Mechanism of activation of the RAF-ERK signaling pathway by oncogenic mutations of B-RAF. Cell. 2004; 116: 855-867.

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