Pergamon

Bioorganic & Medicinal Chemistry Letters 10 (2000) 699–701

BIOORGANIC & MEDICINAL CHEMISTRY LETTERS

Antitumor Agents. Part 202: Novel 2′-Amino Chalcones: Design, Synthesis and Biological Evaluation†

Yi Xia, Zheng-Yu Yang, Peng Xia, Kenneth F. Bastow, Yuka Nakanishi and Kuo-Hsiung Lee*

Natural Products Laboratory, School of Pharmacy, University of North Carolina, Chapel Hill, NC 27599, USA

Received 6 December 1999; accepted 20 January 2000

Abstract—New 4′,5′,2,3,4-substituted 2′-amino chalcones were synthesized and evaluated for cytotoxicity against a panel of human tumor cell lines. Several compounds displayed significant cytotoxicity. The most promising lead molecule (**10**) also had high activity toward multi-drug resistant KB-VIN, and ovarian 1A9 cell lines. 2′-Amino chalcones demonstrated significantly increased antitumor activity compared with the corresponding chalcones, while, the epoxide derivatives generally showed greatly reduced activity.

Chalcones (1,3-diaryl-2-propen-1-ones, **1**) display interesting biological activities, including antimalarial,[1] anti-inflammatory,[2] cytotoxic,[3–5] and anticancer properties.[6,7] A number of chalcones have been reported to be active antimitotic agents inhibiting tubulin polymerization.[8] In our continuing study of antimitotic antitumor agents, we discovered that 2-phenyl-4-quinolones (**3**) and 2-phenyl-2,3-dihydro-4-quinolones (**4**) displayed potent cytotoxicity against a panel of human tumor cell lines.[9–11] Furthermore, some quinolones showed in vivo anticancer activity; in the xenograft ovarian OVCAR-3 model, treated mice demonstrated a 130% increase in life span. Structurally, 2′-amino-chalcones (**2**) are the fragmented analogues of 2-phenyl-4-quinolones and have an uncyclized B ring. However, the synthesis of 2′-amino chalcones for cytotoxic and anticancer properties appears to be an unexplored field. In addition, a number of α,β-unsaturated ketones have demonstrated preferential reactivity toward thiols.[12,13] Alkylation with a cellular thiol such as glutathione (GSH) may also occur with chalcones, leading to adducts at the β-position. Hence, these α,β-unsaturated ketones may be free from the problems of mutagenicity and carcinogenicity that are associated with many alkylating agents used in cancer chemotherapy.[14,15] The aim of the present investigation therefore was to prepare a number of such prototypic molecules and related analogues in order to evaluate their cytotoxic activity (Fig. 1).

As shown in Scheme 1, 2′-amino chalcones (**7**–**11**) were synthesized by a base-catalyzed condensation of appropriately substituted 2-amino acetophenone **5** and aldehyde **6**.[16] Reacting compounds **7**, **9** and **10** with hydrogen peroxide afforded the corresponding α,β-epoxide derivatives **12**–**14**.[17]

The substituted 2′-amino chalcones and derivatives **7**–**14** were assayed for cytotoxicity in vitro against nine human tumor cell lines, including epidermoid carcinoma of the nasopharynx (KB), P-gp-expressing epidermoid carcinoma of the masopharynx (KB-VIN), ostcosarcoma (Hos), melanoma (SKMEL-2), ileocecal carcinoma (HCT-8), breast cancer (MCF-7), lung carcinoma (A-549), glioblastoma (U87-MG), and ovarian cancer (1A9) cell lines.

From the ED_{50} values summarized in Table 1, compounds **7**–**11** showed significant ($ED_{50} \leq 4.0$ mg/mL) cytotoxic activity, especially selectivity against KB, KB-VIN and 1A9 cell lines. Compound **10**, which contained a methylenedioxy moiety at the 4′, 5′ positions and a methoxy group at the 3 position, was the most active compound in this study.

By comparing the cytoxic activities of compounds with different substitutions as well as at different positions, the following conclusions were reached: (a) Introducing

*Corresponding author. Tel.: +1-919-962-0066; fax: +1-919-966-3893; e-mail: khlee@unc.edu

†For part 201 see Ishida, J.; Wang, H. K.; Bastow, K. F.; Hu, C. Q.; Lee, K. H. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 3319.

0960-894X/00/$ - see front matter
PII: S0960-894X(00)00072-X

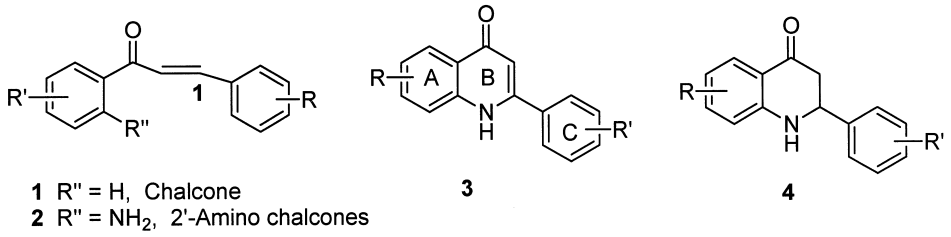
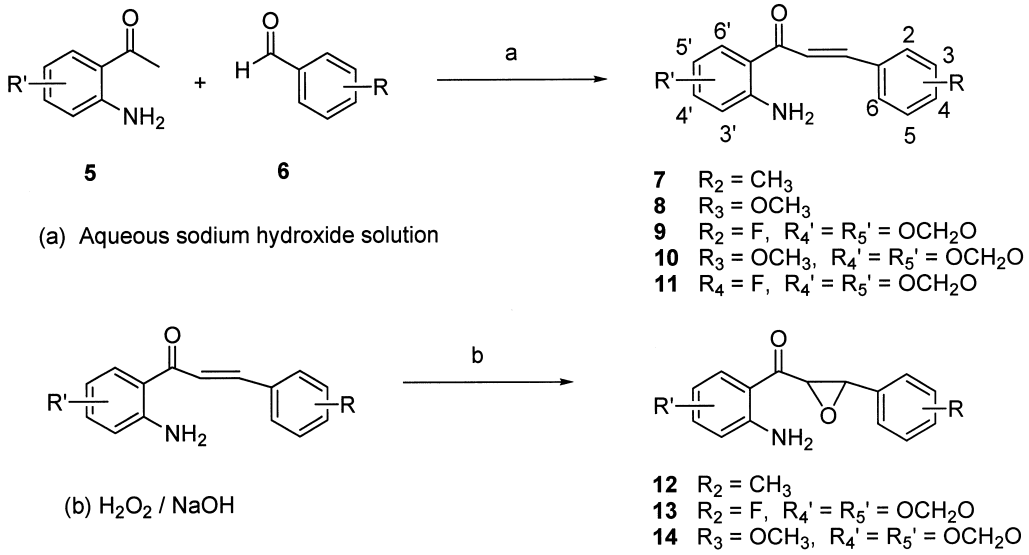


Figure 1.



Scheme 1. General synthetic routes to 2′-amino chalcones.

Table 1. In vitro cytotoxic activities of 4′, 5′, 2,3,4-substituted 2′-amino chalcones[18]

	ED_{50} (μg/mL)[a]								
	KB[b]	KB-VIN[b]	HOS[b]	SKMEL-2[b]	HCT-8[b]	MCF-7[b]	A-549[b]	U87-MG	1A9[b]
7	1.35	1.25	4.00	5.10	9.80	6.10	3.50	>10(34)	1.20
8	0.65	0.30	2.00	3.50	4.50	1.30	1.20	5.10	0.80
9	1.50	0.95	4.00	6.50	3.00	2.60	2.00	7.00	1.50
10	0.52	0.30	2.40	2.30	1.50	0.48	0.45	8.00	0.35
11	3.10	2.20	6.00	9.00	6.50	5.10	4.20	>10(49)	3.50
12	15.50	11.50	>20(47)[c]	>20(45)	>20(41)	19.50	17.00	>20(28)	12.50
13	15.40	2.30	4.00	9.50	4.80	2.30	3.50	9.00	1.85
14	2.00	1.30	4.50	9.80	2.10	1.10	2.00	5.00	1.20
15	18.70	14.00	>20(42)	>20(42)	>20(28)	19.00	18.50	>20(20)	15.00

[a]ED_{50} was the concentration of compound which affords 50% reduction in cell number after 3 days incubation.
[b]Human epidermoid carcinoma of the nasopharynx (KB), pgP-expressing human epidermoid carcinoma of the nasopharynx (KB-VIN), ostcosarcoma (Hos), human melanoma cancer (SKMEL-2), human ileocecal carcinoma (HCT-8), human breast cancer (MCF-7), human lung carcinoma (A-549), and human ovarian cancer (1A9).
[c]Inhibition < 50% at the highest test concentration (percentage observed is given in brackets).

the methylenedioxy moiety at the 4′, 5′ position (**10**) led to enhanced cytotoxic activity compared with the A-ring unsubstituted compound **8**. (b) The methoxy group at the 3-position was greatly beneficial for increased cytotoxicity. Compound **10** was about 3- and 6-times as active as **9** and **11**, respectively, and **8** with a 3-methoxy was also more active than **7**. Compounds **8** and **10** displayed significant cytotoxic effects with ED_{50} values less than 1 μg/mL against KB and 1A9 cell lines. (c) Converting the α/β unsaturated ketones (**7**, **9** and **11**) to the corresponding epoxides (**12**, **13** and **14**) dramatically reduced the cytotoxicity. Thus, although the epoxy group might also act as a second alkylating moiety,[15] the α,β-unsaturated ketone moiety of 2′-amino chalcones appears to play an important role in thiol/enzyme-alkylation, preferentially via Michael addition.[15] This result demonstrated that the double bond is the essential moiety for chalcones as antitumor agents.

In addition, all 2′-amino chalcones showed fairly good activity against nasopharynx (KB), breast (MCF-7), and lung (A549) cell lines as well as increased activity against ovarian cancer (1A9). In comparing chalcones with and without the amino group at the 2′-position **9** was about 40-fold more active than the corresponding 3-methoxy-4′,5′-methylenedioxy chalcone (**15**), which does not contain the 2′-amino group. In addition, 2′-amino chalcones showed better tumor selectivity than the corresponding 2-phenyl-4-quinolones,[10,11] which are cyclic α,β-unsaturated ketones. Additional mechanism studies are ongoing to better understand the results.

In summary, we have discovered a novel class of 2′-amino chalcones as potential antitumor agents. The position and the size of the substituents seem to be important for antitumor activity in the 2′-amino chalcones. Compound **10** with a methylenedioxy moiety at the 4′, 5′ positions and methoxy group at the 3-position is the lead compound with potent cytotoxic activity. Evaluation against multi-drug resistance cells, as well as further SAR studies, are continuing.

Acknowledgements

This investigation was supported by grant CA-17625 from the National Cancer Institute awarded to K. H. Lee.

References and Notes

1. Li, R.; Kenyon, G. L.; Cohen, F. E.; Chen, X.; Gong, B.; Dominguez, J. N.; Davidson, E.; Kurzban, G.; Miller, R. E.; Nuzman, E. O. *J. Med. Chem.* **1995**, *38*, 5031.
2. Ballesteros, J. F.; Sanz, M. J.; Ubeda, A.; Miranda, M. A.; Iborra, S.; Paya, M.; Alcaraz, M. J. *J. Med. Chem.* **1995**, *38*, 2794.
3. Dimmock, J. R.; Kandepu, N. M.; Hetherington, M.; Quail, J. W.; Pugazhenthi, U.; Sudom, A. M.; Chamankhah, M.; Rose, P.; Pass, E.; Allen, T. M.; Halleran, S.; Szydlowski, J.; Mutus, B.; Tannous, M.; Manavathu, E. K.; Myers, T. G.; Clercq, E. D.; Balzarini, J. *J. Med. Chem.* **1998**, *41*, 1014.
4. Yit, C. C.; Das, N. P. *Cancer. Lett.* **1994**, *82*, 65.
5. Satomi, Y. *Int. J. Cancer* **1993**, *55*, 506.
6. Wattenberg, L. W.; Coccia, J. B.; Galhaith, A. R. *Cancer Lett.* **1994**, *83*, 165.
7. Dinkova-Kostova, A. T.; Abeygunawardana, C.; Talalay, P. *J. Med. Chem.* **1998**, *41*, 5287.
8. Edwards, M. L.; Stemerick, D. M.; Sunkara, P. S. *J. Med. Chem.* **1990**, *33*, 1948.
9. Li, L.; Wang, H. K.; Kuo, S. C.; Wu, T. S.; Lednicer, D.; Lin, C.; Hamel, E.; Lee, K. H. *J. Med. Chem.* **1994**, *37*, 3400.
10. Li, L.; Wang, H. K.; Kuo, S. C.; Wu, T. S.; Lednicer, D.; Lin, C.; Hamel, E.; Lee, K. H. *J. Med. Chem.* **1994**, *37*, 1126.
11. Xia, Y.; Yang, Z. Y.; Xia, P.; Bastow, K.; Tachibana, Y.; Kuo, S. C.; Hamel, E.; Hackl, T.; Lee, K. H. *J. Med. Chem.* **1998**, *41*, 1155.
12. Lee, K. H.; Huang, E. S.; Piantadosi, C.; Pagano, J.; Geissman, T. A. *Cancer Res.* **1971**, *31*, 1649.
13. Dimmock, J. R.; Raghavan, S. K.; Logan, B. M.; Bigam, G. E. *Eur. J. Med. Chem.* **1983**, *18*, 248.
14. Benvenuto, J. A.; Connor, T. H.; Monteith, D. K.; Laidlaw, J. L.; Adams, S. C.; Matney, T. S.; Theiss, J. C. *J. Pharm. Sci.* **1993**, *82*, 988.
15. Lee, K. H.; Hall, I. H.; Starness, C. D.; Elgebaly, S. A.; Waddell, T. G.; Hadgraft, R. T.; Ruffner, C. G.; Weidner, I. *Science* **1977**, *196*, 533.
16. Dhar, D. N. *The Chemistry of Chalcones and Related Compounds*; John Wiley and Sons: New York, 1981.
17. All new compounds gave satisfactory analytical and spectroscopic data. Selected spectroscopic data for **2-2′-Amino-3-methoxy-4′,5′-methylenedioxy-chalcone** (**10**): ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.87 (s, 3H, OCH_3), 5.95 (s, 2H, OCH_2O), 6.20 (s, 1H, 3′-H), 6.65 (br, 2H, NH_2), 6.94 (m, 1H, 4-H), 7.14–7.36 (m, 4H, H-6′, H-2, H-5, H-6), 7.48 (d, $J=15.5$ Hz, 1H, H-α), 7.68 (d, $J=15.5$ Hz, 1H, H-β); MS (M^+) 297.10.
18. The cytotoxic assay was performed previously as described in ref 11.