Pergamon

Bioorganic & Medicinal Chemistry Letters, Vol. 4, No. 22, pp. 2701-2704, 1994

0960-894X/94 $7.00+0.00

0960-894X(94)00403-X

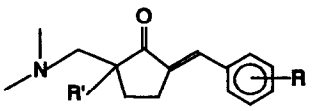
2-(1-CYCLOPENTEN-1-YL)-2-[2-(DIMETHYLAMINO)ETHYL]-5-(E)-BENZYLIDENE CYCLOPENTANONE HYDROCHLORIDES: A NEW SERIES OF MODERATE CYTOTOXIC AGENTS

Haitao Chen[‡*], Zhizhong Ji[+], Lan K. Wong[‡⊗], Jerome F. Siuda[‡*], Ven L. Narayanan[#]

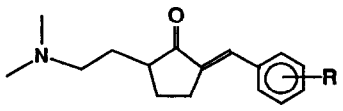
[‡]*School of Pharmacy, University of Pittsburgh, Pittsburgh, Pennsylvania 15261*
[+]*Shenyang College of Pharmacy, Shenyang, P. R. China*
[⊗]*BIOVAIL/IWF Research, Scarborough, Ontario, Canada, M1L 4S4*
[#]*Drug Synthesis & Chemistry Branch, National Cancer Institute, NIH, Bethesda, MD 20205*

Abstract: A series of 2-(1-cyclopenten-1-yl)-2-[2-(dimethylamino)ethyl]-5-(E)-benzylidene cyclopentanone hydrochlorides **5**, were synthesized and demonstrated cytotoxic activity toward human cancer cell lines. A possible mechanism of **5** at the molecular level is suggested.

In previous reports[1,2] on arylidene and alkylidene cyclopentanone Mannich bases, we described the role of the aminomethyl moiety, i.e. Mannich base portion, in cytotoxic activity. We reasoned that substances such as **1a** possessed cytotoxic action because of an ability to form as exocyclic methylene by a 1,2- elimination of the amine. The CH_2=C—C=O unit generated from **1a** could serve as an alkylating agent by a 1,4-Michael addition from a biological nucleophile. This proposal is not inconsistent with other observations.[3] Structure **1b**,[4] and Mannich base homologs such as **2**,[5] did not possess cytotoxic activity possibly due to the inability to act as progenitors of α-methylene cyclopentanones. On the other hand, **1a**, **1b**, and **2** had antiinflammatory properties.[1,4]



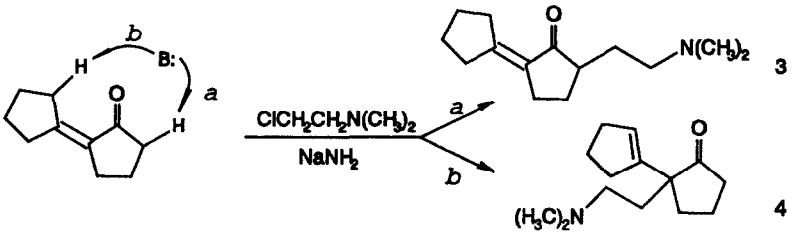
1a, R' = H
1b, R' = CH_3



2

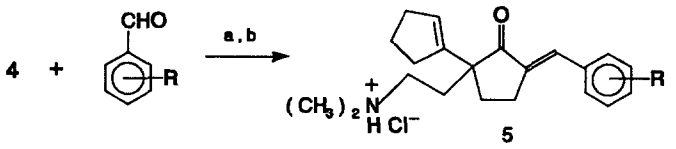
In order to a) test our hypothesis that the Mannich base moiety is necessary for cytotoxic activity in these cyclopentanones, and b) obtain antiinflammatory compounds without cytotoxic properties, we required a structure which could not produce the H_2C=C—C=O unit. An attempt to prepare the Mannich base homolog **3**, from 2-cyclopentylidene cyclopentanone and 2-dimethyl-

aminoethyl chloride through pathway "*a*" was unsuccessful. Rather, abstraction of the proton α to the ethylenic group apparently occurred,[6] resulting in a shift of the double bond and ensuing substitution to give **4**, as described by pathway "*b*". Reaction circumstances thus provided entry to **5** which still met our structural requirements but possessed a cyclopentenyl moiety at the C-2 atom.



Type **5** compounds were synthesized by Claisen-Schmidt condensation of **4** with various benzaldehydes under basic conditions (Scheme 1).[7,8]

Scheme 1



(a) OH^- / MeOH, r.t. (b) HCl

As expected, some compounds of type **5** had significant antiinflammatory activity.[8] Contrary to our expectations, **5a-h** also possessed moderate cytotoxic activity in various human cancer cell lines according to NCI's in vitro anticancer screening[9] (Table 1). The most potent substances were **5e** and **5f**. With the exception of compound **5e**, all compounds gave featureless Mean Graphs which indicated a lack of sub-panel selectivity. (Data not shown.) However, **5e** demonstrated significant selectivity to melanoma cell lines at all three levels, i.e. GI50, TGI and LC50. The characteristics of the Mean Graphs of compound **5e** were completely different from that of any of the other benzylidene cyclopentanone analogs, which showed no subpanel selectivity to melanoma cell lines. Overall, the absence of cytotoxic properties of **1b**, hint to the special effects of the cyclopentenyl group in **5**.

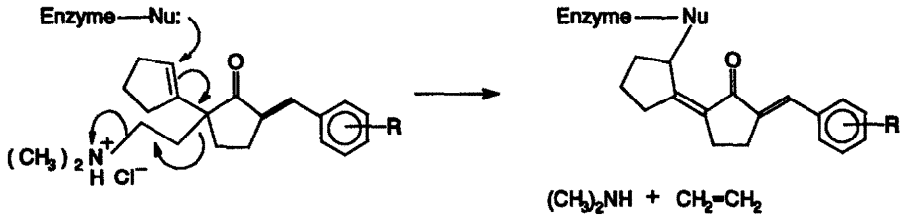
Table 1. Some physical and cytotoxic data for 2-(1-cyclopenten-1-yl)-2-[2-(dimethylamino)ethyl]-5-(E)-benzylidene cyclopentanone hydrochlorides (5).

Compd[a]	R	mp[b] (°C)	Yield (%)	Cytotoxic MG-MID values[c] Log GI50	Log TCI	Log LC50
5a	H	212-4	60	-4.79	-4.49	-4.20
5b	4-OCH_3	204-6	62	-4.75	-4.42	-4.15
5c	2-OCH_3	163-5	45	-4.80	-4.43	-4.15
5d	3-OCH_3	181-3	56	-4.81	-4.52	-4.23
5e	4-Cl	240-2	70	-5.15	-4.72	-4.35
5f	3-Br, 4-OCH_3	215-7	37	-5.35	-4.89	-4.45
5g	3,4-(OCH_2O)	220-2	53	-4.83	-4.52	-4.22
5h	2-Cl	222-4	47	-4.93	-4.56	-4.22

[a] Spectroscopic data including ^1H NMR, IR and MS were consistent with the assigned structures; elemental analysis were within ± 0.3% of the theoretical values. [b] All compounds were recrystallized from EtOH. [c] Meangraph-midpoint values (NCI data). Totally, about 60 human cancer cell lines were used for screening.

Although an α-methylene ketone would not be directly available from **5**, we suggest that alkylation may arise via nucleophilic attack of a biologically important molecule (enzyme ?) at the double bond of the cyclopentenyl group leading to an irreversibly inactivated enzyme (Scheme 2). The resulting structure can undergo a second alkylation via a 1,4- Michael addition thus making **5** a potential bis-alkylating agent.[10] On conjecture that both structural types **1a** and **5** function as alkylating agents of biological nucleophiles, two different mechanisms are plausible in explaining their anti-cancer action. Future research on non-Mannich bases having substituents at the C-2 atom of the cyclopentanone may prove useful in evaluating the mechanism of cytotoxic action as well as uncovering the significant structural parameters of antiinflammatory activity.

Scheme 2



In summary, **5** represents a new series of cytotoxic compounds. All of the synthesized compounds showed no subpanel selectivity except compound **5e** which gave unique selectivity to melanoma cell lines. Replacement of the 2-cyclopentenyl moiety by a saturated cyclopentanone and by other alkenyl groups could be beneficial to future structure-activity relationships. The proposed mechanism for **5** may also provide a new approach to design anticancer agents or other irreversible enzyme inhibitors.

Acknowledgements: We thank Baofeng Zhang and Qinghai Yu for their assistance in the antiinflammatory tests. Appreciation is also extended to Nancy Urista for arranging and typing the manuscript.

References and Notes

1. Chen, H.; Jing, Y.; Ji, Z.; Zhang, B. *Acta Pharmaceutica Sinica.* **1991**, *26*, 183.
2. Chen, H.; Ji, Z.; Wong, L.; Siuda, J.F.; Narayanan, V.L. *Bioorg. & Med. Chem.* In press.
3. (a) Lee, K-H.; Huang, E-S.; Piantadosi, C.; Pagano, J.S.; Geissman, T.A. *Cancer Research.* **1971**, *31*, 1649. (b) Dimmock, J.R.; Taylor, W.G. *J. Pharm. Sci.* **1975**, *64*, 241. (c) Dimmock, J.R.; Phillips, O.A.; Wonko, S.L.; Hickie, R.A.; Tuer, R.G.; Ambrose, S.J.; Reid, R.S.; Mutus, B.; Talpas, C.J. *Eur. J. Med. Chem.* **1989**, *24*, 217.
4. Chen, H.; Ji, Z.; Wong, L.; Siuda, J.F.; Narayanan, V.L. Submitted for publication.
5. Chen, H. Ph.D. Dissertation. Shenyang College of Pharmacy, Shenyang, P. R. China, 1991.
6. Ueberwasser, H. *Ger. Pat.* 1, 059, 901, June 25, 1959. *CA*, **1962**, *56*, 355f.
7. In a typical reaction, 3.2 ml of 5N NaOH was added dropwise to a solution containing 4.0 mmol of the starting cyclopentenyl cyclopentanone and 8.0 mmol of the substituted benzaldehyde. After stirring at room temperature for 12 h, 50 ml of H_2O was added and the solution extracted with ethyl ether. The organic phase was in turn extracted with 6N HCl. The combined acid extracts were basified and re-extracted with ether. After drying, the ether extract was treated with HCl-EtOH to furnish a precipitate which was crystallized from EtOH to give **5** as a pure product.
8. In the rat paw edema test, compounds **5b** and **5d** gave 34% and 42% inhibition of swelling respectively, relative to control.
9. Boyd, M.R. *Cancer: Principles and Practice of Oncology Update*; Devita, V.T., Jr., Ed.; J.B. Lippincott: Philadelphia, 1989; Vol. 3(10) pp 1-12.
10. One may argue that a 1,4-Michael addition can also take place at the benzylidene site. If that were the case, then structure **2** should exhibit some cytotoxic action, but it does not. Furthermore, our preliminary evidence (Reference 2) suggests only monoalkylation of **1a**.

(*Received in USA* 31 *August* 1994; *accepted* 17 *October* 1994)