Pergamon

Bioorganic & Medicinal Chemistry Letters 8 (1998) 2877–2880

BIOORGANIC & MEDICINAL CHEMISTRY LETTERS

POLYCYCLIC AROMATIC COMPOUNDS AS ANTICANCER AGENTS: SYNTHESIS AND BIOLOGICAL EVALUATION OF SOME CHRYSENE DERIVATIVES

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Received 15 June 1998; accepted 4 September 1998

Abstract: Synthesis and biological evaluation of new chrysene derivatives aimed at the development of anticancer agents were carried out.

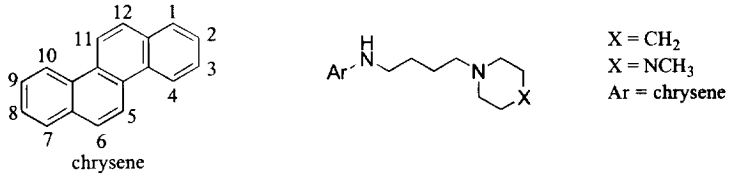
Polycyclic aromatic compounds are widely distributed in nature and are considered to be among the significant environmental carcinogens.[1] Previously, considerable research has been directed towards the synthesis of the polycyclic ring systems[2] and examination of their metabolic activation within target cells. Several hypotheses[3] have been proposed to establish the correlations between the structure of these metabolites, their cellular interactions, and their carcinogenicity. Eventually, most of the polycyclic metabolic products that act as carcinogens, intercalate with or bind covalently to DNA. Examination of several frequently used antitumor agents revealed two common structural features[4]: they have a planar ring system and a basic side chain. It could be predicted, therefore, that in addition to other cellular interactions these compounds would first demonstrate a strong interaction with the lipid domains of the plasma membranes and other membranes within the cell.[5] In some instances, antitumoral, DNA-intercalating drugs have been shown to interact with cell membranes and in some cases have demonstrated antitumor activities without further penetrating the cell structure. This would then put them in a class of drugs that have been called generically membrane stabilizing agents (MSA).[6] These are agents that increase membrane stability against various stressors and often at higher concentration induce membrane destabilization. For example, they may act as anti-hemolytic agents at lower concentrations and cause hemolysis at higher concentrations. In order to determine the importance of these primary interactions with the plasma membrane of tumor cells in antitumor effects, we undertook an exploratory synthetic and biological evaluation of unique polycyclic aromatic compounds. This was based on our belief that the potential use of such compounds as antitumor agents has not been systematically explored,[7]

PII: S0960-894X(98)00520-4

especially when specific modification is applied to enhance the membrane interaction as the primary effector of antitumor activity. On this basis, we began this systematic analysis by synthesizing a number of chrysene derivatives for the first time and studied their biological effects in vitro on a panel of human tumor cell lines.

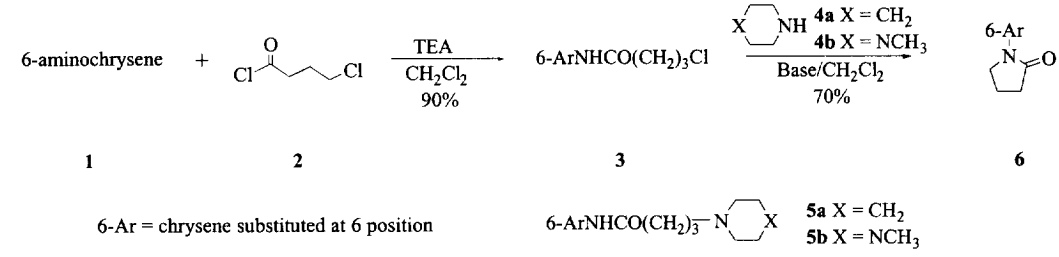
Recently, we have developed an efficient method for the reduction of the aromatic nitro compounds to the aromatic amines by samarium-iodine catalyzed reaction.[8] For this reason, we have decided to undertake a synthetic route for the amino compounds of general structures that have a side chain linked to the polyarene through nitrogen as depicted in Figure 1.

Figure 1



Reaction of 6-amino chrysene **1** with 4-chlorobutyryl chloride **2** in the presence of triethylamine gave the required chloroamide **3** in excellent yield. Condensation of piperidine **4a** or N-methyl piperazine **4b** in the presence of triethylamine or other strong bases, such as NaH and K_2CO_3, failed to produce the required monoamide **5**. It was anticipated that the monoamide **5** would give compounds of general structure by reduction (Figure 1). The structure of the product was deduced to be a cyclic amide **6** formed through intramolecular cyclization (Scheme 1).

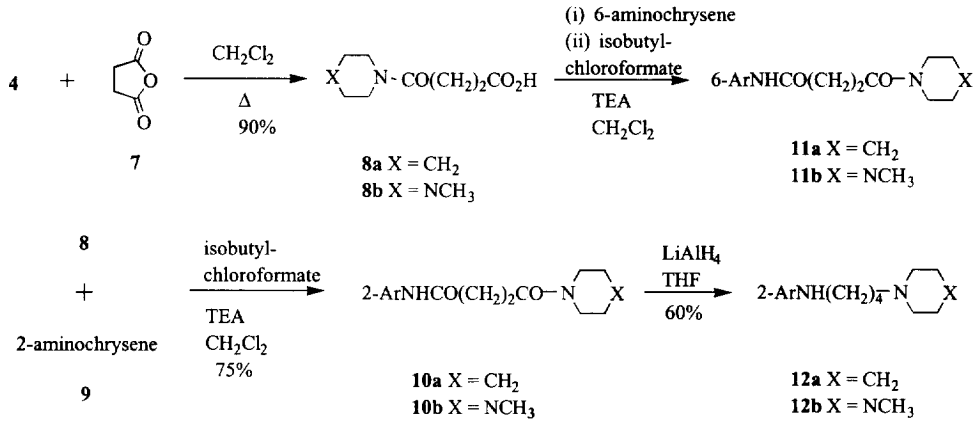
Scheme 1



As an alternative, we prepared the acid **8** in quantitative yield by refluxing succinic anhydride **7** with piperidine **4a** and N-methyl piperizine **4b** using dicholoromethane as solvent (Scheme 2).

Coupling reaction of the acid **8** with commercially available 2-amino chrysene **9** or 6-amino chrysene **1** with DCC[9] gave a poor yield (less than 5%) of the desired products **10** and **11**, respectively. Similar reaction of the acids **8a** with aniline or *p*-anisidine in the presence of DCC gave the amide in excellent yield indicating the difference in reactivity between polycyclic and monocyclic amines. After considerable experimentation, we discovered such coupling reaction can be carried out efficiently by isobutyl chloformate-triethylamine method.[10] The products **10** and **11** were isolated in good yield. Reduction of the diamides **10** to the diamines **12** was carried out by $LiAlH_4$ in refluxing THF (Scheme 2).

Scheme 2



2-Ar and 6-Ar = chrysene substituted at 2 and 6 position, respectively

The products **12** were isolated by crystallization from diethyl ether or by rapid flash chromatography by using neutral alumina as adsorbent and MeOH/EtOAc (10/90) as the eluent.

As is demonstrated in the table, the six chrysene derivatives **10**, **11** and **12** demonstrated consistent antitumor activity against a broad spectrum of test tumor lines (Table 1).

Table 1

Compounds	Solvent (stock)	p388/0 leukemia	BRO melanoma	SKml2 melanoma	HT29 colon	MCF-7 breast
10a	2.5% EtOH	10.5	17.3	13.3	8.5	10.2
10b	2.5% EtOH	7.9	9.5	9.2	4.8	9.8
11a	2.5% EtOH	12.2	15.0	15.9	10.1	11.5
11b	2.5% EtOH	9.8	11.8	10.0	6.6	11.2
12a	2.5% EtOH	2.2	4.5	3.8	2.3	3.0
12b	2.5% EtOH	4.7	8.8	8.7	9.3	12.1
Adriamycin	RPMI-1640	0.8	0.2	0.1	0.5	0.4

IC_{50} (μg/mL)* of **10**, **11**, and **12** in various cell lines

*Data are provided as IC_{50} values (μg/mL). Assays were conducted by 72 h continuous exposure using the MTT method. The final concentration of solvent is <0.625%, which is not toxic to the cells. All dilutions were made in RPMI 1640 with 10% FBS. Adriamycin dilutions were made in medium without FBS.

Compound **12a** demonstrated the greatest inhibitory of tumor cell growth activity against every cell line, which in three instances was less than 1 log value of that of adriamycin. Some general conclusions that can be drawn from the results, based more on the consistency of effect than on statistical significance, would be as follows: (1) In general the 2-chrysene derivatives demonstrated greater inhibitory of tumor cell growth activity than the 6-chrysene derivatives. (2) In general those compounds with a terminal piperizine heterocyclic ring **10b** and **11b** were more effective than those with a piperidine terminal ring **10a** and **11a**. (3) For each of the 2-chrysene derivatives the diamino derivatives **12** demonstrated enhancement of inhibitor of tumor cell growth activity and in these instances, the piperidine terminal ring compound **12a** was the most potent of all. Evidence that

differences in solubility between these varied compounds did not contribute to their differential inhibition of tumor cell growth is derived from two sources. The first, that **10b** and **10a** demonstrated a similar solubility in different solutes while the former demonstrated approximately a two to fourfold greater capacity for tumor cell inhibition. In addition, the hydrochloride salt of **10b** while considerably more soluble than its parent compound demonstrated an identical tumor inhibitory capacity (data not shown). Of interest, when tested in a RBC-hemolytic assay **11b** demonstrated a concentration-dependent hemolysis[10] identical to that of several phenothiazines, well known membrane-stabilizing agents. Despite this we recognize that these agents may well interact at other crucial site within the cell.

While continued development of other analogs is actively underway, **10b** and **12a** have been chosen as lead compounds for in vivo toxicity testing. Moreover, the highly functionalized compounds[12] can be further modified into a variety of other structures of biological significance.

Acknowledgement

This work was supported in part by a grant received from the Robert J. Kleberg, Jr. and Helen C. Kleberg Foundation. The testing of the compounds against tumor lines was performed in the laboratory of Dr. Robert Newman, Department of Pharmacology.

References and Notes

1. For a general review see: Freudenthal, R.; Jones, P. W. *Carcinogenesis-a comprehensive survey*; Raven Press: New York, 1976; vol.1-3.
2. For a recent example see: Harvey, R. G. *Polycyclic aromatic hydrocarbons;* Wiley-VCH, 1997.
3. Di Raddo, P.; Chan, T. H. *J. Org. Chem.* **1982**, *47*, 1427 and references cited therein.
4. For some recent examples: (a) Cherubim, P.; Deady, L. W.; Dorkos, M.; Quazi, N. H.; Baguley, B. C.; Denny, W. A. *Anti-cancer drug design.* **1993**, *8*, 429. (b) Palmer, B. D.; Lee, H. H.; Baguley, B. C.; Denny, W. A. *J. Med. Chem.* **1992,** *35,* 258.
5. Wingard, L. B.; Tritton, T. R. *Cancer Res.* **1985**, *45*, 3529.
6. For an example, see: Jorgensen, K.; Ipsen, J. H. *Biochem. Biophys. Acta.* **1991**, *1062*, 227 and references cited therein.
7. Bair, K. W.; Tuttle, R. L.; Knick, V. C.; Cory, M.; McKee, D. D. *J. Med. Chem.* **1990**, *33*, 2385.
8. Banik, B. K.; Mukhopadhyay, C.; Venkatraman, M. S.; Becker, F. F. *Tetrahedron Lett.* **1998**, in press.
9. Lee, M.; Lown, J. W. *J. Org. Chem.* **1987**, *52*, 5717.
10. Holzapfel, C. W.; Pettit, G. R. *J. Org. Chem.* **1985**, *50*, 2323.
11. Details will be published elsewhere.
12. Some of the compounds described here are potential carcinogens. All reactions and work up were carried out in well-ventilated hood. Compounds **1** and **6** were obtained from Aldrich and ICN. New compounds gave satisfactory spectral data. **12a**: mp 115 °C; ^{1}H NMR (200 MHz, ppm) δ 1.44–2.45 (m, 10H), 3.42–3.50 (br t, 2H), 4.67 (br s, 1H), 7.54–7.76 (m, 6H), 7.90–7.99 (m, 2H), 8.55 (d, J = 9.10 Hz, 1H), 8.67 (d, J = 7.84 Hz, 1H), 8.76 (d, J = 7.20 Hz, 1H); ^{13}C NMR δ 24.48, 25.06, 25.97, 27.32, 44.22, 54,65, 58.97, 97.50, 110.84, 120.28, 121.15, 123.02, 123.20, 123.89, 125,63, 125.97, 126.47, 128.39, 132. 73, 142.24; Anal. calcd for $C_{27}H_{30}N_2$: C, 84.8%; H, 7.9%; N, 7.3%. Found: C 84.48%; H, 7.60%; N, 7.30%.