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Short communication

Novel 6,12-disubstituted chrysene as potent anticancer agent: Synthesis, *in vitro* and *in vivo* study

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ABSTRACT

We describe herein the synthesis of novel 6,12-distributed chrysene as potent anticancer agents. *In vitro* and *in vivo* studies are also reported here.

1. Introduction

Research on PAH and their derivatives has received significant attention from organic and medicinal chemists as well as biologists [1]. In parallel with these efforts there has been a persistent, but relatively limited focus on the use of these molecules as anticancer agents. For example, Bair et al. reported a close correlation between their effectiveness against tumor lines and the configuration of the polyaromatic molecule [2]. This group then developed benzylic aminopropanediols that were predicted to be more effective based on from SAR studies. These compounds were proposed to interact with DNA by intercalation and also suggested to be inhibitors of topoisomerase II. Intercalation has been confirmed for at least two of the most active napthalimides, amonafide and mitonafide and their antitumor activity has been suggested to result from this interaction [3–6]. These interesting reports appeared to us to offer significant opportunities to expand the investigation of PAH-derived compounds to improve their antitumor activities, decrease toxicity and to better identify their crucial targets [7–12].

In prior studies we have reported that a series of mono-substituted chrysene derivatives have demonstrated a structurally related antitumor activity that suggested crucial interactions at the tumor cell membrane as an alternate target for activity and SAR studies indicated the important roles of the nature and length of the appended chain as well as the terminal moiety [13]. Despite the significant activity of a number of these compounds against a spectrum of human and animal lines *in vitro* their *in vivo* activity was limited.

Therefore, to extend the previous studies of these biologically active aromatic compounds this paper describes the synthesis of a few of 6,12-disubstitued chrysene derivatives and their evaluation *in vitro* and *in vivo* against a number of human and animal tumor lines. At least one of these compounds demonstrated reasonable activity *in vivo* and when examined by the NIH-Compare Program was reported to have an “unidentified mode of action”.

2. Synthesis

It has been established that some disubstitued compounds were more active than the compounds which had a single chain or a single aromatic moiety **7c**. The chemistry described in our earlier study can be extended to prepare a new family of compounds of these types by simple chemical manipulation. For example, two amide derivatives **7a**, and **7b** were prepared as shown below (Scheme 1). (**1**) On acetylation afforded 6-acetamidochrysene (**2**). 6-Acetamidochrysene (**2**) on nitration by nitric acid produced the nitro amide **3** which on reduction (hydrazine hydrate and 10% Pd/C) [14–15] and subsequent hydrolysis (20% sulfuric acid in aqueous ethanol) afforded 6,12-diaminochrysene (**5**). A coupling reaction of 6 with 5 in the presence of isobutyl chloroformate afforded the

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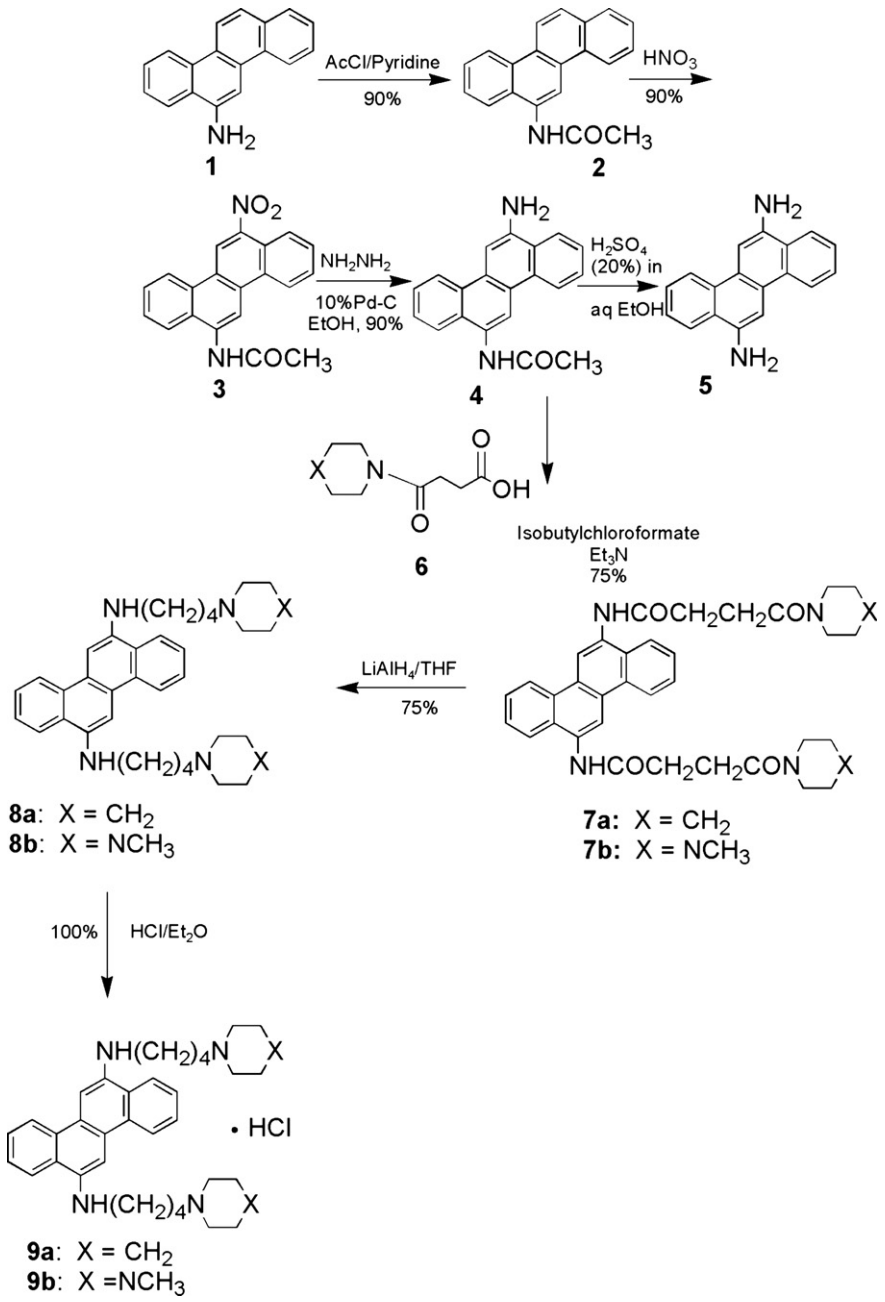

Scheme 1. Synthesis of anticancer agents derived from 6-aminochrysene. Synthesis of 6,12-disubstituted chrysene.

amide **7**. The amide **7** was then reduced to produce the amine **8** and the amine **8** was then converted to the hydrochloride salt **9** (Scheme 1).

2.1. In vitro cytotoxicity

Six human tumor lines of hematopoietic (HL-60) and five of epithelial origin were tested, as well as one mouse lymphoma, P388 which is used as a standard in chemotherapy testing. As indicated in Table 1 the activities of the monosubstituted compounds were consistent with previously reported results (Fig. 1). While **10a**, the single chain amide with a terminal piperidine moiety failed to produce an IC_{50} below 20 μM against any cancer cell line, **10b** with a terminal piperazine ring demonstrated an IC_{50} below 10 μM against 4 cancer cell lines of different derivation. Compound **11a**, the single chain amino derivative with a terminal piperidine moiety demonstrated IC_{50} against all 7 cancer cell lines below 5 μM. This considerable enhancement of anticancer activity is commensurate with the increase in activity that has been reported previously for all related, single chain amino analogues regardless of the terminal moiety.

The effect of substituting amino chains for the amides had an even greater effect than it had for the single chain amino substitution. Compound **8a** with symmetrical piperidine rings had IC_{50} of 2 μM or less against 5/7 lines and <1 μM against 2/7 including PC-3, a human prostate cancer cell line against which cisplatin demonstrated an IC_{50} of 2.1 μM. The amino compound **8b** with terminal *N*-methylpiperazine rings demonstrated an IC_{50} of <4 μM against 1/7 cancer cell lines; <2 μM against 4/7 cancer cell lines and <1 μM against 2/7 cancer cell lines including SKOV-3, an ovarian cancer

Table 1
IC_{50} (μM) of compounds **7a**, **7b**, **8a**, **8b**, and **9b**, against several cancer cell lines; MTT assay (72 h continuous exposure).

Compounds	BRO	HT-29	MCF-7	SKOV-3	PC-3	HL-60	P388
Cisplatin	5.66	16.99	10.05	5.99	2.1	1.66	11.0
10a (10)	>100	33.3	24.5	21.0	50.4	18.8	29.5
10b (8)	41.6	9.3	7.1	11.1	18.4	9.5	6.0
11a (5)	3.4	2.4	2.3	4.4	3.7	1.1	2.2
11b (3)	13.9	14.3	6.4	8.4	10.02	5.3	19.5
7a (4)	44.3	41.1	21.0	22.0	24.4	25.0	37.8
7b (5)	57.3	66.6	75.0	72.2	15.5	42.1	98.0
8a (6)	1.7	1.2	1.4	1.9	0.8	0.8	2.0
8b (5)	3.8	2.1	1.7	0.9	1.2	0.9	1.7
9b (3)	0.6	1.6	1.2	1.0	2.1	0.9	0.8

Data are provided as IC_{50} values (μM). Assays were conducted using 72 h of continuous exposure to drug; relative cell growth was determined 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. The number of run indicates in the brackets.

line against which cisplatin demonstrated an IC_{50} of 5.99 μM. The hydrochloride salt **9b** of the amino compound **8b** might be considered to be the most active of all of these compounds with IC_{50} of <2 μM against 3/7 cancer cell lines and <1 μM against 4/7. In this latter group was BRO, a human melanoma cancer cell line against which no other compound demonstrated a comparable activity and against which cisplatin demonstrated an IC_{50} of 5.66 μM; and <1 μM with P388 against which cisplatin's IC_{50} was 11.0 (Table 1).

2.2. In vivo studies

The effectiveness of **9b** was tested *in vivo* against the human ovarian cancer cell line SKOV-3. The agent was dissolved in PBS, pH 7.4 just prior to injection. The cells were harvested at 80% confluence and viability was tested by trypan blue exclusion. Cells were used only if viability was judged to be in excess of 90%. 6–10 week old nu/nu females were used. The tumor cells were washed in PBS, re-suspended in PBS and injected intra-peritoneally at 0.65×10^6 per mouse. All mices were sacrificed at seven weeks after injection. Administration of **9b** was begun 72 h after the injection of the tumor at 40 mg/k i.p. The regimen consisted of administration of this dose administered for 5 days at 10:00 a.m. each morning of the first and second weeks. Relative to control mice a weight loss of between 5% and 7% was detected in the treated mice with complete restoration of the weights to those of control mice by the end of the third week.

2.3. In vivo results

The results of two *in vivo* runs are summarized in Table 2. In the typical untreated mouse multiple nodules were detected throughout the abdominal cavity and varied in diameter generally from 1 to

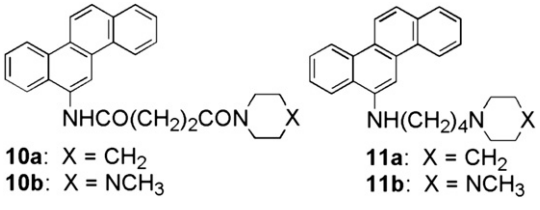

Fig. 1. Anticancer diamide derived from chrysene. Example of anticancer diamide and diamine.

Table 2
Effect of **9b** on intraperitoneal growth of SKOV-3.

	T/M[a]	T/TBM[b]	Tvol/M[c]	Tvol/TBM[d]
Controls (20)	6.5	10.8	1.1 cm^3	1.9 cm^3
40 mg/k (15)	4.2	5.8	0.6 cm^3	0.7 cm^3

[a] Average number of tumors per mouse.
[b] Average number of tumors per tumor bearing mouse.
[c] Total tumor volume per mouse.
[d] Total tumor volume per tumor bearing mouse.

10 mm. Administration of **9b** reduced the tumor number per tumor bearing mouse by 35% and the tumor volume was reduced by 47%.

3. Discussion

This study was aimed at extending our initial findings that a number of newly synthesized compounds with amide or amine linkers, having a chrysene nucleus, demonstrated an interesting degree of *in vitro* antitumor activity against human and animal tumor cell lines. Since even the most active of these compounds, those with amino structure, demonstrated only modest activity against these cancer cell lines when tested *in vivo*, we speculated that bis-compounds bearing a variety of such chains and terminal moieties might reveal important SAR, as well as having the potential for greatly enhanced anticancer activity.

Several findings utilizing amide compounds (**7a** and **7b**) were of interest. While it did not appear surprising that **7a**, the amide variant of **10b** was as inactive as was the latter, the lack of any significant activity by **7b**, the amide variant **11b** was unexpected. When comparing amides, those bearing a piperazine ring as the terminal moiety demonstrated at least limited activity against several tumor cell lines. While we could not determine the cause of this lack of activity of a bis-piperazine it seemed reasonable to suggest that some form of hindrance resulted from the dual binding of the identical terminal moieties perhaps limiting membrane transport.

Compounds **9a**, and **9b** demonstrated a typical effect of the conversion of the amide to amino components of the linker regardless of the nature of the terminal moiety. The amino compound demonstrated activity against almost every cancer cell line tested, regardless of its derivation. Thus, it was of interest that each of the bis-amino compounds **9a** and **9b** demonstrated such antitumor activities ranging from IC_{50} of 1.0–2.5 μM in a few instances to <1.0 μM in several. In evaluation of potential clinical agents, compounds with <1.0 μM activities are considered to be of interest, while recognizing that their toxicity must be taken into account. While one might conclude that the greatly increased basicity of such compounds becomes the overriding element in their activity we must admit that the exact mechanism is uncertain. Further, we have demonstrated that for one of these amino compounds, **9b**, the salt of **8b** demonstrated activity *in vivo* against the human ovarian cancer cell line SKOV-3. Although clearly not curative in the limited regimen used, this tumor is notoriously resistant to many standard antitumor agents suggesting that further study with variants of the regimen may be warranted.

Finally, as a caveat against presupposing that any of these agents has a universal effect against all tumor cell lines, we have demonstrated in a previous publication using human leukemic Jurkat T cells *in vitro*, we demonstrated that while **11a** caused extensive cytotoxicity, **8b** was far less active. This relatively lesser activity of **8b** was also reflected in a greatly diminished degree of apoptotic damage, the apparent mechanism of cell death imparted in this cell line by these compounds [16]. However, selectivity of effect against different tumors is more the rule than the exception for many antitumor compounds.

4. Experimental section

4.1. General methods

All solvents and reagents were obtained from commercial sources and used without purification. Reactions were monitored by TLC using pre-coated silica gel aluminum plates containing a fluorescence indicator. Chemical shifts of ^{1}H NMR spectra were given in parts per million with respect to TMS, and the coupling constant J was measured in Hz. Data are reported as follows: chemical shifts, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet). ^{1}H NMR spectra were recorded in $CDCl_3$ using tetramethylsilane as an internal standard. IR spectra of neat compounds were expressed as wave numbers (cm^{-1}).

4.1.1. 6-Acetamidochrysene (**2**)

To 6-aminochrysene (1 g, 4 mmol) in pyridine (8 mL) at 0 °C was added acetylchloride (326 ml, 4.2 mmol) dropwise with vigorous stirring and the mixture was allowed to stir for further 10 min. The resultant mixture was poured into dilute HCl (10%, 100 mL). The precipitated solid was filtered, washed with dilute HCl (10%) followed by water and dried to furnish of 6-acetamidochrysene (1.160 g, 98%).

4.1.2. 12-Nitro-6-acetamidochrysene (**3**)

To 6-acetamidochrysene (0.5 g, 1.7 mmol) in dry dichloromethane (5 mL), cooled to 0 °C with ice bath was added concentrated nitric acid (1 mL) and the mixture was allowed to stir overnight at room temperature. On completion of the reaction as indicated by TLC, the mixture was diluted with dichloromethane (50 mL), washed with saturated $NaHCO_3$ (25 mL) and water (25 mL). The solvent was then removed and the crude nitro compound was crystallized (dichloromethane/hexane) to yield 12-nitro-6-acetamidochrysene (330 mg, 58%).

4.1.3. 12-Amino-6-acetamidochrysene (**4**)

To a stirred suspension of 12-nitro-6-acetamidochrysene (0.3 g, 0.9 mmol) in ethanol (50 mL) was added 10% Pd/C (133 mg) followed by hydrazine monohydrate (0.85 mL) and the mixture was heated to reflux for 2 h. The mixture was then filtered and the Pd/C was washed with hot ethanol. After evaporation of the solvent the residue was extracted with dichloromethane (50 mL) and washed with water (20 mL). The organic layer was separated, dried over anhydrous Na_2SO_4 and evaporated to provide 12-amino-6-acetamidochrysene (265 mg, 97% yield).

4.1.4. 6,12-Diaminochrysene (**5**)

To a stirred suspension of 12-amino-6-acetamidochrysene (0.24 g, 0.8 mmol) in absolute ethanol (50 mL) was added conc. H_2SO_4 (15 mL) dropwise and the mixture heated to reflux for 1.5 h. The resulting mixture was poured into ice and neutralized with 50% NaOH solution. The precipitated diamine was extracted with ethyl acetate (3 × 50 mL) and the combined organic layer was dried over anhydrous Na_2SO_4. On evaporation of solvent 6,12-diaminochrysene was isolated (158 mg, 76%), mp 282 °C.

4.1.5. N,N-(6,12-Chrysenyl)-bis-(4-(1-piperidinyl)-butane)-1,4-dicarboxiamide (**7a**)

To acid **6** (520 mg, 2.3 mmol) in dry dichloromethane (50 mL) at 0 °C was added triethylamine (0.34 mL, 1.45 mmol) followed by isobutyl chloroformate (0.3 mL, 1.4 mmol) and the mixture was allowed to stir at 0 °C for 10 min. To this mixture was added 2,8-diaminochrysene (190 mg, 0.7 mmol) and allowed to stir overnight at room temperature. On completion of the reaction, HCl (10%, 50 mL) was added and the organic layer was washed with saturated $NaHCO_3$ solution (25 mL). The organic layer was then dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to produce the amide. This was purified by column chromatography over silica gel (methanol/ethyl acetate = 1:4); Yield: 230 mg (53%); mp 260–262 °C; IR (film): 3252, 2934, 2855, 1650, 1538, 1470, 1441, 1225, 1218, 1138, 1013, 978; ^{1}H NMR ($CDCl_3$): 1.6 (bs, 12H), 2.95 (m, 8H), 3.45(dd, J = 5.2 Hz, J = 4.3 Hz, 2H), 3.7 (dd, J = 5.8 Hz, J = 4.6 Hz, 2H), 7.6 (m, 4H), 8.15 (m, 2H), 8.6 (m, 2H), 9.1(s, 1H), 9.45 (s, 1H); Mass: 593, 569, 525, 481, 437, 393, 297, 122; Anal. Calcd for $C_{36}H_{40}O_4N_4$: C, 72.9, H, 6.8, N, 9.5. Found: C, 72.31, H, 6.68, N, 9.19.

4.1.6. N,N-(6,12-Chrysenyl)-bis(4-(4N-methylpiperazinyl)-butane)-1,4-dicarboximide (**7b**)

To acid **6** (434 mg, 2.3 mmol) in dry dichloromethane (50 mL) at 0 °C was added triethylamine (0.32 mL, 1.45 mmol) followed by isobutyl chloroformate (0.290 mL, 1.4 mmol) and the mixture allowed to stir at 0 °C for 10 min. To this mixture was added 6,12-diaminochrysene (180 mg, 0.7 mmol) and the reaction was allowed to stir overnight at room temperature. On completion of the reaction dilute HCl (10%, 50 mL) was added and the organic layer was washed with saturated $NaHCO_3$ solution (25 mL). The organic layer was then dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to furnish the amide. This was purified by column chromatography over silica gel (methanol/ethyl acetate = 1:4) Yield: 198 mg (48%); mp 246–248 °C; IR (cm^{-1}): 3252, 2920, 2850, 1650, 1537, 1442, 1372, 1293, 1255, 1220, 1146, 1022, 1001, 871, 750; ^{1}H NMR ($CDCl_3$) 2.3 (s, 6H), 2.4 (m, 8H), 2.9 (m, 8H), 3.6 (dd, J = 5.4 Hz, J = 4.6 Hz, 2H), 3.8 (dd, J = 5.2 Hz, J = 4.3 Hz, 2H), 7.55 (m, 8H), 8.1 (m, 4H), 8.5 (m, 4H), 8.9 (s, 2H), 9.2 (s, 2H); Mass: 624.28, 623.22, 483.2, 441.2, 423.1, 341.2, 312.3, 183.2, 155.1, 101.17; Anal. Calcd for $C_{36}H_{42}O_4N_6$: C, 69.4, H, 6.8, N, 13.5. Found C, 68.37, H, 6.78, N, 11.33.

4.1.7. General procedure for the reduction of the tetramide **7**

To a cooled suspension of tetra-amide (0.5 mmol) in dry THF (150 mL) was added lithium aluminum hydride (3 mmol, 1 M solution in THF) under argon and the mixture heated to reflux for 21 h under argon. At the end of this time the mixture was cooled and quenched with saturated solution of sodium sulfate. The precipitated aluminum hydroxide was filtered and washed with ethyl acetate. The ethyl acetate layer was washed with water dried and evaporated under vacuum. Purification by column chromatography over silica gel or alumina gave the tetra-amine.

4.1.8. N,N-(6,12-Chrysenyl)-bis-(4-(1-piperidinyl)-butane)-1,4-diamine (**8a**)

mp 186–188 °C; IR (film): 3415, 3032, 2930, 2857, 2801, 2763, 2359, 1595, 1521, 1449, 1354, 1274, 1217, 1110, 1042; ^{1}H NMR ($CDCl_3$): 1.4 (m, 4H), 1.6 (m, 8H), 1.8 (m, 8H), 2.4 (m, 12H), 3.4 (t, 4H), 7.6 (m, 6H), 7.9 (d, 2H, J = 8 Hz), 8.65 (d, 2H, J = 8 Hz); Mass: 537, 475, 398, 313, 269, 226, 206, 199, 193, 179, 139; Anal. Calcd for $C_{36}H_{48}N_4$: C, 80.54, H, 8.9, N, 10.4. Found: C, 80.31, H, 8.80, N, 10.21.

4.1.9. N,N-(6,12-Chrysenyl)-bis-(4-(4N-methylpiperazinyl)-butane)-1,4-diamine (**8b**)

mp 166–168 °C; IR (film): 3383, 2932, 2849, 2798, 1594, 1524, 1452, 1357, 1277, 1225, 1162, 1113, 1048, 1012; ^{1}H NMR ($CDCl_3$): 1.6 (m, 8H), 2.3 (s, 6H), 2.5(m, 20H), 3.5 (t, 4H), 7.6 (m, 6H), 8.0 (d, 2H, J = 8 Hz), 8.6 (d, 2H, J = 8 Hz); UV: 370, 286, 234; Mass: 567, 531, 313, 304, 284, 263, 230, 216, 206, 154, 130; Anal. Calcd for $C_{36}H_{50}N_6$: C, 76.3, H, 8.9, N, 14.8. Found: C, 76-61, H, 8.88, N, 14.67.

4.1.10. Preparation of the salt of the tetramine **8**

The hydrochloride salt of the amine **9** was prepared by mixing it with excess hydrochloric acid solution in ether for 1 h and filtering of

the residue (100% yield). The salt was characterized after regenerating the parent amine by basification–extraction procedure.

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