Stereoselective Synthesis of β-Lactams with Polyaromatic Imines: Entry to New and Novel Anticancer Agents†

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Abstract: We present herein stereoselective synthesis of novel β-lactams using polyaromatic imines following the Staudinger reaction. Consistent mechanisms for these results have been advanced. As a measure of cytotoxicity, some of these compounds have been assayed against nine human cancer cell lines. Structure−activity study has revealed that 1-*N*-chrysenyl and 1-*N*-phenanthrenyl 3-acetoxy-4-aryl-2-azetidinones have potent anticancer activity. The presence of the acetoxy group at C_3 of the β-lactams has proven to be obligatory for their anticancer activity.

Introduction. After the discovery of penicillins and cephalosporins as β-lactam antibiotics and clinically useful active agents, the past few decades have witnessed remarkable growth in the field of β-lactam chemistry.[1] The need for potent effective β-lactam antibiotics as well as more effective β-lactamase inhibitors has motivated synthetic organic and medicinal chemists to design new functionalized 2-azetidinones. Apart from their clinical use as antibacterial agents, these compounds have been used as synthons in the preparation of various heterocyclic compounds of biological significance.[2] For example, suitably substituted hydroxy β-lactams have been used in the semi synthesis of paclitaxel (Taxol) and docetaxel (Taxotere).[3] The potential use of some β-lactams as therapeutic agents for lowering plasma cholesterol levels has been documented as well.[4] Extensive studies of human leukocyte elastase (HLE) inhibitory mechanisms and the biological activity of this class of compounds have also been published.[5] Because of this general trend of β-lactam use, the search for clinically useful β-lactams that are antibiotics or have other medically important properties will continue.[6,7,8]

We have been engaged in the synthesis of β-lactams and several other biologically active compounds.[9] In a continuation of our research in this field, we describe herein stereoselective synthesis of novel β-lactams starting from polyaromatic imines and biological evaluation of some of these β-lactams as anticancer agents for the first time.[10] To our knowledge, there have been no claims that β-lactams as the sole structural units have anticancer activity.[11]

In our earlier publications, we demonstrated synthesis and biological evaluation of some derivatives of polyaromatic amines, which were open-chain amides in which the polycyclic residue was bound (for example **1** and **2**, Figure 1).[12] We anticipated that conformationally restricted analogues of these open chain diamides (**1** and **2**) may increase their potency. Also, it was demonstrated that conformationally restricted amides (β-lactams) lower the cholesterol level in human plasma efficiently.[4b] We envisioned that a β-lactam having a structure as indicated in **3** (Figure 1) would serve as a conformationally restricted analogue of the potent compounds **1b** and **2b**. With this background, the following studies were undertaken.

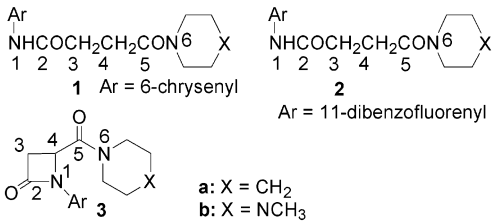
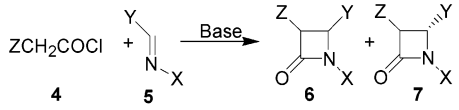


Figure 1.

Synthesis of Novel β-Lactams with Polyaromatic Imines. The Staudinger reaction has been used extensively for the synthesis of β-lactams (for example, **6** and **7**). This reaction requires an imine **5**, base, and acid chloride, **4** (or equivalent). The stereochemistry of resulting β-lactams varies, including cis, trans, and a cis−trans mixture, depending on the substituents present in the imine **5** and acid chloride **4** and conditions of the reactions (Scheme 1).

Scheme 1



In general, the reaction of acyloxy-, alkoxy-, and nitrogen-containing acid chloride with diaryl imines produces cis β-lactam under Staudinger reaction conditions.[13] However, the reaction of polyaromatic imines[14] (**8**, **10**, **12**, **14, 16**, and **18**) with acetoxy, phenoxy, and phthalimido acid chloride in the presence of triethylamine at −78 °C to room temperature produced trans β-lactams (**9**, **11**, **13**, **15, 17**, and **19**, Figure 2), which contrasts sharply with the observation described above. Isomeric polyaromatic imines (**20**, **22**, and **24**) in which the aromatic moieties were interchanged produced cis-β-lactams (**21**, **23**, and **25**) in good yield (Figure 3). Interestingly enough, imines (**26**) derived from cinnamaldehyde and 1-amino pyrene also afforded cis β-lactams **27** and **28** (Figure 4).

Although formation of β-lactams using the Staudinger reaction was discovered more than 90 years ago, surprisingly, there has not been a precedent in the literature regarding the use of tetracyclic or pentacyclic aromatic systems in imine components. Interestingly, the formation of trans β-lactams as seen in the present investigation has not been described in the literature. Some earlier studies were directed toward the formation of trans β-lactams. However, the conditions in those experiments were clearly different from those in the present investigation. For example, synthesis of some

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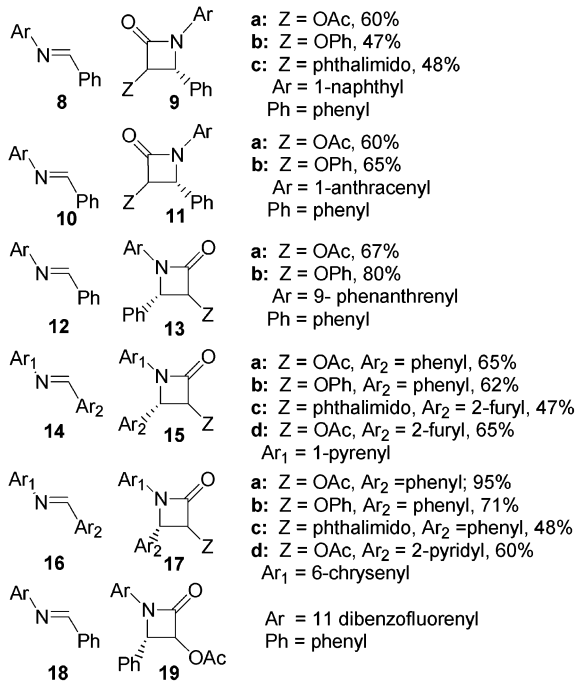


Figure 2.

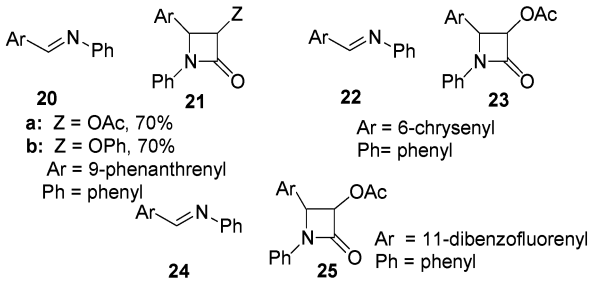


Figure 3.

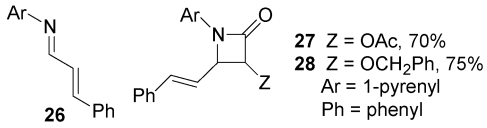
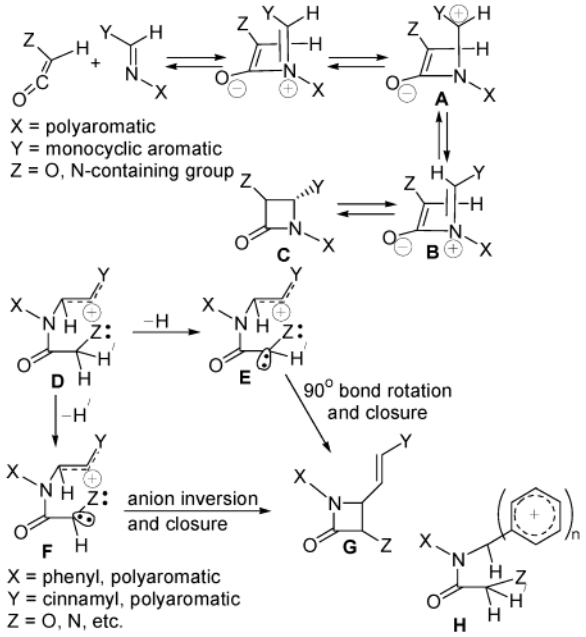


Figure 4.

trans β-lactams was achieved using high-power microwave irradiation and changing the order of the addition of the reagents.[15c,d] Furthermore, in two cases, trans β-lactams were obtained in low yield as the only isolated products using cyclic imines, but they were not derived from an aromatic amine.[15a,b]

Mechanism of β-Lactam Formation with Polyaromaic Imines. The mechanism of β-lactam formation has been investigated extensively. Based on the enormous amount of data in the literature, some predictions have been made. For instance, Georg and Ravikumar established some empirical rules regarding stereoselectivity in the formation of β-lactam rings.[13] On the other hand, computer-assisted theoretical calculations were advanced to explain the stereochemical outcome.[16] Also, low-temperature infrared spectroscopy was used by Lynch et al. to identify the reactive intermediates.[17] In general, two mechanisms have been proposed to explain the product distribution in the β-lactam formation reaction. One of these, the ketene mechanism was observed in the low-temperature infrared spectroscopy study,[17] while the other, acylation of imine mechanism, was believed to be in the path as described previously.[13] Both of these mechanisms have been supported by numerous lines of evidence in several studies. In particular, it has been hypothesized that cycloaddition of the imine occurs from the least hindered side of the ketene, a process that generates zwitterionic intermediates; conrotatory cyclization of these intermediates can then provide cis and trans β-lactams. In addition, the second mechanism proposes acylation of the imine by the acid chloride to form *N*-acyliminium chloride, which produces zwitterionic intermediates (Scheme 2).

Scheme 2



The formation of a trans isomer as observed in the present study can be rationalized through isomerization of the enolates (Scheme 2, **A** to **B**). The electron-withdrawing polyaromatic group at the nitrogen stabilizes the iminium ion. This process allows rotation of the bond (**A** to **B**) and results in trans β-lactam formation **C**. This observation is similar to that described by Just et al., in which formation of a trans isomer having electron-withdrawing nitro-substituted imines was performed.[18] In contrast, the exclusive formation of a cis β-lactam having a polyaromatic group and cinnamyl at C_4 prompted us to develop a hypothesis regarding a mechanism suggested previously by Doyle et al.[19] In this context, extended conjugation of the cinnamyl and polyaromatic system stabilizes the acyliminium ion **D**. Furthermore, the presence of the cinnamyl or polyaromatic system at C_4 outweighs the contribution of the N-polyaromatic system, resulting in cis β-lactam formation. Subsequent proton abstraction from complex **D** would lead to cis β-lactams **G** through **E** (90° bond rotation and closure) or **F** (anion inversion and closure).[13,19] This hypothesis is strengthened further due to possible formation of donor−acceptor complex **H** as proposed by Bose et al.[20] This complex formation effectively stabilizes the transition states of the reaction.

Anticancer Activities of the β-Lactams. These β-lactams were tested using nine human cancer cell

Table 1. In Vitro Cytotoxicity of β-Lactam Compounds on Human Cancer Cell Lines (μM)[a]

compounds	BRO	MCF-7	MDA-231	OVCAR	SKOV	PC-3	HL-60	K-562	HT-29
cisplatin	7.66	10.05	12.33	3.99	5.99	4.66	1.66	2.33	16.99
1b	33.64	40.0	12.23	18.11	11.05	27.29	9.41	12.70	16.70
13a	10.48	10.09	12.49	18.0	18.00	9.3	5.21	4.0	10.49
17a	10.84	9.81	11.98	4.17	6.88	16.32	3.64	4.33	5.66
17d	11.00	14.93	14.46	-	9.0	-	2.5	2.5	15.90
9, **11**, **13b**, **15**, **17b**,**c**, **19**, **23**	>20	>20	>20	>20	>20	>20	>20	>20	>20

[a] All of the in vitro cytotoxicity assays were performed in the Pharmacology and Analytic Core Laboratory of our University as described previously.[12] In summary, an MTT assay was carried out using the nine human cancer cell lines.

lines with cisplatin and diamide **1b** as controls; results are depicted in Table 1.

The initial structure−activity study revealed that regardless of the structure or configuration of the β-lactam component, neither naphthalene (**9**), anthracene (**11**), nor pyrene derivatives (**15**) demonstrated activity against any of these cell lines. In each case, their maximum activity was determined to be at concentrations in excess of 20 μM/mL (a level not considered to have a significant effect). The results of testing of phenanthrene (**13**) and chrysene derivatives (**17**) demonstrated that only β-lactams (**13a**, **17a**, and **17d**) in the trans configuration having the acetoxy moiety were active, whereas when phenoxy and phthalimido (**13b, 17b**, and **17c**) groups were present instead of the acetoxy group, the compounds were inactive. Specifically, on the breast cancer cell line MCF-7, three compounds (cisplatin, **13a**, and **17a**) had almost identical activity, while on the colon cancer cell line HT-29; **17a** was approximately three times as active as cisplatin. Selective differences in cytotoxicity were also evident on the ovarian cancer cell line OVCAR, where cisplatin and **17a** had almost identical activity and **13a** had little.

Several conclusions can be derived from the results of the in vitro studies. It is evident that the minimal structural requirement of the aromatic moiety for cytotoxicity is at least three aromatic rings in an angular configuration. Thus, only phenanthrene **13a** and two chrysene derivatives **17a** and **17d** demonstrated cytotoxicity against the tumor cell lines. The comparable naphthalenes, anthracenes, dibenzofluorenes, and pyrene compounds (**9**, **11**, **13b**, **15, 19**, and **23**) were inactive. Also, the presence of the acetoxy group proved to be obligatory, suggesting that an enzymatic or other alteration at this site was involved in the activation of the compound. Furthermore, only when the β-lactam was in the trans configuration (**17a** vs **23**) did it prove to have greater antitumor activity. These findings suggest that there is an interaction of **13a**, **17a**, and **17d** with a specific receptor or enzyme, which has stringent stereochemical requirements. However, neither the target nor the mechanism of the subsequent antitumor activity has been identified.

For the in vivo assays, K-562 acute leukemia cells, SKOV-3 ovarian carcinoma cells, and HT-29 colon cancer cells were harvested at near confluence and resuspended in RPMI. In general, 1×10^6 cells in 100 μL were inoculated subcutaneously into the right shoulder of female (K-562) mice and male (HT-29) athymic (nu/nu) mice obtained from Harlan laboratories (Frederick, MD). The same number of SKOV-3 cells was injected intraperitoneally into female nu/nu mice. **17a** was dissolved in tissue-culture-grade dimethyl sulfoxide (Sigma) and administered intraperitoneally to the mice in 50-mL volumes. Various treatment schedules and routes were tested, including multiple injections on a twice daily schedule (BID), a three times daily schedule (TID), and an alternate schedule of twice daily injections interspersed with single daily injections within a seven-day regimen (XSID). Furthermore, when compared with standard antitumor agents such as cisplatin and adriamycin, **17a** had negligible toxicity. The maximum **17a** dose eventually selected for in vivo use was 60 mg/kg administered intraperitoneally at approximately 8 a.m. on Monday through Friday and 40 mg/kg at approximately 5 p.m. on Monday, Wednesday, and Friday. This regimen was repeated the following week. Using this method, no deaths have been observed in more than 50 mice, and a maximum weight loss of 3.52 g per animal has been noted. Within 3−5 days of administration of the last dose, the mice's weight rapidly returned to that of the mice in the control group. At that time, in two separate experiments using the regimen described above with HT-29 cells, there was a delay in producing the first consistently measurable tumor (approximately 2 mm in diameter) of 7 ± 2 days. The mice with HT-29 tumors in these groups experienced an average delay in achieving the tumor-growth endpoint of a volume of 1 cm^3 of 9 ± 2 days. The effect of using SKOV-3 cells was even more striking, with many of the treated mice having no tumors.

Conclusion. The compounds described herein are unique, and it appears reasonable to state that they are the first β-lactam derivatives to demonstrate significant in vitro antitumor cytotoxicity and, in the case of **17a**, in vivo activity. The stereochemical outcome of the Staudinger reaction as reported herein will offer our laboratory and others many additional opportunities to use β-lactams in the synthesis of new compounds having anticancer properties. Additional tumor cell lines on which **17a** have shown significant in vitro activity and other new potent β-lactams available from this study will be investigated for their in vitro and in vivo activity.

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