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Bioorganic & Medicinal Chemistry
Bioorganic & Medicinal Chemistry 13 (2005) 3611–3622

Stereocontrolled synthesis of anticancer β-lactams via the Staudinger reaction

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Received 22 January 2005; revised 15 March 2005; accepted 24 March 2005
Available online 12 April 2005

Dedicated to Professor R. L. Dutta of Burdwan University, India for his remarkable lifetime contributions in teaching University students

Abstract—Stereocontrolled synthesis of novel β-lactams using polyaromatic imines following the Staudinger reaction has been accomplished. The effects of domestic microwave irradiation on this type of reaction have been investigated. Formation of *trans*-β-lactams has been explained through isomerization of the enolates formed during the reaction of acid chloride (equivalent) with imines in the presence of triethylamine. A donor–acceptor complex pathway is believed to be involved in the formation of *cis*-β-lactams. The effect of a *peri* hydrogen has been found to be significant in controlling the stereochemistry of the resulting β-lactams. SAR has identified β-lactams with anticancer activity. The presence of an acetoxy group has proven obligatory for their anticancer activity.

1. Introduction

The enchanted β-lactams has had a variety of medicinal applications. In addition to the well-known penicillins and cephalosporins antibiotics, a number of other biologically relevant enzymes have been targeted by β-lactams.[1] The need for potent and effective β-lactam antibiotics as well as more effective β-lactamase inhibitors has motivated chemists to design new β-lactams.[2] These compounds have served as starting materials in the preparation of various heterocyclic compounds of biological significance.[3] Substituted hydroxy β-lactams have been the starting materials in the semi-synthesis of paclitaxel (Taxol) and docetaxel (Taxotere).[4] The medicinal use of some β-lactams as therapeutic agents for lowering plasma cholesterol levels has been documented.[5] Studies of human leukocyte elastase inhibitory mechanisms and the biological activity of this class of compounds have also been published.[6] There have been a few other remarkable developments, such as catalytic asymmetric[7] and polymer-supported[8] synthesis of β-lactams. As a result of this general trend of β-lactam use, the searches for clinically useful β-lactams that are antibacterial and have other medically important properties will continue.[9–11]

We have demonstrated various methods for the synthesis of β-lactams[12] and several biologically active compounds.[13,14] In continuation of our research in this area, we describe herein a full account of our stereocontrolled synthesis of novel anticancer β-lactams starting from imines, with pendent polyaromatic substituents.[14]

In previous publications, we demonstrated synthesis and biological evaluation of some derivatives of polyaromatic amines, which were open-chain amides to which the polycyclic residue was bound (e.g., **1** and **2**, Fig. 1).[13] Structures **1** and **2** suggest that a ring formation using N_1 and C_4 would result in β-lactam **3**. With regard to the above, we envisioned that β-lactam **3** of the general structure shown in Figure 1 would serve as a conformationally constrained analogue of our open-chain compounds (**1** and **2**) that have been shown to have anticancer activity. The initial impetus for this study was to prepare substituted amines and amides, particularly including compounds with polyaromatic substituents, with the goal of investigating such compounds for potential anticancer activity. It was then decided to extend the scope to include a variety of cyclic amides, including β-lactams. Therefore, our goal has been targeted to develop the synthesis of these types of molecules.

Keywords: β-Lactams; Anticancer agents; Staudinger reaction.
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doi:10.1016/j.bmc.2005.03.044

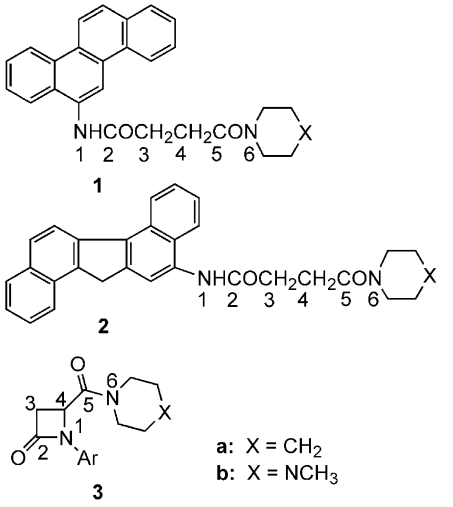


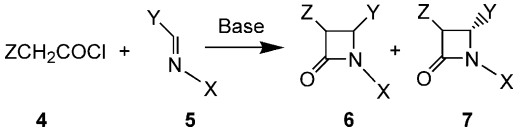
Figure 1.

We are aware from the literature that conformationally constrained molecules often have a greater effect on biological properties when compared to the relatively flexible open-chain compounds.[15–22] On the basis of this hypothesis, we anticipated that conformationally constrained analogues of our open-chain diamides (**1** and **2**) may increase potency. It has been established that β-lactams are more effective at lowering cholesterol in human plasma when compared to open-chain substrates.[5] Therefore, synthesis of β-lactams of type **3** and related compounds is necessary in order to investigate a comparative study with diamides **1** and **2**.

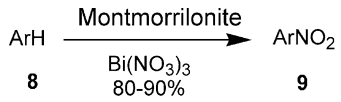
2. Results and discussion

2.1. Synthesis of novel β-lactams with polyaromatic imines

The Staudinger reaction has been used extensively for the synthesis of monocyclic β-lactams (Scheme 1, e.g., **6** and **7**).[12c] This reaction requires an imine **5**, a tertiary base (triethylamine), and acid chloride **4** (or equivalent). While many monocyclic aromatic amines and aldehydes required for the synthesis of imines are commercially available, polycyclic aromatic amines and aldehydes are not. Therefore, preparation of these starting materials is necessary for studying this reaction. In general, nitro compounds are the precursors of the amines. Therefore, an important task is to prepare polycyclic aromatic nitro compounds, particularly those of chrysene, phenanthrene, pyrene, and dibenzofluorene in good yield. Nitration of these hydrocarbons by concentrated nitric acid in sulfuric acid or acetic acid is a widely



Scheme 1.



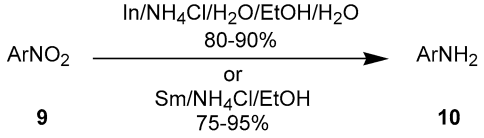
Ar = naphthalene, anthracene, chrysene, pyrene, etc.

Scheme 2.

used reaction for this purpose. The conditions described using mixed acids are not ecologically friendly. However, our recent work culminated in facile synthesis of polyaromatic nitro derivative **9** starting from polyaromatic hydrocarbons (PAHs) **8** through the use of bismuth nitrate impregnated with clay (Scheme 2).[23] The advantages of this method over the classical method are numerous. The presence of clay is essential for the success of this reaction.

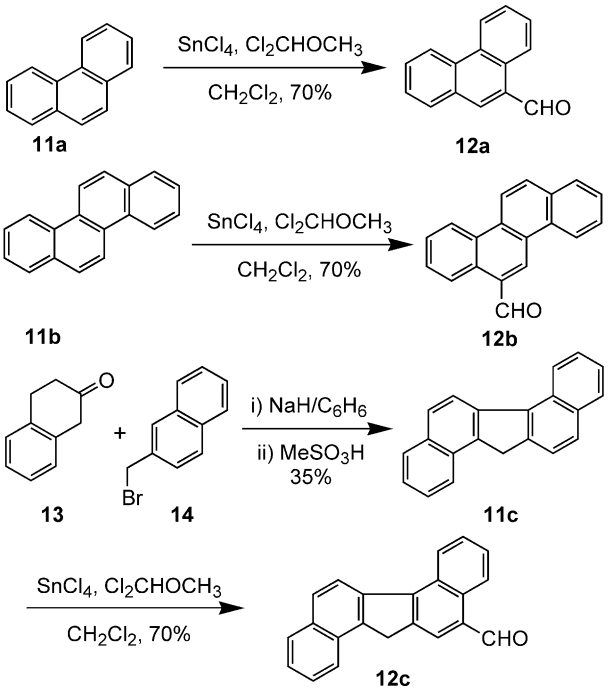
Several methodologies can be used to prepare polyaromatic amines from polyaromatic nitro compounds. For example, catalytic hydrogenation, catalytic transfer hydrogenation, and several new methods have been found to be suitable for the reduction of polyaromatic nitro compound **9** to polyaromatic amine **10**. These methods are not convenient with PAH derivatives. Our recently described indium-[24] and samarium-induced[25] reduction methods offer additional opportunities to achieve this purpose. For example, the indium-induced reaction can be performed in water in the presence of ammonium chloride, while the samarium-induced reaction can elicit a product within a few minutes using ultrasound (Scheme 3). The indium-induced method can be accomplished in 10 g scale. We have reduced 6-nitro chrysene to 6-aminochrysene in more than 90% yield in 10 g scale. The most common hydrogenation using Pd/C has not proved to be successful. Preparation of polyaromatic aldehydes, particularly phenanthrene **12a**, chrysene **12b**, and dibenzofluorene **12c**, has been accomplished using a previously described method[26a] from their respective hydrocarbons **11a**,**b**, and **11c**. Synthesis of dibenzofluorene hydrocarbon **11c** has been achieved by following our one-pot method by reacting β-tetralone **13** and naphthyl bromide **14** in the presence of sodium hydride in benzene and subsequent acid treatment (Scheme 4).[26b] This process involves alkylation, cyclodehydration, and aromatization in a one-pot method.[27]

We initiated preparation of β-lactams by following the Staudinger reaction using these specific amine **10**, aldehyde **12**, and commercially available compounds. The stereochemistry of resulting β-lactams including, cis, trans, and a cis–trans mixture, varies depending on the



Ar = naphthalene, anthracene, chrysene, pyrene, etc.

Scheme 3.



Scheme 4.

substituents present in imine **5** and acid chloride **4** and the conditions of the reactions (Scheme 1). In general, the reaction of acyloxy, alkoxy, and nitrogen-containing acid chloride with diaryl imines produces *cis*-β-lactams under Staudinger reaction conditions.[28] However, reaction of polyaromatic imines (**15**, **17**, **19**, **21**, **23**, and **25**) with acetoxy, phenoxy, and phthalimido acid chloride in the presence of triethyl amine at −78 °C to room temperature produced exclusively *trans*-β-lactams in reasonably good yields (**16**, **18**, **20**, **22**, **24**, and **26**, Scheme 5), which contrasts sharply with the observation described above. According to earlier results, *cis*-β-lactams were expected.[28] The trans stereochemistry of the products has been verified from the NMR data (Section 4). The coupling constant of the C_3 and C_4 hydrogens in the cis-compounds is higher than that of in the trans-products. Also, isomeric polyaromatic imines (**27**, **29**, and **31**) in which the aromatic moieties were interchanged produced exclusively *cis*-β-lactams (**28**, **30**, and **32**) in good yield (Scheme 6). Interestingly, imine **21e** derived from cinnamaldehyde and 1-amino pyrene also afforded *cis*-β-lactam **33** as the only product (Scheme 7).

The critical aspect of the Staudinger reaction, however, was observed when isomeric naphthalenyl (1- and 2-substituted) and anthracenyl (1- and 2-substituted) imines were employed. While the 1-substituted compounds (**15** and **17**) produced only the trans isomers (**16** and **18**), the 2-substituted compounds (**34** and **35**) produced a mixture of cis (**37** and **39**) and trans isomers (**36** and **38**) in a ratio of 1:1. The only structural difference in these compounds was the location of a *peri* hydrogen in these derivatives (**15** and **17**) and (**34** and **35**) (Scheme 8). The *peri* hydrogen in **15** and **17** was closer to the C=N bond than it was in **34** and **35**.

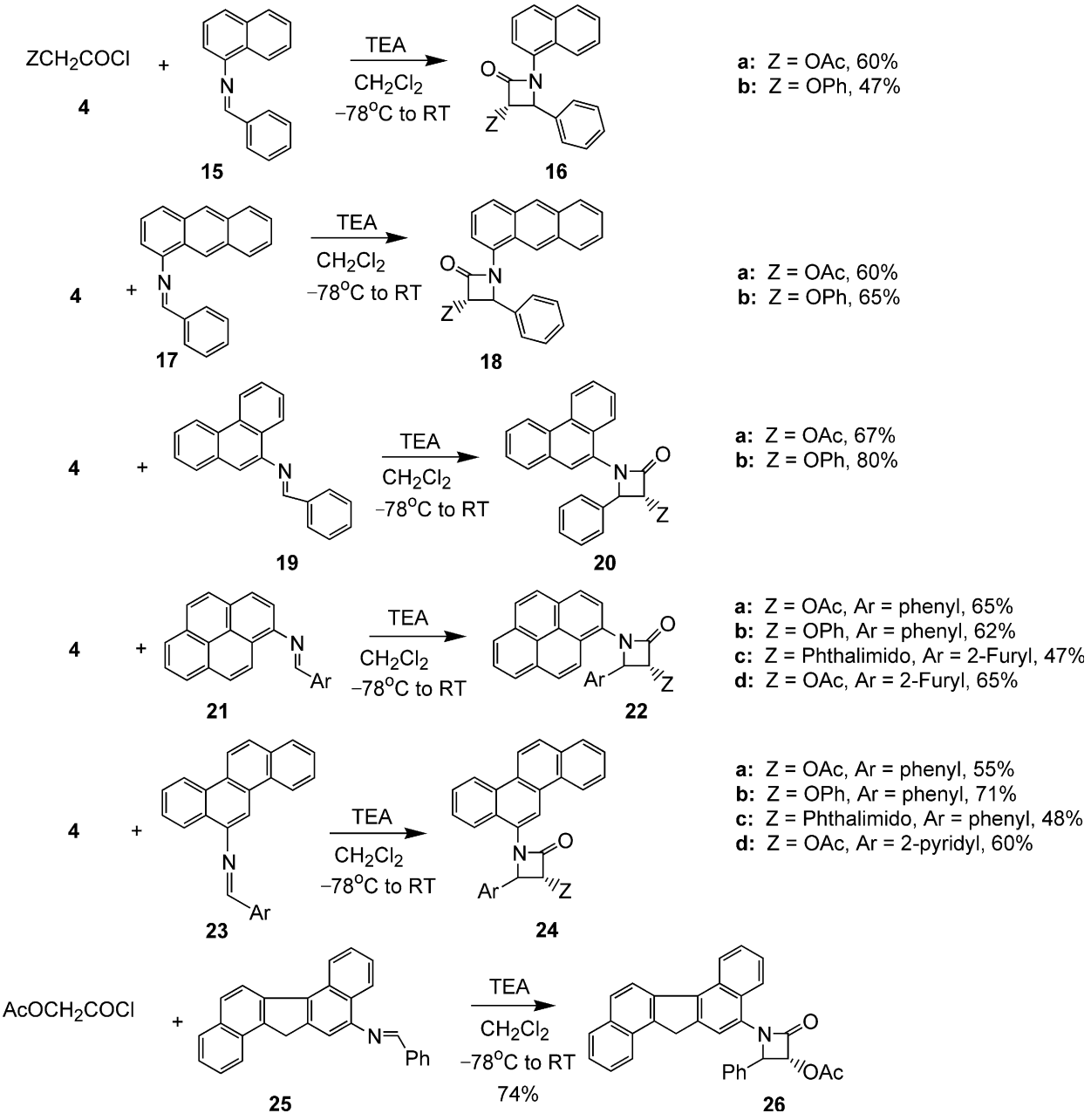
The preparation of β-lactams using the Staudinger reaction was discovered more than 90 years ago. Surprisingly, there has not been a precedent recorded in the literature regarding the use of tetracyclic or pentacyclic aromatic systems in imine components. Notably, the formation of *trans*-β-lactams as seen in the present investigation also has not been described in the literature.[12c] Some previous studies were aimed at the formation of *trans*-β-lactams. However, the experimental conditions in those investigations were clearly different from those in the present one. For example, synthesis of some *trans*-β-lactams was achieved using high-power microwave irradiation and changing the order in which the reagents were added.[29d,e] Furthermore, in two cases, *trans*-β-lactams were formed in low yield as the only isolated products using cyclic imines, but they were not derived from aromatic amines.[29a,b] Structurally, those cyclic imines are completely different than the imines used in this study. The situation became more complicated when a sterically congested cyclic imine produced *cis*-β-lactam.[29c] Since microwave irradiation was helpful in achieving the synthesis of *trans*-β-lactams, we wanted to test this approach under this condition.

2.2. Microwave-induced synthesis of β-lactams

The use of domestic microwave in organic synthesis is well established. This is particularly very interesting because of the unconventional set up for conducting the reaction to take advantage of the specific nature of microwave energy. Irradiation of a solution of imines **15**, **17**, and **23** with acetoxyacetyl chloride in chlorobenzene using a domestic microwave oven[30,31] afforded *trans*-β-lactams **16a**, **18a**, and **24a**, respectively, in comparable yield (Scheme 9).

A large Erlenmeyer flask was the reaction vessel in unmodified domestic microwave oven. Polar solvents like chlorobenzene and DMF can be used. The boiling points of these solvents are much higher than the projected temperature of the reaction. The temperature of the reaction mixture was kept below 110 °C by the proper adjustments of the on–off cycle and a 'heat sink'. Since microwave energy is absorbed by all of the polar molecules effectively, there is no need for a stirrer. A reflux condenser is not required. When irradiated in a microwave oven using chlorobenzene and triethylamine, *cis*-β-lactams **37** and **39** did not isomerize to the more stable *trans*-β-lactams **36** and **38**. Also, the *cis*-β-lactams did not change to *trans*-β-lactams when they were refluxed using ethylene dichloride and triethylamine. These experiments established that there was no isomerization of the *cis*-β-lactams to the more thermodynamically stable *trans*-β-lactams during reaction of imines with acid chlorides (equivalent) at a high temperature and/or under microwave irradiation.

The surprising observation is that irradiation of **15**, **17**, and **23** with **4** under identical conditions afforded the trans product **16a**, **18a**, and **24a** as the only isomers. However, irradiation of **34** and **35** with **4** in chlorobenzene produced mostly *trans*-β-lactams (**36** and **38**).

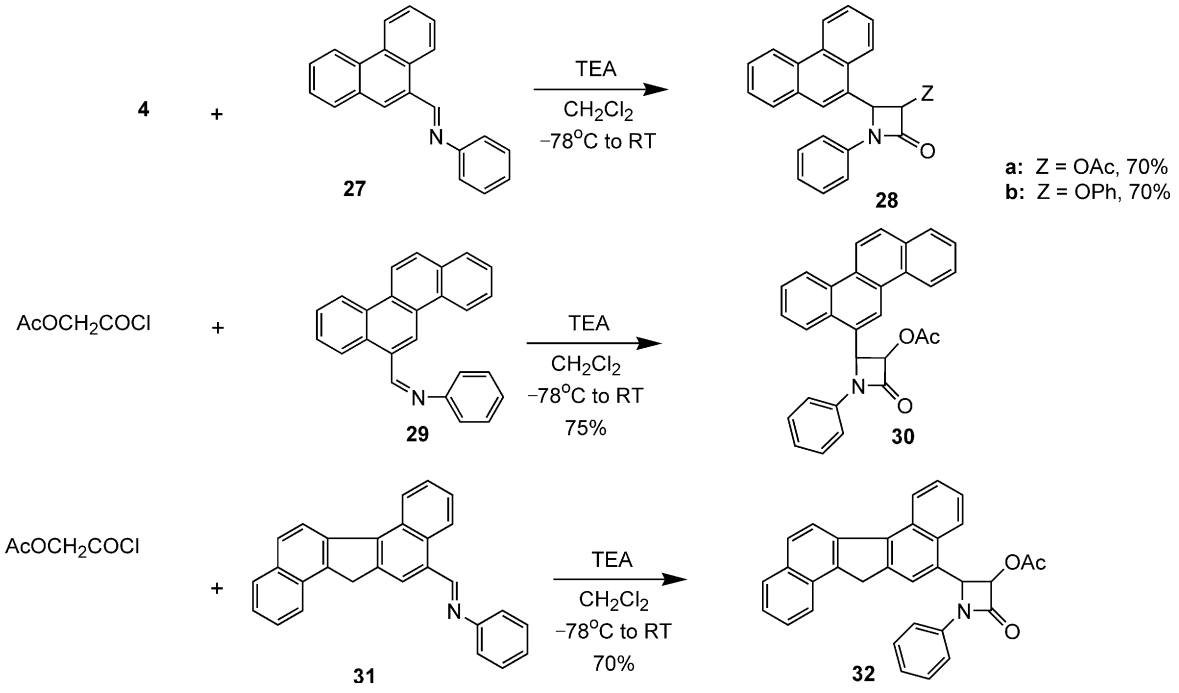


Scheme 5.

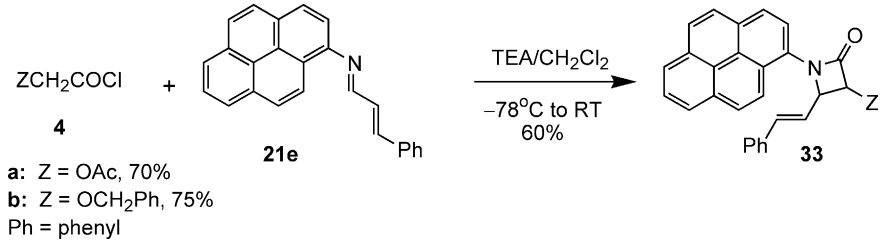
Therefore, the present study clearly indicates that microwave irradiation can accelerate the synthesis of β-lactams with comparable yield. These reactions were performed in unmodified domestic microwave ovens in a matter of minutes using very limited amounts of solvents.

2.3. Mechanism of β-lactam formation with polyaromatic imines

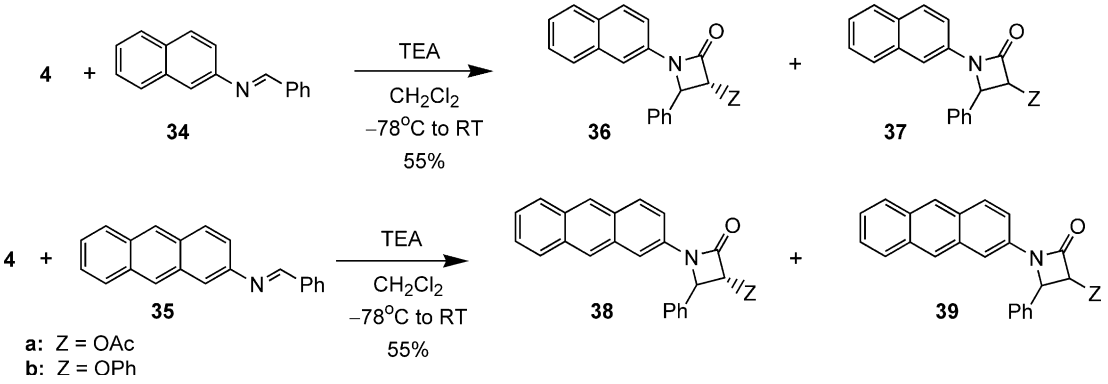
While the mechanism of β-lactam formation has been investigated extensively, the rationale for the observed diastereoselectivity in certain cases remains unknown. It has been shown that the stereoselectivity depends on a number of factors: the structure of the imine, acid chloride (equivalent), sequence of reagent addition, solvent, temperature, and bases. In a large number of observations, *cis*-β-lactam was found to be the exclusive or major product when acid chloride (equivalent) was added dropwise at low to room temperature to the solution of imines and a tertiary base. On the other hand, a *trans*-β-lactam is the major or exclusive product when a tertiary base is slowly added to the imine and acid chloride (equivalent) solution at room to high temperature. Based on the large amount of data in the literature, some predictions concerning their stereoselectivity have been made. For instance, Georg and Ravikumar established some empirical rules regarding stereoselectivity in the formation of β-lactam rings.[28] Also, computer-assisted theoretical calculations have been advanced to explain the stereochemical outcome.[32,33] Cossio and co-workers[32] and Sordo and co-workers[33] explained the stereochemical results on the basis of torquoelectronic



Scheme 6.

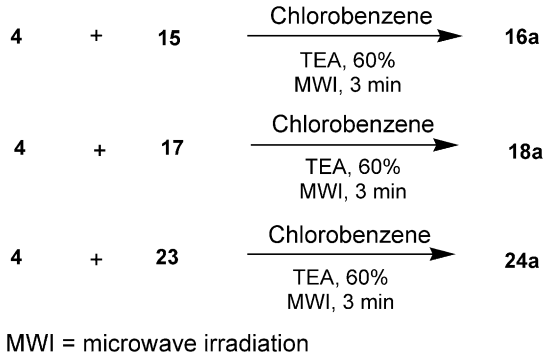


Scheme 7.



Scheme 8.

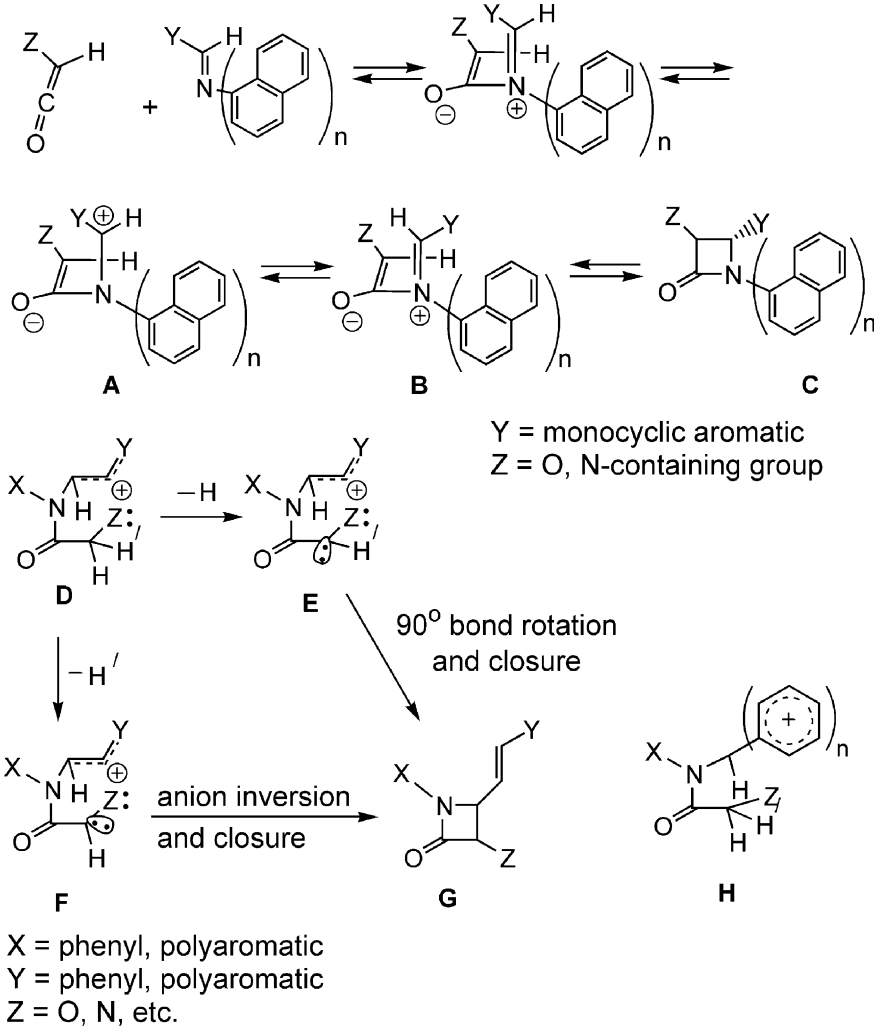
effects. Low-temperature infrared spectroscopy was used by Lynch et al. to identify the reactive intermediates.[34] In general, two mechanisms have been proposed to explain the product distribution in the β-lactam formation reaction. One of these, the ketene mechanism, was observed in a low-temperature infrared spectroscopy study[34] while the other, the acylation of imine mechanism, was believed to be involved as described previously.[28] Both 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 latter mechanism proposes acylation of the imine by the acid



Scheme 9.

chloride to form *N*-acyliminium chloride, which produces zwitterionic intermediates (Scheme 10).

Our current thoughts regarding the likely mechanisms by which this cycloaddition proceeds are described below in brief. Infra-red spectra have shown a strong band at 2200 cm^{-1} when **4** and **23** were reacted in the presence of triethylamine within 30 min after the start of the reaction. This band mostly disappeared after 24 h of reaction. Therefore, involvement of a ketene species is speculated. The formation of a trans isomer as observed in the present study can be rationalized through isomerization of the enolates (Scheme 10, **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 the formation of *trans*-β-lactam **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.[35] 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 previously described by Doyle et al.[36] 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-lactam **G** through **E** (90° bond rotation and closure) or **F** (anion inversion and closure). This hypothesis is further strengthened by the possible formation of donor–acceptor complex **H** as suggested by Bose et al.[37] This complex formation effectively stabilizes the transition states of the reaction.



Scheme 10.

In an elegant study, Cossio et al.[32a] described that the SN_2 intramolecular mechanism favored the preferential or exclusive formation of *trans*-β-lactams, particularly when the reactions were allowed to take place in the absence of a tertiary base in the initial stages of the reaction. Triethylamine was used as one of the reactants at the beginning of our experiment, yet the product was a *trans*-β-lactam in many cases as described above. The use of diisopropylethyl amine as the base could not improve the yield of our products. However, the stereochemistry of the products remained identical. In a recent paper, Lassaletta and co-workers[38] explained the stereoselectivity of *trans*-β-lactam on the basis of steric effects. This paper postulated the isomerization of C=N bond prior to ring closure as a result of severe steric interactions between bulky *N*-benzyloxycarbonyl-*N*-benzylamino group and the alkyl group of hydrazone. Undoubtedly, this mechanism explained our *trans*-selectivity, but could not explain cis selectivity with similar-types of compounds. Formation of a mixture of cis- and trans-isomers with naphthalenyl and anthracenyl imines as observed cannot be explained even when using the mechanisms described above.[32–38] If the electron-withdrawal properties or the steric crowding of the *N*-polyaromatic system are solely responsible for the *trans*-β-lactam formation, then an identical stereochemical distribution would have been observed in the isomeric naphthalenyl and anthracenyl compounds. Comparison of these results and examination of the *N*-polyaromatic systems with which (**19**, **21**, **23**, and **25**) trans isomers were the only products revealed a structural similarity. As stated above, these imines **15** and **17** have a *peri* hydrogen very close to the C=N bond, whereas this *peri* hydrogen is relatively distant from the same bond in imines **34** and **35**. Whether this *peri* hydrogen is accountable for the difference in stereochemical behavior is unknown at this time. However, a critical role for a *peri* nitrogen atom in the biological activity of a number of carboxamides has been demonstrated. But, it has been established that microwave irradiation can alter the stereochemical distribution when naphthalenyl and anthracenyl imines **34** and **35** were used irrespective of the absence of the *peri* hydrogen. In contrast, several other imines (**21e**, **27**, **29**, and **31**) with extended conjugation never produced *trans*-β-lactams even after performing the reactions under forcing conditions.[29e] In this respect, it appears that stabilization of the positive charge by the extended conjugation is the major contributor in dictating the stereochemistry of the final β-lactams.[36] These extensive results also indicate that it is the nature of the C_4 group that controls the isomer distribution in this type of reaction. Therefore, it is conceivable that the mechanism of β-lactam formation reaction by Staudinger reaction is not only very complex, but also unique since it varies considerably with minor structural changes and conditions.

2.4. Anticancer activities of the β-lactams

These β-lactams were tested using nine human cancer cell lines with cisplatin and diamide **1b** as controls. The results are depicted in Table 1.

The structure–activity study revealed that regardless of the structure or configuration of the β-lactam component, neither naphthalene (**16**), anthracene (**18**) nor pyrene derivatives (**22**) demonstrated activity against any of these cell lines. 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 *trans*-acetoxy phenanthrene and chrysene derivatives (**20a**, **24a**, and **24d**) demonstrated activity. Phenoxy and phthalimido (**20b**, **24b**, and **24c**) β-lactams were inactive. Specifically, on the breast cancer cell line MCF-7, three compounds (cisplatin, **20a**, and **24a**) had almost identical activity, while on the colon cancer cell line HT-29; **24a** 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 **24a** had almost identical activity and **20a** had little.

Several conclusions can be derived from the results of the in vitro studies. It is a 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 **20a** and two chrysene derivatives **24a** and **24d** demonstrated cytotoxicity against the tumor cell lines. The comparable naphthalenes, anthracenes, and pyrene compounds (**16**, **18**, **20b**, **22**, **24b–c**, **28**, and **30**) were inactive. Also, the presence of the acetoxy group proved to be obligatory. Acetoxy is a well-established leaving group for reactions with a wide range of nucleophiles. This suggests that an enzymatic or other alteration at this site was involved in the activation of these compounds (**20a**, **24a**, and **24d**). Furthermore, only the *trans*-β-lactams (**20a** and **24a** vs **28a** and **30a**) were proved to have antitumor activity. This study supports that certain conformationally restricted compounds, indeed, can give better activity in biological systems.[5,15–22] In the present study, it has been confirmed that **20a**, **24a**, and **24d** are more potent

Table 1. In vitro cytotoxicity of β-lactams on human cancer cell lines (μM)

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
20a	10.48	10.09	12.49	18.0	18.00	9.3	5.21	4.0	10.49
24a	10.84	9.81	11.98	4.17	6.88	16.32	3.64	4.33	5.66
24d	11.00	14.93	14.46	—	9.0	—	2.5	2.5	15.90
16, **18**, **20b**, **22**, **24b–c**, **28**, **30**, **33**	>20	>20	>20	>20	>20	>20	>20	>20	>20

All of the in vitro cytotoxicity assays were performed using MTT assay.

than **1b** in many cancer lines in vitro. However, neither the target nor the mechanism of the subsequent antitumor activity of these agents has been identified.[14b]

3. Conclusion

We have demonstrated facile synthesis of a number of new anticancer active β-lactams starting from polyaromatic imines. The β-lactam derivatives described herein are unique and they demonstrate reasonable in vitro antitumor cytotoxicity. The stereochemical outcome of the Staudinger reaction as reported herein may offer our laboratory and others many additional opportunities to use β-lactams in the synthesis of biologically active compounds.[39]

4. Experimental

4.1. General methods

All of the 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 hertz. 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 $CDCl_3$ and CD_3OD using tetramethylsilane as an internal standard. IR spectra were expressed as wave numbers (cm^{-1}).

For the preparation of the nitro compound, see Ref. 25. For the preparation of the aldehyde, see Ref. 26.

4.2. Preparation of imine (general procedure)

To a solution of the amine (10 mmol) in toluene (40 mL) was added aldehyde (10 mmol) and the mixture was refluxed overnight using a Dean–Stark water separator (monitored by TLC). When the reaction was over, toluene was evaporated under reduced pressure, and the crude product was used as such for the next reaction.

4.3. Preparation of β-lactam (general procedure)

A solution consisting of acid chloride (1.5 mmol) in dichloromethane (10 mL) was added dropwise to a stirred solution containing imine (1 mmol) and distilled triethylamine (3 mmol) in dry dichloromethane (10 mL) at −78 °C. The reaction mixture was then stirred overnight at room temperature, washed with saturated sodium bicarbonate solution (10 mL), dilute hydrochloric acid (10%, 10 mL), brine (10 mL), dried with anhydrous sodium sulfate, and evaporated to obtain the crude product. Proton NMR was performed to calculate the ratio of the isomeric β-lactams. The pure product (47–80%) was then isolated via column chromatography over silica gel using ethyl acetate–hexanes (1:4) as the solvent.

4.4. Microwave-assisted preparation of the β-lactam (general procedure)

The following caution is recommended. It is standard practice in our laboratories to place the microwave oven inside the hood. Many commercial microwave ovens are equipped with a timer such that heating can be started after the operator has moved away from the hood containing the microwave oven.

The same amount of imine, acid chloride, and triethylamine was placed in an Erlenmeyer flask (125 mL capacity) containing chlorobenzene (2 mL). The flask was then capped with a glass funnel and placed in a microwave oven (G. E. Model, 1450 W). A 500 mL beaker containing 200 mL of water was placed in the oven next to the reaction flask to serve as a 'heat sink'. The mixture was irradiated for 3 min at intervals of 1 min each. After the usual work up as described above, the β-lactam was isolated (60–70% yield).

4.5. *trans*-*N*-(1-Naphthalenyl)-3-acetoxy-4-phenyl-2-azetidine-2-one (16a)

Mp 136–138 °C; IR cm^{-1} (neat) 1757, 1745, 1596, 1576, 1510, 1465, 1456, 1409, 1367, 1340, 1222; ^{1}H NMR ($CDCl_3$): δ (ppm) 2.26 (s, 3H), 5.33–5.34 (d, J = 1.94 Hz, 1H), 5.66–5.67 (d, J = 1.96 Hz, 1H), 7.21–7.39 (m, 7H), 7.52–7.66 (m, 2H), 7.72–7.75 (d, 1H), 7.84–7.85 (d, 1H), 8.22–8.25 (d, 1H). Anal. Calcd for $C_{21}H_{17}NO_3$: C, 76.12; H, 5.17; N, 4.23. Found: C, 76.15; H, 5.19; N, 4.20.

4.6. *trans*-*N*-(1-Naphthalenyl)-3-phenoxy-4-phenyl-2-azetidine-2-one (16b)

Mp 215–217 °C; IR cm^{-1} (neat) 1760, 1596, 1576, 1510, 1494, 1465, 1456, 1406, 1368, 1339, 1290, 1228; ^{1}H NMR ($CDCl_3$): δ (ppm) 5.30–5.31 (d, J = 1.81 Hz, 1H), 5.38–5.39 (d, J = 1.8 Hz, 1H), 6.95–7.06 (m, 3H), 7.23–7.44 (m, 9H), 7.51–7.57 (m, 1H), 7.59–7.67 (m, 1H), 7.72–7.74 (d, 1H), 7.84–7.87 (d, 1H), 8.25–8.27 (d, 1H). Anal. Calcd for $C_{25}H_{19}NO_2$: C, 82.17; H, 5.24; N, 3.83. Found: C, 82.2; H, 5.18; N, 3.79.

4.7. *trans*-*N*-(1-Anthracenyl)-3-acetoxy-4-phenyl-2-azetidine-2-one (18a)

Mp 298–300 °C; IR cm^{-1} (neat) 1752, 1672, 1583, 1457, 1370, 1315, 1273, 1218; ^{1}H NMR ($CDCl_3$): δ (ppm) 2.28 (s, 3H), 5.41–5.42 (d, J = 1.95 Hz, 1H), 5.74–5.75 (d, J = 1.99 Hz, 1H), 7.18–7.20 (d, 1H), 7.26–7.42 (m, 6H), 7.51–7.54 (m, 2H), 7.88–7.91 (d, 1H), 7.99–8.02 (m, 1H), 8.14–8.17 (m, 1H), 8.44 (s, 1H), 8.83 (s, 1H). Anal. Calcd for $C_{25}H_{19}NO_3$: C, 78.72; H, 5.02; N, 3.67. Found: C, 78.69; H, 5.05; N, 3.59.

4.8. *trans*-*N*-(1-Anthracenyl)-3-phenoxy-4-phenyl-2-azetidine-2-one (18b)

Mp 146–148 °C; IR cm^{-1} (neat) 1761, 1622, 1598, 1592, 1541, 1493, 1458, 1406, 1385, 1367, 1339, 1290, 1231; ^{1}H NMR ($CDCl_3$): δ (ppm) 5.38–5.39 (d, J = 1.81 Hz, 1H),

5.47–5.48 (d, J = 1.79 Hz, 1H), 6.99–7.08 (m, 3H), 7.20–7.36 (m, 7H), 7.44–7.56 (m, 4H), 7.88–7.91 (d, 1H), 7.98–8.01 (m, 1H), 8.14–8.18 (m, 1H), 8.44 (s, 1H), 8.85 (s, 1H). Anal. Calcd for $C_{29}H_{21}NO_2$: C, 83.83; H, 5.09; N, 3.3.37. Found: C, 83.79; H, 5.1; N, 3.4.

4.9. *trans*-*N*-(9-Phenanthrenyl)-3-acetoxy-4-phenyl-2-azetidine-2-one (20a)

Mp 152–154 °C; IR cm^{-1} (neat) 1754, 1625, 1599, 1528, 1498, 1455, 1401, 1369, 1280, 1219; ^{1}H NMR ($CDCl_3$): δ (ppm) 2.27 (s, 3H), 5.43–5.44 (d, J = 1.92 Hz, 1H), 5.70–5.71 (d, J = 1.96 Hz, 1H), 7.27–7.29 (m, 3H), 7.40–7.42 (m, 2H), 7.52–7.63 (m, 3H), 7.73–7.78 (m, 3H), 8.29–8.32 (m, 1H), 8.62–8.64 (d, 1H), 8.70–8.73 (m, 1H). Anal. Calcd for $C_{25}H_{19}NO_3$: C, 78.72; H, 5.02; N, 3.67. Found: C, 78.69; H, 5.17; N, 3.70.

4.10. *trans*-*N*-(9-Phenanthrenyl)-3-benzyloxy-4-phenyl-2-azetidine-2-one (20b)

IR cm^{-1} (neat) 1760, 1624, 1597, 1528, 1497, 1482, 1453, 1400, 1368, 1346, 1277, 1208; ^{1}H NMR ($CDCl_3$): δ (ppm) 4.80 (d, J = 1.87 Hz, 1H), 4.94 (d, J = 11 Hz, 1H), 5.32 (d, J = 1.85 Hz, 1H), 7.21–7.26 (m, 6H), 7.34–7.44 (m, 5H), 7.70–7.75 (m, 5H), 8.27–8.30 (m, 1H), 8.61 (d, J = 8 Hz, 1H), 8.66–8.71 (m, 1H). Anal. Calcd for $C_{30}H_{23}NO_2$: C, 83.89; H, 5.39; N, 3.26. Found: C, 83.80; H, 4.89; N, 3.50.

4.11. *trans*-*N*-(1-Pyrenyl)-3-acetoxy-4-phenyl-2-azetidine-2-one (22a)

Mp 130–132 °C; IR cm^{-1} (neat) 1760, 1745, 1601, 1509, 1457, 1410, 1372, 1315, 1283, 1224; ^{1}H NMR ($CDCl_3$): δ (ppm) 2.29 (s, 3H), 5.52–5.53 (d, J = 1.19 Hz, 1H), 5.75–5.76 (d, J = 1.93 Hz, 1H), 7.24–7.27 (m, 3H), 7.41–7.44 (m, 2H), 7.77–7.80 (d, 1H), 7.97–8.10 (m, 4H), 8.19–8.25 (m, 3H), 8.41–8.44 (d, 1H). Anal. Calcd for $C_{27}H_{19}NO_3$: C, 79.98; H, 4.72; N, 3.45. Found: C, 80.0; H, 4.7; N, 3.5.

4.12. *trans*-*N*-(1-Pyrenyl)-3-phenoxy-4-phenyl-2-azetidine-2-one (22b)

Mp 186–187 °C; IR cm^{-1} (neat) 1757, 1599, 1590, 1509, 1493, 1456, 1438, 1410, 1379, 1315, 1276, 1263, 1241, 1227; ^{1}H NMR ($CDCl_3$): δ (ppm) 5.40–5.39 (d, J = 1.79 Hz, 1H), 5.57–5.58 (d, J = 1.68 Hz, 1H), 6.99–7.06 (m, 3H), 7.26–7.34 (m, 5H), 7.46–7.49 (dd, 2H), 7.79–7.81 (d, 1H), 7.97–8.09 (m, 4H), 8.18–8.24 (m, 3H), 8.44–8.47 (d, 1H). Anal. Calcd for $C_{31}H_{21}NO_2$: C, 84.72; H, 4.82; N, 3.19. Found: C, 84.7; H, 4.8; N, 3.2.

4.13. *trans*-*N*-(1-Pyrenyl)-3-phthalimido-4-phenyl-2-azetidine-2-one (22c)

IR cm^{-1} (CH_2Cl_2) 3060, 1760, 1600, 1555; ^{1}H NMR ($CDCl_3$): δ (ppm) 2.21 (s, 3H), 5.43 (d, J = 2.04 Hz, 1H), 6.10 (d, J = 2.05 Hz, 1H), 6.25 (dd, J_1 = 10 Hz, J_2 = 14 Hz, 1H), 6.42 (d, J = 3.8 Hz, 1H), 7.80 (d, J = 9 Hz, 1H), 8.05–8.31 (m, 9H). Anal. Calcd for $C_{31}H_{18}N_2O_4$: C, 77.17; H, 3.76; N, 5.81. Found: C, 76.68; H, 3.45; N, 5.53.

4.14. *trans*-*N*-(6-Chrysenyl)-3-acetoxy-4-phenyl-2-azetidine-2-one (24a)

Mp 174–176 °C; IR cm^{-1} (neat) 1755, 1595, 1515, 1486, 1456, 1440, 1394, 1373, 1314, 1283, 1219; ^{1}H NMR ($CDCl_3$): δ (ppm) 2.36 (s, 3H), 5.54–5.55 (d, J = 1.91 Hz, 1H), 5.77–5.78 (d, J = 1.94 Hz, 1H), 7.26–7.31 (m, 3H), 7.46–7.49 (m, 2H), 7.60–7.71 (m, 2H), 7.77–7.80 (m, 2H), 7.95–7.99 (m, 2H), 8.38–8.41 (m, 1H), 8.45 (s, 1H), 8.50–8.53 (d, 1H), 8.63–8.66 (d, 1H), 8.79–8.82 (m, 1H). Anal. Calcd for $C_{29}H_{21}NO_3$: C, 80.72; H, 4.91; N, 3.25.12. Found: C, 80.69; H, 4.89; N, 3.19.

4.15. *trans*-*N*-(6-Chrysenyl)-3-phenoxy-4-phenyl-2-azetidine-2-one (24b)

Mp 180–182 °C; IR cm^{-1} (neat) 1761, 1596, 1515, 1494, 1456, 1439, 1392, 1346, 1315, 1235; ^{1}H NMR ($CDCl_3$): δ (ppm) 5.42–5.43 (d, J = 1.8 Hz, 1H), 5.59–5.60 (d, J = 1.74 Hz, 1H), 7.0–7.09 (m, 3H), 7.28–7.38 (m, 5H), 7.52–7.55 (m, 2H), 7.59–7.70 (m, 2H), 7.76–7.79 (m, 2H), 7.94–7.98 (m, 2H), 8.41–8.43 (m, 1H), 8.48 (s, 1H), 8.50–8.52 (d, 1H), 8.62–8.65 (d, 1H), 8.78–8.81 (m, 1H). Anal. Calcd for $C_{33}H_{23}NO_2$: C, 85.14; H, 4.98; N, 3.01. Found: C, 85.09; H, 4.79; N, 2.99.

4.16. *trans*-*N*-(6-Chrysenyl)-3-phthalimido-4-phenyl-2-azetidine-2-one (24c)

IR cm^{-1} (neat) 3050, 1760, 1605, 1550; ^{1}H NMR ($CDCl_3$): δ (ppm) 5.67 (d, J = 2.8 Hz, 1H), 5.95 (d, J = 2.8 Hz, 1H), 7.23–7.30 (m, 3H), 7.46–7.49 (m, 2H), 7.62 (m, 2H), 7.77 (m, 4H), 7.92 (m, 4H), 8.50 (m, 2H), 8.60 (m, 2H), 8.75 (m, 1H). Anal. Calcd for $C_{35}H_{22}N_2O_3$: C, 81.07; H, 4.28; N, 5.40. Found: C, 81.0; H, 4.25; N, 5.35.

4.17. *trans*-*N*-(6-Chrysenyl)-3-acetoxy-4-(2′-pyridyl)-2-azetidine-2-one (24d)

Mp 162–164 °C; IR cm^{-1} (neat) 1760, 1600, 1510, 1485, 1450, 1390; ^{1}H NMR ($CDCl_3$): δ (ppm) 2.29 (s, 3H), 5.30 (d, J = 1.5 Hz, 1H), 5.58 (d, J = 1.5 Hz, 1H), 7.16 (dd, J_1 = 5.1 Hz, J_2 = 6.9 Hz, 9H), 7.27 (d, J = 9 Hz, 1H), 7.50–7.98 (m, 7H), 8.36–8.81 (m, 6H). Anal. Calcd for $C_{28}H_{20}N_2O_3$: C, 77.76; H, 4.66; N, 6.48. Found: C, 77.43; H, 4.35; N, 6.18.

4.18. *trans*-*N*-(2′-Dibenzofluorenyl)-3-acetoxy-4-phenyl-2-azetidine-2-one (26)

UV (EtOH): λ_{max} 260 (log ε 4.57), 355 (log ε 4.26); IR cm^{-1} (CH_2Cl_2) 3054, 1755, 1590, 1496, 1456; ^{1}H NMR ($CDCl_3$): δ (ppm) 2.28 (s, 3H), 4.00 (1H, AB_q, J = 22.68 Hz), 5.42, (d, J = 1.2 Hz, 1H), 5.70 (d, J = 1.2 Hz, 1H), 7.23–7.40 (m, 8H), 7.67–7.87 (m, 2H), 7.88–7.90 (m, 3H), 8.35–8.38 (m, 2H), 8.42–8.50 (m, 1H); ^{13}C NMR ($CDCl_3$): δ (ppm) 20.67, 36.29, 65.29, 81.03, 117.50, 121.41, 124.04, 124.08, 124.62, 125.61,

125.78, 126.50, 126.91, 127.68, 127.82, 128.59, 129.01, 129.99, 130.19, 131.82, 135.28, 136.96, 141.28, 141.13, 163.29, 169.77. Anal. Calcd for $C_{32}H_{23}NO_3$: C, 81.86; H, 4.94; N, 2.98. Found: C, 81.58; H, 5.02; N, 3.09.

4.19. *cis*-*N*-(1-Phenyl)-3-acetoxy-4-phenanthrenyl-2-azetidine-2-one (28a)

Mp 192–194 °C; IR cm^{-1} (neat) 1761, 1599, 1497, 1451, 1408, 1372, 1265, 1217; ^1H NMR ($CDCl_3$): δ (ppm) 1.40 (s, 3H), 6.11–6.13 (d, $J = 5.17$ Hz, 1H), 6.53–6.54 (d, $J = 5.22$ Hz, 1H), 7.11–7.16 (m, 1H), 7.26–7.33 (m, 2H), 7.45–7.49 (m, 2H), 7.54–7.59 (m, 1H), 7.65–7.78 (m, 5H), 7.97–8.0 (d, 1H), 8.67–8.7 (d, 1H), 8.76–8.79 (d, 1H). Anal. Calcd for $C_{25}H_{19}NO_3$: C, 78.72; H, 5.02; N, 3.67. Found: C, 78.69; H, 4.99; N, 3.59.

4.20. *cis*-*N*-(1-Phenyl)-3-phenoxy-4-phenanthrenyl-2-azetidine-2-one (28b)

IR cm^{-1} (neat) 1752, 1596, 1493, 1452, 1435, 1405, 1375, 1264, 1227; ^1H NMR ($CDCl_3$): δ (ppm) 5.80–5.82 (d, $J = 5.39$ Hz, 1H), 6.17–6.19 (d, $J = 5.32$ Hz, 1H), 6.68–6.71 (m, 2H), 6.83–6.88 (m, 1H), 7.04–7.14 (m, 3H), 7.30–7.35 (m, 2H), 7.50–7.77 (m, 8H), 7.96–7.98 (d, 1H), 8.68–8.71 (d, 1H), 8.78–8.81 (d, 1H). Anal. Calcd for $C_{29}H_{21}NO_2$: C, 83.83; H, 5.09; N, 3.37. Found: C, 83.79; H, 5.1; N, 3.33.

4.21. *cis*-*N*-(1-Phenyl)-3-acetoxy-4-chrysenyl-2-azetidine-2-one (30)

IR cm^{-1} (neat) 1755, 1748, 1598, 1497, 1383, 1368, 1264, 1255, 1216; ^1H NMR ($CDCl_3$): δ (ppm) 8.89–8.56 (d, 1H), 8.73–8.70 (d, 1H), 8.64 (s, 1H), 8.41–8.37 (m, 1H), 8.11–8.09 (d, 1H), 8.05–8.02 (d, 1H), 7.98–7.95 (m, 1H), 7.79–7.95 (m, 1H), 7.79–7.72 (m, 2H), 7.62–7.58 (m, 2H), 7.59–7.52 (m, 1H), 7.51–7.29 (t, 2H), 7.14–7.10 (t, 1H), 6.59–6.57 (d, $J = 5.2$ Hz, 1H), 6.28–6.26 (d, $J = 5.18$ Hz, 1H), 1.37 (s, 3H); ^{13}C NMR ($CDCl_3$): δ (ppm) 169.1, 162.6, 136.9, 132.1, 130.8, 130.2, 129.4, 129.3, 128.4, 128.3, 128.1, 127.1, 127.0, 126.9, 126.8, 126.6, 126.42, 124.9, 123.9, 123.1, 122.8, 120.7, 120.4, 117.6, 75.2, 59.2, 19.7. Anal. Calcd for $C_{29}H_{21}NO_3$: C, 80.72; H, 4.91; N, 3.25. Found: C, 80.52; H, 4.69; N, 3.0.

4.22. *cis*-*N*-(1-Phenyl)-3-acetoxy-4-(2-dibenzofluorenyl)-2-azetidine-2-one (32)

IR cm^{-1} (CH_2Cl_2): 3050, 1758, 1590, 1490, 1456; ^1H NMR ($CDCl_3$): δ (ppm) 8.98–8.69 (d, 1H), 8.58–8.55 (d, 1H), 8.11–7.93 (m, 5H), 7.74–7.46 (m, 5H), 7.35–7.30 (t, 3H), 7.15–7.10 (t, 1H), 6.50–6.48 (d, $J = 5.17$ Hz, 1H), 6.24–6.22 (d, $J = 5.03$ Hz, 1H), 4.25–4.24 (d, 2H), 1.42 (s, 3H). Anal. Calcd for $C_{32}H_{23}NO_3$: C, 81.86; H, 4.94; N, 2.98. Found: C, 81.58; H, 5.02; N, 3.09.

4.23. *cis*-*N*-(1-Pyrenyl)-3-acetoxy-4-cinnamyl-2-azetidine-2-one (33a)

IR cm^{-1} (CH_2Cl_2): 3070, 1755, 1600, 1558; ^1H NMR ($CDCl_3$): δ (ppm) 2.21 (s, 3H), 5.30 (dd, $J_1 = 5$ Hz, $J_2 = 8$ Hz), 6.12 (d, $J = 5.2$ Hz, 1H), 6.25–6.38 (m, 1H), 6.65–6.70 (m, 1H), 7.8–8.38 (m, 14H). Anal. Calcd for $C_{29}H_{21}NO_3$: C, 80.72; H, 4.91; N, 3.25. Found: C, 80.69; H, 4.89; N, 3.19.

4.24. *cis*-*N*-(1-Pyrenyl)-3-benzyloxy-4-cinnamyl-2-azetidine-2-one (33b)

IR cm^{-1} (CH_2Cl_2): 3055, 1756, 1600, 1550; ^1H NMR ($CDCl_3$): δ (ppm) 4.80 (dd, $J_1 = 9$ Hz, $J_2 = 12$ Hz, 2H), 5.12 (dd, $J_1 = 4$ Hz, $J_2 = 8$ Hz, 1H), 5.20 (d, $J = 5.5$ Hz, 1H), 6.46–6.62 (m, 2H), 7.18–7.45 (m, 8H), 7.84–8.24 (m, 11H). Anal. Calcd for $C_{34}H_{25}NO_2$: C, 85.15; H, 5.25; N, 2.92. Found: C, 84.89; H, 5.01; N, 2.75.

Acknowledgements

We gratefully acknowledge the partial financial support for this research from The University of Texas, M. D. Anderson Cancer Center. B.K.B. is grateful to The University of Texas—Pan American for academic and research facilities.

References and notes

1. For recent examples, see: (a) Southgate, R.; Branch, C.; Coulton, S.; Hunt, E. In *Recent Progress in the Chemical Synthesis of Antibiotics and Related Microbial Products*; Lukacs, G., Ed.; Springer: Berlin, 1993; Vol. 2, p 621; (b) Kidwai, M.; Sapra, P.; Bhushan, K. R. *Curr. Med. Chem.* **1999**, *6*, 195–215; (c) Bose, A. K.; Manhas, M. S.; Banik, B. K.; Srirajan, V. In *The Amide Linkage: Selected Structural Aspects in Chemistry, Biochemistry, and Material Science*; Greenberg, A., Breneman, C. M., Liebman, J. F., Eds.; Wiley-Interscience: New york, 2000, pp 157–214, Chapter 7 (β-Lactams: Cyclic Amides of Distinction); (d) *β-Lactams: Synthesis, Stereochemistry, Synthons and Biological Evaluation; Current Medicinal Chemistry*; Banik, B. K., Ed.; ; Bentham Science, 2004; Vol. 11.
2. Buynak, J. *Curr. Med. Chem.* **2004**, *11*, 1951–1964.
3. (a) Manhas, M. S.; Banik, B. K.; Mathur, A.; Vincent, J. E.; Bose, A. K. *Tetrahedron* **2000**, *56*, 5587–5601; (b) Bose, A. K.; Mathur, C.; Wagle, D. R.; Manhas, M. S. *Tetrahedron* **2000**, *56*, 5603–5619; (c) Ojima, I. *Acc. Chem. Res.* **1995**, *28*, 383–389; (d) Banik, B. K.; Manhas, M. S.; Bose, A. K. *J. Org. Chem.* **1994**, *59*, 4714–4716; (e) Banik, B. K.; Manhas, M. S.; Bose, A. K. *J. Org. Chem.* **1993**, *58*, 307–309.
4. Suffness, M. *Taxol Science and Applications*; CRC: Boca Raton, FL, 1995.
5. (a) Clader, J. W.; Burnett, D. A.; Caplen, M. A.; Domalski, M. S.; Dugar, S.; Vaccaro, W.; Sher, R.; Browne, M. E.; Zhao, H.; Burrier, R. E.; Salisbury, B.; Davis, H. R. *J. Med. Chem.* **1996**, *39*, 3684–3693; (b) Burnett, D. A.; Caplen, M. A.; Darris, H. R., Jr.; Burrier, R. E.; Clader, J. W. *J. Med. Chem.* **1994**, *37*, 1734–1736; (c) Burnett, D. A. *Curr. Med. Chem.* **2004**, *11*, 1873–1887; (d) Clader, J. W. *J. Med. Chem.* **2004**, *47*, 1–9.
6. Finke, P. E.; Shah, S. K.; Fletcher, D. S.; Ashe, B. M.; Brause, K. A.; Chandler, G. O.; Dellea, P. S.; Hand, K. M.; Maycock, A. L.; Osinga, D. G.; Underwood, D. J.; Weston, H.; Davies, P.; Doherty, J. B. *J. Med. Chem.* **1995**, *38*, 2449–2462, and earlier references.

7. For catalytic asymmetric synthesis, see: (a) Taggi, A. E.; Hafez, A. M.; Wack, H.; Young, B.; Drury, W. J., III; Lectka, T. *J. Am. Chem. Soc.* **2000**, *122*, 7831–7832; (b) Magriotis, P. A. *Angew. Chem.* **2001**, *113*, 4507–4509; (c) Hodous, B. L.; Fu, G. C. *J. Am. Chem. Soc.* **2002**, *124*, 1578–1579; (d) Cordova, A.; Watanabe, S.; Tanaka, F.; Notz, W.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2002**, *124*, 1866–1867; (e) France, S.; Weatherwax, A.; Taggi, A. E.; Lectka, T. *Acc. Chem. Res.* **2004**, *37*, 592–600.
8. For polymer-supported synthesis, see: (a) Ruhland, B.; Bhandari, A.; Gordon, E. M.; Gallop, M. A. *J. Am. Chem. Soc.* **1996**, *118*, 253–254; (b) Furman, B.; Thurmer, R.; Kaluza, Z.; Lysek, R.; Voelter, W.; Chmielewski, M. *Angew. Chem., Int. Ed.* **1999**, *38*, 1121–1123; (c) Gordon, K.; Bolger, M.; Khan, N.; Balasubramanian, S. A. *Tetrahedron Lett.* **2000**, *41*, 8621–8625; (d) Schunk, S.; Enders, D. *Org. Lett.* **2000**, *2*, 907–910; (e) Annunziata, R.; Benaglia, M.; Cinquini, M.; Cozzi, F. *Chem. Eur. J.* **2000**, *6*, 133–138; (f) Gordon, K. H.; Balasubramanian, S. *Org. Lett.* **2001**, *3*, 53–56; (g) Schunk, S.; Enders, D. *J. Org. Chem.* **2002**, *67*, 8034–8042; (h) Delpiccolo, C. M. L.; Mata, E. G. *Tetrahedron: Asymmetry* **2002**, *13*, 905–910.
9. Serine protease: (a) Mascaretti, O. A.; Boschetti, C. E.; Danelon, G. O.; Mata, E. G.; Roveri, O. A. *Curr. Med. Chem.* **1995**, *1*, 441–470; (b) Edwards, P. D.; Bernstein, P. R. *Med. Res. Rev.* **1994**, *14*, 127–194; (c) Sandanayaka, V. P.; Prashad, A. S.; Yang, Y.; Williamson, T.; Lin, Y. I.; Mansour, T. S. *J. Med. Chem.* **2003**, *46*, 2569–2571.
10. Buynak, J. D.; Rao, A. S.; Fod, G. P.; Carver, C.; Carver, C.; Adam, G.; Geng, B.; Bachmann, B.; Shobassy, S.; Lackey, S. *J. Med. Chem.* **1997**, *40*, 3423–3433, and references cited therein.
11. Bonneau, P. R.; Hasani, F.; Plouffe, C.; Malenfant, E.; Laplante, S. R.; Guse, I.; Ogilvie, W. W.; Plante, R.; Davidson, W. C.; Hopkins, J. L.; Morelock, M. M.; Cordingley, M. G.; Deziel, R. *J. Am. Chem. Soc.* **1999**, *121*, 2965–2973 and references cited therein.
12. (a) Ghatak, A.; Becker, F. F.; Banik, B. K. *Heterocycles* **2000**, *53*, 2769–2772; (b) Banik, B. K.; Ghatak, A.; Becker, F. F. *J. Chem. Soc., Perkin Trans. 1* **2000**, 2179–2181; (c) Banik, B. K.; Becker, F. F. *Tetrahedron Lett.* **2000**, *41*, 6551–6554; (d) Ng, S.; Banik, I.; Okawa, A.; Becker, F. F.; Banik, B. K. *J. Chem. Res.* **2001**, 118–119; (e) Dasgupta, S. K.; Banik, B. K. *Tetrahedron Lett.* **2002**, *43*, 9445–9447; (f) Banik, B. K.; Samajdar, S.; Banik, I. *Tetrahedron Lett.* **2003**, *44*, 1699–1701; (g) Banik, B. K.; Banik, I.; Hackfeld, L. *Heterocycles* **2003**, *59*, 505–508; (h) Banik, B. K.; Adler, D.; Nguyen, P.; Srivastava, N. *Heterocycles* **2003**, *61*, 101–104; (i) Banik, B. K.; Banik, I.; Samajdar, S.; Wilson, M. *Heterocycles* **2003**, *63*, 283–296.
13. (a) Becker, F. F.; Banik, B. K. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 2877–2880; (b) Banik, B. K.; Venkatraman, M. S.; Mukhopadhyay, C.; Becker, F. F. *Tetrahedron Lett.* **1998**, *39*, 7247–7250; (c) Becker, F. F.; Mukhopadhyay, C.; Hackfeld, L.; Banik, I.; Banik, B. K. *Bioorg. Med. Chem.* **2000**, *8*, 2693–2699; (d) Banik, B. K.; Ghatak, A.; Mukhopadhyay, C.; Becker, F. F. *J. Chem. Res.* **2000**, 108–109; (e) Mukhopadhyay, C.; Becker, F. F.; Banik, B. K. *J. Chem. Res.* **2001**, 28–31; (f) Banik, B. K.; Becker, F. F. *Bioorg. Med. Chem.* **2001**, *9*, 593–605; (g) Banik, B. K.; Becker, F. F. *Curr. Med. Chem.* **2001**, *8*, 1513–1533; (h) *Current Approaches to the Development of New Chemotherapeutic Agents*; Banik, B. K., Ed.; *Current Medicinal Chemistry*; Bentham Science, 2001; Vol. 8; (i) Banik, B. K.; Samajdar, S.; Banik, I. *J. Org. Chem.* **2004**, *69*, 213–216; (j) Also see: Becker, F. F.; Banik, B. K. U.S. Patent 6,015,811, 2000; (k) Becker, F. F.; Banik, B. K. U.S. Patent 6,184,224, 2001; (l) Becker, F. F.; Banik, B. K. U.S. Patent 6,362,200, 2002.
14. (a) Banik, I.; Becker, F. F.; Banik, B. K. *J. Med. Chem.* **2003**, *46*, 12–15; (b) Banik, B. K.; Becker, F. F.; Banik, I. *Bioorg. Med. Chem.* **2004**, *12*, 2523–2528. Presented at the American Chemical Society (ACS) National Meeting, Orlando, FL, April 2002, MEDI-213. We sent this paper for presentation to the ACS on October 31, 2001 and it was accepted on December 16, 2001. The drug synthesis and chemistry branch of the NCI tested **24a** in their 60 cell lines and sent us the report on August 8, 2001. This indicates that we are the pioneer in this field.
15. It has also been demonstrated that UAB-8, a conformationally constrained analogue of retinoic acid, has a favorable toxicological profile relative to the original molecule. For example, see: Lin, T. H.; Rogers, T. S.; Hill, D. L.; Simpson-Herren, L.; Farnell, D. R.; Kochhar, D. M.; Alam, M.; Brouillette, W. J.; Muccio, D. D. *Toxicol. Appl. Pharmacol.* **1996**, *139*, 310–316.
16. Rigid tricyclic indole analogues of melatonin have also been synthesized, and the superiority of the cis constrained isomer over trans as an agonist has been experimentally proved. For example, see: Garratt, P. J.; Vonhoff, S.; Rowe, S. J.; Sugden, D. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 1559–1564.
17. Angular polyaromatic systems, phenalene derivatives appeared to be promising restricted ligands for melatonin receptors. For example, see: Mathe-Allainmat, M.; Gaudy, F.; Sicic, S.; Dangy-Caye, A.-L.; Shen, S.; Bremont, B.; Benatalah, Z.; Langlois, M.; Renard, P.; Delagrange, P. *J. Med. Chem.* **1996**, *39*, 3089–3095.
18. Conformationally constrained anesthetic steroids that modulate $GABA_A$ receptors have been studied. For example, see: Anderson, A.; Boyd, A. C.; Clark, J. K.; Fielding, L.; Gemmell, D. K.; Hamilton, N. M.; Maidment, M. S.; May, V.; McGuire, R.; McPhail, P.; Sansbury, F. H.; Sundaram, H.; Taylor, R. *J. Med. Chem.* **2000**, *43*, 4118–4125.
19. The discovery of conformationally constrained Taxol analogues (constrained on the C_{13} side chain) that can retain the biological activity of the natural product is an addition to this principle. For example, see: Barboni, L.; Lambertucci, C.; Appendino, G.; Vander Velde, D. G.; Himes, R. H.; Bombardelli, E.; Wang, M.; Snyder, J. P. *J. Med. Chem.* **2001**, *44*, 1576–1587.
20. One of the most well-known strategies in nucleoside analogue synthesis is replacement of the carbohydrate group by relatively constrained acyclic chains. For example, see: Hernandez, A. I.; Balzarini, J.; Karlsson, A.; Camarasa, M. J.; Perez, M. J. *J. Med. Chem.* **2002**, *45*, 4254–4263.
21. Conformationally restricted compounds that are more efficient than their flexible analogues include linezolid derivatives. For example, see: Selvakumar, N.; Srinivas, D.; Khera, M. K.; Kumar, M. S.; Mamidi, R. N. V. S.; Sarnaik, H.; Charavaryamath, C.; Rao, B. S.; Raheem, M. A.; Das, J.; Iqbal, J.; Rajagopalan, R. *J. Med. Chem.* **2002**, *45*, 3953–3962.
22. Conformationally restricted compounds that are more efficient than their flexible analogues include nicotine derivatives. For example, see: Ullrich, T.; Krich, S.; Binder, D.; Mereiter, K.; Anderson, D. J.; Meyer, M. D.; Pyerin, M. *J. Med. Chem.* **2002**, *45*, 4047–4054.
23. (a) Samajdar, S.; Becker, F. F.; Banik, B. K. *Tetrahedron Lett.* **2000**, *41*, 8017–8020; (b) Samajdar, S.; Becker, F. F.; Banik, B. K. *Arkivoc* **2001**, 27–30; For some examples of bismuth nitrate-catalyzed reactions from our laboratory, see: (c) Samajdar, S.; Basu, M. K.; Becker, F. F.; Banik, B. K. *Synth. Commun.* **2002**, *32*, 1917–1921; (d) Samajdar, S.; Becker, F. F.; Banik, B. K. *Synth. Commun.* **2001**, *31*, 2691–2695; (e) Srivastava, N.; Dasgupta, S.; Banik, B. K.

Tetrahedron Lett. **2003**, *44*, 1191–1194; (f) Srivastava, N.; Banik, B. K. *J. Org. Chem.* **2003**, *68*, 2109–2114; (g) Banik, B. K.; Banik, I.; Renteria, M.; Dasgupta, S. *Tetrahedron Lett.* **2005**, *46*, 2643.

24. (a) Banik, B. K.; Suhendra, M.; Banik, I.; Becker, F. F. *Synth. Commun.* **2000**, *30*, 3745–3754; (b) Banik, B. K.; Banik, I.; Becker, F. F. *Org. Synth.* **2004**, *81*, 188–194; For some examples of indium-induced reactions from our laboratory, see: (c) Banik, B. K.; Samajdar, S.; Banik, B. K.; Zegrocka, O.; Becker, F. F. *Heterocycles* **2001**, *55*, 227–230; (d) Banik, B. K.; Banik, I.; Hackfeld, L.; Becker, F. F. *Heterocycles* **2001**, *56*, 467–470; (e) Banik, B. K.; Hackfeld, L.; Becker, F. F. *Synth. Commun.* **2001**, *31*, 1581–1586.
25. (a) Banik, B. K.; Mukhopadhyay, C.; Venkatraman, M. S.; Becker, F. F. *Tetrahedron Lett.* **1998**, *39*, 7243–7247; (b) Basu, M. K.; Becker, F. F.; Banik, B. K. *Tetrahedron Lett.* **2001**, *41*, 6551–6554; For some examples of samarium-induced reactions from our laboratory, see: (c) Banik, B. K.; Zegrocka, O.; Banik, I.; Hackfeld, L.; Becker, F. F. *Tetrahedron Lett.* **1999**, *40*, 6731–6734; (d) Banik, B. K.; Zegrocka, O.; Becker, F. F. *J. Chem. Res.* **2000**, 321–322; (e) Ghatak, A.; Becker, F. F.; Banik, B. K. *Tetrahedron Lett.* **2000**, *41*, 3793–3796; (f) Basu, M. K.; Becker, F. F.; Banik, B. K. *J. Chem. Res.* **2000**, 406–407; (g) Basu, M. K.; Banik, B. K. *Tetrahedron Lett.* **2001**, *42*, 187–191; (h) Banik, B. K. *Eur. J. Org. Chem.* **2002**, 2431–2444; (i) Samajdar, S.; Banik, B. K. *Chem.—Indian J.* **2003**, *1*, 230; (j) Banik, B. K. *Chem.—Indian J.* **2003**, *1*, 149; (k) Banik, B. K.; Venkatraman, M. S.; Banik, I.; Basu, M. K. *Tetrahedron Lett.* **2004**, *45*, 4737–4739; (l) Banik, B. K.; Banik, I.; Samajdar, S.; Cuellar, R. *Tetrahedron Lett.* **2005**, *46*, 2319–2321.
26. (a) Bair, K. W.; Andrews, C. W.; Tuttle, R. L.; Knick, V. C.; Cory, M.; McKee, D. D. *J. Med. Chem.* **1991**, *34*, 1983–1990; (b) Harvey, R. G.; Pataki, J.; Cortez, C.; DiRaddo, P.; Yang, C. *J. Org. Chem.* **1991**, *56*, 1210.
27. Banik, B. K.; Mukhopadhyay, C.; Becker, F. F. *Synth. Commun.* **2001**, *31*, 2399–2403.
28. Georg, G. I.; Ravikumar, V. T. In *The Organic Chemistry of β-Lactams*; Georg, G. I., Ed.; VCH: New York, 1992.
29. (a) Alcaide, B.; Vicente-Rodriguez, A. *Tetrahedron Lett.* **1999**, *40*, 2005–2006; (b) Afonso, A.; Rosenblum, S. B.; Puar, M. S.; McPhail, A. T. *Tetrahedron Lett.* **1998**, *39*, 7431–7434; (c) Bolli, M. H.; Marfurt, J.; Grisostomi, C.; Boss, C.; Binkert, C.; Hess, P.; Treiber, A.; Thorin, E.; Morrison, K.; Buchmann, S.; Bur, D.; Ramuz, H.; Clozel, M.; Fischli, W.; Weller, T. *J. Med. Chem.* **2004**, *47*, 2776–2795; (d) Endo, M.; Droghini, R. *Bioorg. Med. Chem. Lett.* **1993**, *3*, 2483–2486; (e) Bose, A. K.; Banik, B. K.; Manhas, M. S. *Tetrahedron Lett.* **1995**, *36*, 213–216.
30. Microwave activation has become very popular and useful technology in organic and medicinal chemistry. For some recent examples, see: (a) Perreux, L.; Loupy, A. *Tetrahedron* **2001**, *57*, 9199–9223; (b) Lidstrom, P.; Tierney, J.; Wathey, B.; Westman, J. *Tetrahedron* **2001**, *57*, 9225–9287; (c) Bose, A. K.; Manhas, M. S.; Ganguly, S. N.; Sharma, A. H.; Banik, B. K. *Synthesis* **2002**, 1578–1591; (d) Bose, A. K.; Banik, B. K.; Lavlinskaia, N.; Jayaraman, M.; Manhas, M. S. *Chemtech* **1997**, *27*, 18–24, and references cited therein.
31. One of us was extensively involved in the microwave-assisted β-lactam synthesis. For example, see: (a) Bose, A. K.; Manhas, M. S.; Ghosh, M.; Shah, M.; Raju, V. S.; Bari, S. S.; Newaz, S. N.; Banik, B. K.; Barakat, K. J.; Chaudhury, A. G. *J. Org. Chem.* **1991**, *56*, 6968–6970; (b) Banik, B. K.; Manhas, M. S.; Kaluza, Z.; Barakat, K. J.; Bose, A. K. *Tetrahedron Lett.* **1992**, *33*, 3603–3606; (c) Banik, B. K.; Manhas, M. S.; Newaz, S. N.; Bose, A. K. *Bioorg. Med. Chem. Lett.* **1993**, *3*, 2363–2368; (d) Bose, A. K.; Banik, B. K.; Barakat, K. J.; Manhas, M. S. *Synlett* **1993**, 575–577; (e) Bose, A. K.; Manhas, M. S.; Banik, B. K.; Robb, E. W. *Res. Chem. Intermediate* **1994**, *20*, 1–20; (f) Banik, B. K.; Manhas, M. S.; Robb, E. W.; Bose, A. K. *Heterocycles* **1997**, 405; (g) Banik, B. K.; Jayaraman, M.; Srirajan, V.; Manhas, M. S.; Bose, A. K. *J. Ind. Chem. Soc.* **1997**, *74*, 951; (h) Banik, B. K.; Barakat, K. J.; Wagle, D. R.; Manhas, M. S.; Bose, A. K. *J. Org. Chem.* **1999**, *64*, 5746–5753.
32. (a) Arrieta, A.; Lecea, B.; Cossio, F. P. *J. Org. Chem.* **1998**, *63*, 5869–5876; (b) Cossio, F. P.; Arrieta, A.; Lecea, B.; Ugalde, J. M. *J. Am. Chem. Soc.* **1994**, *116*, 2085–2093; (c) Cossio, F. P.; Ugalde, J. M.; Lopez, X.; Lecea, B.; Palomo, C. *J. Am. Chem. Soc.* **1993**, *115*, 995–1004; For an excellent discussion of mechanism of β-lactam formation, see: Hegedus, L. S.; Montgomery, J.; Narukawa, Y.; Snustad, D. C. *J. Am. Chem. Soc.* **1991**, *113*, 5784–5791.
33. Lopez, R.; Sordo, T. L.; Sordo, J. A.; Gonzalez, J. *J. Org. Chem.* **1993**, *58*, 7036–7037.
34. Lynch, J. E.; Riseman, S. M.; Laswell, W. L.; Tschaen, D. M.; Volante, R. P.; Smith, G.; Shinkai, I. *J. Org. Chem.* **1989**, *54*, 3792–3796.
35. Just, G.; Ugolini, A.; Zamboni, R. *Synth. Commun.* **1979**, *9*, 117–121.
36. Doyle, T. W.; Belleau, B.; Luh, B. Y.; Ferrari, C. F.; Cunningham, M. P. *Can. J. Chem.* **1977**, *55*, 468–507.
37. Bose, A. K.; Chiang, Y. H.; Manhas, M. S. *Tetrahedron Lett.* **1972**, 4091–4094.
38. Diez, E.; Fernandez, R.; Marques-Lopez, E.; Martin-Zamora, E.; Lassaletta, J. M. *Org. Lett.* **2004**, *6*, 2749–2752; For a similar and elegant contribution, also see: Fernandez, R.; Ferrete, A.; Lassaletta, J. M.; Llera, J. M.; Martin-Zamora, E. *Angew. Chem., Int. Ed.* **2002**, *41*, 831.
39. The research in β-lactam may have untapped therapeutic potential. It has been demonstrated recently that certain β-lactam antibiotics have potential for treating neurological diseases. For an example, see: Miller, T. M.; Cleveland, D. W. *Science* **2005**, *307*, 361–362.