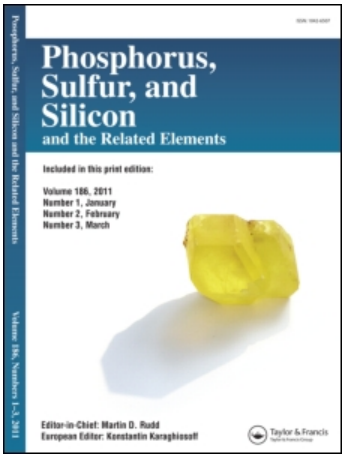

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Petra, Osiris, and Molinspiration Together as a Guide in Drug Design: Predictions and Correlation Structure/Antibacterial Activity Relationships of New *N*-Sulfonyl Monocyclic β-Lactams

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PETRA, OSIRIS, AND MOLINSPIRATION TOGETHER AS A GUIDE IN DRUG DESIGN: PREDICTIONS AND CORRELATION STRUCTURE/ANTIBACTERIAL ACTIVITY RELATIONSHIPS OF NEW *N*-SULFONYL MONOCYCLIC β-LACTAMS

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We report in this article the design and calculated molecular properties of 18 new mono-cyclic β-lactams 4–21, on the basis of one hypothetical antibacterial pharmacophore structure designed to interact with both of Gram-positive bacteria and Gram-negative bacteria. The in vitro biological evaluation of these compounds allowed us to point out new potential non-nucleoside hits, with MIC values in the range of 2–8 μg/mL active against* Staphylococcus aureus*,* Bacillus subtilis*,* Escherichia coli*, and* Pseudomonas aeruginosa*. A correlation structure/antibacterial activities relationship of these monocyclic β-lactams is described.

Supplemental materials are available for this article. Go to the publisher's online edition of* Phosphorus, Sulfur, and Silicon and the Related Elements *to view the free supplemental file.

Keywords Antibacterial activity; drug design; N-sulfonyl β-lactams; virtual screening

INTRODUCTION

The β-lactam system has been shown to be an efficient precursor for many synthetic industrial antibiotics including penicillin derivatives.[1] Although antibiotic-containing rings fused to the β-lactam ring display interesting biological properties, they become less efficient because of emergence of new MDR-bacterial and viral strains. So the pharmaceutical industry turned to other derivatives that are versatile intermediates for the synthesis of important products such as penams, cephems, clavulanates, monobactams, carbapenems, and trinems.[2,3] Monocyclic β-lactams have also attracted much attention owing to their

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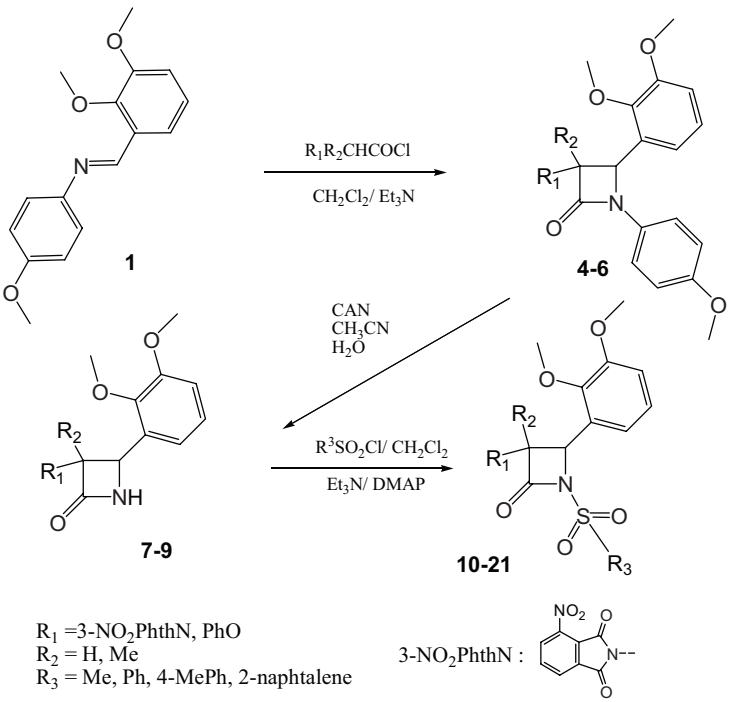
important pharmacological properties.[4] Some monocyclic β-lactams containing the phthalimido group have shown good antibacterial activity.[5,6] Recently scientists have found that monocyclic β-lactams are also inhibitors of cytomegalovirus protease,[7,8] inhibitors of thrombin and tryptase,[9,10] cholesterol absorption inhibitors,[11,12] human leukocyte elastase (HLE) inhibitors,[13,14] porcine pancreatic elastase (PPE) inhibitors,[15] cysteine protase inhibitors,[16,17] and anticancer agents.[18,19] In addition to their diverse current uses as pharmaceuticals, β-lactams are of interest as synthetic building blocks[20,21] and in the semi synthesis of Taxol.[22] Selective bond cleavage of the strained β-lactam ring coupled with further interesting synthetic transformations renders these fascinating molecules powerful synthetic building blocks.[23,24] In addition, the existence of the methoxy group on the molecules enhances the various biological activities.[25] The high synthetic utility and pharmacological importance of the β-lactam family have prompted us to realize a pharmacological study of the antibacterial activity of the compounds **4–21** (Scheme 1).



Scheme 1 General synthesis of monocyclic β-lactams **4–21**.

Previously, antibacterial screening showed that compounds bearing a formyl, hydroxy, or nitroso side chain in position 3 are highly active against *Mycobacterium tuberculosis*.[26,27] From general structure–activity relationship observations, it appears that functionalized side chain(s) such as [X-(C)n-Y], where (X,Y = O,N) and (n = 2,3), are crucial for bioactivity. These atoms or centers that have critical interactions with the bacterial cell receptor constitute the pharmacophore and are vital for antimicrobial activities. These interactions must have typically precise geometric requirements that are readily described in terms of the distances between the terminal atoms and their orientation in the pharmacophore sites.[28b]

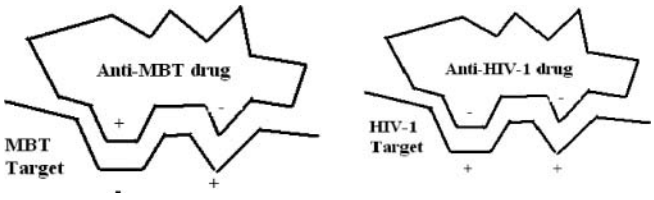


Figure 1 Possible interactions between antibacterial or anti-HIV-1 drugs and their specific biological targets.

As an extensive continuation of our study on the structure–antibacterial activity relationships in β-lactam derivatives, we performed an investigation of compounds **4**–**21**, because they represent an attractive model for a theoretical and experimental study of the pharmacophore, and their medical applications because of the large variability and combination in their substituents (R^1, R^2, and R^3). Moreover, given the current interest in selective drugs through the development of molecules that recognize simultaneously specific bacterial and HIV-1 sites, we became interested in the combined synthesis and antibacterial and anti-HIV screenings of heterocycles having two or more flexible pharmacophore systems (O=C−C−O and O−C−O−N) as is postulated in Figure 1.

The main interesting tasks of this work are as follows: (i) Develop robust prediction models for the heterocycles/bacteria inhibitory properties (solubility, MT inhibition, stability, selectivity, etc.) of small molecules with the estimation of confidence of these models; (ii) interpret the calculated/predicted results for the design of new compounds; (iii) perform docking or pharmacophore modeling based on crystal structures to support the lead optimization process; (iv) combine the antibacterial pharmacophore site with a selective anti-HIV pharmacophore site without altering activity of the first one; (v) find the right molecule for the right target.

RESULTS AND DISCUSSION

Chemistry

Monocyclic β-lactams **4–6** (Scheme 1) were obtained by the [2+2] cycloaddition of imine **1** with ketenes derived from acyl chlorides **2**, **3**, and phenoxyacetyl chloride in the presence of triethylamine in dry dichloromethane at –10 °C, as it was previously reported recently.[29] Compounds **4–21** are stable at ambient temperature. Their structures have been determined by IR, MS, and NMR (^{1}H and ^{13}C) spectroscopy.[29]

Antibacterial Activity and Preliminary Observations

The antibacterial activity of compounds **4–21** is represented in Table I (available in the Supplemental Materials online).

PETRA Calculations

PETRA is a program package comprising various empirical methods for the calculation of physicochemical properties in organic molecules. All methods are empirical in nature and have been developed over the last 20 years in the research group of Gasteiger.[30]

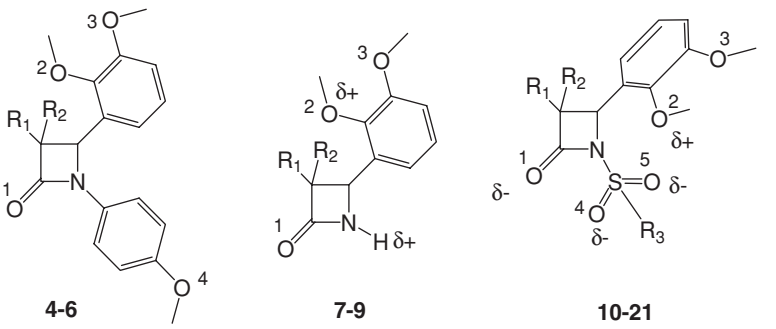
The following chemical effects can be quantified: heats of formation, bond dissociation energies, sigma charge distribution, π-charge distribution, inductive effect, resonance effect, delocalization energies, and polarizability effect.[30]

In order to check the apparent antibacterial activity of compound 19 and to look for evidence of structure–activity via Gram-positive and Gram-negative bacteria, we performed Petra calculations[30] with 4–21 (Table II, available in the Supplemental Materials online).

The PETRA software calculations confirmed that all compounds 4–21 have a clear preference for forming antibacterial dipolar pharmacophore sites though their estimated partial π charges respectively for two oxygen atoms are of different charges (–0.1784 e and +0.0435 e) for compound 17 for example. The PETRA calculations with the other β-lactam derivatives 4–21 are shown and are summarized in Table II.

Compound 21 has the same partial π-charges [–0.1779 e for O of SO_2 and +0.0436 e for O of methoxy almost as tightly as 17, but its activity, as evidenced by a lack of observable antibacterial results, is considerably better (2–8 for 21 instead of 8–128 μg/mL for 17). In the light of these observations, the lack of antibacterial activity by the latter three compounds (10, 17, and 21) is explicable in terms of the existence of dipolar pharmacophore site (O---O).

The increase in activity could be due to the increase of the hydrophobic character that the alkyl and alkyloxy groups confer on the molecule. Hydrophobic molecules with rigid, planar structures such as aromatic rings, have been shown to have the ability to insert into membranes and induce localized permeability changes leading to leakage out of the membrane.[31] The combination of methoxy, sulfonyl, and Pho groups (**18**–**21**), while also hydrophobic and very easily inserted into the membrane, are much less likely to cause disruption of the lipid packing order. That can be explained by possible cell membrane facility, as the 2-naphtalene group is too lipophylic to have this type of effect. The enhanced antibacterial inhibition observed in the presence of **17**, **18**, **19**, and **21** is then more likely due to its interaction with some intracellular target. The presence of a strong or poor electron-withdrawing group must alter the nature of the compound in such a way as to promote binding to the target(s) (Scheme 2).



Scheme 2

Osiris Calculations

The Osiris Property Explorer used in this article is an integral part of Actelion's in-house substance registration system.[32] It allows a user to draw chemical structures

and calculates on-the-fly various drug-relevant properties whenever a structure is valid. Prediction results of compounds **4–21** molecular properties (solubility, druglikeness, and drug-score) are abstracted (Table III, available online in the Supplemental Materials).

Molinspiration Calculations

cLogP (octanol/water partition coefficient) is calculated by the methodology developed by Molinspiration as a sum of fragment-based contributions and correction factors. The method is very robust and is able to process practically all organic and most organometallic molecules. Molecular polar surface area (PSA) is calculated based on the methodology published by Ertl et al.[33] as a sum of fragment contributions. O- and N-centered polar fragments are considered. PSA has been shown to be a very good descriptor characterizing drug absorption, including intestinal absorption, bioavailability, Caco-2 permeability, and blood-brain barrier penetration.[33] Prediction results of compounds **4–21** molecular properties (TPSA, GPCR ligand, and ICM) are valued (see Table IV in the Supplemental Materials online).

β-Lactam **4** is among the least active substances to have been evaluated as antibacterial agents in this series (MIC $>$ 128 μg/mL). Accordingly, an effort was initiated to establish a pharmacophore hypothesis to delineate the requirements of the active site via a comprehensive program of analogue synthesis and evaluation of the effects of structural modification(s) on antibacterial activity of **4**.

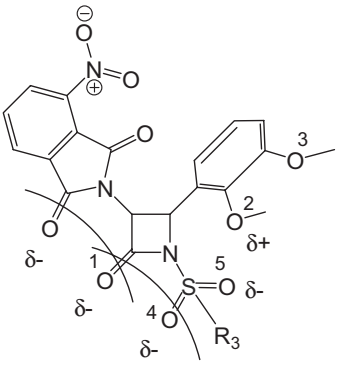
We then set out to determine the resultant in vitro effects of chemical alterations in each region. The unsubstituted N atom of β-lactam-ring of **7–9** endowed antibacterial activity (MIC $>$ 128 μg/mL). The modulating antibacterial effect(s) of substituents having different electronegative properties, located at the N(1) and C(3) sites comprising the SO_2 and 3-NO_2PhthN or PhO substituents of C(3), were ascertained next.

A combination of the PhO (R_1) and 2-naphthalene (R_3) substituents located respectively at the 3,1-positions on the β-lactam ring of **21** generated higher antibacterial activity relative to **4–20** in both the Gram-positive and Gram-negative inhibition tests. However, in general a 2,3-dimethoxyphenyl of the position 4 of β-lactam proved to be unhelpful as a substituent. We postulate that the strong tendency to form a ($O^{\delta+}$---$O^{\delta-}$) dipolar pharmacophore site in the predominant (*cisoidal*) form is likely to be responsible for the lack of biological activity observed with these semi π-conjugated β-lactam derivatives. If this hypothesis is correct, by modifying **21**, we may be able to modulate the degree of interaction of the compound with various bacteria.

CONCLUSIONS AND PERSPECTIVES

The functionalized β-lactam compounds **4–21** can easily be prepared.[29] These compounds typically could form the highly interesting combined two or more pharmacophore sites in one molecule. A number of important points emerge concerning their antibacterial properties. The positive results we have recorded, while encouraging for purposes of new drug design, confirm that very likely most of these compounds could be used without great risk of toxicity in diverse antibacterial activity. Based on their structural properties, these compounds may be useful as antitubercular agents with high activity or as potential antiviral agents (Scheme 3).[34]

These results prompt two pertinent observations: (i) This type of β-lactam can furnish an interesting model for studying the interaction of antibiotics with HIV-integrase target



Scheme 3

because the possible negative center-bonding of a O^1 and O of 3-NO_2PhthN group to the positively charged centers of catalytic integrase domain is generally favored; (ii) the flexible pharmacophore site(s) geometric conformation enables us to prepare molecules for multi-therapeutic materials (anti-HIV and anti-*Mycobacterium tuberculosis*).

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