Journal of Medicinal Chemistry

Brief Article

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Design, Synthesis, and Antiviral Evaluation of Purine-β-lactam and Purine-aminopropanol Hybrids

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Supporting Information

ABSTRACT: Purine-β-lactam chimera were prepared as a novel class of hybrid systems through *N*-alkylation of 6-benzylamino- or 6-benzyloxypurine with (ω-haloalkyl)-β-lactams, followed by reductive ring opening of the β-lactam ring by $LiEt_3BH$ to provide an entry into the class of purine-aminopropanol hybrids. Both new types of hybrid systems were assessed for their antiviral activity and cytotoxicity, resulting in the identification of eight purine-β-lactam hybrids and two purine-aminopropanol hybrids as promising lead structures.

INTRODUCTION

The synthesis of novel chemical entities via the fusion of two biologically relevant moieties has emerged as a new strategy within drug discovery programs, for example, in the development of new anticancer, anti-Alzheimer, and antimalarial agents.[1] Important motives for the implementation of the concept of molecular hybridization relate to the search for highly active novel entities able to circumvent drug resistance or the exploitation of active transport mechanisms by linking bioactive units to moieties that are recognized and actively transported into mammalian cells. In addition to these biological perspectives, hybrid systems allow for the design of new organic structures through selective modification of one of both entities, and the selective elaboration of one substructure might provide access to functionalized target compounds with biological interest because of the conservation of the second bioactive moiety.

Purines have been a fruitful source of inspiration for medicinal chemists for many years.[2] As a result, a broad variety of bioactive purine derivatives has been designed, which has led to the launch of several powerful drugs with diverse applications.[3] In that respect, major advances have been made concerning the treatment of viral infections by purine derivatives, as exemplified by the well-known drugs acyclovir (anti-herpes)[4] and abacavir (anti-HIV).[5] A totally different heterocyclic system endowed with pronounced biological activities is the β-lactam nucleus. This small-ring azaheterocycle comprises the key structural motif in β-lactam antibiotics and has been identified as crucial for the bioactivity.[6] Next to their antibacterial properties, β-lactams also exhibit other pharmacological activities enabling their use in different therapeutic areas.[7] Examples in that respect include the inhibition of HIV-1 protease,[8] antitumor activity,[9] antimalarial activity,[10] and cholesterol absorption inhibition.[11] On the other hand, β-lactams have been shown amply to be excellent synthons in organic chemistry, especially toward the selective preparation of stereodefined target compounds.[12]

The study of new hybrid systems in which purines and β-lactams are combined comprises an unexplored field of research. The concept of nucleoside-β-lactam chimera as potentially bioactive systems has been introduced in 1995, although only three pyrimidine-β-lactam hybrids were prepared and their bioactivity was not assessed.[13] These systems were synthesized through the Ugi reaction using a β-amino acid, an aldehyde, and an isocyanide. More recently, an alternative approach toward similar combinations of β-lactams and nucleobases (both purine- and pyrimidine-based) has been described based on the Kinugasa reaction starting from *N*-propargyl nucleobases.[14] However, mixtures of diastereomers were obtained, and the resulting hybrids exhibited no or weak (for uracil derivatives) antibacterial activity. Apart from the latter study, no reports on purine-β-lactam hybrids are available.

As purines are known to be eligible templates for the synthesis of antiviral agents, the antiviral evaluation of new purine-β-lactam hybrids could thus provide new anchor points within this field. Furthermore, the inherent reactivity of the β-lactam nucleus allows for selective transformations of these hybrids to afford functionalized purine derivatives with a predetermined stereochemistry in their side chain, and the final purine-containing targets might also be of interest with regard to the treatment of viral infections. Hence, the objective of the present study involves the design, synthesis, and antiviral evaluation of a set of new purine-β-lactam hybrids and the corresponding β-lactam ring-opening products.

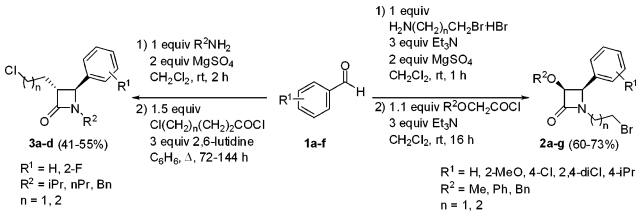
RESULTS AND DISCUSSION

The synthetic strategy deployed in this research is based on the coupling of a nucleophilic purine system with an ω-haloalkyl-substituted β-lactam unit as the electrophilic moiety. In particular, both 1- and 3-(ω-haloalkyl)-β-lactams **2** and **3**

Received: March 20, 2012
Published: April 23, 2012

were selected to undergo fusion with either 6-benzylamino- or 6-benzyloxypurine through *N*-alkylation. These halogen-containing β-lactams **2** and **3** have previously been prepared and explored synthetically by us,[15] pointing to their potential as synthons in organic chemistry. Their preparation includes initial imination of substituted benzaldehydes **1** with a ω-bromoalkylamine hydrobromide or a primary amine, followed by a Staudinger [2 + 2]-cyclocondensation with a ketene in situ prepared from alkoxyacetyl chloride or an ω-chloroalkanoyl chloride, thus resulting in the diastereoselective synthesis of *cis*-1-(ω-bromoalkyl)-β-lactams **2** or *trans*-3-(ω-chloroalkyl)-β-lactams **3**, respectively (Scheme 1). The observed *cis*-selectivity

Scheme 1. Staudinger Synthesis of *cis*-1-(ω-Bromoalkyl)-β-lactams 2 and *trans*-3-(ω-Chloroalkyl)-β-lactams 3

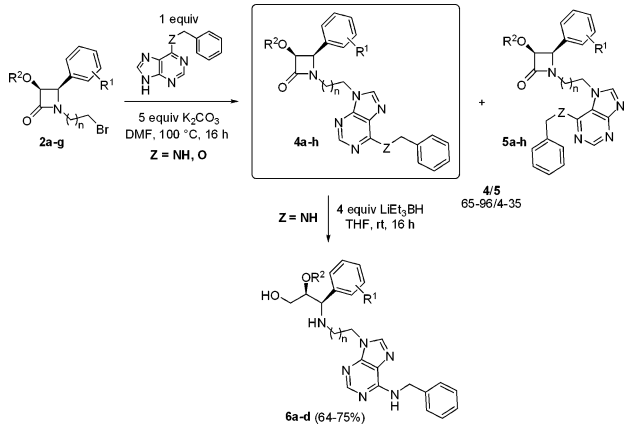


in the formation of β-lactams **2** could be deduced from their ^{1}H NMR spectra, as the coupling constants between the protons at C3 and C4 were 4.4 Hz ($CDCl_3$).[15a,b,16] Also the *trans*-stereochemistry of azetidin-2-ones **3** was unambiguously assigned based on the coupling constants between the C3 and C4 protons, as the observed *J* values of 1.7−1.9 Hz (^{1}H NMR, $CDCl_3$) correspond well with those reported in the literature for *trans*-β-lactams.[15c,16] Furthermore, it is known that the use of Bose−Evans ketenes (alkoxyketenes) favors the formation of the *cis*-β-lactams, whereas the use of the Moore ketene (chloroketene) generally results in the formation of the thermodynamically more stable *trans*-β-lactams.[17]

In the next part, ω-haloalkyl-substituted β-lactams **2** and **3** were deployed as electrophiles for a nucleophilic substitution with 6-benzylamino- or 6-benzyloxypurine. *N*-Alkylation of purines indeed comprises a privileged strategy for the functionalization of the purine nucleus and is thus frequently encountered in purine syntheses.[18] A minor drawback of this approach involves the competition between *N*9- and *N*7-alkylation, although it is known that the introduction of certain substituents at the 6-position favors the formation of *N*9 isomers at the expense of their *N*7 counterparts.[19] In this work, 6-benzylamino- and 6-benzyloxypurine were chosen for the synthesis of new hybrid structures. In addition to its potential influence on the regioselectivity of the alkylation reaction, the possible removal of the benzyl group in the final stage of the process might be of interest for other purposes.

Thus, treatment of *cis*-1-(ω-bromoalkyl)-β-lactams **2** with 1 equiv of 6-benzylamino- or 6-benzyloxypurine and 5 equiv of K_2CO_3 in DMF afforded a mixture of *N*9- and *N*7-alkylation products **4** and **5** after heating for 16 h at 100 °C (Scheme 2).[19e,20] Spectroscopic analysis revealed the *N*9 isomers **4** to be the main constituents (ratio **4**/**5** (65−96)/(4−35)). Evidence for this assignment stems from a comparison of the chemical shifts of the C2 and C8 protons of the major regioisomer with data reported in the literature.[21] The main isomers **4** could be isolated in pure form through column chromatography on silica gel in moderate to good yields (37−84%). A significantly higher regioselectivity was obtained for the alkylation of 6-

Scheme 2. *N*-Alkylation of 6-Benzylamino- or 6-Benzyloxypurine and $LiEt_3BH$-Mediated Ring Opening of the Resulting Purine-β-lactam Hybrids 4



benzylaminopurine (*N*9/*N*7 (72−96)/(4−28)) as compared to 6-benzyloxypurine (*N*9/*N*7 65/35). This can be explained considering the intramolecular hydrogen bridge formation between the proton of the benzylamino group and the *N*7 atom of the purine nucleus in 6-benzylaminopurine, thus lowering the nucleophilicity of this *N*7 atom.

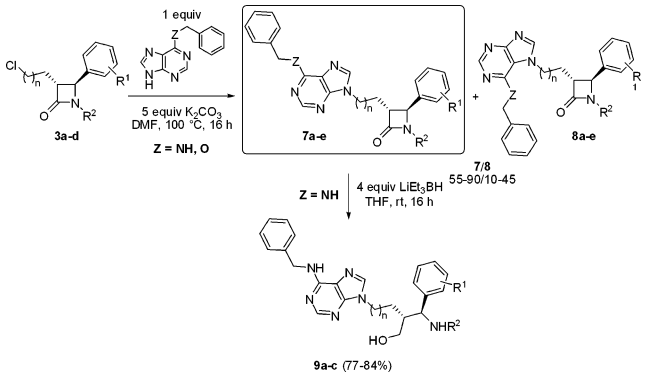
The above-described method constitutes a convenient approach toward β-lactam-purine hybrids **4** as a new class of scaffolds with potential applications in different fields. In addition to their biological interest as a combination of pharmacophores, the presence of the small-ring azaheterocyclic unit enables further synthetic elaboration. A useful transformation of the azetidin-2-one system involves reductive ring opening toward functionalized aminopropanols, as these entities are structural motifs in different drugs and bioactive agents. For example, aminopropanols are key units in β-blockers,[22] antitumor agents,[23] and broad-spectrum antibiotics.[24] Thus, reductive ring opening of the azetidin-2-one moiety in hybrids **4** could provide access to another type of hybrid system composed of a purine unit and an aminopropanol unit. As $LiAlH_4$ is known to be a suitable reagent for the reductive ring opening of β-lactams,[15a,25] initial attempts were focused on the use of this reagent under different reaction conditions to affect the reduction of azetidin-2-ones **4**. However, variation of the reaction temperature (rt to 100 °C), reaction time (2−48 h), molar equivalents of $LiAlH_4$ (2−5), and solvent (THF, 2-methyl-THF, (di)glyme, 1,4-dioxane, MTBE, and combinations thereof) led to recovery of the starting material or to the desired product contaminated with a significant number of side products (>60%). To avoid the possible interference of the purine ring with the strong reducing agent $LiAlH_4$, other hydride sources were evaluated as well ($SiHCl_3$, $LiBH_4$, $LiEt_3BH$). Eventually, optimal results were obtained after treatment of purine-β-lactam hybrids **4a−d** with 4 equiv of $LiEt_3BH$ in THF at room temperature for 16 h, leading to a full conversion of the starting products to the contemplated aminopropanols **6** with minimal formation of side products (<30%) (Scheme 2). Finally, column chromatography on silica gel afforded analytically pure samples used for spectroscopic analysis and biological testing.

In analogy with the above-described results, *trans*-3-(ω-chloroalkyl)-β-lactams **3** were also used as synthons for the preparation of novel purine-β-lactam and purine-aminopropanol hybrids. Thus, coupling between the purine moiety

dx.doi.org/10.1021/jm300383k | J. Med. Chem. 2012, 55, 5637−5641

and the β-lactam core was achieved through *N*-alkylation (DMF, K_2CO_3, 100 °C, 16 h),[19,20] affording a mixture of *N*9 and *N*7 products **7** and **8** (Scheme 3). Again, selective *N*9-

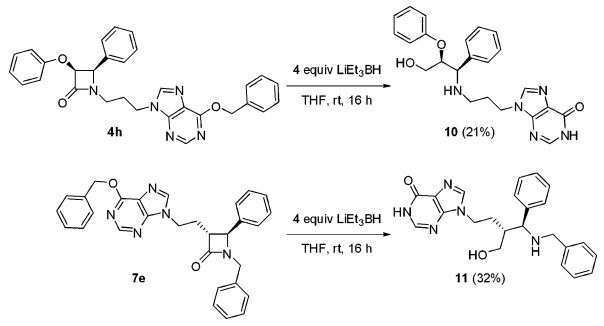
Scheme 3. *N*-Alkylation of 6-Benzylamino- or 6-Benzyloxypurine $LiEt_3BH$-Mediated Ring Opening of the Resulting Purine-β-lactam Hybrids 7



alkylation was observed for 6-benzylaminopurine (*N*9/*N*7 (88−90)/(10−12)), whereas a less pronounced preference was noted for 6-benzyloxypurine (*N*9/*N*7 (55−65)/(35−45)). The main isomers **7** could be isolated in pure form through column chromatography on silica gel in moderate yields (39−60%). Subsequently, reductive ring opening of purine-β-lactam hybrids **7a−c** was affected by using $LiEt_3BH$ in THF, providing a convenient entry into novel purine-aminopropanol hybrids **9** (Scheme 3).

Whereas the 6-benzylaminopurine unit remained intact upon treatment of hybrids **4a−d** and **7a−c** with $LiEt_3BH$, analysis of the reaction mixtures obtained after reaction of 6-benzyloxypurines **4h** and **7e** pointed to a reductive removal of the benzyl group upon treatment with $LiEt_3BH$ in THF (Scheme 4). Isolation of the main reaction products via column

Scheme 4. Synthesis of Purin-6-one Hybrids 10 and 11



chromatography (SiO_2), albeit in low yield, allowed the identification of these compounds as purin-6-one-amino-propanol hybrids **10** and **11**.

Considering the established reputation of purines as potent antiviral agents, 20 novel purine-β-lactam and purine-amino-propanol hybrids prepared in this study were screened for their antiviral activity against nine different viruses, i.e., human immunodeficiency virus type 1 (HIV-1), human hepatitis C virus (HCV), human respiratory syncytial virus (RSV), influenza virus (Flu), dengue-2 virus (Denv-2), chikungunya virus (ChikV), cytomegalovirus (CMV), hepatitis B virus (HBV), and coxsackie B virus (CoxV). The most promising results of these biotestings are summarized in Table 1. These potential lead compounds were selected based on the results for

Table 1. Antiviral Activities of the Most Promising Compounds

compd	virus	SI[a]	CC_{50} (μM)[b]	EC_{50} (μM)[c]
4b	CoxV	>28.09	>100.00	3.56
	RSV	5.79	46.60	8.05
	ChikV	>5.75	>98.36	17.11
4c	RSV	17.94	40.14	2.24
4e	HBV	4.52	>50.00	11.07
4f	ChikV	4.53	58.97	13.01
4h	CMV	4.13	70.78	17.15
	CoxV	>34.05	>100.00	2.94
6a	HBV	9.19	31.86	3.47
	RSV	4.29	8.23	1.92
	ChikV	6.19	71.20	11.51
7b	CMV	4.29	30.72	7.16
	CoxV	17.11	47.37	2.77
7c	RSV	9.71	75.64	7.79
7d	CoxV	11.55	48.23	4.17
9c	RSV	>4.25	>100.00	23.55

[a]The selectivity index (SI) is calculated as CC_{50}/EC_{50}. [b]The toxicity is expressed as CC_{50} (50% cytotoxic concentration). [c]The antiviral activity is expressed as EC_{50} defined as the concentration of compound achieving 50% inhibition of the virus-reduced signals compared to the uninfected cell control.

both their antiviral efficacies and their in vitro toxicity profiles (SI > 4). The assay principles and methods are described in the Supporting Information. Detailed results of these biological studies are also in the Supporting Information.

None of the tested hybrids showed antiviral activity against Flu, HIV-1, Denv-2, and the HCV replicon assay. On the other hand, moderate to good activities were registered against RSV, ChikV, CMV, HBV, and CoxV. It is important to note that from the 20 compounds tested in these screenings, 10 different purine derivatives were identified as potentially interesting templates for further elaboration, i.e., β-lactams **4b**,**c**,**e**,**f**,**h** and **7b−d** and aminopropanols **6a** and **9c**. This observation certainly confirms the broad applicability of functionalized purines as privileged motifs in antiviral research. In addition, 8 of these 10 lead compounds belong to the class of purine-β-lactam hybrids, pointing to the potential interest in the further elaboration of these new scaffolds in terms of studies on mode of action, structure−activity relationships, and possible additive or synergistic interactions between the pharmacophoric units. Although purine-β-lactam hybrids were initially only considered as synthetic intermediates to provide a convenient entry into the novel class of purine-aminopropanol hybrids, the former type of chimera proved to be more relevant as antiviral lead compounds compared to the latter hybrid systems. The details regarding the chemical structures of hybrids **4**, **6**, **7**, and **9** are provided in Table 2.

In conclusion, a new protocol was established for the efficient synthesis of purine-β-lactam hybrids through *N*-alkylation of purines with ω-haloalkyl-substituted β-lactams. Furthermore, these dual systems were converted into new purine-amino-propanol hybrids through reductive ring opening of the β-lactam moiety. Both classes of hybrid systems were screened for their antiviral activities and cytotoxicity, revealing interesting opportunities for further study on these scaffolds. In particular,

dx.doi.org/10.1021/jm300383k | J. Med. Chem. 2012, 55, 5637−5641

Table 2. Chemical Structures of Hybrids 4, 6, 7, and 9

compd	Z	*n*	R^1	R^2
4a	NH	1	4-Cl	Ph
4b	NH	2	H	Ph
4c	NH	2	2,4-Cl_2	Bn
4d	NH	2	4-^{i}Pr	Me
4e	NH	1	H	Bn
4f	NH	1	2-MeO	Ph
4g	NH	1	H	Ph
4h	O	2	H	Ph
6a	NH	1	4-Cl	Ph
6b	NH	2	H	Ph
6c	NH	2	2,4-Cl_2	Bn
6d	NH	2	4-^{i}Pr	Me
7a	NH	1	H	^{i}Pr
7b	NH	2	H	^{n}Pr
7c	NH	2	2-F	^{i}Pr
7d	O	1	H	^{i}Pr
7e	O	1	H	Bn
9a	NH	1	H	^{i}Pr
9b	NH	2	H	^{n}Pr
9c	NH	2	2-F	^{i}Pr

8 purine-β-lactam hybrids and 2 purine-aminopropanol hybrids were identified as promising templates for further elaboration.

EXPERIMENTAL PART

General. ^{1}H NMR spectra were recorded at 300 MHz (JEOL ECLIPSE+) with $CDCl_3$ as solvent and tetramethylsilane as internal standard. ^{13}C NMR spectra were recorded at 75 MHz (JEOL ECLIPSE+) with $CDCl_3$ as solvent and tetramethylsilane as internal standard. Mass spectra were obtained with a mass spectrometer Agilent 1100, 70 eV. IR spectra were measured with a Spectrum One FT-IR spectrophotometer. High resolution electron spray (ES) mass spectra were obtained with an Agilent Technologies 6210 series time-of-flight instrument. Melting points of crystalline compounds were measured with a Büchi 540 apparatus. The purity of all tested compounds was assessed by HRMS analysis and/or HPLC analysis, confirming a purity of ≥95%.

Synthesis of Purine-β-lactam Hybrids 4 and 7. General Procedure. To a solution of *cis*-1-(ω-bromoalkyl)-β-lactam **2** (10 mmol) or *trans*-3-(ω-chloroalkyl)-β-lactam **3** (10 mmol) in dimethylformamide (60 mL) were added potassium carbonate (50 mmol) and 6-benzylaminopurine (10 mmol) or 6-benzyloxypurine (10 mmol). After being stirred for 16 h at 100 °C, the mixture was poured into water (60 mL) and extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layers were washed with brine (6 × 60 mL) and dried over anhydrous $MgSO_4$. Filtration of the drying agent and removal of the solvent in vacuo afforded the crude purine-β-lactam hybrid **4** or **7**, which was purified by means of column chromatography on silica gel.

Synthesis of Purine-aminopropanol Hybrids 6, 9, and 11. General Procedure. To an ice-cooled solution of purine-β-lactam hybrid **4** or **7** (1 mmol) in dry THF (10 mL) was added $LiEt_3BH$ (1 M in THF, 4 mL) in small portions. After being stirred for 16 h at room temperature, the mixture was cooled to 0 °C and water was added to quench the excess of $LiEt_3BH$. The resulting suspension was filtered over Celite, and the filtrate was poured into water (10 mL) and extracted with CH_2Cl_2 (3 × 10 mL). Drying ($MgSO_4$), filtration of the drying agent, and removal of the solvent in vacuo afforded the crude purine-aminopropanol hybrid **6**, **9**, or **11**, which was purified by means of column chromatography on silica gel, albeit sometimes in low yield (10–60%).

ASSOCIATED CONTENT

Supporting Information

Spectral data of **4a–h**, **6a–d**, **7a–e**, **9a–c**, and **11** and bioassay principles, methods, and results. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

The authors are indebted to Ghent University, Belgium, and the Research Foundation–Flanders (FWO-Vlaanderen), Belgium, for financial support. K.M. is Aspirant of the Research Foundation–Flanders (FWO-Vlaanderen).

ABBREVIATIONS USED

HIV-1, human immunodeficiency virus type 1; HCV, human hepatitis C virus; RSV, human respiratory syncytial virus; Flu, influenza virus; Denv-2, dengue-2 virus; ChikV, chikungunya virus; CMV, cytomegalovirus; HBV, hepatitis B virus; CoxV, coxsackie B virus

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