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Short communication

Synthesis and antimicrobial activities of monoindolyl- and bisindolyloximes

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Abstract – Six monoindolyl- and bisindolyloximes structurally related to protein kinase C inhibitors bisindolylmaleimides were synthezised. They did not have protein kinase C inhibitory properties but exhibited interesting antimicrobial activities. Their antibacterial activities against several strains of pathogenic and non-pathogenic Gram-positive and Gram-negative bacteria are described. The bisindolyl monooxime isomers exhibited a marked activity against the three strains of *Staphylococcus aureus* tested and against *Escherichia coli* 1507E. © Elsevier, Paris

indolyl oximes / antimicrobial activity / pathogenic bacteria

1. Introduction

The ever increasing incidence of infection resulting from bacteria resistant to currently available therapy has prompted the continuing need to develop new antibacterial agents [1–3]. The different antibacterial agents may act via various mechanisms [4, 5]. They can be inhibitors of cell wall synthesis (β-lactam antibiotics including penicillins, cephalosporins, monobactams, carbapenems or others such as vancomycin), inhibitors of protein synthesis (macrolides such as erythromycin, aminoglycosides, tetracyclines, chloramphenicol, oxazolidinones), inhibitors of nucleic acid synthesis with four different modes of action: by direct interaction with DNA, by inhibition of DNA topoisomerases (quinolones, 2-pyridones), by inhibition of DNA synthesis or inhibition of RNA synthesis (fluoroquinolones, rifamycins, coumarin antibiotics). They can also target other essential cellular metabolic functions like membrane transport, fatty acid synthesis, lipopolysaccharide biosynthesis, folic acid metabolism (sulfonilamides, trimethoprim).

Emergence of bacterial resistance to a number of antimicrobial agents such as β-lactam antibiotics, macrolides, quinolones, and vancomycin [6, 7] is a crucial problem which led to the development of series of analogues of the known drugs as well as the research for new drugs owning quite different structures.

In the course of search for new protein kinase C inhibitors structurally related to bisindolyl maleimides *(figure 1)* [8–10] and interacting with the ATP binding site of the enzyme, we synthezised mono-indolyl and bisindolyloximes. Compounds **1**–**6** *(figure 2)*, as already observed for amides [11] in which the rigid upper heterocycle was missing, were found to be inactive toward protein kinase C. However, except compound **4**, they exhibited strong antimicrobial properties against Gram-positive bacteria *Bacillus cereus* and *Streptomyces chartreusis*. Compound **4** was active against Gram-negative bacterium *Escherichia coli*. These results prompted us to test their antimicrobial activities against bacterial pathogens. In this paper, we describe the synthesis and the antimicrobial activities of indolyloximes **1**–**6**.

2. Chemistry

Monooximes **1** and **2** and dioxime **3** were prepared in two steps from commercial indole-glyoxalyl chloride: reaction with indolylmagnesium bromide, leading to bis-3-indolylglyoxal [12], followed by treatment with hydroxylamine hydrochloride (1 eq. for **1** and **2**, 10 eq.

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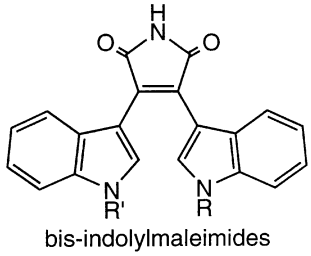

Figure 1.

for **3**) in ethanol in the presence of pyridine *(figure 2)*. Both isomers **1** and **2** could be easily separated by chromatography. Their structures were assigned from ^{13}C NMR spectra. The signals of the quaternary carbon (C=N) were observed at 105.4 ppm in compound **2** and 154.4 ppm in compound **1**, which is in agreement with *anti* configuration for **1** and *syn* configuration for **2** [13]. Compound **4** was prepared in two steps from bis-(3-indolylglyoxal): N-methylation of both indole nitrogens [14] followed by reaction with hydroxylamine hydrochloride (1 eq.). Two isomers were obtained but they could not be separated by chromatography since *syn* isomer was converted to *anti* isomer on the silicagel chromatography column. Oximes **5** and **6** were prepared from 3-indoleglyoxylic acid. Esterification was performed using sulfuric acid in methanol, reaction of the methyl ester with hydroxylamine hydrochloride (1 eq.) yielded isomers **5** and **6** which could be isolated independently. In the ^{13}C NMR spectra, the signal of the quaternary carbon (C=N) was observed at 148.0 ppm for *anti* isomer **5** and at 144.2 ppm for *syn* isomer **6**.

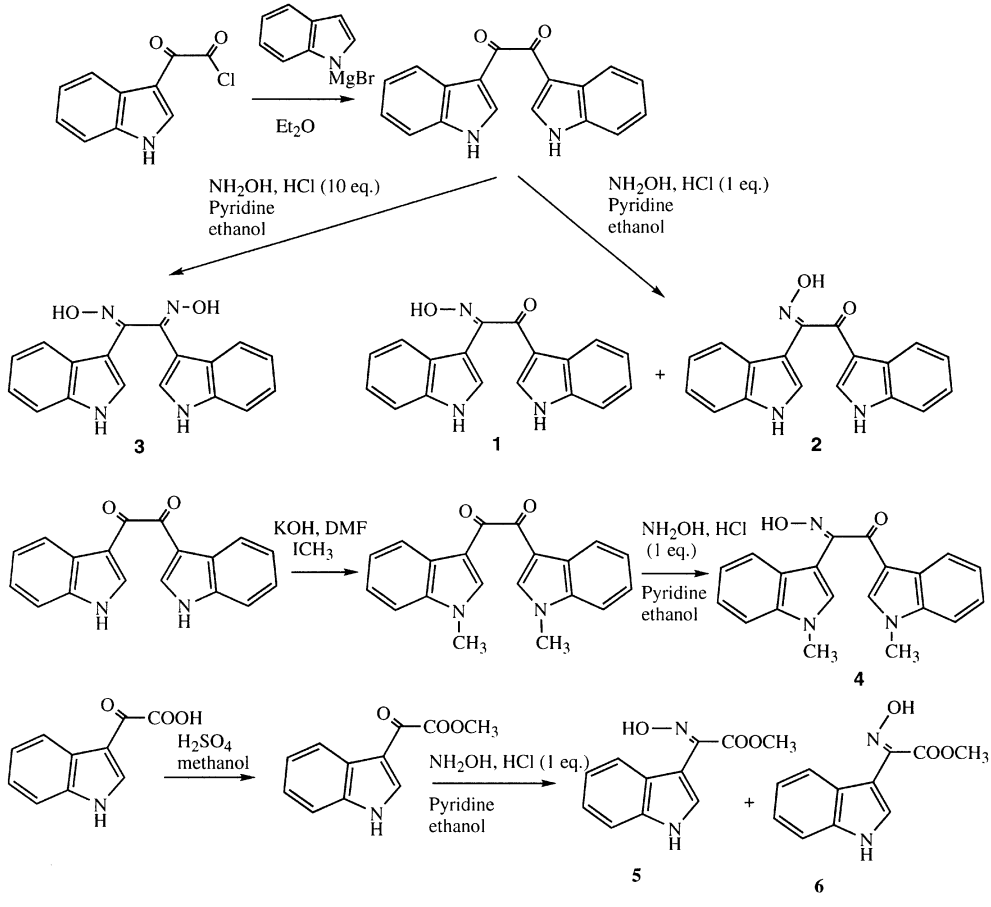

Figure 2.

Table I. In vitro growth inhibitory effect of compounds **1–6** against different microorganisms. [a]

Compounds	*B. cereus* ATCC 14579	*S. chartreusis* NRRL 11407	*E. coli* ATCC 11303	*C. albicans* IP 444
1	++	+++ sp ++++	–	–
2	+++	++++ sp ++++	±	–
3	+	++ sp ++	–	–
4	–	– sp ++++	++	–
5	+	+++	+	–
6	–	+++	–	–

[a] The size of zones of growth inhibition was 13–15 mm (++++), 10–12 mm (+++), 8–9 mm (++), 6–7 mm (+); sp (inhibition of sporulation): ++++ (28–35 mm), ++: 12 mm.

3. Biological results and discussion

Antibiogram tests were performed on a Gram-negative bacterium *E. coli*, a yeast *Candida albicans* and two Gram-positive bacteria *B. cereus*, *S. chartreusis*. The inhibition of sporulation of *S. chartreusis* was examined *(table I)*. None of the compounds **1**–**6** tested had any activity against *C. albicans.* Surprisingly, oxime **4** exhibited a non-negligible antimicrobial activity against Gram-negative *E. coli* without any growth inhibition toward Gram-positive bacteria *B. cereus* and *S. chartreusis*. Oxime **2** was weakly active against *E. coli*. Oximes **1**, **2**, **3** and **5** were active against the two Gram-positive bacteria tested, **6** was only active against *S. chartreusis*. Compound **2** had the strongest antibacterial activity against both *B. cereus* and *S. chartreusis*.

Compounds **1**–**6** were tested against six strains of pathogenic Gram-positive bacteria (*Staphylococcus aureus* SG511, SG 285 and Exp54146, *Streptococcus pyogenes* A561 and 77A, *Enterococcus faecium* M78L) and eleven strains of pathogenic Gram-negative bacteria (*Serratia* RG 2532, *Proteus mirabilis* A235, *Proteus vulgaris* A232, *Escherichia coli* UC1894, 078, TEM, 1507E, DC0 and DC2, *Salmonella typhimurium* MZ11 and *Klebsiella pneumoniae* 52145). The MICs were determined. Only the bisindolylmonooximes **1** and **2** exhibited a noticeable activity against *S. aureus* SG511, 285 and *S. aureus* Exp54146 as well as against *E. coli* 1507E *(table II)*.The *syn* oxime **2** was weakly active against *E. faecium* M78L. The *anti* oxime **1** was weakly active against *S. pyogenes* A561 and *E. coli* DC2.

The main interest of the work is the antimicrobial activity of the monooximes **1** and **2** toward *S. aureus*. To have an insight into the mode of action of these compounds, we tested their inhibitory potencies against protein kinase C (PKCα). The IC_{50} observed were > 100 mg/mL. Therefore the antibacterial activity cannot be due to PKC inhibition.

Peptidoglycan is an essential constituent of the cell wall of eubacteria. Its biosynthesis is a complex process involving many steps, both in the cytoplasm and in the cell membrane. Among the cytoplasmic steps, four ADP-forming ligases catalyse the assembly of the peptide moiety by successive additions of L-alanine, D-glutamate, a diaminoacid (most frequently diaminopimelate or lysine) and D-alanyl-D-alanine to UDP-*N*-acetylmuramic acid [15]. UDP-*N*-acetylmuramoyl-L-alanine:D-glutamate ligase (Mur D) is responsible for the addition of D-glutamic acid to UDP-*N*-acetylmuramic acid and therefore can be a potential target for new antibacterial agents. Since several structurally related indolocarbazoles were found to be Mur D inhibitors (unpublished results), the antimicrobial potencies of compounds **1** and **2** could be due, at least partially, to this enzyme inhibition. We are now investigating this hypothesis. Moreover, the major problem with compounds in these series is their insolubility. Their antimicrobial properties could be markedly increased by introducing on the indole moieties substituents that are known to facilitate membrane crossing such as hydroxy groups. To conclude, oximes **1** and **2** represent new structures able to exhibit interesting antimicrobial activities especially against *S. aureus*. Chemical investigations have to be extended in this field.

Table II. In vitro antimicrobial activities against six strains of pathogenic Gram-positive bacteria (MICs in μg/mL reading after 24 h) compared to those of the known antibiotic Ofloxacine determined in identical conditions.

Strains	MIC μg/mL		
	1	**2**	Ofloxacine
S. aureus SG511	20	20	0.15
S. aureus 285	40	40	0.15
S. aureus Exp54146	160	40	0.30
S. pyogenes A561	160	> 160	1.20
S. pyogenes 77A	> 160	> 160	2.50
E. faecium M78L	> 160	160	0.60
E. coli TEM	> 160	> 160	0.15
E. coli 1507E	80	40	0.15
E. coli DC0	> 160	> 160	0.60
E. coli DC2	160	> 160	0.30

4. Experimental protocols

4.1. Chemistry

IR spectra were recorded on a Perkin-Elmer 881 spectrometer (ν in cm^{-1}), NMR spectra on a Bruker AC 400 (^1H: 400 MHz, ^{13}C: 100 MHz) (chemical shifts δ in ppm, the following abbreviations are used: singlet (s), doublet (d), triplet (t), multiplet (m), tertiary carbons (C *tert.*), quaternary carbons (C *quat.*)). Mass spectra (EI) and (FAB+) were determined at Cesamo (Talence) on a high-resolution Fisons Autospec-Q spectrometer. Chromatographic purifications were performed with a flash Geduran SI 60 (Merck) 0.040–0.063 mm column.

*4.1.1. Anti 1,2-bis(3-indolyl)-2-(hydroxyimino)-ethan-1-one **1** and Syn 1,2-bis(3-indolyl)-2-(hydroxyimino)-ethan-1-one **2***

A mixture of 1,2-bis(3-indolyl)-glyoxal (300 mg, 1.04 mmol), NH_2OH, HCl (72 mg, 1.04 mmol), pyridine (1.5 mL) and absolute ethanol (7.5 mL) was refluxed for 6 h. After removal of the solvent, the residue was dissolved in EtOAc and washed with brine. The organic phase was dried over $MgSO_4$. After removal of the solvent, the residue was purified by flash chromatography (eluent, cyclohexane–EtOAc 5:5) to give **1** (170 mg, 0.56 mmol, 54% yield) and **2** (121 mg, 0.40 mmol, 38% yield) as white powders.

***1*:** M.p. 110–113 °C. IR (KBr): $\nu_{CO,\ C=N}$ 1610, 1620 cm^{-1}, $\nu_{NH,OH}$ 3200–3380 cm^{-1}. HRMS (FAB+) M^+ Calc. for $C_{18}H_{13}N_3O_2$ 303.1007 Found 303.1005. ^1H-NMR (400 MHz, DMSO-d_6) δ: 7.19 (1H, t, J = 7.3 Hz), 7.25 (1H, t, J = 7.3 Hz), 7.30 (2H, m), 7.49 (1H, d, J = 7.8 Hz), 7.58 (1H, m), 7.95 (1H, s), 8.19 (1H, d, J = 7.8 Hz), 8.29 (1H, m), 10.75 (1H, s), 11.47 (1H, s), 12.10 (1H, s). ^{13}C-NMR (100 MHz, DMSO-d_6) δ: 111.9, 112.5, 120.3, 121.0, 121.9, 122.1, 122.4, 123.1, 127.3, 136.6 (C *tert.* arom.), 108.9, 115.3, 124.3, 124.9, 136.8, 136.9 (C *quat.* arom.), 154.4 (C=N), 188.0 (C=O).

***2*:** M.p. 195–198 °C. IR (KBr): $\nu_{CO,\ C=N}$ 1610, 1620 cm^{-1}, $\nu_{NH,OH}$ 3100–3380 cm^{-1}. HRMS (FAB+) M^+ Calc. for $C_{18}H_{13}N_3O_2$ 303.1007 Found 303.1006. ^1H-NMR (400 MHz, DMSO-d_6) δ: 6.93 (1H, t, J = 7.5 Hz), 7.12 (1H, t, J = 7.5 Hz), 7.32 (3H, m), 7.49 (1H, d, J = 8.0 Hz), 7.58 (1H, m), 8.13 (1H, s), 8.36 (1H, m), 8.42 (1H, s), 11.55 (3H, broad s, 2NH + OH). ^{13}C-NMR (100 MHz, DMSO-d_6) δ: 111.8, 112.5, 119.6, 120.4, 121.4, 121.5, 122.2, 123.2, 131.4, 137.2 (C *tert.* arom.), 105.0, 116.0, 124.9, 125.8, 135.2, 136.8 (C *quat.* arom.), 150.4 (C=N), 186.8 (C=O).

*4.1.2. 1,2-bis(3-indolyl)-1,2-bis(hydroxyimino)-ethane **3***

A mixture of 1,2-bis(3-indolyl)-glyoxal (2.585 g, 8.97 mmol), NH_2OH, HCl (6.23 g, 89.70 mmol), pyridine (13 mL) and absolute ethanol (65 mL) was refluxed for 6 h. After idendical work-up as described above, **1** was obtained as a white powder (2.0125 g, 6.32 mmol, 71% yield). M.p. 189–192 °C. HRMS (FAB+) M^+ Calc. for $C_{18}H_{14}N_4O_2$ 318.1116 Found 318.1115. IR (KBr): $\nu_{C=N}$ 1640 cm^{-1}, $\nu_{NH,OH}$ 3200–3600 cm^{-1}. ^1H-NMR (400 MHz, acetone-d_6) δ: 7.15 (2H, t, J = 7.2 Hz), 7.19 (2H, s), 7.22 (2H, t, J = 7.0 Hz), 7.44 (2H, d, J = 7.9 Hz), 8.21 (2H, d, J = 7.7 Hz), 10.65 (2H, s), 11.32 (2H, s). ^{13}C-NMR (100 MHz, acetone-d_6) δ: 109.8, 124.3, 136.9 (C *quat.* arom.), 111.7, 119.9, 121.9, 122.0, 127.3 (C *tert.* arom.), 149.4 (C=N).

*4.1.3. Anti 1,2-bis(3-N-methylindolyl)-2-(hydroxyimino)-ethan-1-one **4***

A mixture of 1,2-bis[3-(N-methyl-indolyl)]-glyoxal (283 mg, 0.89 mmol), NH_2OH, HCl (62 mg, 0.89 mmol), pyridine (1.5 mL) and absolute ethanol (7.5 mL) was refluxed for 6 h. After idendical work-up as described above, **4** was obtained as an off-white powder (176 mg, 0.53 mmol, 60% yield). M.p. 255–256 °C. IR (KBr) $\nu_{C=O,C=N}$ 1610, 1620 cm^{-1}, ν_{OH} 3300–3550 cm^{-1}. HRMS (EI) M^+ Calc. for $C_{20}H_{17}N_3O_2$: 331.1320. Found: 331.1320. ^1H NMR (400 MHz, DMSO-d_6): 3.76 (3H, s, NCH_3), 3.88 (3H, s, NCH_3), 7.24 (1H, dt, J_1 = 7.9 Hz, J_2 = 0.8 Hz), 7.31 (1H, dt, J_1 = 8.3 Hz, J_2 = 1.2 Hz), 7.33 (1H, s), 7.36 (1H, dt, J_1 = 7.4 Hz, J_2 = 1.0 Hz), 7.38 (1H, dt, J_1 = 7.2 Hz, J_2 = 1.7 Hz), 7.51 (1H, d, J = 8.2 Hz), 7.60 (1H, dd, J_1 = 6.8 Hz, J_2 = 1.9 Hz), 8.02 (1H, s), 8.21 (1H, d, J = 7.8 Hz), 8.30 (1H, d, J = 6.9 Hz), 10.82 (1H, s, N=OH). ^{13}C NMR (100 MHz, DMSO-d_6): 32.5, 33.1 (NCH_3); 108.0, 114.2, 124.7, 125.5, 137.2, 137.6 (C *quat.* arom.); 110.1, 110.9, 120.5, 121.2, 122.1, 122.2, 122.5 (2C), 123.2, 131.2 (C *tert.* arom.); 154.0 (C=N); 187.4 (C=O).

4.1.4. Methyl 2-indolyl-2-oxo-ethanoate

Commercial indolyl-glyoxylic acid (1 g, 5.28 mmol) was added to a solution of concentrated H_2SO_4 (1.6 mL) in methanol (6.2 mL). The mixture was refluxed for 3 h. After neutralization with NaOH and extraction with EtOAc, the organic phase was washed with brine, dried over $MgSO_4$. After removal of the solvent, the residue was purified by flash chromatography (eluent, EtOAc) to give methyl 2-indolyl-2-oxo-ethanoate as a yellow solid (934 mg, 4.57 mmol, 87% yield). M.p.: 218–220 °C. IR (KBr) $\nu_{C=O}$ 1730, 1740 cm^{-1}, ν_{NH} 3240 cm^{-1}. HRMS (FAB+) $(M + H)^+$ Calc. for $C_{11}H_{10}NO_3$: 204.0661.

Found: 204.0647. ^{1}H NMR (400 MHz, DMSO-d_6): 3.95 (3H, s, OCH_3), 7.35 (2H, t, J = 7.5 Hz), 7.60 (1H, d, J = 7.5 Hz), 8.20 (1H, d, J = 7.5 Hz), 8.50 (1H, s), 12.45 (1H, s, N_{indole}–H). ^{13}C NMR (100 MHz, DMSO-d_6): 52.5 (CH_3), 112.7, 121.1, 122.8, 123.8, 138.3 (C *tert.* arom.), 112.4, 125.4, 136.7 (C *quat.* arom.), 163.9, 178.6 (C=O).

*4.1.5. Anti Methyl-2-hydroxyimino-2-(3-indolyl)-ethanoate **5** and Syn Methyl-2-hydroxyimino-2-(3-indolyl)-ethanoate **6***

A mixture of methyl 2-indolyl-2-oxo-ethanoate (275 mg, 1.355 mmol), NH_2OH, HCl (94 mg, 1.355 mmol), pyridine (2.3 mL) and absolute ethanol (10 mL) was refluxed for 6 h. After idendical work-up as described for **1**, **5** (142 mg, 0.651 mmol, 48% yield) and **6** (100 mg, 0.460 mmol, 34% yield) were obtained as off-white powders.

***5*:** M.p.: 134–135 °C. IR (KBr) $\nu_{C=N}$ 1610 cm^{-1}, $\nu_{C=O}$ 1720 cm^{-1}, $\nu_{OH,NH}$ 3340, 3440 cm^{-1}. HRMS (EI) M^+ Calc. for $C_{11}H_{10}N_2O_3$: 218.0691. Found: 218.0692. ^{1}H NMR (400 MHz, DMSO-d_6): 3.89 (3H, s), 7.17 (1H, dt, J_1 = 7.8 Hz, J_2 = 0.7 Hz), 7.25 (1H, dt, J_1 = 8.2 Hz, J_2 = 1.3 Hz), 7.51 (1H, d, J = 8.1 Hz), 7.54 (1H, d, J = 2.5 Hz), 8.02 (1H, d, J = 7.8 Hz), 11.26 (1H, s), 11.65 (1H, s). ^{13}C NMR (100 MHz, DMSO-d_6): 52.1 (OCH_3); 107.0, 123.9, 136.9 (C *quat.* arom.); 112.8, 121.2, 121.4, 122.7, 127.4 (C *tert.* arom.); 148.0 (C=N); 164.7 (C=O).

***6*:** M.p.: 146–147 °C. IR (KBr) $\nu_{C=N}$ 1630 cm^{-1}, $\nu_{C=O}$ 1710 cm^{-1}, $\nu_{OH,NH}$ 3200–3500 cm^{-1}. HRMS (EI) M^+ Calc. for $C_{11}H_{10}N_2O_3$: 218.0691. Found: 218.0691. ^{1}H NMR (400 MHz, DMSO-d_6): 3.86 (3H, s), 7.10 (1H, dt, J_1 = 7.9 Hz, J_2 = 1.0 Hz), 7.19 (1H, dt, J_1 = 8.2 Hz, J_2 = 1.2 Hz), 7.36 (1H, d, J = 8.0 Hz), 7.50 (1H, d, J = 8.1 Hz), 8.13 (1H, d, J = 2.8 Hz). ^{13}C NMR (100 MHz, DMSO-d_6): 52.3 (OCH_3); 111.9, 119.9, 120.0, 121.6, 130.6 (C *tert.* arom.); 103.7, 124.8, 135.3 (C *quat.* arom.); 144.2 (C=N); 165.5 (C=O).

4.2. Antibiogram tests and MIC determinations

Five strains were tested, three Gram positive bacteria (*B. cereus* ATCC 14579, *S. chartreusis* NRRL 11407, *S. griseus* ATCC 23345), a Gram negative bacterium (*E. coli* ATCC 11303) and a yeast (*Candida albicans* 444 from Pasteur Institute). Antimicrobial activity was determined by the conventional paper disk (Durieux No. 268, 6 mm in diameter) diffusion method using the following nutrient media: Mueller–Hinton (Difco) for *B. cereus* and *E. coli*, Sabouraud agar (Difco) for *C. albicans* and Emerson agar (0.4% beef extract, 0.4% peptone, 1% dextrose, 0.25% NaCl, 2% agar, pH 7.0) for the *Streptomyces* strains. Products **1**–**6** were dissolved in DMSO and a paper disk containing each of the products (300 mg) was placed on Petri dishes. Growth inhibition was examined after 24 h incubation at 27 °C.

MICs were determined by a two-fold microdilution method in Mueller–Hinton broth (Diagnostic Pasteur). The medium was supplemented with 4% globular extract (Diagnostic Pasteur) to support the growth of streptococci. The MIC was defined as the lowest concentration which prevents the growth after 24 h incubation at 37 °C in ambient atmosphere.

4.3. Protein kinase C inhibition

Protamine sulphate was from Merck (Darmstadt, Germany). Unless specified, chemicals were from Sigma (St. Louis, MO). [γ-^{33}P] ATP (1000–3000 Ci/mmol) was obtained from Amersham. Recombinant baculoviruses from protein kinase C subtypes were supplied by Dr. Silvia Stabel, Köln, Germany.

Expression and partial purification of PKCs together with measurements of activities were carried out as previously described [16].

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