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# Synthesis and Antimicrobial Activity of Some Isoindolin-1-ones Derivatives

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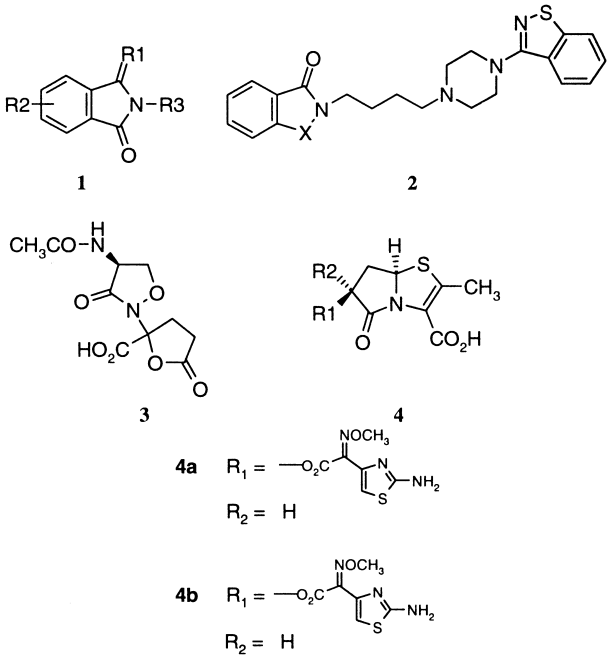
**Abstract**—A range of *N*-substituted isoindolin-1-ones was prepared and their potential as novel antimicrobial agents was investigated. MIC values for active compounds were determined and reported. © 2000 Published by Elsevier Science Ltd.

*N*-Substituted isoindolin-1-one derivatives have generated considerable interest lately as they have been reported as having diverse biological activity. Compound **1**, for instance, is an inhibitor of thromboxane $A_2$-induced vasoconstriction,[1] and compound **2** is a potential anti-psychotic agent due to its action as an antagonist of dopamine $D_2$ and serotonin 5-$HT_2$ receptors.[2] Other examples of biologically active isoindolinones include anxiolytics and reverse transcriptase inhibitors.[3,4]

As we recognised the γ-lactam functionality contained within the *N*-substituted isoindolin-1-ones, it was interesting to note the report on lactivicin (**3**), a monocyclic γ-lactam isolated from *Empedobacter lactamgenus* and *Lysobacter albus*, as having β-lactam-like biological activity. Lactivicin is moderately active against Gram negative bacteria, highly active against Gram positive bacteria, but inactive against fungi.[5]

In addition two bicyclic γ-lactams (**4a** and **4b**) derived from penems were found to have low but demonstrable activity against a wide range of Gram positive and Gram negative bacteria.[6]

We wished to further explore the diverse biological activity of the *N*-substituted isoindolin-1-ones and as there have been reports of γ-lactams having antimicrobial activity[5,6] (*vide infra*), a range of *N*-substituted isoindolin-1-ones were synthesised and subjected to antimicrobial testing.




In this communication we wish to report the synthesis and antimicrobial activity, expressed as minimum inhibitory concentrations (MIC values) of *N*-substituted isoindolin-1-one derivatives **5**, **6**, **7** and **8** and present them as a novel class of bicyclic aromatic γ-lactam antibacterial compounds.

Compounds **5a**–**j** (Table 1) were prepared by refluxing the corresponding amino acid with *o*-phthalaldehyde in

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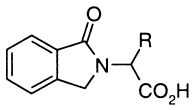
acetonitrile. After 12 h the hot reaction mixture was filtered to remove unreacted amino acid and on cooling the desired isoindolin-1-one crystallised and could be isolated simply by filtration. Yields ranged from 33–87%.[7]



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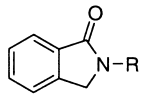

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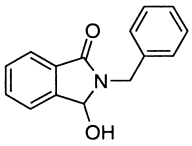

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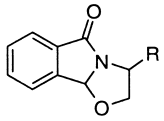

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Compounds **6a–c** (Table 2) were prepared by combining the corresponding amino acid with *o*-phthalaldehyde in either acetonitrile, chloroform or diethyl ether with catalytic amounts of acetic acid at temperatures ranging from 0–80 °C. Yields of 70–78% were obtained.[8]

Compound **7** (Table 1) was prepared by adding the corresponding primary amine to phthalaldehyde acid

**Table 2.** Structures of inactive compounds

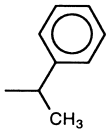
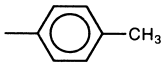
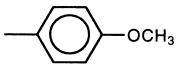
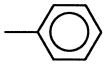
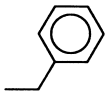
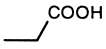
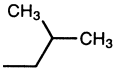
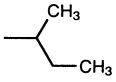
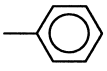
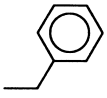
| Compound | R | Configuration |
|---|---|---|
| **6a** |  | (*S*) |
| **6b** |  | |
| **6c** |  | |
| **8a** |  | (*R*,*S*) |
| **8b** |  | (3*R*) |
| **8c** |  | (3*S*) |

**Table 1.** MIC values (mg/mL) of *N*-substituted isoindolin-1-ones

| Compound | R | Configuration | B.s.[a] | M.r.[b] | S.a.[c] | E.c.[d] | P.a.[e] |
|---|---|---|---|---|---|---|---|
| **5a** |  | (*S*) | 0.729 | 1.62 | 1.62 | 1.62 | 3.6 |
| **5b** |  | (*R*) | 0.328 | 2.61 | 1.62 | 3.6 | 3.6 |
| **5c** |  | (*S*) | 0.729 | 2.61 | 3.6 | 1.62 | 3.6 |
| **5d** |  | (*S*) | 0.147 | 2.61 | 3.6 | 0.729 | 1.62 |
| **5e** |  | (*S*) | 1.62 | 1.62 | 3.6 | 1.62 | 3.6 |
| **5f** |  | (*R*) | 1.62 | 1.62 | 3.6 | 3.6 | 3.6 |
| **5g** |  | (*R*,*S*) | 0.729 | 3.6 | 3.6 | 3.6 | 3.6 |
| **5h** |  | (*R*,*S*) | 0.729 | 1.175 | 3.6 | 1.62 | 3.6 |
| **5i** |  | (*S*) | 0.529 | 0.729 | Zero growth inhibition | 1.62 | 3.6 |
| **5j** |  | (*S*) | 1.175 | 2.61 | Zero growth inhibition | 3.6 | 3.6 |
| **7** | | (*R*,*S*) | Zero growth inhibition | 1.62 | Zero growth inhibition | 2.61 | 3.6 |
| DMSO controls | | | Zero growth inhibition | Zero growth inhibition | Zero growth inhibition | Zero growth inhibition | Zero growth inhibition |

[a]B.s. = *Bacillus subtilis*.
[b]M.r. = *Micrococcus roseus*.
[c]S.a. = *Staphylococcus aureus*.
[d]E.c. = *Escherichia coli*.
[e]P.a. = *Pseudomonas aeruginosa*.

chloride and triethylamine in chloroform. The reaction mixture was left overnight at room temperature and then extracted with dilute hydrochloric acid. The chloroform solution was dried over anhydrous potassium carbonate and concentrated. Purification was achieved by recrystallisation from chloroform–ether mixtures. Yields of 45–50% were obtained.[9]

Compounds **8a**–**c** (Table 2) were prepared by refluxing the corresponding amino alcohol and 2-formylbenzoic acid under Dean–Stark conditions in toluene for 12 h. Purification was achieved by flash chromatography with diethyl ether/light petroleum ether mixtures as eluents. Yields of 70–72% were obtained.[10]

Compounds **5**–**8** were subjected to in vitro microbiological testing and determination of MIC values.

Antimicrobial activity was determined by using the direct agar plate technique.[11] A range of Gram positive and negative bacteria, an *Aspergillus* sp and *Candida albicans* were used in the initial screen. Substances **5a**–**j** and **7** were found to be active against Gram positive as well as Gram negative bacteria with only substance **8a** having activity against the *Aspergillus* sp. and *Candida albicans*. Structures of inactive compounds are given in Table 2.

Compounds **5a**–**j** and **7** showing antibacterial activity in the initial test were further subjected to determination of MIC values. A standard microdilution technique[12] was used for the determination of MIC values using the following organisms: Gram positive bacteria (*Bacillus subtilis, Micrococcus roseus, Staphylococcus aureus*) and Gram negative bacteria (*Escherichia coli*, *Pseudomonas aeruginosa*). Suspensions of bacteria were standardised at $5\times10^6$ colony forming units per mL (CFU/mL) and test compounds were disolved in water containing 0.2% DMSO. The MIC values are given in Table 1.

The COOH functional group present in compounds **5a**–**j** seems to be necessary for antibacterial activity for that specific series as compounds **6a**–**c** lacking this group but similar in structure to compounds **5a**–**j** showed no antibacterial activity in the initial screening test.

Compounds **5a**–**j** and **7** exhibited antimicrobial activity similar to β-lactam antibiotics (MIC values for ampicillin and amoxycillin ranges from 0.02.0 μg/mL) and other γ-lactams such as the monocyclic lactivicin[5] and the bicyclic penems (**4a** and **b**).[6] Lactivicin and the bicyclic penems (**4a** and **b**) had activity against Gram positive and Gram negative bacteria but not against fungi. This corresponds well with the results obtained with the *N*-substituted isoindolin-1-one compounds tested in this study.

In conclusion, we report that *N*-substituted isoindolin-1-ones derived from available amino acids constitute a novel class of bicyclic aromatic γ-lactam antibacterial agents, with the carboxylic acid derivatives displaying the greatest activity.

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