
Fabrice Anizon, Bruno Pfeiffer, Michelle Prudhomme

To cite this version:


HAL Id: hal-00016530
https://hal.archives-ouvertes.fr/hal-00016530
Submitted on 27 Feb 2007
Synthesis of pyridino[3′,2′:4,5]pyrrolo[3,2-g]pyrrolo-[3,4-e]indolizin-1,3-dione and pyrrolo[3,2-c]pyrazole skeletons

Fabrice Anizon, Bruno Pfeiffer and Michelle Prudhomme

aLaboratoire SEESIB, Université Blaise Pascal, UMR 6504 du CNRS, 63177 Aubière, France
bInstitut de Recherches SERVIER, Division Recherche et Cancérologie, 125 Chemin de ronde, 78290 Croissy sur Seine, France

Received 5 October 2005; revised 14 November 2005; accepted 16 November 2005
Available online 2 December 2005

Abstract—A three step synthesis of an isogranulatinimide analogue, in which the imidazole moiety is replaced by a pyrrole unit and the indole heterocycle is replaced by a 7-azaaindole moiety is described. Moreover, a novel synthetic pathway to the pyrrolo[3,2-c]-pyrazole skeleton is reported.

© 2005 Elsevier Ltd. All rights reserved.

I. Introduction

Granulatimide and isogranulatimide are aromatic alkaloids isolated from the brazilian ascidian Didemnum granulation (Fig. 1). These compounds have been identified as cell cycle G2 checkpoint inhibitors. In response to DNA damage, cell cycle checkpoints are activated. Their role consists in blocking the cell cycle to allow time for DNA repair. In more than 50% of cancer cells, the p53 gene is mutated. The G1 checkpoint is dependent on the p53 protein. Therefore, in the p53-mutated cells, the G1 checkpoint is lacking. These cells will be more sensitive to DNA damaging agents in the presence of a G2 checkpoint inhibitor, than healthy cells in which G1 checkpoint remains intact. Granulatimide and isogranulatimide, as well as staurosporine and UCN-01, are G2 checkpoint inhibitors. Compounds structurally related to granulatimide and isogranulatimide have been recently synthesized by our group. A series of compounds related to isogranulatimide, in which the imidazole moiety was replaced by a pyrrole heterocycle has been described (Fig. 1).

In this letter, we report the synthesis of an isogranulatimide analogue bearing a pyrrole moiety instead of the imidazole heterocycle, and a 7-azaaindole unit instead of an indole heterocycle. Azaindoles are biososters of indole. They are found in many natural and synthetic compounds of biological interest. The replacement of a carbon atom by a nitrogen atom may modify the affinity for the binding site of the target enzyme(s), due to the modification of the electronic distribution on the aromatic framework and also due to the presence of a supplementary lone electron pair, which may induce additional hydrogen bonds. Moreover, a novel two-step synthesis of a pyrrolo[3,2-c]pyrazole is reported.

2. Chemistry

The preparation of compound 5 is outlined in Scheme 1. In indole series, 2,2′-pyrrolylindole was prepared from 3-bromoidindle and pyrrole in an acidic medium. In these conditions, the coupling between 3-bromo-7-azaaindole and pyrrole did not occur. For the preparation of 7-azaaindoles, acid-catalyzed Fischer indolization from pyridylhydrazones is not favored. A 7-azaaindole framework could be built by thermal cyclization from the hydrazone prepared from 2-hydrazinopyridine and the appropriate ketone. Heating 2-acetylpyrrole in 2-hydrazinopyridine at 160 °C allowed the isolation of hydrazone I in 94% yield (Scheme 1). Unfortunately, the 7-azaaindole derivative 3 could not be obtained by thermal indolization. Heating 1 at 245 °C in diethylene glycol led to decomposition of starting material. When the reaction was performed in nitrobenzene at 200 °C, pyrazole 2 was isolated in 40% yield after purification by flash chromatography. Only few methods are described in the literature for the synthesis of
pyrrolo[3,2-c]pyrazoles.\textsuperscript{25,26} The pyrrolo[3,2-c]pyrazole nucleus is found in more complex or related structures\textsuperscript{27-33} or condensed aromatic systems of biological interest.\textsuperscript{34,35} However, to our knowledge, this synthetic pathway has never been described previously. The structure of compound 2 has been confirmed from NMR spectroscopic data (\textsuperscript{1}H-\textsuperscript{1}H COSY, \textsuperscript{13}C-\textsuperscript{1}H HSQC, \textsuperscript{13}C-\textsuperscript{1}H HMBC, \textsuperscript{15}N-\textsuperscript{1}H HMBC correlations), which allowed the assignments of the signals (Fig. 2). A possible mechanism for the formation of compound 2 could involve an azomethine imine intermediate, which would undergo electrocyclization.\textsuperscript{30,37}
Compound 3 was obtained in 42% yield by coupling 3-picoline and 2-cyanopyrrole in the presence of LDA. A Michael addition between compound 3 and maleimide in refluxing toluene in the presence of SnCl₄ allowed the obtention of compound 4 in poor yield. As previously observed, a Michael addition could not be performed from 7-azaindenole and maleimide in acetic acid. Finally, coupling of compound 3 with maleimide was successfully carried out in a mixture of MeOH/CH₂Cl₂ 1:2 at 50 °C giving the Michael adduct 4 in 54% yield. Compound 5 was obtained in 14% yield by cyclization of 4 in refluxing nitrobenzene in the presence of Pd black followed by filtration and purification by flash chromatography. This step probably involves the oxidation of the succinimide to maleimide prior to the cyclization.

In summary, a new isoguaninatulimic analogue was prepared in three steps via a 2,2'-pyrrol-7-azaindenole intermediate. In parallel, the synthesis of a pyrrole[3,2-c]-pyrazole derivative was performed in two steps. This method could be applied to obtain analogues bearing various substituents. The pyrrole[3,2-c]-pyrazole nucleus is found in structures of biological interest. The biological activities of the new compounds are under investigation.

References and notes


40. Procedure for the preparation of 3 and spectral data: a solution of LDA was prepared at 0 °C from a 2.0 M solution of butyllithium in cyclohexane (8.1 mL) and diisopropylamine (2.26 mL) in THF (20 mL). The solution was stirred at 0 °C for 10 min before addition of 3-picoline (522 μL, 5.38 mmol). The mixture was stirred at 0 °C for 10 min then cooled to −78 °C before addition of 2-cyanopyrrole (455 μL, 5.38 mmol). The mixture was stirred at 0 °C for 1.5 h. A solution of LDA was added (9 mmol—prepared from 2.0 M butyllithium in cyclohexane (4.5 mL) and diisopropylamine (1.26 mL) in THF (10 mL) and the reaction mixture was heated at 45 °C for 5 h. After cooling and addition of brine, the mixture was extracted with EtOAc. The organic phase was dried over MgSO4, filtered, and evaporated. Compound 3 was isolated after purification by flash chromatography (eluent THF/CH2Cl2 1:9 then 2:5) as a purple solid (11.5 mg, 0.024 mmol, 42% yield). Mp > 150 °C (decomposition). IR (KBr) νcm−1 3420 cm−1. HRMS (FAB+) [M+H]+ caked for C13H34N3 184.0875, found 184.0872. 1H NMR (400 MHz, DMSO-d6): δ 6.64 (1H, d, J = 2.0 Hz), 6.77 (1H, d), 6.95 (1H, m), 7.03 (1H, dd, J1 = 8.0 Hz, J2 = 5.0 Hz), 7.86 (1H, dd, J1 = 8.0 Hz, J2 = 1.5 Hz), 8.13 (1H, dd, J1 = 5.0 Hz, J2 = 1.5 Hz), 11.41 (1H, br s, NH), 11.81 (1H, br s, NH). 13C NMR (100 MHz, DMSO-d6): δ 93.0, 107.0, 108.9, 115.6, 119.8, 126.5, 141.3 (CH), 121.2, 124.3, 133.1, 149.1 (C).

41. Procedure for the preparation of 4 and spectral data: a mixture of 3 (100 mg, 0.546 mmol) and maleic acid (530 mg, 5.46 mmol) in water (2 mL) was heated at 80 °C for 48 h. Methanol was evaporated and after addition of brine, the aqueous mixture was extensively extracted with EtOAc. The organic phase was dried over MgSO4, filtered, and evaporated. Compound 4 was isolated after purification by flash chromatography (eluent EtOAc/cyclohexane from 5:5 to 8:2) as an off-white solid (82.6 mg, 0.295 mmol, 54% yield). Mp > 200 °C (decomposition). IR (KBr) νcm−1 1700, 1770 cm−1. 1H NMR (500 MHz, DMSO-d6): δ 2.77 (1H, dd, J1 = 18.0 Hz, J2 = 5.5 Hz), 2.32 (1H, dd, J1 = 18.0 Hz, J2 = 10.0 Hz), 4.60 (1H, dd, J1 = 10.0 Hz, J2 = 5.5 Hz), 6.26 (1H, m), 6.57 (1H, br s), 7.05 (1H, br s), 7.07 (1H, dd, J1 = 8.0 Hz, J2 = 4.5 Hz), 7.59 (1H, d, J = 7.5 Hz), 8.21 (1H, d, J = 4.5 Hz), 11.11 (1H, br s, NH), 11.50 (1H, br s, NH), 11.64 (1H, br s, NH). 13C NMR (100 MHz, DMSO-d6): δ 37.2 (CH3), 38.9 (CH), 109.1, 109.4, 115.6, 120.5, 125.4, 142.3 (CH atom), 104.2, 118.7, 122.2, 130.9, 145.3 (C), 177.9, 179.9 (C=O).

42. Procedure for the preparation of 5 and spectral data: a mixture of 4 (82 mg, 0.295 mmol) and Pb black (31.4 mg) in nitrobenzene (5 mL) was refluxed for 7 h. The reaction mixture was filtered over flash silica gel (eluent dichloromethane then THF). Compound 5 was isolated after purification by flash chromatography (eluent THF/CH2Cl2 1:9 then 2:5) as a purple solid (11.5 mg, 0.024 mmol, 42% yield). Mp > 300 °C. IR (KBr) νcm−1 1720, 1760 cm−1. 1H NMR (400 MHz, DMSO-d6): δ 7.16 (1H, dd, J1 = 4.0 Hz, J2 = 2.5 Hz), 7.23 (1H, dd, J1 = 4.0 Hz, J2 = 1.0 Hz), 7.40 (1H, dd, J1 = 8.0 Hz, J2 = 4.5 Hz), 8.30 (1H, dd, J1 = 2.5 Hz, J2 = 1.0 Hz), 8.49 (1H, dd, J1 = 4.5 Hz, J2 = 1.5 Hz), 8.76 (1H, dd, J1 = 8.0 Hz, J2 = 1.5 Hz), 11.17 (1H, br s, NH), 13.24 (1H, br s, NH). 13C NMR (100 MHz, DMSO-d6): δ 101.1, 114.7, 116.4, 117.2, 130.0, 145.3 (CH), 101.3, 114.4, 116.8, 122.2, 124.2, 133.3, 151.2 (C), 166.4, 169.1 (C=O).