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Exploring the Synthesis of New 1-(4-Substitutedphenylamino) imidazo[1,5-a]indol-3-one Derivatives as Cyclized Analogs of Leucettines

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ABSTRACT

New 1-arylaminoimidazo[1,5-*a*]indol-3-ones were synthesized as cyclized derivatives of leucettine L41, a low molecular weight inhibitor of the DYRKs/CLKs protein kinases with potential applications in Alzheimer's disease and Down syndrome. In this first approach, access to the desired 1-aminoimidazo[1,5-*a*]indol-3-ones involved 5 steps and was explored with a series of various primary amines and polar secondary amines in order to introduce molecular diversity on *N*-1 position. The 5 step synthesis of the 1-arylaminoimidazo[1,5-*a*]indol-3-ones was achieved and the limiting step of this process was the final cyclization *via* a sulphur/nitrogen displacement from methylsulfanyl thiourea intermediates. Good results were obtained for isothioureas derived from primary amines. The 1-arylaminoimidazo[1,5-*a*]indol-3-ones were evaluated on a panel of five protein kinases (DYRK1A, CK1, CDK5/p25, GSK3 α/β and CLK1).

INTRODUCTION

Leucettamine B, a natural marine alkaloid comprising a 2-aminoimidazoline-4-one scaffold, was isolated in 1993 from the sponge *Leucetta microraphis* Haeckel (*Calcarea*) of the Argulpelu Reef in Palau (Chan *et al.*, 1993). Several total synthesis of Leucettamine B have been reported (Molina *et al*., 1994, Roué *et al.*, 1999, Chérouvrier *et al.*, 2001 and 2002, Debdab *et al.*, 2009). Other marine natural products containing the 2-aminoimidazoline-4-one core, such as polyandrocarpamine A (Cimino *et al.*, 1982), hymenialdisine (Meijer et al., 2000, Xu et al., 1997, and Papeo *et al.*, 2005) and zorrimidazolone (Aiello *et al.*, 2011), are subject to intensive research by organic chemists, biochemists and biologists.

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Among these molecules, (*Z*) hymenialdisine was identified as nanomolar inhibitor of various protein kinases (glycogen synthase kinase 3β (GSK3β, casein kinase 1 (CK1) and different cyclin-dependent kinases (CDKs) (Wan *et al.*, 2004).

Protein kinases catalyze phosphorylation on serine, threonine and tyrosine residues and regulate protein functions, stability and localization. They constitute very attractive therapeutic targets for the pharmaceutical industry in the search for new clinical drugs.

Recently our group reported the patented synthesis of leucettamine B derivatives (Bazureau *et al.*, 2009), collectively named leucettines, as low molecular weight inhibitors (Debdab *et al*., 2011 and Tahtouh *et al.*, 2012) of DYRKs (dual specificity, tyrosine phosphorylation regulated kinases) (Aranda *et al.*, 2011) and CLKs (cdc2-like kinases) (Hagiwara *et al.*, 2005), two families of kinase involved in alternative pre-mRNA splicing and Alzheimer's disease/Down syndrome.

A detailed structure/activity relationship (SAR) study led to the selection of leucettine L41 (Figure 1) as a potent inhibitor of DYRKs and CLKs. To understand the kinase/inhibitor selectivities and to generate models for structure-based optimization, leucettine L41, was co-crystallized with DYRK1A and found to bind in the ATP pocket of this kinase by two direct polar interactions and hydrogen bonds (Debdab *et al.,* 2011). Considering these biological results, particularly the hydrogen bonding network in the co-crystal structure, it was of interest to explore the building of 1-phenylamino imidazo[1,5-*a*]indol-3-one (Figure 1) which can be considered as an analog of leucettine L41 obtained by the ring closure of N-C atoms between the *N*-1 position of the 2-aminoimidazoline-4-one platform and the C-6 position of the 1,3-benzodioxol-5-ylidene moiety. Here, we describe the synthesis of new 2-phenylamino imidazo[1,5-*a*]indol-3-ones without substituents on the indolone moiety and evaluate their effects on five purified protein kinases.

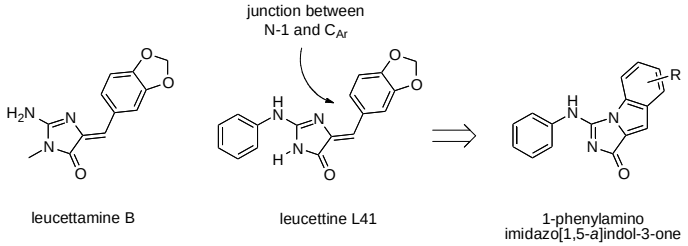


Fig. 1: Leucettamine B, Leucettine L41 and cyclized derivatives.

MATERIALS AND METHOD

Materials and instruments

All reagents and solvents were purchased from Acros, Aldrich Chimie, and Fluka France and were used without further purification. Solvents were evaporated with a BUCHI rotary evaporator. Melting points were determined on a Kofler melting point apparatus and were uncorrected. ^{1}H NMR spectra were recorded on BRUKER AC 300 P (300 MHz) spectrometer, ^{13}C NMR spectra on BRUKER AC 300 P (75 MHz) spectrometer. Chemical shifts are expressed in parts per million downfield from tetramethylsilane as an internal standard. Data are given in the following order: *d* value, multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad), number of protons, coupling constants *J* is given in Hertz. The mass spectra (HRMS) were taken respectively on a MS/MS ZABSpec Tof Micromass (EBE TOF geometry) at an ionizing potential of 8 eV and on a VARIAN MAT 311 at an ionizing potential of 70 eV in the "Centre Régional de Mesures Physiques de l'Ouest" (CRMPO, Rennes). Elemental analyses were performed on a Carlo Erba 1106 apparatus.

Methods

Standard procedure for the synthesis of N-carbamothioyl-1H-indole-2-carboxamide 6(a-f) and N-carbothioyl-1H-indole-2-carboxamide 6(f,g).

In a 50 ml two-necked round-bottomed flask provided with a magnetic stirrer and condenser, a suspension of commercial indole-2-carboxylic acid **1** (1 g, 6.2 mmol) was vigorously stirred at room temperature in 25 ml of benzene. To this mixture was added dropwise phosphorous trichloride [0.85 g, 0.54 ml, 6.2 mmol for compounds **6(a-e)** or 1.7 g, 1.08 ml, 12.4 mmol for compounds **6(f,g)**] during 30 min. at 25°C under a stream of Ar. The reaction mixture was heated in oil bath at 80°C during 1 hr. After cooling down to room temperature, the reaction mixture was filtered on a Buchner funnel (porosity N°4) and the resulting filtrate was concentrated until a final volume of 5 ml in a rotary evaporator under reduced pressure. This concentrated solution was poured in a 50 ml round bottomed flask provided with a magnetic stirrer and condenser. To this solution were added successively 30 ml of acetone p.a. and potassium thiocyanate (603 mg, 6.2 mmol). This suspension was stirred at 25°C during 1 hr and primary amine **4** (6.2 mmol) or morpholine **5a** or 4-methylpiperazine **5b** (6.2 mmol) was added in one portion. The reaction mixture was stirred vigorously at 25°C during 1 hr, then the solvent was removed in a rotary evaporator under reduced pressure. The resulting crude oil crystallized at standing room temperature that gave the desired product **6** as yellowish powder, which was submitted to purification by recrystallization in absolute ethanol (1-3 ml).

*N-(4-Methylphenylcarbamothioyl)-1H-indole-2-carboxamide (**6a**)*

Compound **6a** was prepared in 9% yield (173 mg) from *p*-toluidine **4a** (628 mg, 598 µl, 6.2 mmol) according to the standard procedure. Mp = 200-202°C. ^{1}H NMR (DMSO-d_6) δ: 2.32 (s, 3H), 7.09 (dd, 1H, *J* = 7.4, 0.9 Hz, Ar), 7.22 (d, 2H, *J* = 7.7 Hz, Ar), 7.25-7.35 (m, 1H, Ar), 7.49 (d, 1H, *J* = 8.4 Hz, Ar), 7.55 (d, 2H, *J* = 7.7 Hz, Ar), 7.68 (d, 1H, *J* = 7.8 Hz, Ar), 7.78 (s, 1H, Ar), 11.48 (br s, 1H, NH), 12.07 (br s, 1H, NH), 12.58 (br s, 1H, NH). ^{13}C NMR (DMSO-d_6) δ: 20.57 (CH_3), 108.50, 112.58, 120.36, 122.43, 124.28, 125.21, 126.75, 128.40, 129.06, 135.46, 135.61, 137.78, 161.42 (C=O), 178.82 (C=S). HRMS, *m/z*: 332.0835 found (calculated for $C_{17}H_{15}N_3ONaS$ $[M+Na]^+$ requires 332.0839).

*N-(Phenylcarbamothioyl)-1H-indole-2-carboxamide (**6b**)*

Compound **6b** was prepared in 9% yield (165 mg) from aniline **4b** (578 mg, 567 µl, 6.2 mmol) according to the standard procedure. Mp = 201-203°C. ^{1}H NMR (DMSO-d_6) δ: 7.05-7.18 (m, 1H, Ar), 7.24-7.38 (m, 3H, Ar), 7.38-7.52 (m, 3H, Ar), 7.69 (d, 2H, *J* = 7.8 Hz, Ar), 7.81 (s, 1H), 11.50 (br s, 1H, NH), 12.00 (br s, 1H, NH), 12.63 (br s, 1H, NH). ^{13}C NMR (DMSO-d_6) δ: 108.52, 112.58, 120.38, 122.46, 124.39, 125.25, 126.28, 126.75, 127.51, 128.65, 130.16, 137.81, 138.01, 141.25, 161.43 (C=O), 178.93 (C=S). HRMS, *m/z*: 318.0676 found (calculated for $C_{16}H_{13}N_3ONaS$ $[M+Na]^+$ requires 318.0671).

*N-[(4-Fluorophenyl)carbamothioyl]-1H-indole -2- carboxamide (**6c**)*

Compound **6c** was prepared in 18% yield (350 mg) from 4-fluoroaniline **4c** (690 mg, 588 µl, 6.2 mmol) according to the standard procedure. Mp = 199-201°C. ^{1}H NMR (DMSO-d_6) δ: 7.05-7.13 (m, 1H, Ar), 7.16-7.34 (m, 4H, Ar), 7.49 (d, 1H, *J* = 8.7

Hz, Ar), 7.63-7.72 (m, 2H, Ar), 7.80 (s, 1H, Ar), 11.53 (s, 1H, NH), 11.99 (s, 1H, NH), 12.50 (s, 1H, NH). ^{13}C NMR (DMSO-d_6) δ: 108.52, 109.69, 112.58, 114.94, 120.38, 122.46, 125.25, 126.75, 126.95, 127.06, 131.29, 132.12, 132.24, 137.81, 161.35 (C=O), 179.52 (C=S). HRMS, *m/z*: 336.0590 found (calculated for $C_{16}H_{12}N_3O^{19}FNaS$ $[M+Na]^+$ requires 336.0577).

*N-[(3-Fluorophenyl)carbamothioyl]- 1H-indole-2-carboxamide **(6d)***

Compound **6d** was prepared in 75% yield (1.46 g) from 3-fluoroaniline **4d** (690 mg, 595 µl, 6.2 mmol) according to the standard procedure. Mp = 202-203°C. ^{1}H NMR (DMSO-d_6) δ: 7.15 (dd, 1H, *J* = 7.4, 1.1 Hz, Ar), 7.22 (d, 1H, *J* = 7.7 Hz, Ar), 7.25-7.30 (m, 1H, Ar), 7.33-7.49 (m, 3H, Ar), 7.55 (m, 1H, Ar), 7.65 (d, 1H, *J* = 7.8 Hz, Ar), 7.70 (s, 1H, Ar), 11.48 (br s, 1H, NH), 12.00 (br s, 1H, NH), 12.50 (br s, 1H, NH). ^{13}C NMR (DMSO-d_6) δ: 108.62, 109.21, 112.18, 114.75, 120.47, 122.42, 125.45, 126.72, 126.98, 127.00, 131.20, 132.05, 132.21, 137.74, 161.35 (C=O), 179.42 (C=S). HRMS, *m/z*: 336.0584 found (calculated for $C_{16}H_{12}N_3O^{19}FNaS$ $[M+Na]^+$ requires 336.0576).

*N-(Phenylmethylcarbamothioyl)-1H-indole-2-carboxamide **(6e)***

Compound **6e** was prepared in 80% yield (1.53 g) from benzylamine **4e** (665 mg, 679 µl, 6.2 mmol) according to the standard procedure. Mp = 196-198°C. ^{1}H NMR (DMSO-d_6) δ: 4.63 (s, 2H, CH_2Ar), 7.12-7.22 (m, 1H, Ar), 7.29-7.38 (m, 3H, Ar), 7.42-7.52 (m, 3H, Ar), 7.73 (d, 2H, *J* = 7.8 Hz, Ar), 7.80 (s, 1H, Ar), 11.58 (br s, 1H, NH), 11.94 (br s, 1H, NH), 12.60 (br s, 1H, NH). ^{13}C NMR (DMSO-d_6) δ: 55.32 (CH_2), 108.52, 112.58, 120.28, 122.66, 124.49, 125.24, 126.09, 126.71, 127.62, 128.64, 131.01, 137.42, 138.11, 141.21, 161.12 (C=O), 178.02 (C=S). HRMS, *m/z*: 332.0941 found (calculated for $C_{17}H_{15}N_3ONaS$ $[M+Na]^+$ requires 332.0936).

*N-(Morpholine-4-carbothioyl)-1H-indole-2-carboxamide **(6f)***

Compound **6f** was prepared in 78% yield (1.40 g) from morpholine **5a** (541 mg, 546 µl, 6.2 mmol) according to the standard procedure. Mp = 180-182°C. ^{1}H NMR (DMSO-d_6) □: 3.75 (s, 4H, CH_2), 3.72 (s, 4H, CH_2), 7.32 (d, 1H, *J* = 7.7 Hz, Ar), 7.35-7.43 (m, 2H, Ar), 7.68 (d, 1H, *J* = 7.8 Hz, Ar), 7.80 (s, 1H, Ar), 11.50 (br s, 1H, NH), 12.52 (br s, 1H, NH). HRMS, *m/z*: 312.3430 found (calculated for $C_{14}H_{15}N_3O_2NaS$ $[M+Na]^+$ requires 312.3426).

*N-[(4-Methylpiperazine)-4-carbothioyl]-1H-indole-2-carboxamide **(6g)***

Compound **6g** was prepared in 75% yield (1.41 g) from 4-methylpiperazine **5b** (628 mg, 695 µl, 6.2 mmol) according to the standard procedure. Mp = 190-192°C. ^{1}H NMR (DMSO-d_6) δ: 2.72 (s, 3H, Me), 3.75 (t, 4H, CH_2), 3.98 (t, 4H, CH_2), 7.30 (d, 1H, *J* = 7.7 Hz, Ar), 7.45-7.53 (m, 2H, Ar), 7.60 (d, 1H, *J* = 7.8 Hz, Ar), 7.75 (s, 1H, Ar), 11.42 (br s, 1H, NH), 12.42 (br s, 1H, NH). HRMS, *m/z*: 325.3846 found (calculated for $C_{15}H_{18}N_4ONaS$ $[M+Na]^+$ requires 325.3844).

*Standard procedure for the synthesis of methylsulfanyl derivatives **7(a-g).***

To a solution of compound **6** (1.81 mmol) in acetone p.a. (5 ml) mixed in a 50 ml round-bottomed flask provided with a magnetic stirrer and a condenser, was added successively methyl iodide MeI (770 mg, 335 µl, 5.43 mmol, 3 equiv) and anhydrous potassium carbonate K_2CO_3 (250 mg, 1.81 mmol). This reaction mixture was heated at 56°C in oil bath during 60 min. under vigorous magnetic stirring. After cooling down to room temperature, 35 ml of deionized water was poured in the reaction mixture, then the resulting suspension was stored in a refrigerator (4°C) during 12 hr. The crystallized compound **7** was collected by filtration on a Buchner funnel (porosity N°4) and was dried under high vacuum (10^{-2} Torr) at 25°C for 1 hr. The product **7** was further used without purification.

*N-[(4-Methylphenylamino)methylsulfanyl -methylene]-1H-indole-2-carboxamide **(7a)***

Compound **7a** was prepared in 66% yield (386 mg) from *N*-(4-methylphenylcarbamothioyl)-1*H*-indole-2-carboxamide **6a** (560 mg, 1.81 mmol) according to the standard procedure. Mp = 152-154°C. Yellowish Powder. ^{1}H NMR (DMSO-d_6) δ: 2.32 (s, 3H, Me_{Ar}), 2.52 (s, 3H, SMe), 6.97-7.06 (m, 1H, Ar), 7.12 (s, 1H, Ar), 7.17-7.26 (m, 3H, Ar), 7.37 (d, 2H, *J* = 8.0 Hz, Ar), 7.45 (d, 1H, *J* = 8.3 Hz, Ar), 7.63 (d, 1H, *J* = 7.8 Hz, Ar), 11.17 (br s, 1H, NH), 11.51 (br s, 1H, NH). ^{13}C NMR (DMSO-d_6) δ: 14.27 (Me_{Ar}), 20.55 (SMe), 106.99, 112.46, 119.73, 121.87, 123.93, 124.68, 129.43, 127.14, 134.92, 135.17, 135.89, 137.35, 160.02 (C=O). HRMS, *m/z*: 346.0988 found (calculated for $C_{18}H_{17}N_3ONaS$ $[M+Na]^+$ requires 346.0984).

*N-[(Phenylamino)methylsulfanyl- methylene]- 1H-indole-2-carboxamide **(7b)***

Compound **7b** was prepared in 52% yield (291 mg) from *N*-(phenylcarbamothioyl)-1*H*-indole-2-carboxamide **6b** (534 mg, 1.81 mmol) according to the standard procedure. Mp = 150-152°C. Yellowish Powder. ^{1}H NMR (DMSO-d_6) δ: 2.52 (s, 3H, SMe), 6.98-7.14 (m, 2H, Ar), 7.18-7.30 (m, 3H, Ar), 7.37-7.46 (m, 3H, Ar), 7.52 (d, 2H, *J* = 8.0 Hz, Ar), 11.03 (br s, 1H, NH), 11.54 (br s, 1H, NH). ^{13}C NMR (DMSO-d_6) δ: 22.63 (SMe), 100.23, 106.99, 112.46, 119.81, 121.78, 123.91, 124.68, 127.18, 129.43, 134.90, 135.21, 135.96, 137.35, 160.02 (C=O). HRMS, *m/z*: 332.0833 found (calculated for $C_{17}H_{15}N_3ONaS$ $[M+Na]^+$ requires 332.0828).

*N-[(4-Fluorophenylamino)methylsulfanyl-methylene]-1H-indole-2-carboxamide **(7c)***

Compound **7c** was prepared in 69% yield (409 mg) from *N*-[(4-fluorophenyl)carbamothioyl]-1*H*-indole-2-carboxamide **6c** (567 mg, 1.81 mmol) according to the standard procedure. Mp = 148-150°C. Yellowish Powder. ^{1}H NMR (DMSO-d_6) δ: 2.52 (s, 3H, SMe), 7.41-7.50 (m, 2H, Ar), 7.54 (d, 2H, *J* = 6.2 Hz, Ar), 7.62 (d, 2H, *J* = 7.7 Hz, Ar), 7.77-7.84 (m, 2H, Ar), 7.98 (d, 1H, *J*

= 7.6 Hz, Ar), 10.90 (br s, 1H, NH), 11.54 (br s, 1H, NH). ^{13}C NMR (DMSO-d_6) δ: 32.77 (SMe), 106.26, 115.49, 115.79, 121.91, 123.99, 131.79, 132.89, 133.01, 134.81, 135.05, 137.36, 160,08 (C=O). HRMS, *m/z*: 350.0736 found (calculated for $C_{17}H_{14}N_3O^{19}FNaS$ $[M+Na]^+$ requires 350.0733).

*N-[(3-Fluorophenylamino) methylsulfanyl-methylene]-1H-indole-2-carboxamide (**7d**)*

Compound **7d** was prepared in 62% yield (367 mg) from *N*-[(3-fluorophenyl)carbamothioyl]-1*H*-indole-2-carboxamide **6d** (567 mg, 1.81 mmol) according to the standard procedure. Mp = 149-151°C. Yellowish Powder. ^{1}H NMR (DMSO-d_6) δ: 2.53 (s, 3H, SMe), 7.02 (s, 1H, Ar), 7.10-7.37 (m, 6H, Ar), 7.45 (d, 1H, *J* = 8.3 Hz, Ar), 7.63 (d, 1H, *J* = 7.8 Hz, Ar), 11.03 (br s, 1H, NH), 11.55 (br s, 1H, NH). ^{13}C NMR (DMSO-d_6) δ: 22.61 (SMe), 100.30, 106.99, 112.36, 119.84, 121.68, 123.86, 124.10, 127.11, 129.43, 134.90, 135.18, 135.95, 137.45, 160.05 (C=O). HRMS, *m/z*: 350.0738 found (calculated for $C_{17}H_{14}N_3O^{19}FNaS$ $[M+Na]^+$ requires 350.0733).

*N-[(Phenylmethylamino)methylsulfanyl-methylene]-1H-indole-2-carboxamide (**7e**)*

Compound **7e** was prepared in 65% yield (380 mg) from *N*-(phenylmethylcarbamothioyl)-1*H*-indole-2-carboxamide **6e** (560 mg, 1.81 mmol) according to the standard procedure. Mp = 152-154°C. Yellowish Powder. ^{1}H NMR (DMSO-d_6) δ: 2.52 (s, 3H, SMe), 4.60 (s, 2H, CH_2Ar), 7.00-7.08 (m, 2H, Ar), 7.16-7.25 (m, 3H, Ar), 7.35-7.42 (m, 3H, Ar), 7.50 (d, 2H, *J* = 8.0 Hz, Ar), 11.05 (br s, 1H, NH), 11.62 (br s, 1H, NH). ^{13}C NMR (DMSO-d_6) δ: 24.63 (SMe), 52.22 (CH_2Ar), 100.34 , 106.99, 112.32, 119.87, 121.68, 123.85, 124.10, 127.11, 129.43, 134.90, 135.14, 135.95, 137.45, 160.12 (C=O). HRMS, *m/z*: 346.0990 found (calculated for $C_{18}H_{17}N_3ONaS$ $[M+Na]^+$ requires 346.0984).

*Methyl N-(1H-indol-2-carbonyl)morpholine-4 -carboximidothioate (**7f**)*

Compound **7f** was prepared in 59% yield (324 mg) from *N*-(morpholine-4-carbothioyl)-1*H*-indole-2-carboxamide **6f** (522 mg, 1.81 mmol) according to the standard procedure. Mp = 158-160°C. Yellowish Powder. ^{1}H NMR (DMSO-d_6) δ: 2.33 (s, 3H, SMe), 3.70 (s, 8H, CH_2), 6.94 (s, 1H, Ar), 7.01 (dd, 1H, *J* = 11.0, 3.9 Hz, Ar), 7.12-7.19 (m, 1H, Ar), 7.41 (d, 1H, *J* = 8.2 Hz, Ar), 7.58 (d, 1H, *J* = 7.9 Hz, Ar), 11.45 (br s, 1H, NH). HRMS, *m/z*: 326.0941 found (calculated for $C_{15}H_{17}N_3O_2NaS$ $[M+Na]^+$ requires 326.0939).

*Methyl N-(1H-indol-2-carbonyl)- 4-methylpiperazine-1-carboximidothioate (**7g**)*

Compound **7g** was prepared in 64% yield (367 mg) from *N*-[(4-methylpiperazine)-4-carbothioyl]-1*H*-indole-2-carboxamide **6g** (547 mg, 1.81 mmol) according to the standard procedure. Mp = 162-164°C. Yellowish Powder. ^{1}H NMR (DMSO-d_6) δ: 1.69 (s, 3H, MeN), 3.28 (s, 3H, SMe), 3.61-3.71 (m, 4H, Ar), 4.23-4.34 (m, 4H, Ar), 6.97 (s, 1H, Ar), 7.19-7.43 (m, 2H, Ar), 7.45-7.57 (m, 1H, Ar), 7.75 (d, 1H, *J* = 8.0 Hz, Ar), 10.16 (br s, 1H, NH). HRMS, *m/z*: 339.1260 found (calculated for $C_{16}H_{20}N_4ONaS$ $[M+Na]^+$ requires 339.1256).

*Standard procedure for the synthesis of 1-amino-imidazo[1,5-a]indol-3-one derivatives **8(a-g).***

In a 50 ml round-bottomed flask provided with a magnetic stirrer and condenser was added successively compound **7** (3 mmol), 5 ml of anhydrous dimethylformamide Me_2NCHO and lithium hydride LiH [powder, 30 mesh, 95%] (50 mg, 6.3 mmol, 2.1 equiv). The reaction mixture was stirred vigorously at room temperature under a stream of argon during 6 hr. After addition of cold deionized water (35 ml), the resulting reaction mixture was stored in a refrigerator (4°C) during 12 hr. The insoluble compound **8** was collected by filtration on a Buchner funnel (porosity N°4) and washed with deionized water (3x10 ml). The crude product **8** was purified by recrystallization in absolute ethanol and dried under high vacuum (10^{-2} Torr) at 25°C for 2 hrs that gave the desired product **8** as yellowish powder.

*1-(4-Methylphenylamino)imidazo[1,5-a]indol-3-one (**8a**)*

Compound **8a** was prepared in 32% yield (264 mg) from *N*-[(4-methylphenylamino)methylsulfanyl-methylene]-1*H* -indole-2-carboxamide **7a** (970 mg, 3 mmol) according to the standard procedure. Mp = 152-154°C. ^{1}H NMR (DMSO-d_6) δ: 2.30 (s, 3H, Me_{Ar}), 6.98 (d, 2H, *J* = 8.2 Hz, Ar), 7.17 (d, 2H, *J* = 8.1 Hz, Ar), 7.19 (s, 1H, =CH, Ar), 7.29 (dd, 1H, *J* = 7.4, 1.6 Hz, Ar), 7.49 (dd, 1H, *J* = 7.4, 1.1 Hz, 1H), 7.80 (d, 1H, *J* = 8.0 Hz, Ar), 7.99 (d, 1H, *J* = 8.2 Hz, Ar), 11.22 (br s, 1H, NH). ^{13}C NMR (DMSO-d_6) δ: 20.48 (CH_3), 103.75, 113.33, 122.04, 122.94, 123.90, 126.93, 129.57, 129.64, 131.66, 132.18, 132.76, 138.87, 143.23, 160.36 (C-3, C=O). HRMS, *m/z*: 298.0959 found (calculated for $C_{17}H_{13}N_3ONa$ $[M+Na]^+$ requires 298.0950). Anal. Calcd. for C, 74.17; H, 4.76; N, 15.26. Found: C: 74.11; H, 4.73; N, 15.24.

*1-(Phenylamino)imidazo[1,5-a]indol-3-one (**8b**)*

Compound **8b** was prepared in 34% yield (267 mg) from *N*-[(phenylamino)methylsulfany l-methylene]- 1*H*-indole-2-carboxamide **7b** (928 mg, 3 mmol) according to the standard procedure. Mp = 212-214°C. ^{1}H NMR (DMSO-d_6) δ: 7.07-7.17 (m, 3H, Ar), 7.21 (s, 1H, =CH, Ar), 7.30 (dd, 1H, *J* = 7.6, 1.4 Hz, Ar), 7.34-7.41 (m, 2H, Ar), 7.50 (dd, 1H, *J* = 7.3 Hz, Ar), 7.81 (d, 1H, *J* = 8.0 Hz, Ar), 7.99 (d, 1H, *J* = 8.1 Hz, Ar), 11.26 (br s, 1H, NH). ^{13}C NMR (DMSO-d_6) δ: 103.88, 113.32, 122.16, 122.99, 123.83, 123.94, 126.99, 129.08, 129.71, 131.69, 132.22, 145.87, 160.56 (C-3, C=O). HRMS, *m/z*: 284.0979 found (calculated for $C_{16}H_{12}N_3ONa$ $[M+Na]^+$ requires 284.0902). Anal. Calcd. for C, 73.55; H, 4.24; N, 16.08. Found: C: 73.69; H, 4.26; N, 16.11.

*1-(4-Fluorophenylamino)imidazo[1,5-a]indol-3-one (**8c**)*

Compound **8c** was prepared in 27% yield (226 mg) from *N*-[(4-fluorophenylamino)methylsulfanyl -methylene]-1*H*-indole-2-carboxamide **7c** (982 mg, 3 mmol) according to the standard

procedure. Mp = 211-213°C. ^{1}H NMR (DMSO-d_6) δ: 7.06-7.23 (m, 5H, Ar), 7.30 (dd, 1H, *J* = 7.5, 1.2 Hz, Ar), 7.49 (dd, 1H, *J* = 7.6, 1.8 Hz, Ar), 7.80 (d, 1H, *J* = 8.0 Hz, Ar), 7.97 (d, 1H, *J* = 8.2 Hz, Ar), 11.28 (br s, 1H, NH). ^{13}C NMR (DMSO-d_6) δ: 104.05, 113.32, 115.51, 115.81, 123.02, 123.64, 123.75, 123.94, 127.02, 129.65, 131.69, 132.20, 139.58, 142.38, 157.42, 160.33 (C-3, C=O). HRMS, *m/z*: 302.0703 found (calculated for $C_{16}H_{10}N_3O^{19}FNa$ $[M+Na]^+$ requires 302.0700). Anal. Calcd. for C, 68.81; H, 3.61; N, 15.05. Found: C: 68.89; H, 3.64; N, 15.09.

*1-(3-Fluorophenylamino)imidazo[1,5-a]indol-3-one (**8d**)*

Compound **8d** was prepared in 52% yield (436 mg) from *N*-[(3-fluorophenylamino)methylsulfanyl-methylene]-1*H*-indole-2-carboxamide **7d** (982 mg, 3 mmol) according to the standard procedure. Mp = 220-222°C. ^{1}H NMR (DMSO-d_6) δ: 6.88-7.00 (m, 3H, Ar), 7.23 (s, 1H, =CH, Ar), 7.26-7.44 (m, 2H, Ar), 7.50 (dd, 1H, *J* = 7.3, 1.7 Hz, Ar), 7.81 (d, 1H, *J* = 8.0 Hz, Ar), 7.96 (d, 1H, *J* = 8.2 Hz, Ar), 11.35 (br s, 1H, NH). ^{13}C NMR (DMSO-d_6) δ: 104.32, 109.19, 109.49, 110.30, 110.58, 113.30, 123.08, 123.99, 127.09, 129.69, 130.46, 131.71, 132.23, 139.95, 148.04, 160.37 (C-3, C=O). HRMS, *m/z*: 302.0704 found (calculated for $C_{16}H_{10}N_3O^{19}FNa$ $[M+Na]^+$ requires 302.0700). Anal. Calcd. for C, 68.81; H, 3.61; N, 15.05. Found: C: 68.86; H, 3.62; N, 15.07.

*1-(Phenylmethylamino)imidazo[1,5-a]indol-3-one (**8e**)*

Compound **8e** was prepared in 22% yield (181 mg) from *N*-[(phenylmethylamino)methylsulfanyl-methylene]-1*H* -indole-2-carboxamide **7e** (970 mg, 3 mmol) according to the standard procedure. Mp = 222-224°C. ^{1}H NMR (DMSO-d_6) δ: 4.66 (s, 2H, CH_2Ar), 7.13 (s, 1H, =CH, Ar), 7.19-7.31 (m, 2H, Ar), 7.32-7.53 (m, 5H, Ar), 7.76 (d, 1H, *J* = 7.7 Hz, Ar), 7.93 (d, 1H, *J* = 7.1 Hz, Ar), 11.60 (br s, 1H, NH). ^{13}C NMR (DMSO-d_6) δ: 51.48 (CH_2), 103.02, 113.13, 122.64, 123.74, 126.57, 126.70, 127.31, 128.30, 129.66, 131.54, 131.96, 139.85, 140.05, 160.33 (C-3, C=O). HRMS, *m/z*: 298.0959 found (calculated for $C_{17}H_{13}N_3ONa$ $[M+Na]^+$ requires 298.0950). Anal. Calcd. for C, 74.17; H, 4.76; N, 15.26. Found: C: 74.21; H, 4.77; N, 15.27.

Biochemistry

Protein kinase assay buffers

Buffer A: 10 mM $MgCl_2$, 1 mM EGTA, 1 mM DTT, 25 mM Tris-HCl pH 7.5, 50 µg heparin/ml.

Buffer B: 60 mM β-glycerophosphate, 15 mM *p*-nitrophenyl-phosphate, 25 mM Mops (pH 7.2), 5 mM EGTA, 15 mM $MgCl_2$, 1 mM DTT, 1 mM sodium vanadate, 1 mM phenylphosphate.

Kinase preparations and assays

Kinase activities for each enzyme were assayed in buffer A or B, with their corresponding substrates, in the presence of 15 µM ATP in a final volume of 30 µL. After 30 min incubation at 30°C, the reaction was stopped by harvesting, using a FilterMate harvester (Packard), onto P81 phosphocellulose papers (GE Healthcare) which were washed in 1% phosphoric acid. Scintillation fluid was added and the radioactivity measured in a Packard counter. Blank values were subtracted and activities calculated as pmoles of phosphate incorporated during the 30 min incubation. The activities were expressed in % of the maximal activity, i.e. in the absence of inhibitors. Controls were performed with appropriate dilutions of DMSO.

CDK5/p25 (human, recombinant) was prepared as previously described (Leclerc *et al.*, 2001). Its kinase activity was assayed in buffer B, with 1 mg histone H1/ml, in the presence of 15 µM [γ-^{33}P] ATP (3,000 Ci/mmol; 10 mCi/ml) in a final volume of 30 µl. After 30 min incubation at 30°C, 25 µl aliquots of supernatant were spotted onto 2.5 x 3 cm pieces of Whatman P81 phosphocellulose paper, and, 20 s later, the filters were washed five times (for at least 5 min each time) in a solution of 10 ml phosphoric acid/liter of water. The wet filters were counted in the presence of 1 ml ACS (Amersham) scintillation fluid.

DYRK1A (rat, recombinant, expressed in *Escherichia coli* as a GST fusion protein, provided by Dr. W. Becker) was purified by affinity chromatography on glutathione–agarose and assayed as described for CDK5/p25 using myelin basic protein (1 mg/ml) as a substrate.

Casein kinase 1 (CK1δ/ε) (porcine brain, native) was assayed with 0.67 µg of CKS peptide (RRKHAAIGpSAYSITA), a CK1 specific substrate obtained from Millegen (Labege, France) (Reinhardt *et al.*, 2007).

GSK-3 α/β (porcine brain, native) was assayed, as described for CDK5/p25 but in Buffer A and using a GSK-3 specific substrate (GS-1: YRRAAVPPSPSLSRHSSPHQSpEDEEE) (pS stands for phosphorylated serine) (Primot *et al.*, 2000). GS-1 was synthesized by Millegen (Labege, France).

CLK1 (mouse, recombinant, expressed in *Escherichia coli* as GST fusion proteins) was assayed in buffer A (+ 0.15 mg BSA /ml) with RS peptide (GRSRSRSRSRSR) (1µg/assay).

RESULTS AND DISCUSSION

For the preparation of the cyclized derivative of leucettine L41, the planned retrosynthesis of 1-aminoimidazo[1,5-*a*]indol-3-ones (Figure 2) involved firstly, a ring closure by intramolecular sulphur/nitrogen displacement; secondly, activation of the carbon sulphur double bond by classical *S*-alkylation with an halogenoalcane; thirdly, thiourea synthesis by addition of primary or secondary amine on isothiocyanate function and fourthly, nucleophilic addition of thiocyanate anion on the indole-2-carbonyl halide In order to synthesize the desired new 1-aminoimidazo[1,5-*a*]indol-3-ones **8** (Scheme 1), commercial indole-2-carboxylic acid **1** was treated successively by phosphorous trichloride (Katritzky *et al.*, 2004) under reflux at 85°C during 2 hrs followed by addition of potassium isothiocyanate in acetone at room temperature for a supplementary reaction time of 1 hr (Abu-El-Halawa *et al.*, 2008). Initial attempts to isolate the indole-2-carbonyl isothiocyanate **3** for complete caracterization by ^{1}H, ^{13}C NMR and HRMS analyses failed. This can be explained by the instability of intermediate **3** in the reaction medium during its preparation (Kutschy *et al.*, 2000).

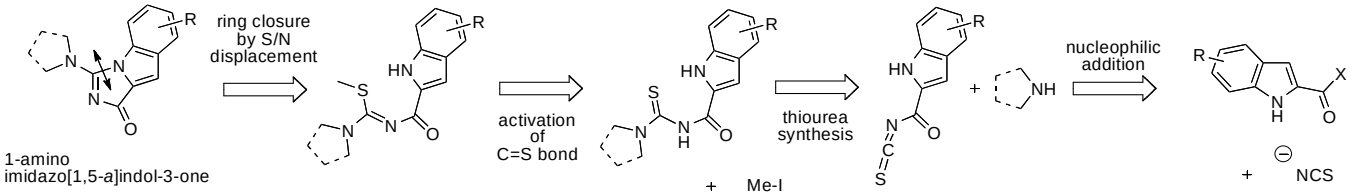
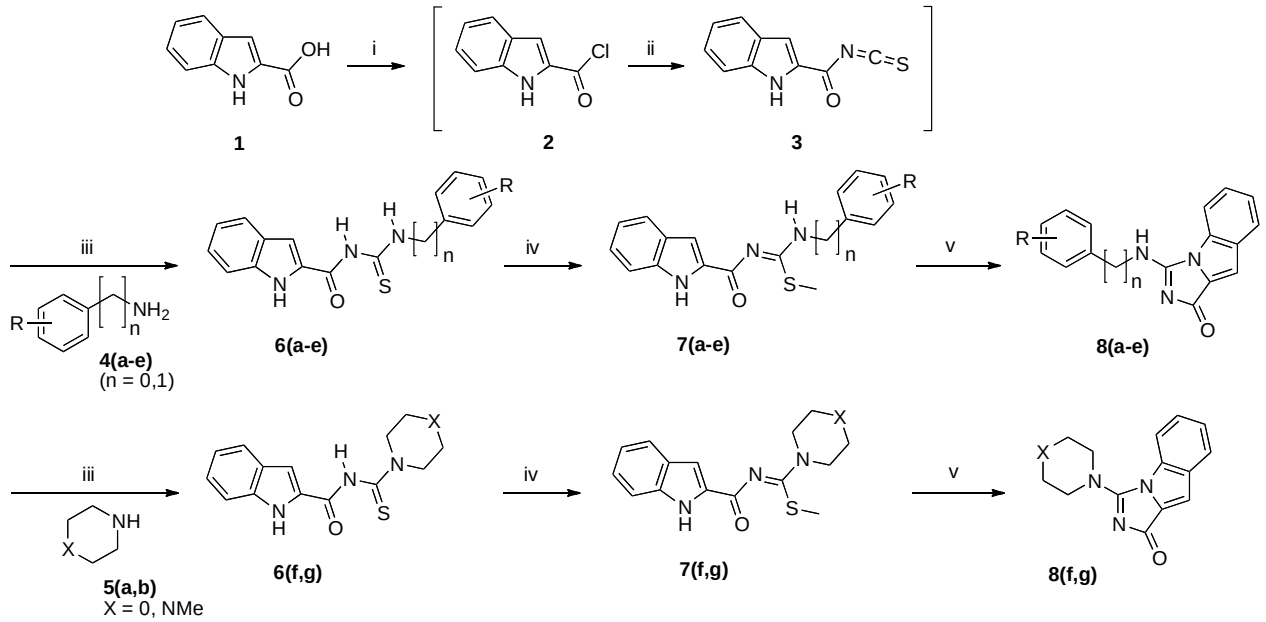


Fig. 2: Retrosynthetic strategy towards new 1-aminoimidazo[1,5-*a*]indol-3-ones



Scheme. 1: *Reagents and reaction conditions:* (i) PCl_3 2 equiv, C_6H_6, 2 hrs, 85°C. (ii) KSCN 1 equiv, acetone, 1 hr, 25°C. (iii) **4** or **5** 1 equiv, 1 hr, 25°C. (iv) MeI 3 equiv, K_2CO_3 1 equiv, acetone, 1 hr, reflux. (v) LiH 2 equiv, dry DMF, 6 hrs, 25°C.

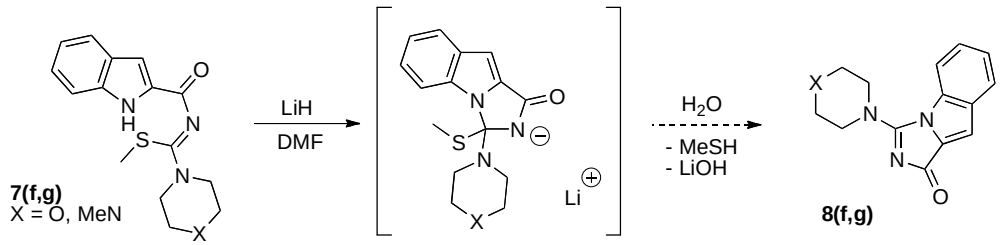


Fig. 3: Possible transient intermediate during reaction of methylsulfanyl isothioureas **7(f,g)** in the presence of lithium hydride.

To obtain the desired product *N,N'*-disubstituted thioureas **6** from indole-2-carboxylic acid **1** in a reasonable yield, we decided to avoid isolation and purification of the indole-2-carbonyl chloride **2** and indole-2-carbonyl isothiocyanate **3** intermediates due to their instability under the hydrolytic work-up conditions. With the aim of introducing diversity on the *N*-1 position of the desired 1-aminoimidazo[1,5-*a*]indol-3-ones **8**, we examined the reactivity of indole-2-carbonyl isothiocyanate **3** with five primary amines **4(a-c)** (*i.e. p*-toluidine **4a**, aniline **4b**, 4-fluoroaniline **4c**, 3-fluoroaniline **4d** and benzylamine **4e**) and two polar secondary cyclic amines **5(a,b)** (*i.e.* morpholine **5a** and *N*-methylpiperazine **5b**). The reaction of the intermediate **3** with the amines **4** and **5** afforded the corresponding thioureas **6(a-g)** as yellowish solids, which were purified by recrystallization from EtOH. As shown in Table 1, the *N,N'*-disubstituted thioureas **6** were synthesized in low to good yields (9-80%). In order to prepare the desired 1-aminoimidazo[1,5-*a*]indol-3-ones **8** by cyclization, *via* intramolecular sulphur/nitrogen displacement, it was necessary to activate the C=S bond of the *N,N'*-disubstituted thioureas **6** with a halogenoalcane. *S*-alkylation of these *N,N'*-disubstituted thioureas **6** was realized with 3 equivalents of methyl iodide in refluxed acetone in the presence of powdered potassium carbonate. Compounds **7(a-g)** were obtained in 52-69% yields. To investigate the scope and limitation of the cyclization depicted in Scheme 1, we screened the reactivity of various bases in appropriate solvent (Et_3N, pyridine, piperidine in acetonitrile, *tert*-BuOK in *tert*-BuOH, AcONa in AcOH, NaH in THF or 1,4-dioxane). No cyclization took place and starting compounds were recovered, thus indicating, that the choice of the base and the solvent was essential for successful ring closure. In fact, the lithium hydride (2 equivalents) in dry dimethylformamide mediated cyclization of compounds **7**. This cyclization proceeded

via intramolecular nucleophilic attack of the deprotonated indole nitrogen on the highly electrophilic carbon atom of the enamide bond C=N bearing the methylsulfanyl leaving group of the isothioureas **7**. The 1-aminoimidazo[1,5-*a*]indol-3-ones **8** were easily isolated after quenching the crude reaction mixture with cold deionized water and the insoluble compound **8** was collected by filtration and was recrystallized from EtOH.

As can be seen in Table 1, cyclization worked well with methylsulfanyl isothioureas **7(a-e)** derived from primary amines **4(a-e)** while, on the contrary, cyclization failed with compounds **7(f,g)** derived from cyclic secondary amines **5(a,b)** even in the presence of ten-fold excess of lithium hydride. This might be explained by the decrease of the electrophilic character on the carbon atom of the enamide C=N bond or by the bulky effect of morpholine-1-yl or *N*-methylpiperazine-1-yl moiety in the possible transient intermediate (Figure 3) which decreases the leaving character of the methylsulfanyl group.

Table. 1: Results for the preparation of compounds **6(a-g)**, **7(a-g)** and 1-amino imidazo[1,5-*a*]indol-3-one derivatives **8(a-g)**.

Compound	R	n	X	Yield[a] (%)
6a	4-Me	0	-	9
6b	H	0	-	9
6c	4-F	0	-	18
6d	3-F	0	-	75
6e	H	1	-	80
6f	-	-	O	78
6g	-	-	NMe	75
7a	4-Me	0	-	66
7b	H	0	-	52
7c	4-F	0	-	69
7d	3-F	0	-	62
7e	H	1	-	65
7f	-	-	O	59
7g	-	-	NMe	64
8a	4-Me	0	-	32
8b	H	0	-	34
8c	4-F	0	-	27
8d	3-F	0	-	52
8e	H	1	-	22
8f	-	-	O	-
8g	-	-	NMe	-

[a] Isolated yields.

As can be seen in Table 1, compounds **8(a-e)** were isolated in yields ranging from 27 to 52%. The structure identification of these five new 1-aminoimidazo[1,5-*a*]indol-3-ones **8(a-e)** were based on the ^{1}H and ^{13}C assignments and was performed extensive 1D and 2D NMR spectroscopy. Examination of the ^{1}H NMR spectra in DMSO-d_6 showed that the CH= proton of the indolyl moiety of **8(a-e)** appears at low field (7.13 ppm < δ_{indol} < 7.21 ppm).

It is interesting to note that there is only one signal for the NH proton in the ^{1}H NMR spectra of **8(a-e)** (11.22 ppm < δ_{NH} < 11.60 ppm), which strongly indicates the cyclized structure of these compounds. For the methylsulfanyl precursors **7(a-e)**, we observed two separated signals for the NH protons. As example, in the ^{1}H NMR spectrum of **7a** in DMSO-d_6, the first NH broad singulet appears at 11.17 ppm and the second shifted to 11.51 ppm. The five new 1-aminoimidazo [1,5-*a*]indol-3-ones **8(a-e)** were evaluated against five different and representative kinases. Harmine (a natural β-carboline alkaloid known to be a potent inhibitor of DYRK1A (Tahtouh *et al.*, 2012 and Göckler *et al.*, 2009)) was also used as positive control and its IC_{50} values were compared with those obtained for the compounds **8**. Results given in Table 2 demonstrated that 1-aminoimidazo[1,5-*a*]indol-3-ones **8** are inactive against DYRK1A, CK1, CDK5/p25, GSK3 α/β and CLK1, except for compound **8b** for which an IC_{50} value of 9 µM was determined.

Table 2: Effects of the 1-amino imidazo[1,5-*a*]indol-3-one derivatives **8(a-e)**.on the catalytic activity of four purified protein kinases[a].

Compound	DYRK1A	CK1	CDK5/p25	GSK3α/β	CLK1
8a	>10	>10	>10	>10	>10
8b	9	>10	>10	>10	>10
8c	>10	>10	>10	>10	>10
8d	-	-	-	-	-
8e	>10	>10	>10	>10	>10
Leucettine L41	0.040	-	-	>10	0.090
Harmine	0.029	1.5	>10	>10	0.072
(R)-Roscovitine	11	2.3	0.2	130	NT

[a]Compounds were tested at various concentrations on each kinase as described in Experimental Section. IC_{50} values, calculated from the dose-response curves, are reported in µM. -, inactive at the highest concentration tested (10 µM); >10, inhibitory but IC_{50} > 10 µM.

CONCLUSION

In summary, we worked out the synthesis in 5 steps of new 1-aminoimidazo[1,5-*a*]indol-3-ones **8(a-e)** without substituents on the indole moiety. The key step of this sequence is the ring closure by intramolecular sulphur/nitrogen displacement in basic medium with S-methylsulfanyl thioureas **7** derivatives issued from primary amines.

Among these cyclized compounds **8**, only **8b** presented modest micromolar inhibition activity on DYRK1A (IC_{50} 9 mM). Now, we are interested in further explorations for introduction of molecular diversity with appropriate groups on the indole moiety of compounds **8**, in order to increase the biological properties of these new 1-aminoimidazo[1,5-*a*]indol-3-ones with potential applications in Alzheimer's disease/Down syndrome.

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COMPETING INTERESTS

LM, JPB and FC are co-inventors on the Leucettine patent (Bazureau *et al.*, 2009). LM is founder of *ManRos Therapeutics*, which has the exclusive exploitation license for Leucettines.

REFERENCES

Abu-El-Halawa R, Sarabi A, El-Abadelah M.M. Facile synthesis of 2-(substituted amino)-4*H*-thieno[3,2-*e*]-1,3-thiazin-4-ones. Monatsh. Chem. 2008; 139: 1251-1255. doi: 10.1007/s00706-008-0920-6.

Aiello A, Fattorusso E, Imperatore C, Irace C, Luciano P, Menna M, Santamaria R, Vitalone R. Zorrimidazolone, a bioactive alkaloid from the non-indigenous mediterranean stolidobranch *Polyandrocarpa zorritensis*. Mar Drugs 2011; 9: 1157-1165. doi: doi:10.3390/md9061157.

Aranda S, Laguna A, de la Luna S. DYRK family of protein kinases: evolutionary relationships, biochemical properties, and functional roles. FASEB J. 2011; 25: 449-462. doi: 10.1096/fj.10-165837.

Bazureau JP, Carreaux F, Renault S, Meijer L, Lozach O. Imidazolone derivatives, preparation method thereof and biological use of same. Patent WO 2009/05032 A2, April 23th 2009.

Chan GW, Mong S, Hemling ME, Freyer AJ, Offen PM, De Brosse CW, Sarau HM, Westley JW. New leukotriene B4 receptor antagonist: leucettamine A and related imidazole alkaloids from the marine sponge Leucetta microraphis. J Nat Prod 1993; 56: 116-121. doi: 10.1021/np50091a016.

Chérouvrier JR, Boissel J, Carreaux F, Bazureau JP. A stereoselective route to 3-methyl-2-methylsulfanyl-5-yliden-3,4-dihydro-imidazol-4-one derivatives and precursor of Leucettamine B. Green Chem 2001; 3: 165-169. doi: 10.1039/B101928G.

Chérouvrier JR, Carreaux F, Bazureau JP. Microwave-mediated solventless synthesis of new derivatives of marine alkaloid Leucettamine B. Tetrahedron Lett 2002; 43: 3581-3584. doi: 10.1016/S0040-4039(00)00575-0.

Cimino G, de Rosa S, de Stefano S, Mazzarella L, Puliti R, Sodano G. Isolation & X-ray crystal structure of a novel bromo-compound from two marine sponges. Tetrahedron Lett 1982; 23: 767-768. doi: 10.1016/S0040-4020(96)01153-2.

Debdab M, Carreaux F, Renault S, Soundararajan M, Fedorov O, Filippakopoulos P, Lozach O, Babault L, Tahtouh T, Baratte B, Ogawa Y, Hagiwara M, Eisenreich A, Rauch U, Knapp S, Meijer L, Bazureau JP. Design, synthesis and biological evaluation of leucettines, a class of potent CLK and DYRK kinases inhibitors derived from the marine sponge leucettamine B. Modulation of alternative RNA splicing. J Med Chem 2011; 54: 4172-4186. doi: 10.1021/jm200274d.

Debdab M, Renault S, Eid S, Lozach O, Meijer L, Carreaux F, Bazureau JP. An efficient method for the preparation of new analogs of leucettamine B under solvent-free microwave irradiation. Heterocycles 2009; 78: 1191-1203. doi: 10.3987/COM-08-11594.

Göckler N, Jofre G, Papadopoulous C, Soppa U, Tejedor FJ, Becker W. Harmine specifically inhibits protein kinase DYRK1A and interferes with neurite formation. FEBS J 2009; 276: 6324-37. doi: 10.1111/*j*.1742-4658.2009.07346.x.

Hagiwara M. Alternative splicing: a new drug target of the post-genome era. Biochim Biophys Acta 2005; 1754: 324-331. doi: 10.1016/j.chembiol.2010.11.009.

Katritzky AR, Singh SK, Bobrov S. Novel synthesis of bicycles with fused pyrrole, indole, oxazole, and imidazole rings. J Org Chem 2004; 69: 9313-9315. doi: 10.1021/jo0485334.

Kutschy P, Suchy M, Dzuriulla M, Takasugu M, Kovacik V. A new approach to imidazo[1,5-a]indole derivatives. Collect Czech Chem Commun 2000; 65: 1163-1172. doi: 10.1135/cccc20001163.

Leclerc S, Garnier M, Hoessel R, Marko D, Bibb JA, Snyder GL, Greengard P, Biernat J, Mandelkow EM, Eisenbrand G, Meijer L. Indirubins inhibit glycogen synthase kinase-3 beta and CDK5/p25, two protein kinases involved in abnormal tau phosphorylation in Alzheimer's disease. A property common to most cyclin-dependent kinase inhibitors? J Biol Chem 2001; 276: 251-260. doi: 10.1074/jbc.M002466200.

Meijer L, Thunnissen AMWH, White A, Garnier M, Nikolic M, Tsai LH, Walter J, Cleverley KE, Salinas PC, Wu YZ, Biernat J, Mandelkow EM, Kim SH, Pettit GR. Inhibition of cyclin-dependent kinases, GSK-3β and casein kinase 1 by hymenialdisine, a marine sponge constituent. Chem Biol 2000; 7: 51-63. doi: 10.1016/S1074-5521(00)00063-6.

Molina P, Almendros P, Fresneda PM. An iminophosphorane-mediated efficient synthesis of the alkaloid leucettamine B of marine of origin. Tetrahedron Lett. 1994; 35: 2235-2236. doi: 10.1016/S0040-4039(00)76806-7.

Papeo G, Posteri H, Borghi D, Varasi M. A new glycociamidine ring precursor: syntheses of (Z)-hymenialdisine, (Z)-2-debromohymenialdisine, and (±)-endo-2-debromohymenialdisine. Org Lett 2005; 7: 5641-5644. doi: 10.1021/ol052266m.

Primot A, Baratte B, Gompel M, Borgne A, Liabeuf S, Romette JL, Costantini F, Meijer L. Purification of GSK-3 by affinity chromatography on immobilised axin. Protein Expr & Purif 2000; 20: 394-404. doi: 10.1006/prep.2000.132.

Reinhardt J, Ferandin Y, Meijer L. Purification CK1 by affinity chromatography on immobilised axin. Protein Expr & Purif 2007; 54:101-109. doi: 10.1016/j.pep.2007.02.020.

Roué N, Bergman J. Synthesis of the marine alkaloid leucettamine B. Tetrahedron 1999; 55: 14729-14738. doi: 10.1016/S0040-4020(99)00918-7.

Tahtouh T, Elkins JM, Filippakopoulos P, Soundararajan M, Burgy G, Durieu E, Cochet C, Schmid RS, Lo DC, Delhommel F, Oberholzer AE, Pearl LH, Carreaux F, Bazureau JP, Knapp S, Meijer L. Selectivity, cocrystal structures, and neuroprotective properties of Leucettines, a family of protein kinase inhibitors derived from the marine sponge alkaloid Leucettamine B. J Med Chem 2012; 55: 9312-9330. doi: 10.1021/jm301034u.

Wan Y, Hur W, Cho CY, Liu Y, Adrian FJ, Lozach O, Bach S, Mayer T, Fabbro D, Meijer L, Gray NS. Synthesis and target identification of hymenialdisine analogs. Chem. Biol 2004; 11: 247-259. doi: doi: 10.1016/j.chem biol.2004.01.015.

Xu YY, Yakushijin K, Horne DA. Synthesis of C(11)N(5) Marine sponge alkaloids: (±)-hymenin, stevensine, hymenialdisine, and debro- mohymenialdisine. J Org Chem 1997; 62: 456-464. doi: 10.1021/jo9619746.

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