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A biomimetic synthesis of coelenterazine analogs

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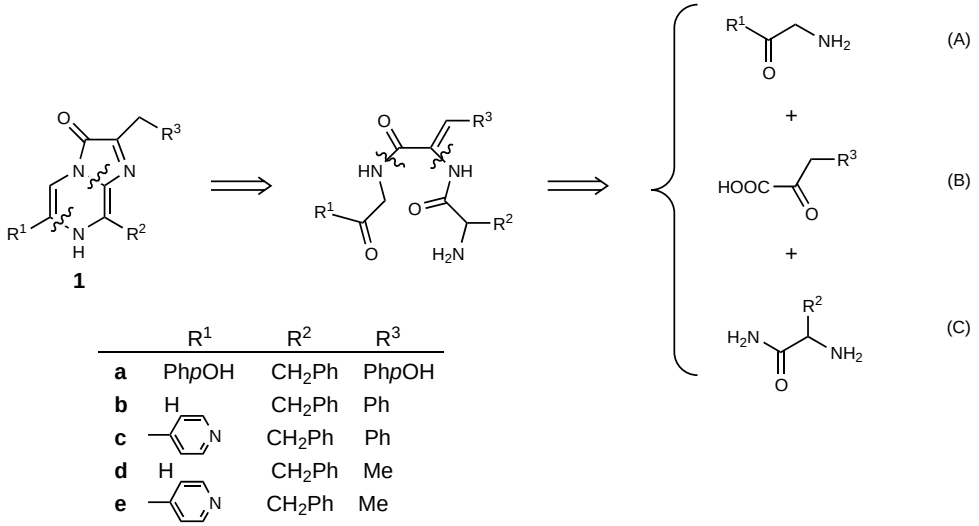
Abstract—*N*-(Trifluoroacetyl)dehydrodipeptides **2**–**3** were coupled to aminomethylene dimethylacetal derivatives **4**–**5**. The resulting pseudo-tripeptides **6** were stepwise deprotected (carbonyl function (**7**) then amine function) and in situ cyclized into imidazolopyrazines **1**. © 2002 Elsevier Science Ltd. All rights reserved.

Coelenterazine **1a** (luciferin) is an imidazopyrazine derivative involved in the luminescence reactions of various marine organisms.[1] Recently, we demonstrated that **1a** and related compounds (Scheme 1) show high antioxidative properties in cells submitted to oxidative stress induced by reactive oxygen species (ROS).[2] This led us to consider imidazopyrazine bicyclic systems as potential lead structures in medicinal chemistry for the discovery of new antioxidants.[3]

Accordingly, we examined different synthetic strategies for the construction of such molecules. The major methods reported in the literature were based on the formation of the imidazole ring by cyclization of adequately substituted pyrazines or by reaction of bifunctional reagents with 2-aminopyrazines.[4] This strategy was very fully applied to the synthesis of coelenterazine **1a** and other luciferins.[5]

A biomimetic approach towards luciferin models had been proposed 30 years ago,[6] but remained unexploited until now. Recent publications on the biosynthesis of the GFPs (green fluorescent proteins) chromophore[7] stimulated our interest in the preparation of com-



	R^1	R^2	R^3
a	Ph*p*OH	CH_2Ph	Ph*p*OH
b	H	CH_2Ph	Ph
c		CH_2Ph	Ph
d	H	CH_2Ph	Me
e		CH_2Ph	Me

Scheme 1.

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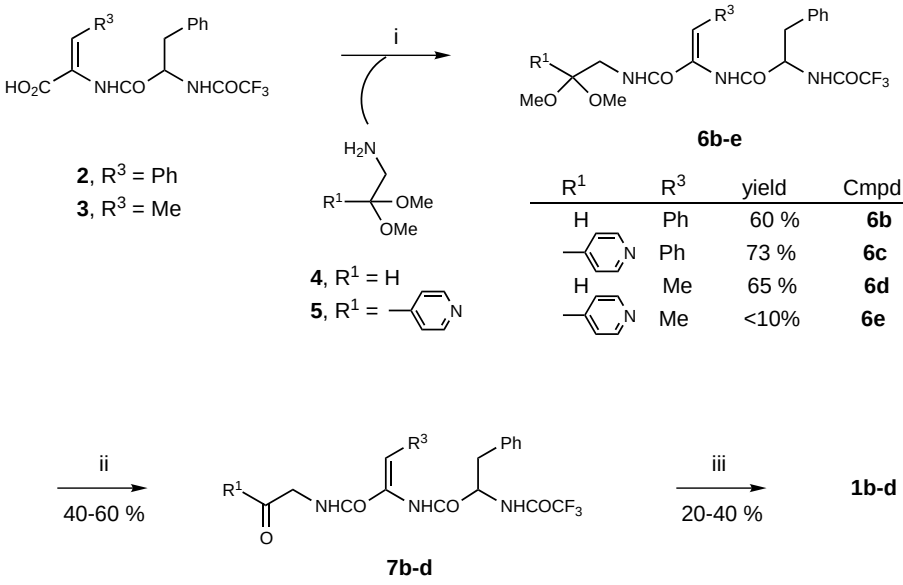
pounds **1** from dehydropeptide precursors via a double intramolecular dehydration (Scheme 1): the building blocks of this strategy are β-aminoketone A (or protected synthetic equivalent) on the one hand, and pyruvic derivative B and α-aminoamide C on the other hand, which condensation gives dehydrodipeptide compounds[8] (**2**–**3** for instance, see Scheme 2). In applying this scheme, we were interested in the modification of substituents R^1 and R^3 of the natural coelenterazine (**1a**), and particularly in the introduction of a pyridyl substituent in position R^1 as a potential bioisosteric group of phenol.

Dehydrodipeptide **2** (α,β-dehydro-*N*-[*N*-(trifluoroacetyl)-1-phenylalanyl]-phenylalanine; Scheme 2) was prepared according to known procedures. Briefly, *N*-(Boc)-(*S*)-phenylalaninamide[9] was deprotected with trifluoroacetic acid and then acylated with trifluoroacetic anhydride to furnish *N*-(trifluoroacetyl)-phenylalalinamide[10] which was condensed with phenylpyruvic acid.[11a] The reactivity of the conjugated acid **2** was first tested with benzylamine: the corresponding benzylamide was isolated in 80% yield by using diisopropylcarbodiimide/hydroxybenzotriazole (HOBT) as activating agent. Similar reaction with α-aminoacetophenone hydrochloride failed, whatever the coupling conditions used: peptide **7** ($R_1 = R_3 = Ph$) was not formed because dimerization of α-aminoacetophenone occurred more rapidly. Therefore, we envisaged the use of 2-hydroxyphenethylamine as synthetic equivalent of α-aminoacetophenone. The coupling product with **2** could indeed be obtained (73% yield), but the subsequent oxidation of the alcohol intermediate into **7** ($R_1 = R_3 = Ph$) failed (tested conditions: MnO_2, $KMnO_4$, CAN, $RuCl_3$, Swern, Dess–Martin). At this stage, we turned to acetal derivatives **6** as precursors of **7** (Scheme 2). Reaction of **2** with aminoacetaldehyde dimethyl acetal (**4**) (commercially available compound) was performed in the presence of *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide (WSC) and *N*-hydroxybenzotriazole (HOBT) to yield **6b**[12] (*N*-2,2-dimethoxyethyl α,β-dehydro-*N*-[*N*-(trifluoroacetyl)-1-phenylalanyl]-phenylalaninamide). The *Z*-configuration of the C=C double bond was unambiguously confirmed by X-ray diffraction analysis of a monocrystal of **6b**. The corresponding pyridyl derivative **6c**[12] (*N*-2-pyridyl-2,2-dimethoxyethyl α,β-dehydro-*N*-[*N*-(trifluoroacetyl)-1-phenylalanyl]-phenylalaninamide) was similarly prepared from **2** and 2,2-dimethoxy-2-(4-pyridyl)-ethylamine (**5**) obtained via the Neber rearrangement of 4-acetylpyridine (*E*)-oxime tosylate.[13]

Deprotection of the carbonyl function was realized, in moderated yield, by treatment with trimethylsilylbromide (for **6b**) or trimethylsilyliodide generated in situ[14] (for **6c**). The resulting compounds **7b**–**c**[15] were next treated under smooth basic conditions allowing trifluoroacetamide deprotection and subsequent intramolecular cyclization as controlled by HPLC analysis of the crude mixtures. Imidazopyrazines **1b**–**c**[16] were isolated, in modest yield, after acidification and precipitation of the corresponding hydrochloride salts. Aromatic protons, typical of the pyrazine moiety, appeared in ^1H NMR at 8.37 δ and 8.50 δ for **1b** and 8.20 δ for **1c**. The characteristic UV pattern of colenterazine derivatives was recorded.[17]

Starting from dehydrodipeptide **3**[11b] (α,β-dehydro-*N*-[*N* - (trifluoroacetyl) - 1 - phenylalanyl] - methylalanine; Scheme 2), we similarly obtained intermediate **6d**[12] by coupling with aminoacetaldehyde dimethylacetal (**4**). Unfortunately, the same reaction performed with the corresponding pyridyl derivative **5** led to a very low yield of precursor **6e**, which could not be purified by column chromatography. Other methods of peptide coupling were tested without success. Unmasking the



R^1	R^3	yield	Cmpd
H	Ph	60 %	**6b**
N	Ph	73 %	**6c**
H	Me	65 %	**6d**
N	Me	<10%	**6e**

Scheme 2. *Reagents and conditions*: (i) WSC, HOBT, Et_3N, THF, 17 h, 20°C; (ii) TMSBr, $CHCl_3$, 20°C, 6 h or TMSI, $CHCl_3$, 50°C, 8 h; (iii) K_2CO_3, CH_3CN–H_2O (10:1), 10^{-3} M solution of precursor, reflux, 4 h then aqueous HCl.

carbonyl function of **6d** as usual (compound **7d**[15]) followed by basic treatment and acidification gave imidazopyrazine **1d**[16] in modest yield (Scheme 2). The typical pattern of the ethyl substituent was visible in ^{1}H NMR (t at 1.18 δ and q at 3.61 δ). The required mass was observed in APCI (atmospheric pressure chemical ionization).

We could not improve the synthesis of compounds **1** by varying the final cyclization conditions. Changing the sequence of reactions, i.e. amine deprotection and subsequent cyclization in acidic medium, furnished untractable mixtures. Thus, our attempt to develop a convergent biomimetic synthesis of pyridyl-substituted luciferin derivatives was somewhat disappointing: only compound **1c** has been prepared on a small scale. In our opinion, the classical approach towards imidazopyrazines making use of pre-formed 1,4-pyrazine heterocycles remains the best route.[18]

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12. **Compounds 6b–d**: **General procedure**:
To a solution of α,β-dehydro-*N*-[*N*-(trifluoroacetyl)-1-phenylalanyl]-phenylalanine (1.00 g, 2.46 mmol, 1 equiv.) in THF (20 mL) were added: triethylamine (342 μL, 2.5 mmol, 1.01 equiv.), aminoacetaldehyde dimethylacetal (273 μL, 2.5 mmol, 1.01 equiv.) and hydroxybenzotriazole (339 mg, 2.5 mmol, 1.01 equiv.). The mixture was stirred at 0°C and *N*-(3-dimethylaminopropyl)-*N′*-ethylcarbodiimide (472 mg, 2.46 mmol, 1 equiv.) was added. Then, the mixture was stirred at room temperature during the night. The precipitate was filtered and the filtrate was evaporated under vacuo. The residue was diluted in CH_2Cl_2 (50 mL), washed with a solution of 0.1N HCl (3×15 mL), brine (15 mL) and then dried over $MgSO_4$ and concentrated under vacuo. Column chromatography on silica gel (CH_2Cl_2/AcOEt: 75/25) gave compound **6b** (0.70 g, 59% yield).
Compound **6b**: white solid; mp 61.5–62.5°C; R_f 0.25 (SiO_2; CH_2Cl_2–EtOAc, 75:25); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.94 (dd, J=13.7 Hz, 5.6 Hz, 1H), 3.18 (dd, J=13.7 Hz, 8.2 Hz, 1H), 3.30 (s, 6H), 3.34 (dd, J=5.8 Hz, 5.2 Hz, 2H), 4.37 (t, J=5.2 Hz, 1H), 4.82 (ddd, J=8.2 Hz, 8.0 Hz, 5.6 Hz, 1H), 6.69 (t, J=5.8 Hz, NH), 6.88 (s, 1H), 7.12–7.20 (m, 10H), 7.85 (d, J=8.0 Hz, NH), 8.76 (s, NH); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 36.9, 41.2, 53.8, 53.9, 54.8, 102.0, 115.4, 127.1, 127.8, 128.5, 128.6, 129.0, 129.1, 129.3, 132.8, 135.2, 157.2, 165.9, 169.3. Anal. calcd for $C_{24}H_{26}F_3N_3O_5$ (493.48): C, 58.41; H, 5.31; N, 8.52%. Found: C, 57.99; H, 5.29; N, 8.4%.
Compound **6c**: white solid; mp 96–97.5°C; R_f 0.21 (SiO_2; CH_2Cl_2–EtOAc, 60:40); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.87 (dd, J=13.9 Hz, 8.4 Hz, 1H), 3.06 (dd, J=13.9 Hz, 7.7 Hz, 1H), 3.21 (s, 6H), 3.68 (dd, J=14.1 Hz, 5.4 Hz, 1H), 3.81 (dd, J=14.1 Hz, 6.3 Hz, 1H), 4.74 (ddd, J=8.4 Hz, 7.7 Hz, 7.0 Hz, 1H), 6.42 (dd, J=6.3 Hz, 5.4 Hz, NH), 6.67 (s, 1H), 6.97–7.19 (m, 10H), 7.45 (d, J=6.1 Hz, 2H), 8.06 (d, J=7.0 Hz, NH), 8.39 (d, J=6.1 Hz, 2H), 9.05 (s, NH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 37.1, 43.7, 49.3, 49.4, 55.1, 101.0, 114.3, 122.8, 127.4, 128.0, 128.1, 128.7, 128.8, 129.1, 129.6, 132.8, 135.1, 148.4, 149.6, 157.6, 165.0, 169.3. Anal calcd for $C_{29}H_{29}F_3N_4O_5$ (570.56): C, 61.05; H, 5.12; N, 9.82%. Found: C, 61.46; H, 5.46; N, 9.56%.
Compound **6d**: colorless oil; R_f 0.21 (SiO_2; CH_2Cl_2–EtOAc, 60:40); ^{1}H NMR (acetone-d_3, 500 MHz) δ 1.53 (d, J=7.2 Hz, 3H), 3.14 (dd, J=13.7 Hz, 5.3 Hz, 1H), 3.28 (dd, J=5.5 Hz, 2.4 Hz, 2H), 3.30 (s, 6H), 3.34 (dd, J=13.7 Hz, 6.4 Hz, 1H), 4.39 (t, J=5.5 Hz, 1H), 4.88 (ddd, J=6.8 Hz, 6.4 Hz, 5.3 Hz, 1H), 6.54 (q, J=7.2 Hz, 1H), 6.99 (t, J=2.4 Hz, NH), 7.24 (m, 1H), 7.31 (m, 2H), 7.35 (m, 2H), 8.75 (s, NH), 8.75 (d, J=6.8 Hz, NH); ^{13}C NMR (acetone-d_3, 500 MHz) δ 13.3, 38.0, 42.0, 53.7, 54.0, 56.4, 103.2, 116.8, 127.7, 129.3, 130.2, 130.3, 131.1, 137.6, 157.8, 164.8, 169.5; MS (APCI) m/z=431.2 (M, 15%), 430.2 (M–1, 100%), ($C_{19}H_{24}F_3N_3O_5$).
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15. **Compounds 7b–d**: **General procedure**:
To a solution of compound **6b** (100 mg, 0.2 mmol, 1 equiv.) in $CHCl_3$ (1 mL) was added trimethylsilyl bromide (160 mg, 1.01 mmol, 5 equiv.). The mixture was stirred for 6 h at room temperature and then hydrolyzed with H_2O (0.5 mL) and diluted with $CHCl_3$ (10 mL). The organic phase was washed with H_2O (3×2 mL), dried over $MgSO_4$ and concentrated under vacuo. Column chromatography on silica gel (CH_2Cl_2–AcOEt, 60:40) gave compound **7b** (51 mg, 55% yield).
Compound **7b**: yellow solid; mp 83.4–85.2°C; R_f 0.22 (SiO_2; CH_2Cl_2–EtOAc, 60:40); ^1H NMR ($CDCl_3$, 500 MHz) δ 3.06 (dd, $J=13.4$ Hz, 5.6 Hz, 1H), 3.20 (dd, $J=13.4$ Hz, 8.2 Hz, 1H), 4.13 (d, $J=5.8$ Hz, 2H), 4.82 (ddd, $J=8.2$ Hz, 8.0 Hz, 5.6 Hz, 1H), 6.74 (t, $J=5.8$ Hz, NH), 7.12 (s, 1H), 7.16–7.33 (m, 10H), 7.40 (d, $J=8.0$ Hz, NH), 7.99 (s, NH), 9.54 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 37.2, 50.3, 54.8, 115.4, 127.4, 128.7, 128.8, 129.1, 129.2, 129.4, 131.1, 132.7, 135.0, 157.5, 165.6, 169.3, 196.9; MS (FAB$^+$) m/z 448 ($C_{22}H_{20}F_3N_3O_4$).
Compound **7c**: yellow foam; R_f 0.27 (SiO_2; CH_2Cl_2–EtOAc, 30:70); ^1H NMR ($CDCl_3$, 300 MHz) δ 2.95–3.30 (m, 2H), 4.72 (d, $J=5.2$ Hz, 2H), 4.92 (dd, $J=8.0$ Hz, 7.0 Hz, 1H), 7.0–7.3 (m, 13H), 7.64 (d, $J=5.9$ Hz, 2H), 8.49 (s, NH), 8.78 (d, $J=5.9$ Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 37.4, 47.1, 54.8, 115.9, 120.7, 127.5, 128.8, 128.9, 129.1, 129.2, 129.4, 132.7, 135.1, 140.1, 150.8, 151.1, 165.4, 169.3, 194.1; MS (FAB$^+$) m/z 525 ($C_{27}H_{23}F_3N_4O_4$).
Compound **7d**: yellow foam; R_f 0.25 (SiO_2; CH_2Cl_2–EtOAc, 30:70); ^1H NMR ($CDCl_3$, 300 MHz) δ 1.70 (d, $J=7.2$ Hz, 3H), 3.30–3.50 (m, 2H), 4.31 (d, $J=5.4$ Hz, 2H), 5.00 (m, 1H), 6.72 (q, $J=7.2$ Hz, 1H), 6.82 (m, 5H), 7.58 (d, $J=7.2$ Hz, NH), 7.73 (s, NH), 9.76 (s 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.7, 38.0, 50.4, 55.4, 113.7, 127.7, 128.4, 129.1 (×2), 129.4 (×2), 131.8, 135.1, 164.7, 164.8, 168.8, 196.8; MS (APCI) $m/z=386.0$ (M, 100%), 387.0 (M+1, 15%) ($C_{17}H_{18}F_3N_3O_4$).
16. **Compounds 1b,c**: **General procedure**:
To a solution of K_2CO_3 (15 mg, 0.11 mmol, 1 equiv.) in H_2O (1 mL) and acetonitrile (40 mL) was added a solution of pseudotripeptide **7b** (50 mg, 0.11 mmol, 1 equiv.) in acetonitrile (50 mL). The mixture was stirred for 4 h under reflux, cooled to room temperature and acidified with a solution of 1N HCl. White precipitate was filtered and the filtrate was concentrated under vacuo to furnish crude compound **1b** (15 mg, 40% yield).
Compound **1b** (hydrochloride): brown solid; R_f 0.25 (SiO_2; hexane–iPrOH, 20:80); ^1H NMR ($CDCl_3$, 300 MHz) δ 3.84 (s, 2H), 4.23 (s, 2H), 7.20–7.60 (m, 10H), 8.37 (d, $J=2.1$ Hz, 1H), 8.50 (d, $J=2.1$ Hz, 1H); UV (10^{-4} M; H_2O–CH_3CN) λ_{max} (A) 433 (0.28), 269 (0.47), 207 (0.66).
Compound **1c** (hydrochloride): brown solid; ^1H NMR (CD_3OD, 200 MHz) δ 3.49 (s, 2H), 4.23 (s, 2H), 7.20–7.60 (m, 10H), 7.7–7.85 (m, 4H), 8.20 (s, 1H); UV (10^{-4} M; H_2O–CH_3CN) λ_{max} (A) 398 (0.17), 282 (0.59), 208 (0.72).
Compound **1d** (hydrochloride): brown solid; ^1H NMR (CD_3OD, 300 MHz) δ 1.18 (t, $J=7.2$ Hz, 3H), 3.32 (s, 2H), 3.61 (q, $J=7.2$ Hz, 2H), 7.16–7.36 (m, 4H), 7.81 (d, $J=7.2$ Hz, 1H), 7.91 (dd, $J=7.2$ Hz, 1.8 Hz, 1H); MS (APCI in positive mode) $m/z=254.1$ (M+1), ($C_{15}H_{13}N_3O$).
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