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SYNTHESIS AND IDENTIFICATION OF A NOVEL 6,5,6 -TRICYCLIC LACTAM

Joel P. Cooper,*[†] Jeff E. Cobb,[†] Barry G. Shearer,[†] Douglas J. Minick,[§] and Randy D. Rutkowske [§]

[†]Department of Medicinal Chemistry, [§]Department of Computational, Analytical and Screening Sciences

GlaxoSmithKline, Research Triangle Park, North Carolina, 27709, U.S.A.

Abstract - While incorporating oxazoles into known PPARγ agonist an unexpected 6,5,6-tricylic lactam was isolated as the major product.

INTRODUCTION

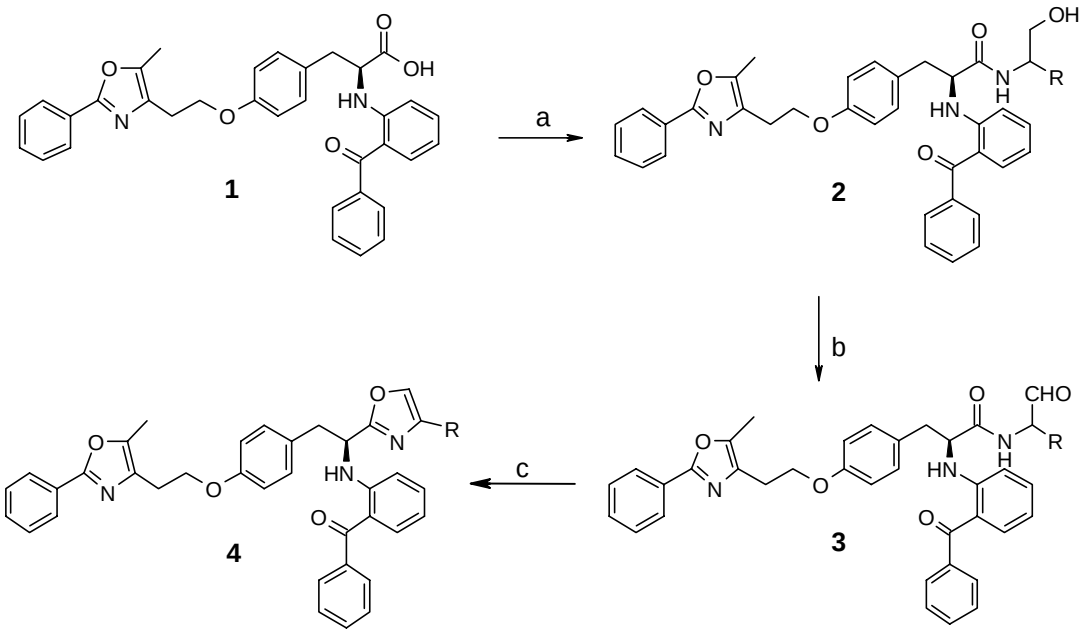
We recently described a novel series of tyrosine-based PPARγ agonist exemplified by GI262570.[1] A series of oxazole targets included in this work were synthesized via cyclodehydration of substituted aldehyde amides. During the course of this work, an unexpected tricyclic lactam was isolated as the major product from one of the cyclodehydration reactions. In this report we describe the synthesis and structural characterization of the unexpected tricyclic compound (**5**). A proposed mechanism for the formation of tricyclic lactam (**5**) is also presented.

RESULTS AND DISCUSSION

The standard protocol for the synthesis of our oxazole targets involved coupling acid (**1**) (GI262570) with a variety of amino alcohols as illustrated in Scheme 1. Oxidation of the intermediate alcohol (**2**) and subsequent cyclodehydration using Ph_3P, I_2 and Et_3N according to the procedure of Wipf [2] provided the desired oxazole (**4**). In general, the reactions provided the desired oxazole in moderate yields. However, in the case of the valinal amide (**3**) (R = *i*-Pr) we encountered an interesting result. While oxazole (**4**) (R = *i*-Pr) was obtained, it was the minor product isolated in only 11% yield. An unknown major product was isolated in 41% yield as a yellow foam.

^{1}H NMR spectrum of the major product indicated the loss of the aniline NH, both by the absence of the NH proton and the loss of coupling between the NH and the adjacent C-6 methine proton. The C-6 methine proton also showed a downfield shift of 1.1 ppm from the precursor aldehyde (**3**) and 0.4 ppm

Scheme 1



a) Amino alcohol, HOBT, EDC, NEt_3, CH_2Cl_2; b) TPAP, NMO, CH_2Cl_2; c) I_2, PPh_3, NEt_3, CH_2Cl_2

from the desired oxazole (**4**) (R = *i*-Pr). The isopropyl methine proton was absent and the normal doublet associated with an isopropyl substituent was replaced by two nonequivalent methyl singlets at δ 1.32 and 0.80 ppm. The ^{1}H NMR also indicated that the phenyl oxazole moiety was unchanged. ^{13}C NMR analysis indicated the absence of the phenyl ketone carbonyl peak at 195 ppm and is replaced by a carbon at 114 ppm. The amide carbonyl is retained at 168 ppm. Based on the above spectroscopic analysis, the tricyclic lactam structure (**5**) (Figure 1) was proposed as the major product. Similar tricyclic lactams have been reported in the literature. [3]

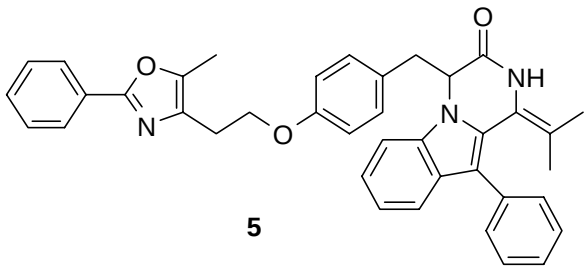


Figure 1. Proposed tricyclic lactam structure

Additional NMR experiments were conducted to further confirm the proposed structure. The *ortho* protons of the C-7 phenyl ring are highly deshielded and have a NOE coupling with the protons of the C-16 methyl group at δ 1.32 ppm (Figure 2). These results are consistent for structure (**5**).

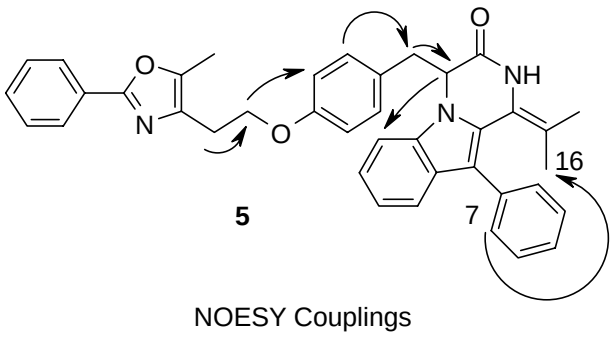


Figure 2. Observed NOESY couplings for compound (**5**)

Energy minimization studies of compound (**5**) show the 6,5,6 ring system being planar, with the C-7 phenyl group being anti periplanar and shielding the C-16 methyl group (Figure 3), as the lowest energy confirmation. (Note: The tyrosine phenyl ring and oxazole have been omitted for clarity). This accounts for the upfield shift and the non-equivalence of the vinylic methyls. The two ortho protons of the C-7 phenyl group are deshielded by the phenyl ring of the indole moiety, consistent with the observed downfield shift for these protons in the NMR spectra.

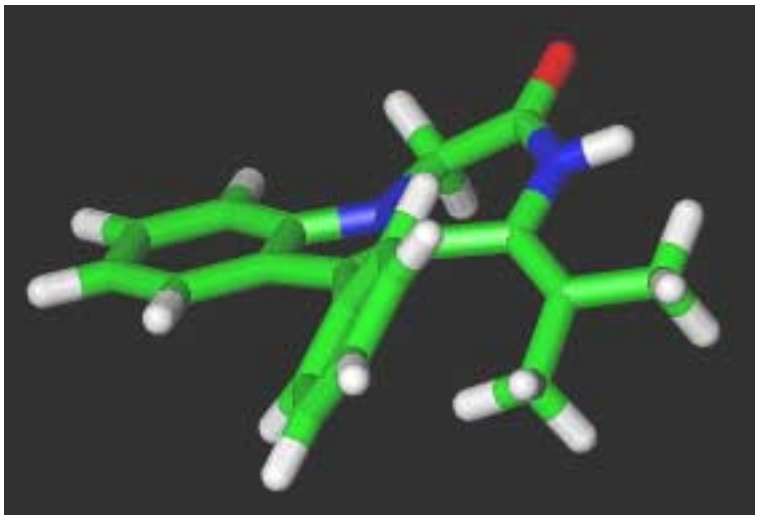


Figure 3. Lowest energy conformation for the 6,5,6-tricyclic ring

Evaluation of the IR spectrum of compound (**5**) showed bands at 3409 and 1679 cm^{-1} which were assigned to NH and C=O stretching modes, respectively. The strong, broad amide II band (in-plane NH bend) generally observed near 1520 cm^{-1} for non-cyclic amides but absent in IR spectra of cyclic amides was not observed in the spectrum of compound (**5**). These observations strongly support the presence of a 6-membered lactam. Intensified carbon-hydrogen bands at 1392 cm^{-1} and 1375 cm^{-1} are diagnostic for the presence of methyl groups on a sp^2-hybridized carbon, consistent with the vinylic methyl substituents present in (**5**). These observed results further support the proposed structure (**5**).

HR FAB$^+$ MS spectral data observed for compound (**5**) provided good support for the structure proposed in Figure 1. The exact mass of **5** was determined to be 594.2755 Da. This value fits the emperical formula $C_{39}H_{36}N_3O_3$ (calculated 594.2756 Da, Δ = 0.1 mmu), which corresponds to the protonated molecular formula of the proposed structure. This experimental molecular weight is also 36 a.m.u. less than the molecular weight of the starting material (**3**) in Scheme 1, providing supportive evidence that compound (**5**) was formed by the loss of 2 moles of water from **3**. Finally, the major fragment ion in the FAB$^+$ mass spectrum of **5** was observed at m/z 301. This ion was assigned to the tricyclic fragment in the proposed structure, which is formed by facile cleavage of the *p*-oxybenzyl side chain.

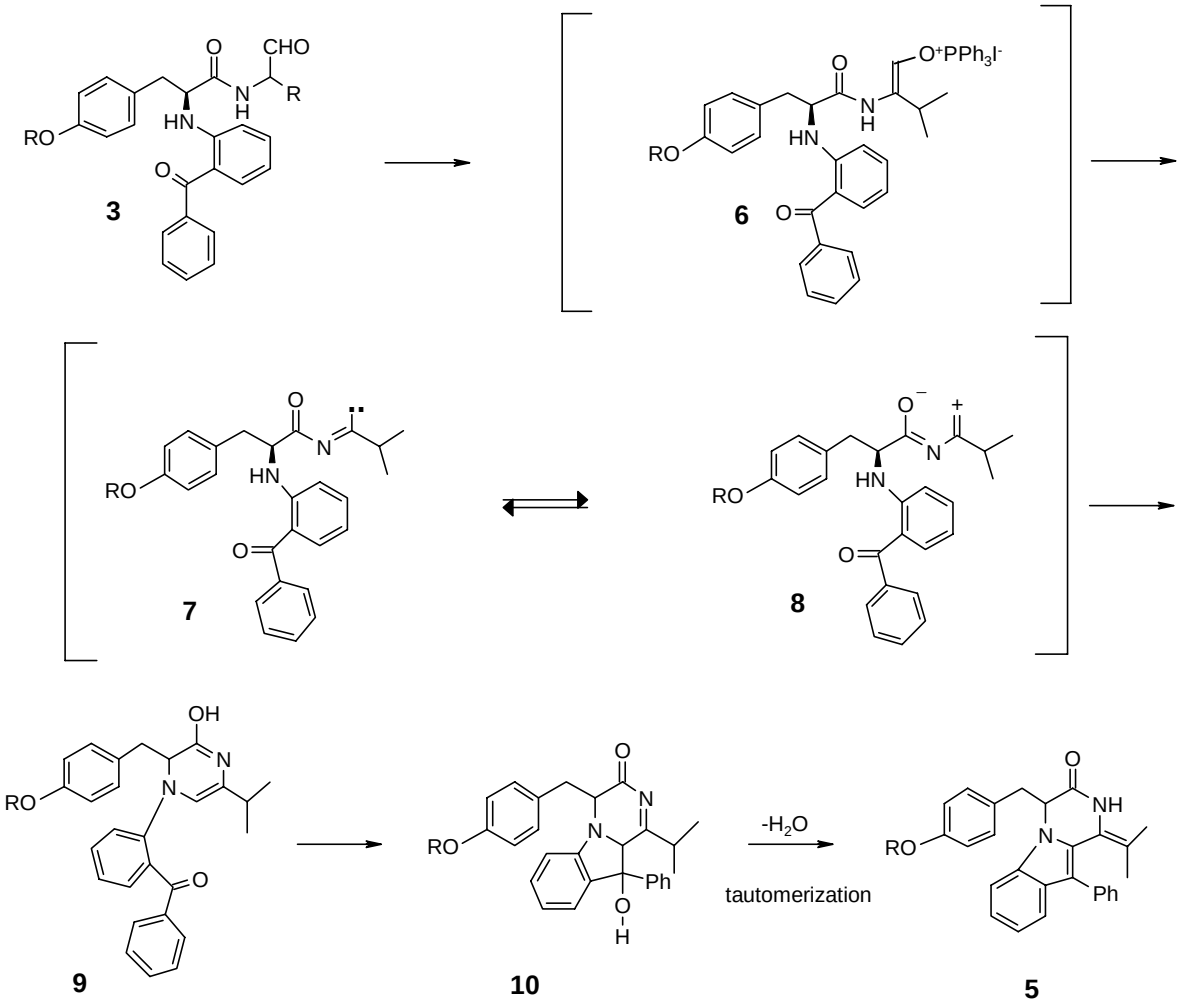


Figure 4. Proposed mechanism for formation of the tricyclic lactam

A mechanism for the conversion of **3** to **5** is proposed (Figure 4) and is based upon mechanistic considerations first proposed by Wipf. [2] Formation of the enol phosphonium salt (**6**) followed by loss of triphenylphosphine oxide would give a highly reactive acyliminocarbene (**7**-**8**). Seidel and Huisgen[4] and Williams [5] have previously reported the cyclization of acyliminocarbenes to yield oxazoles. However,

competing addition into the intermediate by the basic nitrogen of the aminobenzophenone moiety and subsequent proton transfer produces intermediate (**9**). Deprotonation of the C-4 carbon and addition into the benzophenone carbonyl gives alcohol (**10**). Subsequent loss of water and tauteromization to the exocyclic double bond gives compound (**5**). It is unclear why in this case nitrogen addition into the acylimino carbene, appears to be favored over oxygen addition. It is also unclear if the reaction is specific to the valinal amide series. Cyclization to the tricyclic lactam, may have occurred with the other formyl amides, but as minor products in amounts insufficient to be isolated or observed.

The unknown major product (**5**) isolated from the cyclodehydration of intermediate (**4**) was unanticipated. The compilation of the above ^{1}H NMR, IR and HRMS spectral data are all consistent with the assigned tricyclic lactam structure (**5**).

EXPERIMENTAL

All commercial chemicals and solvents are reagent grade and were used without further purification unless otherwise noted. ^{1}H and ^{13}C spectra were obtained on 400 MHz and 500 MHz Unity Plus NMR spectrometers. IR spectral data were taken using a Bruker Equinox 55 FT-IR spectrometer equipped with a room-temperature DTGS detector. Spectra were acquired at 4 cm^{-1} resolution. Solution-phase spectra were taken of samples dissolved in spectrophotometric-grade chloroform (Aldrich). FAB^{+} MS spectral data were measured using a VG 70SQ spectrometer operating at 10,000 ppm resolution. The exact MS was determined using a magic bullet matrix doped with PEG for mass calibration.

***N*-(2-Benzoylphenyl)-*N*-[(1*S*)-1-hydroxymethyl-2-methylpropyl]-*O*-[2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)ethyl]-*D*-tyrosinamide (2):** GI 262570X (0.81 g, 1.49 mmol), *R*-(-)-valinol (0.18 g, 1.79 mmol), HOBT (0.22 g, 1.64 mmol) and triethylamine (0.52 mL, 3.73 mmol) were dissolved in CH_2Cl_2 (20 mL). The reaction was stirred at rt for 5 min and then EDC (0.34 g, 1.79 mmol) was added. The reaction was stirred for 16 h at rt. The reaction was diluted with CH_2Cl_2 (50 mL), washed with water (100 mL), dried over $MgSO_4$, filtered and concentrated. The crude material was purified by flash chromatography (98:2, CH_2Cl_2:MeOH) to afford 0.88 g (94%) of the desired product as a yellow solid. ^{1}H NMR ($CDCl_3$, 400 MHz) 9.42 (s, 1H), 8.85 (bs, 1H), 7.96 (dd, 2H, J = 7.4, 8.0 Hz), 7.59 (m, 12H), 7.20 (s, 1H), 6.79 (dd, 3H, J = 9.9 Hz), 6.54 (t, 2H, J = 7.7 Hz), 4.91 (q, 1H, J= 7.0 Hz), 4.18 (t, 2H, J = 6.8 Hz), 3.26 (t, 2H, J = 6.4), 2.93 (t, 2H, J = 6.7), 2.79 (d, 1H, J=6.8 Hz), 2.35 (s, 3H), 1.08 (dd, 6H, J = 5.4 Hz, J = 5.4 Hz).

{2-[((1*R*)-1-(4-Isopropyl-1,3-oxazol-2-yl)-2-{4-[2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]phenyl}ethyl)amino]phenyl}(phenyl)methanone (4) and 3-methylene-1-(1-methylethylidene)-4-{4-[2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]benzyl}-10-phenyl-1,2,3,4-tetrahydropyrazino[1,2-*a*]indole. (5): *N*-(2-Benzoylphenyl)-*N*-[(1*S*)-1-hydroxymethyl-2-methylpropyl]-

O-[2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)ethyl]-*D*-tyrosinamide (0.47 g, 0.74 mmol) and *N*-methylmorpholine (0.35 g, 2.98 mmol) were dissolved in CH_2Cl_2 (10 mL) and dried over $MgSO_4$. The solution was filtered and celite (0.50 g) was added. The reaction was stirred for 5 min and then TPAP (0.06 g, 0.19 mmol) was added. The reaction was stirred for 5 min and then filtered through a pad consisting of 3" of celite on top of 3" of silica. The product was eluted with CH_2Cl_2. The organics were concentrated to afford 0.14 g (29%) of the aldehyde. The aldehyde was dissolved in CH_2Cl_2 (10 mL) and added to a solution of iodine (0.11 g, 0.21 mmol), triphenylphosphine (0.11 g, 0.43 mmol) and triethylamine (0.12 mL, 0.86 mmol) in methylene chloride (5 mL). The reaction was stirred at rt for 1.5 h. The reaction was poured into a saturated solution of $Na_2S_3O_3$ and shaken. The organics were removed and the aqueous was extracted with ether (100 mL). The organics were dried over $MgSO_4$, filtered and concentrated. The crude material was purified by flash column eluted with Hex:EtOAc (1:1) to give 0.015 g (0.024 mmol, 11%) of the oxazole (**4**) and 0.052 g (41%) of the lactam (**5**).

Oxazole (**4**): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.02 (d, 1H, *J* = 7.08 Hz), 7.96 (dd, 2H, *J* = 7.4, 8.0 Hz), 7.59 (d, 2H, *J* = 8.2 Hz), 7.49 (d, 1H, *J* = 7.1 Hz), 7.44 - 7.39 (m, 6H), 7.29 (t, 1H, *J* = 7.1 Hz), 7.20 (s, 1H), 7.07 (d, 2H, *J* = 8.6 Hz), 6.79 (dd, 3H, *J* = 9.9 Hz), 6.54 (t, 1H, *J* = 7.7 Hz), 4.91 (q, 1H, *J*= 7.0 Hz), 4.18 (t, 2H, *J* = 6.8 Hz), 3.26 (t, 2H, *J* = 6.4), 2.93 (t, 2H, *J* = 6.7), 2.79 (m, 1H), 2.35 (s, 3H), 1.08 (dd, 6H, *J* = 5.4 Hz, 5.4 Hz). *Anal*. Calcd for $C_{39}H_{37}N_3O_4$: C, 76.57; H, 6.10; N, 6.87. Found: C, 76.82; H, 6.24; N, 6.66. LRMS M +H 612.

Lactam (**5**): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.91 (dd, 2H, *J* = 3.6, 4.1 Hz), 7.74 (d, 1H, *J* = 8.0 Hz), 7.41 – 7.34 (m, 8H), 7.28 (d, 2H, *J* = 3.7 Hz), 7.24 – 7.12 (m, 3H), 6.70 (d, 2H, *J* = 8.6 Hz), 6.57 (d, 2H, *J* = 8.5 Hz), 5.29 (t, 1H, *J* = 4.4 Hz), 4.08 (t, 2H, *J* = 6.6 Hz), 3.38 (d, 2H, *J* = 4.3 Hz), 2.89 (t, 1H, *J* = 6.6 Hz), 2.32 (s, 3H), 1.32 (s, 3H), 0.80 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 168.06, 157.96, 145.01, 136.02, 134.65, 132.65, 130.80, 129.80, 129.37, 128.68, 128.63, 127.85, 127.68, 126.99, 126.05, 125.88, 122.94, 120.71, 119.92, 119.51, 118.97, 114.37, 114.16, 108.51,66.50, 59.27, 41.48, 38.15, 26.33, 21.90, 18.60, 10.23 ^{13}C NMR ($CDCl_3$, 100 MHz) dept δ 130.80, 129.81, 129.37, 128.68, 128.63, 126.05, 125.88, 122.94, 120.71, 119.92, 114.16, 108.51, 66.50 (CH_2), 59.27, 38.15 (CH_2), 26.33 (CH_2), 21.90, 18.60, 10.23 Calcd for $C_{39}H_{35}N_3O_3 \cdot H_2O$: C, 76.57; H, 6.10; N, 6.87. Found: C, 75.49; H, 5.73; N, 6.74.

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