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Concise and regiospecific syntheses of tri-substituted 1,2,4-triazoles

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Abstract

Novel tri-substituted 1,2,4-triazoles are synthesized *via* complementary, regiospecific routes as part of a lead finding exercise. A key feature of one of the syntheses is recognition of an intrinsic regioselectivity toward deprotonation in the 1-phenylguanazole substrate.

Keywords: Isomers; Peptide mimetics; Regiochemistry; Triazoles

As part of an exploratory study of potentially interesting receptor ligands, we desired a rapid entry into a series of novel heteroaromatic neurokinin-1 (NK_1) receptor antagonists. Such compounds are candidates for therapeutic intervention in processes such as pain transmission and neurogenic inflammation [1]. The 1,2,4-triazole scaffold was chosen for its synthetic accessibility and ability to deploy those functionalized aromatic rings which are believed to be key determinants for high affinity receptor binding [2,3]. This is a recurring structural theme and is exemplified in a number of published non-peptide NK_1 antagonists such as CP-99,994 [3] and L-733,060 [4] (**Fig. 1**).

Diphenyl cyanocarbonimidate **1** has previously been employed in the construction of the triazole nucleus [5]. The phenoxy leaving groups can be replaced in a stepwise manner with heteronucleophiles and heterocyclization to di-substituted triazoles is effected when the second nucleophile in the sequence is hydrazine (**Scheme 1**, *Eqn. 1*). Whilst this has proved to be an

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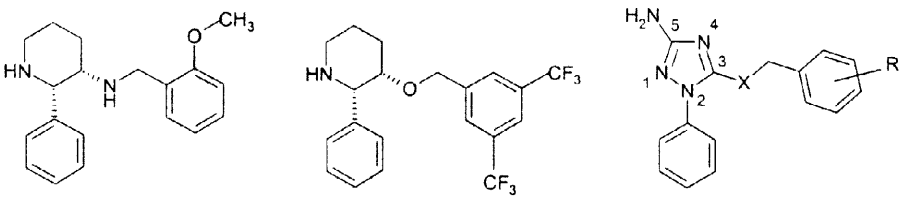
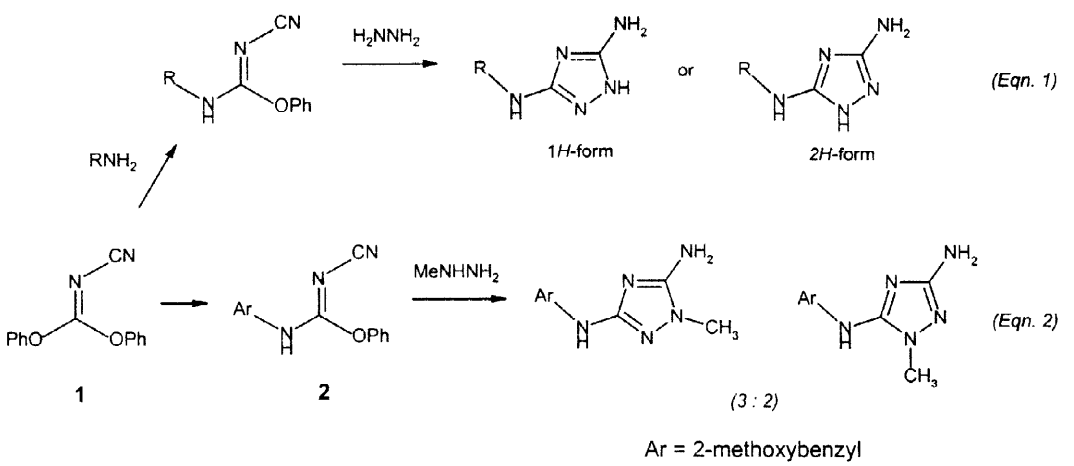


Fig. 1 CP-99,994 L-733,060 Triazole-based analogues

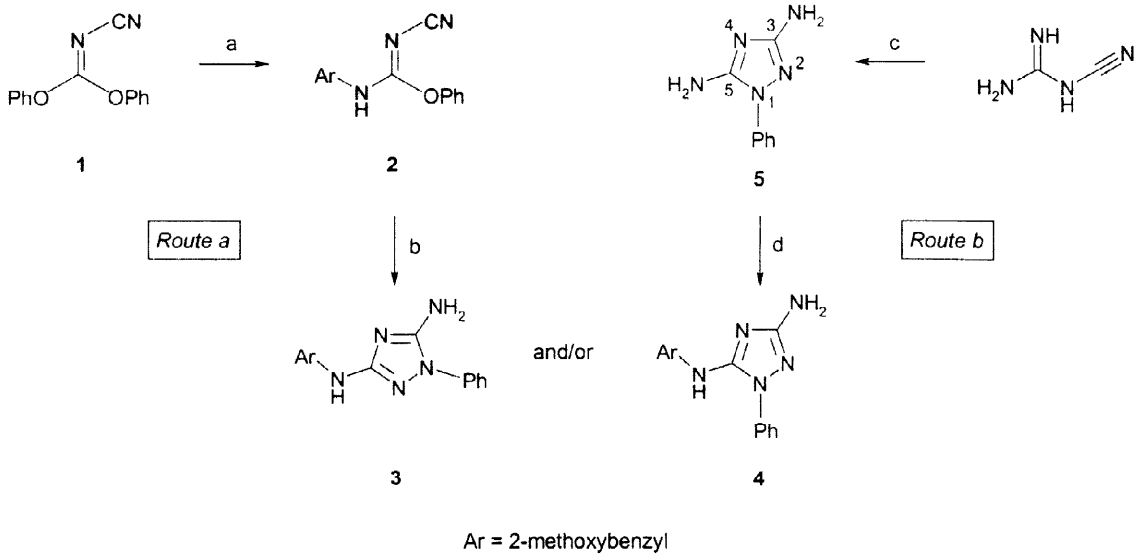
expedient synthetic method, its application to tri-substituted triazoles *via* mono-substituted hydrazines exposes the need for regiochemical control (**Scheme 1**, *Eqn. 2*) [6,7]. Use of phenylhydrazine, as required by retrosynthetic analysis of our primary target class (**Fig. 1**, X = NH, R = 2-MeO), was similarly recognized as capable of affording a mixture of regioisomers **3** and **4** (**Scheme 2**, *Route a*) [7], although only the latter was targeted as a potential NK_1 antagonist on account of the *ortho* disposition of its aryl substituents.



Scheme 1.

In practice, reaction of the isourea **2** with phenylhydrazine was seen to give rise to a single new component. ^{1}H NMR experiments (1D-NOEDIF) revealed an enhancement of some of the aromatic signals upon irradiation of the exocyclic primary amine signal at δ 6.2, suggesting that compound **3** had been formed exclusively. After recrystallizing the compound from ethyl acetate, the regiochemical assignment was confirmed by X-ray crystallographic analysis (**Fig. 2a**).

This regiochemical outcome could be reversed by constructing the heterocyclic ring from an undifferentiated substrate. Thus, *N*-cyanoguanidine and phenylhydrazine react to form 1-phenylguanazole **5** irrespective of their orientation upon cyclization (**Scheme 2**, *Route b*) [8]. Once formed, however, the ring system manifests an exploitable pK_a difference between the C5



Scheme 2. *Reagents and conditions:* (a) 2-Methoxybenzylamine, propan-2-ol (89%); (b) $PhNHNH_2$ (solvent), 100 °C, 11 h (86%); (c) $PhNHNH_2$, H_3O^+, reflux, 6 h (41%); (d) (i) 1M KO^{t}Bu in THF (1 eq.), -15 °C; (ii) 2-methoxybenzyl bromide (1 eq.).

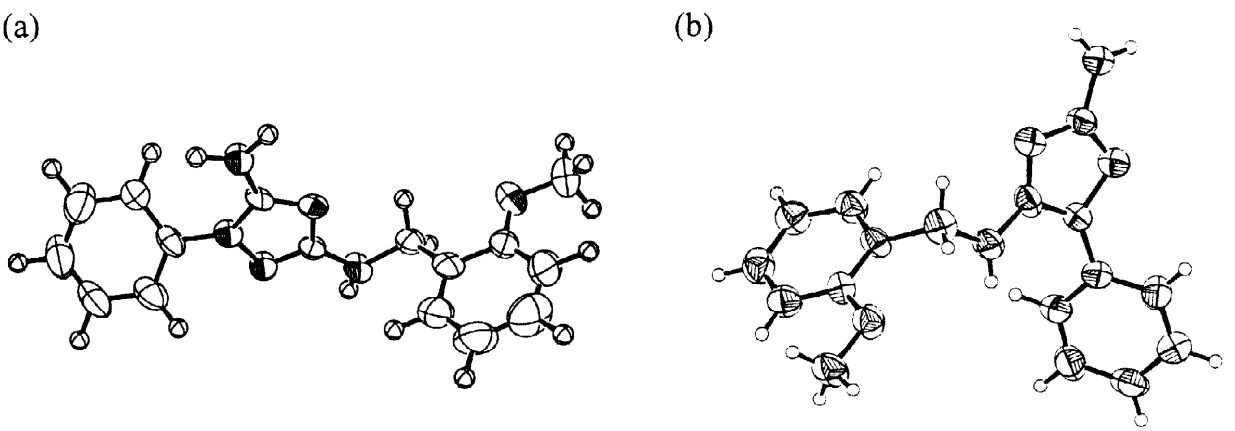
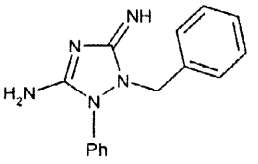


Fig. 2. *ORTEP diagrams of (a) compound 3 and (b) compound 4 (showing 50% displacement ellipsoids).*

amino group (cpK_a -7.05) and its C3 counterpart (cpK_a -5.05) [9]. Alkylation of **5** (**Scheme 2**, step d) resulted in the detection of a single major product in a crude reaction mixture which did not include isomer **3**. Following purification, crystals of the product were obtained from ethanol (~30% recovery). A comparison of the ^{1}H NMR spectrum with that of compound **3** revealed a similar signature, but with differences in the chemical shifts of the NH and NH_2 signals [10]. These observations were consistent with the formation of isomer **4**, and indicated a successful discrimination between the C3 and C5 amino groups in the *N*-alkylation reaction. As before, an X-ray crystallographic analysis was performed to verify the structure (**Fig. 2b**). Alkylation of **5**

with benzyl chloride and methyl iodide has previously been reported to afford **6** and **7** respectively, although the reactions were conducted at 135-140 °C in methanol for 10 h [8].



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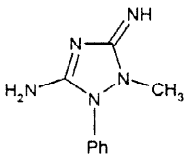

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Compound **4** was biologically characterized through a cloned human NK_1 receptor binding assay, and was found to exhibit a moderate K_i value of 2.4 μM in its ability to displace [^{3}H]-SP binding to membranes from CHO cells transfected with human NK_1 receptor cDNA.

In conclusion, we have delineated a short, regiospecific pathway to the desired *ortho*-di-substituted aminotriazole **4** which complements an alternative route leading to the regioisomer **3** [11]. In the process, we have discovered a novel, achiral NK_1 receptor-binding ligand by introducing established pharmacophoric functionality to a heteroaromatic scaffold. The hitherto unfunctionalized amino group provides an optional synthetic handle from which to append additional receptor-probing functionality [12] for the further exploitation of this compound class.

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[9] ACD/pK_a Calculator software, version 1.0, Advanced Chemistry Development Inc., Toronto, Ontario.

[10] **3**: ^{1}H NMR (200 MHz, DMSO-d_6) δ ppm 7.6-6.8 (9 H, m, aromatic), 6.21 (2 H, s, NH_2), 5.92 (1 H, t, J = 5 Hz, $ArCH_2NH$), 4.29 (2 H, d, J = 5 Hz, $ArCH_2NH$), 3.82 (3 H, s, OCH_3). **4**: ^{1}H NMR (200 MHz, DMSO-d_6) δ ppm 7.6-6.85 (9 H, m, aromatic), 6.71 (1 H, t, J = 5 Hz, $ArCH_2NH$), 5.15 (2 H, s, NH_2), 4.43 (2 H, d, J = 5 Hz, $ArCH_2NH$), 3.82 (3 H, s, OCH_3).

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