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Design and synthesis of 1,3,5-trisubstituted 1,2,4-triazoles as CYP enzyme inhibitors

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ABSTRACT

A series of 1,3,5-trisubstituted 1,2,4-triazoles was designed and synthesized as potential inhibitors of steroidogenic CYP enzymes. The 1,2,4-triazole is part of the core structure fixing the geometry of the substances. A pyridine moiety was introduced as heme-binder. The target compounds were synthesized in two to four steps using silver carbonate mediated ring closure and Suzuki cross coupling reaction as key synthetic transformations. Biological testing of the synthesized compounds for the inhibition of the most important steroidogenic CYPs revealed compounds **29a** and **30** as moderate inhibitors of aldosterone synthase (CYP11B2).

1,2,4-Triazoles are a class of heterocycles which are very important in organic synthesis. However, in nature 1,2,4-triazoles are uncommon and only a few examples have been described so far. The first report of an occurrence of 1,2,4-triazole in nature dates to the year 1985 when L-1,2,4-triazole-3-alanine **1** (Fig. 1) was isolated from a *Streptomyces sp.* strain.[1] The compound acts as a histidine antagonist.[2,3] Further (and only) examples of natural products containing 1,2,4-triazole are the antibiotic Essramycin **2**[4] and 1-(β-D-ribofuranosyl)-1,2,4-triazole **3**[5] isolated from the sea urchin *Glyptocidaris crenularis*. Both compounds were published very recently as natural products but the latter one is already known in the literature as a synthetic compound.[6]

Medicinal chemists involved in drug discovery also paid a lot of attention on 1,2,4-triazoles. In the past years many triazole containing drugs were discovered. The most important application of 1,2,4-triazoles is as biocides but also as drugs for usage for instance in cancer or immunosuppressed patients for prophylaxis and treatment of life-threatening invasive fungal infections.[7] Figure 1 illustrates posaconazole[8,9] **4**, fluconazole[10] **5,** and triadimenol[11] **6** as examples for antifungal drugs (**4**, **5**) or fungicide (**6**), respectively. All of these compounds inhibit the biosynthesis of ergosterol which is important for the growth of the cell membrane in yeast and fungi. The molecular target is the cytochrome P450 (CYP) enzyme CYP51A1 (lanosterol-14α-demethylase).[12,13]

Further examples of CYP enzyme inhibitors containing 1,2,4-triazole are letrozole **7**[14] and anastrozole **8**.[15] Both compounds are potent inhibitors of aromatase CYP19. These substances are depicted in Figure 2.

In all of the above mentioned CYP inhibitors the 1,2,4-triazole moiety is responsible for the interaction of the compound with the heme of the CYP enzyme.[16] Our group has been working for more than 20 years on steroidogenic CYP enzymes and is highly experienced in the development of potent and selective inhibitors of CYP11B1,[17a,b] CYP11B2,[18a–h] CYP17,[19a–i] and CYP19.[20a–f] In this Letter we report on the design of new inhibitors of steroidogenic CYP enzymes which bear 1,2,4-triazole as part of the core structure. By adding nitrogen containing heterocycles as heme-binders, such as pyridine, inhibitors of steroidogenic CYP enzymes should be developed. The synthesized compounds were tested in our established assay system in order to evaluate their potency on the most important steroidogenic CYP enzymes CYP11B1, CYP11B2, CYP17, and CYP19.

The design strategy starts from 1,2,4-triazole as the central element of the core structure. We know from previously described CYP enzyme inhibitors that the triazole scaffold is well tolerated and is suitable as drug component. Compared to a benzene core a triazole moiety possesses a higher hydrophilicity resulting in a better solubility of the inhibitors. Furthermore, its basicity is significantly lower compared to an imidazole core. A second reason for choosing a 1,2,4-triazole as central core is the characteristic geometry of the resulting inhibitors. As we do not want the triazole to

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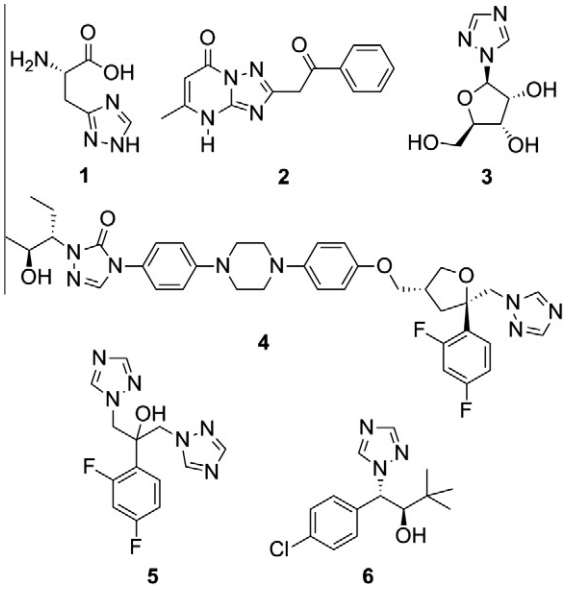


Figure 1. Natural products and antifungal drugs bearing a 1,2,4-triazole moiety.

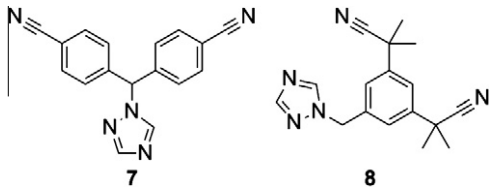


Figure 2. Aromatase inhibitors letrozole **7** and anastrozole **8**.

act as heme binder it needs to be shielded by appropriate substituents. The interaction with the heme shall be achieved by a pyridyl substituent which is connected to the 5-position of the triazole via a short variable (n = 0, 1) alkyl or phenyl linker. In the 3-position either a phenyl group or a 3- or 4-methoxyphenyl group (R_1 = H, OMe) is linked to the triazole. The methoxy group (R_1) is supposed to act as H-bond acceptor in a similar way as the natural steroidal substrates. The resulting 3-aryl-1,2,4-triazole core structure mimics the A- and B-ring of the natural steroidal substrate. The 1-position of the triazole is furthermore substituted by a methyl, phenyl or, benzyl group (R_2). The increasing bulkiness of those substituents could give insights into the shape of the active site. We know from previous SAR in other inhibitor classes that for instance a benzyl group may exploit a subpocket present in CYP11Bs, thus increasing the selectivity toward other steroidogenic CYP enzymes.[18e] The resulting general structures of the desired inhibitors are visualized in Figure 3.

For compounds with R_2 = Ph the synthesis starts from benzaldehyde **9a** or 4-methoxybenzaldehyde **9b**, respectively, which is condensed with phenylhydrazine **10** to give hydrazones **11a**,**b** which were used in the next step without further purification (Scheme 1).[21] Hydrazones **11** are converted to the corresponding hydrazonyl chlorides **12** by the reaction with *n*-chlorosuccinimide in the presence of dimethylsulfide. The chlorine was displaced by primary amines **13** following the approach by Buzykin to give the triazene intermediates **14a**–**e**[22,23] which were not isolated and immediately cyclized to the final products **15**. The desired 1,3,5-substituted 1,2,4-triazoles **15a**–**e** were obtained after cyclization of intermediates **14** mediated by silver carbonate.[21]

The 1,2,4-triazoles with benzyl substituent in 1-position (R_2 = Bn) **20** were readily prepared via ring closure of the initially

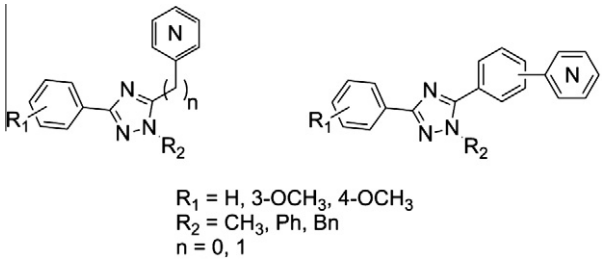
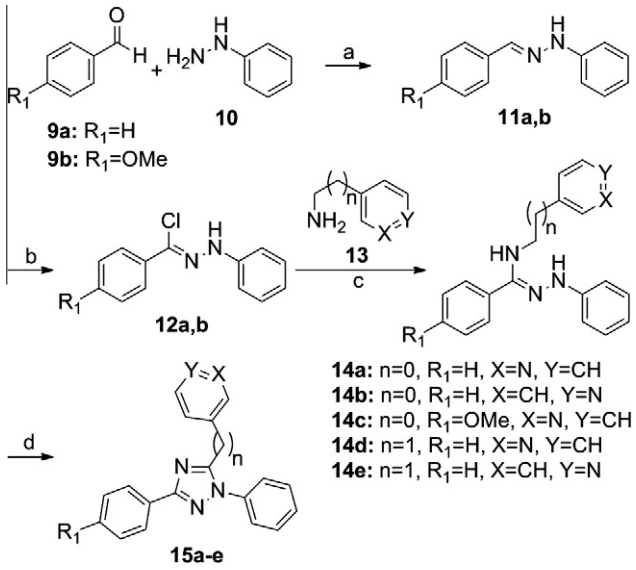


Figure 3. General structures of the synthesized compounds.



Scheme 1. Reagents and conditions: (a) toluene, rt, 12 h; (b) NCS, DMS, CH_2Cl_2, 0 °C to −78 °C to rt, 46–49% (over two steps); (c) **13**, TEA, CH_3CN, rt, 12 h; (d) Ag_2CO_3, CH_3CN, rt, 2 h, 48–77% (over two steps).

formed *N*′-benzyl benzohydrazonamide **18** with substituted heteroaryl acid chlorides **19** (Scheme 2). The intermediate benzohydrazonamide **19** was synthesized from ethyl benzimidate **16** which was reacted with benzyl hydrazine **17**. This reaction sequence afforded compounds **20a**–**c**. Removal of the bromine substituent of **20a** using palladium and hydrazine yielded **20d**. A Suzuki cross coupling reaction of **20a** with (3-methoxyphenyl) boronic acid under Pd catalysis and microwave irradiation led to compound **20e**.

The synthesis of 1-methyl substituted 1,2,4-triazoles (R_2 = Me) is outlined in Scheme 3. Ethyl 4-methoxybenzimidate **21a** was reacted with 5-bromonicotinoyl chloride to give intermediate **23** which was used in the next step without further purification and was subsequently cyclized under mild conditions with methylhydrazine via an Einhorn–Brunner reaction[24] yielding compound **24**.

The preparation of compounds **29a**,**b** and **30** proceeded in a similar manner as for compound **24** (Scheme 4). After cyclization the intermediates **27a**,**b** were reacted with either 3-pyridine boronic acid **28a** or 4-pyridine boronic acid **28b** in a Pd-catalyzed Suzuki cross coupling reaction to afford the desired target substances **29a**,**b** and **30**.

The **14** synthesized 1,3,5-trisubstituted 1,2,4-triazoles **15a**–**e**, **20a**–**e**, **24**, **29a**,**b** and **30** were tested in our established screening system with regard to their ability to inhibit the most important human steroidogenic CYP enzymes CYP11B1, CYP11B2, CYP17, and CYP19. The assays were performed as described previously for CYP11B1,[17a] CYP11B2,[17a] CYP17,[25] and CYP19.[25b,26] After the