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Synthesis and molecular docking of 1,2,3-triazole-based sulfonamides as aromatase inhibitors

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ABSTRACT

A series of 1,4-disubstituted-1,2,3-triazoles (**13**–**35**) containing sulfonamide moiety were synthesized and evaluated for their aromatase inhibitory effects. Most triazoles with open-chain sulfonamide showed significant aromatase inhibitory activity (IC_{50} = 1.3–9.4 μM). Interestingly, the *meta* analog of triazole-benzene-sulfonamide (**34**) bearing 6,7-dimethoxy substituents on the isoquinoline ring displayed the most potent aromatase inhibitory activity (IC_{50} = 0.2 μM) without affecting normal cell. Molecular docking of these triazoles against aromatase revealed that the compounds could snugly occupy the active site of the enzyme through hydrophobic, π–π stacking, and hydrogen bonding interactions. The potent compound **34** was able to form hydrogen bonds with Met374 and Ser478 which were suggested to be the essential residues for the promising inhibition. The study provides compound **34** as a potential lead molecule of anti-aromatase agent for further development.

1. Introduction

Breast cancer is one of the leading causes of cancer-related mortality among women worldwide from different age groups. The vast majority of breast cancers in postmenopausal women are deriving from estrogens production.[1–3] Estrogens are biosynthesized from androgens catalyzed by aromatase (CYP19), an enzyme belonging to the P450 family of monooxygenase heme proteins. Two main strategies to control or block breast cancer progression include binding of the estrogen receptors (ERs) with receptor antagonists (ERAs such as tamoxifen), and inhibiting the production of estrogen with aromatase inhibitors (AIs).[3] AIs were found to have less side effects than ERAs owing to the the lack of estrogenic activity on uterus and vasculature.[3]

Triazoles are common pharmacophore found in a diverse range of biologically active molecules due to their potential structural features (i.e., capability of hydrogen bonding, stable to metabolic degradation and less undesired effects).[4] Among the AIs, letrozole (**1**) and anastrozole (**2**), both containing 1,2,4-triazole ring, were approved by the Food and Drug Administration (FDA) and using as the first-line therapy in the treatment of breast cancer in postmenopausal women since they have been shown to be superior to tamoxifen.[3] Based on the AIs, the triazole ring plays a pivotal role in chelation with heme iron.[5] Along the line, Touaibia group has studied on an aromatase inhibitory activity of various substituted-1,2,3-triazole letrozole-based analogs.[6] The results revealed that 1,2,3-trizole (**3**) analog of letrozole showed equipotent activity to the parent compound. In addition, the 1,4-disubstituted-1,2,3-triazole (**4**) was shown to be the most potent compound (IC_{50} = 1.36 μM) among the tested 1,4-disubstituted-1,2,3-triazole series. Aromatase inhibitors **1**–**4** are shown in Figure 1. However, the interaction mode of the 1,4-disubstituted-1,2,3-triazole series with the target enzyme remains to be explored.

Recently, 1,4-disubstituted-1,2,3-triazoles bearing 1,2,3,4-tetrahydroisoquinoline (THIQ) and its open-chain derivatives **5** (Fig. 2) with cytotoxic activity against four cancer cell lines (e.g., HuCCA-1, HepG2, A549 and MOLT-3) have been reported by our group.[7,8] Based on the molecular docking study, an aldoketo reductase 1C3 (AKR1C3) has been identified to be a plausible target responsible for anticancer activity of the THIQ analogs.[8]

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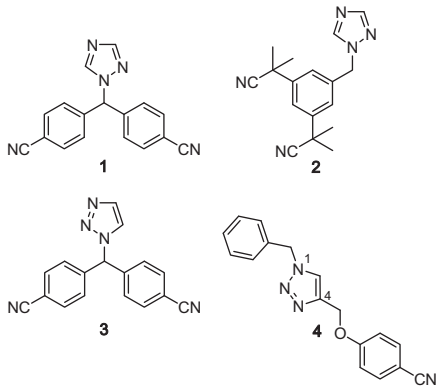


Figure 1. Aromatase inhibitors containing triazole **1**–**4**.

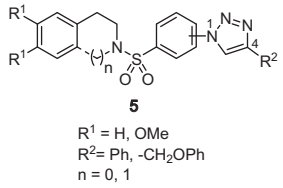


Figure 2. Cytotoxic agents containing triazole **5**.

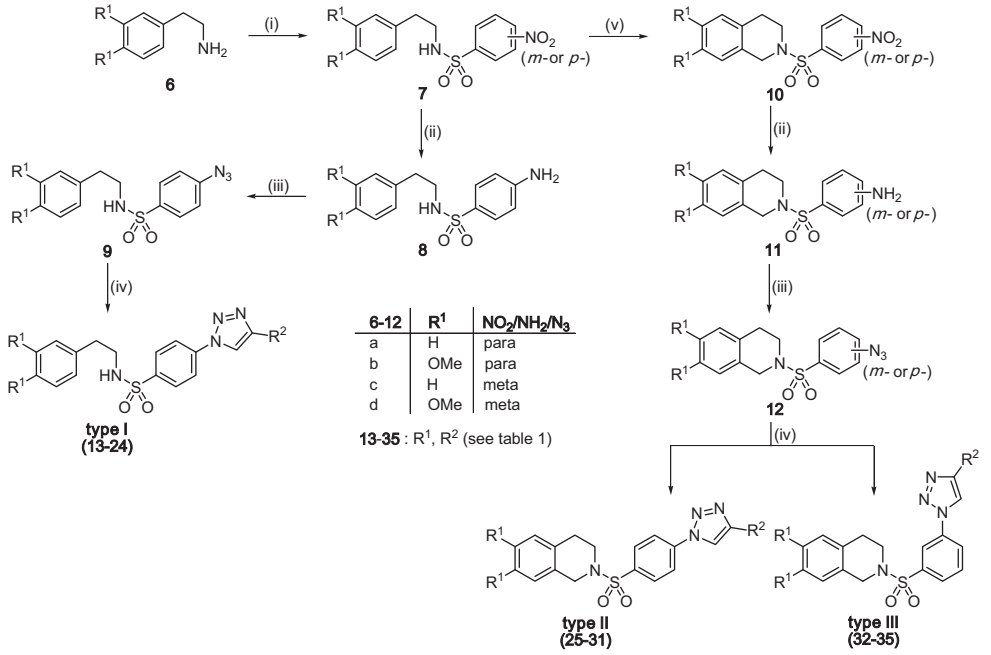
In general, two structural features of the aromatase active site associate with highly hydrophobic and H-bonding interactions.[9] Therefore, to design and seek for a novel class of aromatase inhibitor, many in-house 1,2,3-triazoles (series I and II) and four novel 1,2,3-triazoles of THIQ (series III) were synthesized through the Click reaction, and evaluated for their aromatase inhibitory effects. Herein, the molecules of rational designed inhibitors (Fig. 2) bearing THIQ, benzene, naphthalene and coumarin rings might be anticipated in forming hydrophobic interaction. In addition, various functional groups of the designed compounds such as sulfonamide, triazole, ether and carbonyl moieties would participate in hydrogen bonding formation. Moreover, molecular docking of the synthesized compounds against the aromatase was also performed to give insights into their binding modes governing the investigated aromatase inhibitory activities.

2. Results and discussion

2.1. Chemistry

The synthesis of triazoles (e.g., types I and II) has been previously reported by our group.[7,8] The open chain THIQ analogs of triazoles **13**–**24** (type I) were prepared through a sequential sulfonation/reduction/diazotization/cycloaddition reactions (route a; steps i–iv) as outlined in Scheme 1. In the same manner, the synthesis of triazoles type II **25**–**31** and type III **32**–**35** was carried out via route b (steps i–v) in which an additional step (i.e., step v) was performed using the Pictet–Spengler reaction to form isoquinoline ring (**10**) prior to steps ii–iv.

Structures of the novel 1,2,3-triazoles **32**–**35** were confirmed based on their ^{1}H NMR, ^{13}C NMR, HRMS and IR spectra. For instance the triazole **34**, its ^{1}H NMR spectra revealed two triplets at δ 2.86 and 3.47 ppm which were assigned to the methylene protons of C4- and C3-THIQ, respectively. The methylene protons at C1-THIQ ring appeared as a singlet at δ 4.31 ppm whereas two methoxy protons at C6- and C7-positions of the THIQ part were noted as a singlet at δ 3.83 ppm. In addition, the methylene protons of –CH_2O– group were found to be displayed as a singlet at δ 5.39 ppm. Aromatic protons of THIQ ring (H-5 and H-8) displayed as two singlets at δ 6.54 ppm and 6.56 ppm. Two methine protons of coumarin ring appeared as a multiplet at δ 6.92–6.98 (H-6 and H-8). The rest of three methine protons of coumarin moiety were observed as three doublets at δ 6.30 (J = 9.5 Hz), δ 7.39 (J = 9.2 Hz) and δ 7.63 (J = 9.5 Hz) ppm, which were assigned to methine protons of C3, C5 and C4, respectively. A triplet at δ 7.70 ppm (J = 8.0 Hz), two doublets at δ 7.87 (J = 7.8 Hz) and 7.99 ppm (J = 7.6 Hz) and a singlet at δ 8.17 ppm were attributed



Scheme 1. Synthesis of 1,2,3-triazole-based sulfonamides **13**–**35** through the Click reaction. Reagents and conditions: (i) 3- or 4-benzenesulfonyl chloride, Na_2CO_3, CH_2Cl_2, rt; (ii) $SnCl_2{\cdot}2H_2O$, EtOH, reflux; (iii) $NaNO_2$, HCl/CH_3COOH, 0 °C, NaN_3, rt; (iv) ≡–R^2, $CuSO_4{\cdot}5H_2O$, sodium ascorbate, t-BuOH/H_2O, rt; (v) $(CH_2O)_n$, HCOOH, reflux; route a = steps i–iv; route b = steps i–v.