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Research paper

Analogue based drug design, synthesis, molecular docking and anticancer evaluation of novel chromene sulfonamide hybrids as aromatase inhibitors and apoptosis enhancers

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ABSTRACT

Twenty novel chromene derivatives carrying different sulfonamide moieties (**3**–**22**) were designed and synthesized. All the newly prepared compounds were evaluated for their *in vitro* anticancer activity against breast cancer cell line (T47D). Most of the synthesized compounds showed good to moderate activity (IC_{50} = 8.8–108.9 μM), where compound **16** (IC_{50} = 8.8 μM) exhibited higher activity compared to doxorubicin (IC_{50} = 9.8 μM). In order to determine the mechanism of the anticancer activity in T47D cells, the effect of the most potent compounds (**5**–**8**, **11**–**14**, and **16**–**18**) on the aromatase activity was tested. Most of the selected compounds showed significant inhibitory effect on the aromatase activity, with compound **18** showing IC_{50} = 4.66 μM. Furthermore, apoptosis studies were conducted on two of the most potent compounds (**8** & **16**) to estimate the proapoptotic potential of our compounds. Both induced the levels of active caspase 3, caspase 8 and caspase 9. Moreover, they surprisingly boosted the Bax/Bcl2 ratio 5936 & 33,000 folds, respectively compared to the control. Moreover, they showed mild cytotoxic effect (IC_{50} = 183.8 μM & 172.04 μM, respectively) in normal breast cells 184A1. Finally, a molecular docking study was performed to investigate the probable interaction with the aromatase enzyme.

1. Introduction

Breast cancer is one of the majority distinguished commonly spread cancer among women in different age groups [1]. It was categorized as the second leading cause of mortality among women. This tumor is illustrated by excess production of estrogen receptors for endogenous estrogens which is equally expressed in pre and postmenopausal breast tissue [2,3]. This accounts for the pathological effects of estrogens triggering cancer cell proliferation. As a matter of fact, intratumoral local estrogen production is controlled by the aromatase enzyme (CYP19), a member of the cytochrome P450 which controls *in situ* aromatization of C19 androgens to C18 estrogens [4,5]. Thus, one of the lucrative therapeutic approaches of treating estrogen-dependent breast cancer is the inhibition of bioconversion of androgens to estrogens by aromatase inhibitors (AIs) as a safer alternative to blockade of estrogen receptors by estrogen receptor antagonists (ERAs) [4–6].

AIs are comprised of two major classes on basis of their structural chemotype; namely steroidal and non-steroidal AIs. By virtue of their fewer incidence of side effects due to lack of estrogenic activity on the uterus and vasculature, non-steroidal AIs are gaining much popularity over the past few decades [6,7].

Recently, Pingaew et al. reported the synthesis of 1, 4-disubstituted-1, 2, 3-triazole derivatives bearing sulfonamide moiety (Fig. 1) which showed significant anti-proliferative activity [10]. This was proved by evaluating their aromatase inhibitory activity [10]. Interestingly, many of the tested sulfonamides exhibited marked aromatase inhibitory activity (IC_{50} = 0.2–9.4 μM).

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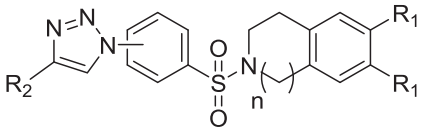
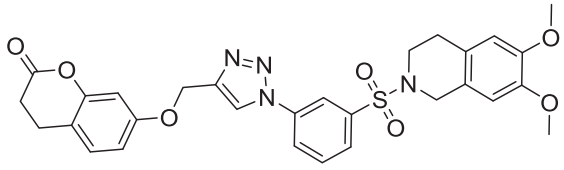


R_1 = H, OMe
R_2 = Ph, -CH_2-OPh
n= 0,1



Lead compound (A)

Fig. 1. Cytotoxic agents revealed by Pingaew et al. [7] and the most active compound (A) against the aromatase enzyme (IC_{50} = 0.2 μM).

Moreover, their molecular docking was adopted to explore their binding modes with the aromatase [10]. The results revealed that most of their active compounds could snugly bind to the aromatase through H-bonding and $\pi-\pi$ stacking without chelation of the heme iron. The most active compound (A) (IC_{50} = 0.2 μM) displayed H-bonding interactions with Met 374 which is suggested to be the essential amino acid residue for the inhibitory activity. This was supported by the fact that such amino acid participated in a water-mediated H-bonding that facilitates the interaction between the aromatase and the C3-keto oxygen of androstanedione (ASD) to undergo enolization; the first step involved in its conversion to estrogen. Compound (A) showed an IC_{50} of 0.2 μM against the aromatase enzyme, thus it represents a good platform for the design of novel non-steroidal AIs [10].

Accordingly, based on their SAR findings we designed a novel series of chromene derivatives carrying different sulfonamide moieties, the designing strategy of which is illustrated in Fig. 2. Our design strategy is three folds; i. tetrahydroisoquiniline ring (THIQ) of the compound (**A**) was replaced with different acyclic and heterocyclic amines aiming to retain hydrophobic interactions with the receptor, ii. The tetrazole ring was replaced with semi-rigid open chain linker, finally, iii. The privileged chromene moiety was preserved to attain proper hydrophobic interaction with CYP19. All of the newly synthesized compounds will be evaluated for their *in vitro* anticancer activity against breast cancer cell line (T47D). It has been reported that the aromatase enzyme is overexpressed in this cell line [11]. Moreover, the most potent molecules will be evaluated for inhibition of the aromatase enzyme. Aromatase inhibition in cancer cells triggers apoptosis which synergistically augments the anti-tumor effect [12]. Considering these literature findings, the apoptotic effect of two of the most potent compounds will be evaluated to trace the apoptotic potency of our compounds. Finally, molecular docking of the compounds with the aromatase enzyme will be performed to explore their binding mode in a proof-of-concept study.

2. Results and discussion

2.1. Chemistry

The aim of this work was to design and synthesize a novel series of benzenesulfonamide incorporating biologically active chromene moieties to evaluate their anticancer activity. Thus, interaction of 3-acetyl-2-*H*-chromen-2-one **1** with dimethylformamide dimethyl acetal (DMF-DMA) under reflux in dry xylene gave the strategic starting material (*E*)-3-(3-(dimethylamino)acryloyl)-2*H*-chromen-2-one **2**. Compound **2** can be represented by three isomeric structures (**2a**–**c**) (Scheme 1). Enaminone **2** was assigned an *E*-configuration based on its ^{1}H-NMR spectrum which exhibited that the coupling constant of the doublet signals for olefinic protons equals to 12.4 Hz correlated to *E*-isomers. The behavior of enaminone **2** towards sulfa-drugs and dapsone was investigated. Thus, when enaminone **2** was reacted with sulfa-drugs and/or dapsone in absolute ethanol and glacial acetic acid (2:1), the corresponding chromene-sulfonamide derivatives **3**–**22** (Schemes 2 and 3) were obtained in good yield. The structures of the obtained compounds were established on the basis of microanalysis, IR, ^{1}H-NMR, ^{13}C-

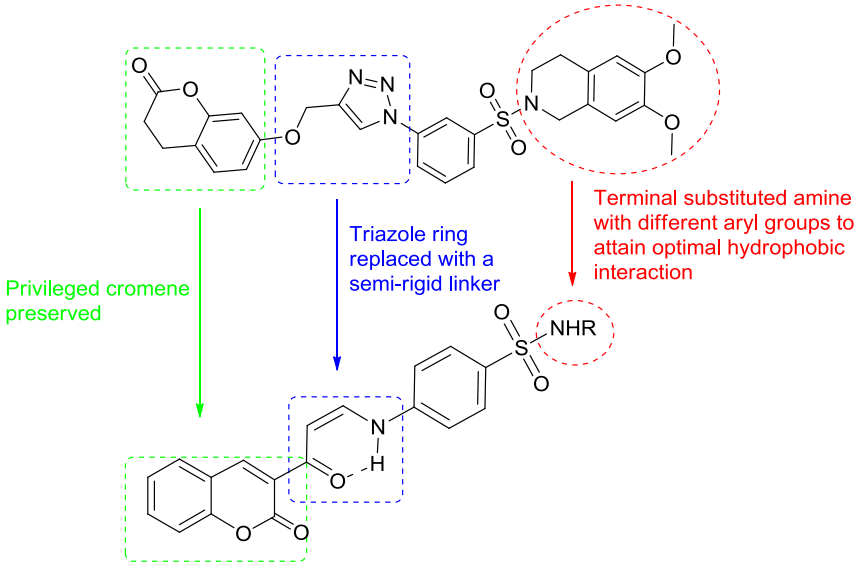


Fig. 2. Analogue-based design of chromene sulfonamide derivatives **3**–**20** as AIs.