Bioorganic & Medicinal Chemistry Letters 23 (2013) 1760–1762

Contents lists available at SciVerse ScienceDirect

Bioorganic & Medicinal Chemistry Letters

journal homepage: www.elsevier.com/locate/bmcl

Design, synthesis and aromatase inhibitory activities of novel indole-imidazole derivatives

Rui Wang, Hong-Fan Shi, Jing-Feng Zhao, Yan-Ping He, Hong-Bin Zhang, Jian-Ping Liu *

Key Laboratory of Medicinal Chemistry for Natural Resource (Yunnan University), Ministry of Education, School of Chemical Science and Technology, Yunnan University, Kunming 650091, PR China

ARTICLE INFO

Article history:
Received 31 October 2012
Revised 9 January 2013
Accepted 15 January 2013
Available online 26 January 2013

Keywords:
Indole-imidazole derivatives
Breast cancer
Aromatase inhibitor (AI)
Structure–activity relationship
Synthesis

ABSTRACT

A series of novel indole-imidazole derivatives have been prepared and evaluated in vitro on the aromatase inhibitory activities. The results suggested that proton or a small electron-withdrawing group at *para*-position of the phenyl ring would enhance the inhibitory activities and any bulky group should be avoided in order to keep a relative small volume for this kind of molecules.

A great majority of breast cancers are hormone-dependent,[1] and it is widely accepted that estrogen plays an important role in the genesis and evolution of breast tumors.[2] Aromatase (CYP19), a cytochrome P450 enzyme, is responsible for the conversion of androgens including androstenedione and testosterone into estrogens,[3] therefore it is considered as a particularly attractive target for inhibition in the endocrine treatment of hormone-dependent breast cancer. Non-steroidal aromatase inhibitors (NSAIs, Fig. 1), such as aminoglutethimide (**1**),[4] anastrozole (**2**, Arimidex™)[5] and letrozole (**3**, Femara™),[6] competitively inhibit the enzymatic activity of aromatase in a reversible manner and play an important role in the endocrine treatment for hormone-dependent breast cancers.

Potent AIs still remain an attractive subject, and lots of interesting compounds have been developed by different groups working in this field.[7–10] Recently, with letrozole as led compound, we designed and prepared several series of potential AI compounds. In order to find some more suitable structures for AI activities, compared with the led compound, our research focused on the geometry and molecular flexibility changes of the designed compounds. We also made an imidazole group in our designed molecules to keep it connected with oxyferryl of the haem group in the structure of aromatase according to Ghosh's discovery.[11]

In this Letter, we designed a novel class of indole-imidazole derivatives (**10a–s**, Fig. 1) based on some structure–activity relationship studies[12–19] which reported that indole derivatives, such as compound **4** (Fig. 1),[18] showed a high potent as aromatase inhibitors. Compared with letrozole and compound **4**, phenyl group was moved from central methine to the nitrogen atom in indole ring. This movement would make two hydrophobic aromatic rings closer, and at the same time newly formed methylene group in the molecules **10a–s** would make the connected angles and possible configurations between two hydrophobic aromatic rings and imidazole group more flexible. Here we reported the synthesis and primary aromatase inhibitory activities of the new derivatives and to the best of our knowledge, there were no such compounds reported.

Our synthesis journey was shown in Scheme 1. The precursors **6a–d** were synthesized by aldol condensation of ethyl azidoacetate and commercially available 4-substituted benzaldehydes **5a–d** in the presence of sodium ethoxide.[20] The key step in the formation of the 6-substituted indoles skeleton intermediates **7a–d** was readily accomplished by using $Rh_2(OAc)_4$ as a catalyst,[21,22] refluxing in toluene. The corresponding compounds **8a–s** were prepared from precursors **7a–d** by arylation with a set of 4-substituted bromobenzenes,[23] and further reduced to corresponding alcohols **9a–s**. Finally, the target compounds **10a–s** were prepared by treatment of *N*-phenyl-indole alcohols **9a–s** with 1,1′-carbonyldiimidazole (CDI) in dry acetonitrile.[24,25] The structures of all target compounds, as well as main intermediates, were confirmed mainly by proton and carbon-13 NMR spectroscopy. Compound **10d** was further verified by the single X-ray crystallography (Fig. 2).[26] The crystal structure of compound **10d** had been deposited at the Cambridge Crystallographic Data Centre and allocated the deposition number CCDC 869637.

* Corresponding author. Tel.: +86 871 5031119; fax: +86 871 5035538.
E-mail address: jpliu@ynu.edu.cn (J.-P. Liu).

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http://dx.doi.org/10.1016/j.bmcl.2013.01.045

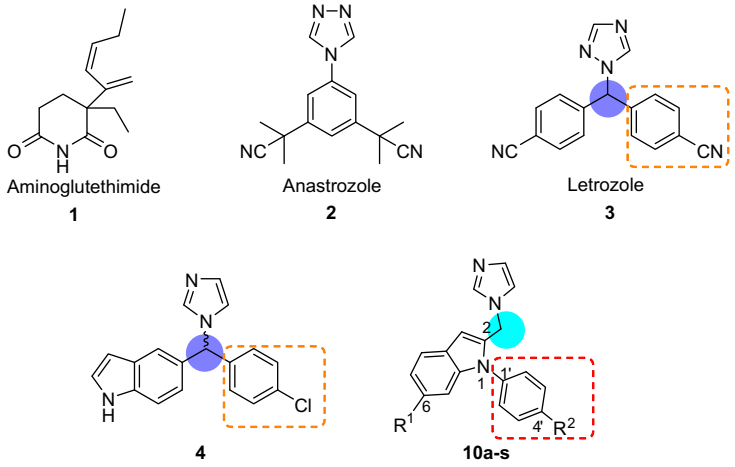
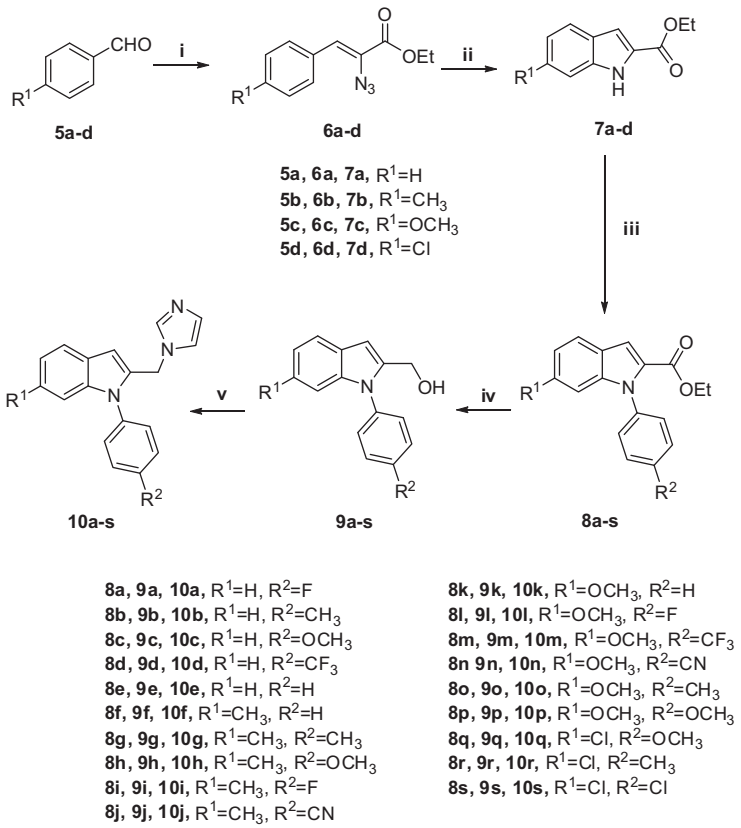


Figure 1. Non-steroidal aromatase inhibitors (NSAIs).



Scheme 1. Synthesis of indole-imidazole derivatives. Reagents and conditions: (i) N_2CH_2COOEt, NaOEt, −50 °C, 8–12 h, 38.6–59.4%; (ii) $Rh_2(OAc)_4$, toluene, reflux, 1–2 h, 51.7–58.6%; (iii) $BrC_6H_4R^2$, K_3PO_4, CuI, *N*,*N*′-dimethylehtylenediamine, toluene, reflux, 24 h, 50.7–81.6%; (iv) LAH, THF, 0 °C to rt, 0.5–4 h, 51.3–87.9%; (v) CDI, CH_3CN, 48–72 h, 71.6–89.1%.

The primary aromatase inhibitory activities of all new compounds were determined according to the reported method,[27–29] with human placental microsomes served as source of P450 arom, and ELISA assay (EIA method) was used to measure the estrone level with commercial estrone ELISA kit.[30] The results were summarized in Table 1 (IC_{50} value, defined as the concentrations corresponding to 50% activity inhibition).

As shown in Table 1, potential AI efficacies of structural variation in the C-6 position of the indole ring and *para*-position of the phenyl group were explored. Most of the test compounds exhibited moderate activities in the aromatase inhibition assay. Compound **10e**, with no substituted group in both C-6 and C-4′, showed nearly the same AI activity as letrozole, while compound **10d**, with trifluoromethyl (CF_3) group at C-4′, showed the highest potent inhibitory activity against aromatase and over 3-fold higher than that of letrozole. Trifluoromethyl group, an interesting building block in the drug constructions,[31–33] which possibly increased aromatase–small molecule interaction with its electron-withdrawing and metabolic stability properties, is worth further studies and should be pay more attention in the future AI drug candidates. It was observed from Table 1 that the compounds with proton or a small electron-withdrawing group at C-4′ tended to enhance the inhibitory activities while those with electron-donating group exhibited lower activities. Generally AI activities of the compounds decreased when proton at C-6 position of the indolyl group was replaced by other bulky groups, but **10k** exhibited an excep-

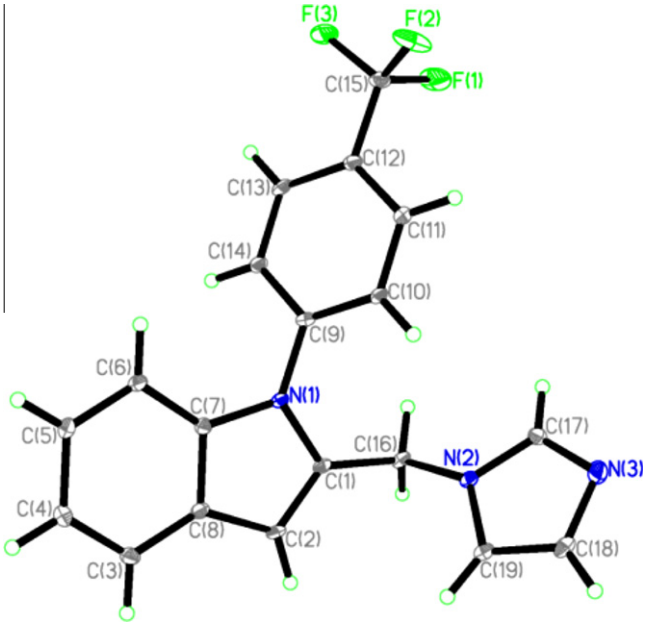


Figure 2. Ortep diagram of compound **10d**.

Table 1
Structures and in vitro CYP19 inhibitory activities of indole-imidazole derivatives **10a–s**

Compounds	R^1	R^2	IC_{50}[a] (nM)	RP[b]
10a	H	F	9.01 ± 0.62	1.8346
10b	H	CH_3	148.93 ± 12.61	0.1110
10c	H	OCH_3	77.36 ± 6.31	0.2137
10d	H	CF_3	4.93 ± 0.23	3.3529
10e	H	H	16.58 ± 1.39	0.9970
10f	CH_3	H	21.39 ± 1.76	0.7728
10g	CH_3	CH_3	164.01 ± 14.63	0.1008
10h	CH_3	OCH_3	138.72 ± 11.46	0.1192
10i	CH_3	F	56.83 ± 5.18	0.2909
10j	CH_3	CN	27.01 ± 1.92	0.6120
10k	OCH_3	H	6.23 ± 0.51	2.6576
10l	OCH_3	F	48.93 ± 4.36	0.3378
10m	OCH_3	CF_3	25.56 ± 2.14	0.6467
10n	OCH_3	CN	46.92 ± 4.13	0.3523
10o	OCH_3	CH_3	57.43 ± 4.96	0.2878
10p	OCH_3	OCH_3	111.09 ± 10.47	0.1488
10q	Cl	OCH_3	203.34 ± 18.91	0.0813
10r	Cl	CH_3	235.33 ± 22.49	0.0702
10s	Cl	Cl	217.43 ± 20.67	0.0760
Letrozole	—	—	16.53 ± 1.24	1.00

[a] Values are the mean of at least three experiments performed in triplicate.
[b] Relative potency RP = IC_{50} (letrozole)/IC_{50} (tested compound).

tionally higher IC_{50}. According to Ghosh et al. report,[11] the volume of the binding pocket of aromatase is no more than 400 Å^3. Since the volume of compound **10d** is about 390 Å^3 from our X-ray crystallographic data, it is obvious that any bulky group attached to our derivatives would make the whole volume of the derivatives too big to fit into aromatase properly.

In conclusion, some 1-aryl-2-((1*H*-imidazol-1-yl)methyl)-6-substituted-1*H*-indole compounds were synthesized and potential AI activities of these compounds were studied. It was showed that proton or a small electron-withdrawing groups on the C-4′ position of the phenyl ring, connected to the indole nitrogen, might enhance AI activities, and any bulky group should be avoided in order to keep a relative small value for these kinds of molecules. The similar derivatives of imidazole group replaced by triazole or other heterocycle groups were also under investigation.

Acknowledgments

This research was supported by the National Natural Science Foundation of China (Grant No. 20562012, 21162033) and the National Basic Research Program of China (973 Program: 2009CB522300). We would like to acknowledge Dr. Meng-Xiang Su, China Pharmaceutical University, Mr. Hong-Jun Kang, Kunming Baker Norton Pharmaceutical Co., Ltd, for their great help and discussion in vitro AI tests.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bmcl.2013.01.045.

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