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# Discovery of a novel class of aldol-derived 1,2,3-triazoles: Potent and selective inhibitors of human cytochrome P450 19A1 (aromatase)

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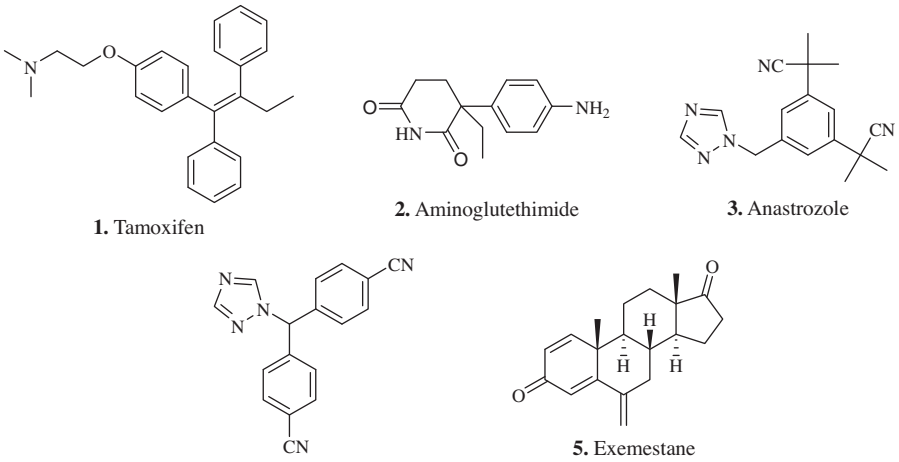
ABSTRACT

The discovery of a novel five-component 1,2,3-triazole-containing pharmacophore that exhibits potent and selective inhibition of aromatase (CYP 450 19A1) is described. All compounds are derived from an initial aldol reaction of a phenylacetate derivative with an aromatic aldehyde. Structure–activity data generated from both *syn*- and *anti*-aldol adducts provides initial insights into the requirements for both potency and selectivity.



Cancer is a leading cause of mortality among women, with breast cancer alone comprising 30%[1,2] of all new cases (estimated 230,480 cases) diagnosed in the US in 2011.[2] Currently, one out of eight American women will develop breast cancer in her lifetime.[2] Approximately 70–80% of postmenopausal breast cancer patients have hormone-dependent (estrogen-dependent) breast




**1.** Tamoxifen **2.** Aminoglutethimide **3.** Anastrozole **4.** Letrozole **5.** Exemestane

**Scheme 1.** Commonly used drugs for the treatment of breast cancer, including the estrogen receptor antagonist tamoxifen **1**, non-steroidal aromatase inhibitors aminoglutethimide **2**, Anastrozole **3** and Letrozole **4** as well as the steroidal aromatase inhibitor exemestane **5**.

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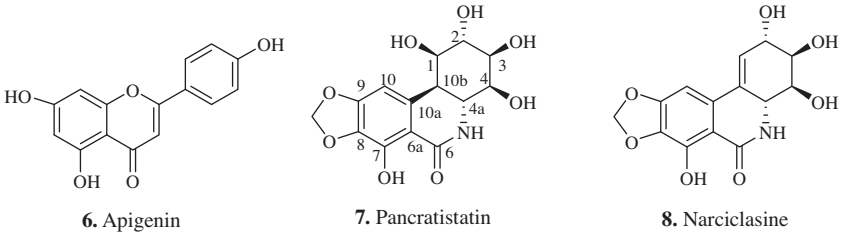
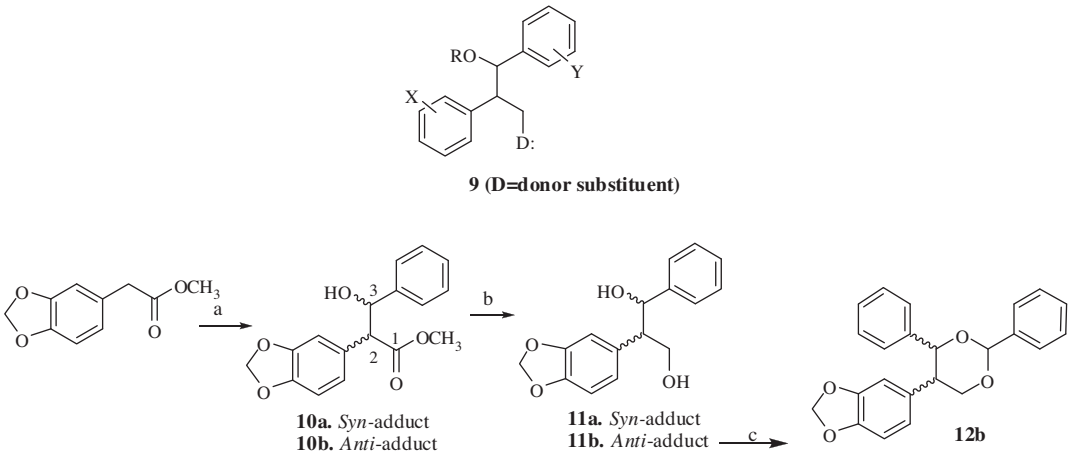



**Scheme 2.** Flavonoid aromatase inhibitor apigenin **6**, as well as cytotoxic alkaloid representatives of the Amaryllidaceae including pancratistatin **7** and narciclasine **8**.




**Scheme 3.** Anti-selective aldol reaction of methyl (3,4-methylenedioxy)phenylacetate and benzaldehyde. Reagents and conditions: (a) LiHMDS, THF, −78 °C to rt, 3 h, 90%; (b) $LiAlH_4$, THF, 0 °C to rt, 3 h, 95%; (c) BDMA, TsOH, DCM, rt, 1 h, 94%.

cancer.[3] For over two decades tamoxifen **1** (Scheme 1) has been used as the standard anti-estrogen in treating such tumors.[4a–f] Tamoxifen and its metabolites function as selective estrogen receptor modulators (SERM).[4f] Their antagonist action in breast tissue prevents estrogen binding and resulting downstream effects that include cancer cell proliferation and the activation of survival and anti-apoptosis pathways.[4d,e] Estradiol, the most potent endogenous estrogen, is biosynthesized from androgens by the cytochrome P450 19A1 enzyme complex (CYP19A1) called aromatase.[5] Aromatase activity has been demonstrated in breast tissue in vitro and expression of aromatase shown to be highest in or near breast tumor sites.[5d–f] Aromatase inhibitors (AIs) have emerged over the last 15 years as modulators of the growth-stimulatory effects of estrogens in estrogen-dependent breast cancer. Nonsteroidal aromatase inhibitors can be divided into three classes (Scheme 1) as aminoglutethimide-like **2** molecules, imidazole/triazole derivatives, and flavonoids.[6] Anastrozole **3** and Letrozole **4** are currently approved AIs for the treatment of metastatic estrogen-dependent breast cancer.[6e–j] Steroidal inhibitors that have been developed to date, such as Exemestane **5**, build upon the basic androstenedione nucleus and incorporate substituents at varying positions on the steroid.[6k] Use of an aromatase inhibitor as initial therapy, or after treatment with tamoxifen is now recommended as adjuvant hormonal therapy for postmenopausal women with hormone-dependent breast cancer.[3] Despite their clinical success, negative side effects and partial selectivity of existing AIs are significant issues which must be addressed. AIs are associated with osteoporosis, reproductive problems and androgenic side effects. These compounds also partly inhibit cytochromes 1A1, 1A2, 2D6, 2C8/9 and 3A4, all of which are involved in the metabolism of xenobiotics, thus increasing the likelihood of drug–drug interactions in patients. These factors in combination necessitate the development of more selective AIs for the treatment of ER positive breast cancer. The activity of flavonoids as aromatase inhibitors has been demonstrated both in vitro and in vivo.[6l,m] We recently

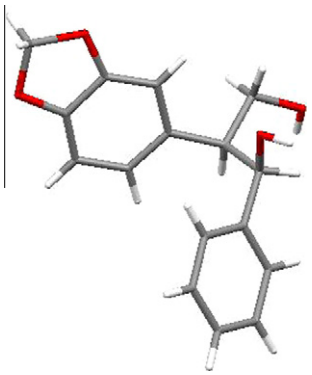


**Figure 1.** X-ray structure of *syn*-aldol derived 1,3-diol **11a**.

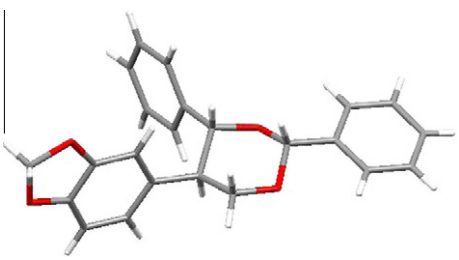
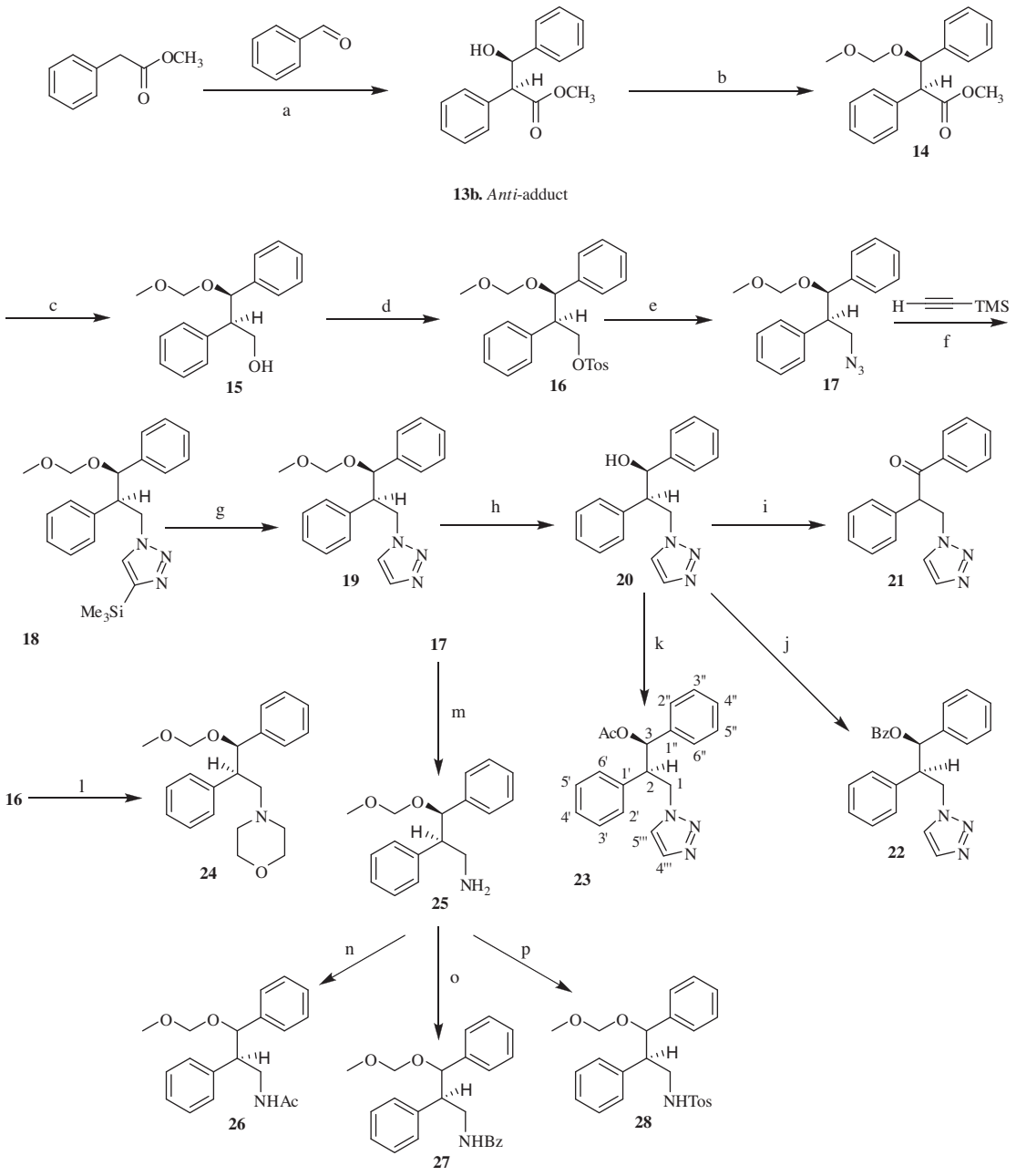


**Figure 2.** X-ray structure of *anti*-aldol derived benzylidene **12b**.

reported the non-selective aromatase inhibitory activity of several flavonoids, with apigenin **6** (Scheme 2) being the most active ($K_i$ 1.0 μM).[6n]

Our research group has been involved in several areas of research pertaining to alkaloids of the Amaryllidaceae,[7] including the polyhydroxylated isoquinolines pancratistatin **7** and narciclasine **8** (Scheme 2).[8] Both compounds exhibit potent antiproliferative activity to a number of cancer cell lines.[8c] In addition to cytotoxic activity, we have monitored P450 activities in order to gauge off-target effects, for example we demonstrated several pancratistatin and seco-analogs to exhibit potent human cytochrome P450 3A4 inhibitory activity.[7l–p] Structural analysis of compounds **2–4**, **6–8** and our synthetic SAR studies[7] revealed to us a possible common pharmacophore, depicted as the general structure **9** (Scheme 3). This novel composition consists of five independent fragments (two functionalized aryl rings, one oxygenated substituent, one donor-substituent and a core unit of undefined stereochemistry). In this letter, we report the synthesis of a range of derivatives of this structural type and the development of potent and selective AIs based on this scaffold.

We elected to pursue an aldol-based approach to compounds of type **9**, based on earlier work involving *anti*-[7i,k] and *syn*-selective[7n] directed aldol reactions of phenylacetates. The selective generation of (*E*)- or (*Z*)-enolates of phenylacetic esters[9] and aldol reaction with aromatic aldehydes leads to the respective *anti*- or *syn*-aldol adducts.[9h,i] In the present case, we wished to access both *syn*- and *anti*-diasteromers in order to assess activity in both series. The reaction of the lithium enolate of methyl 3,4-methylenedioxyphenylacetate




**Scheme 4.** Synthesis of functionalized 1,2,3-triazoles and derivatives in the *anti*-aldol series. Reagents and conditions: (a) LiHMDS, −78 °C to rt, 3 h, 90%; (b) MOMCl, DIPEA, DCM, 0 °C to rt, 8 h, 95%; (c) $LiAlH_4$, THF, 0 °C to rt, 3 h, 91%; (d) TosCl, py, DCM, rt, 5 h, 93%; (e) $NaN_3$, DMF, rt, 6 h, 83%; (f) Cu(I)I, THF, rt, 8 h, 83%; (g) TBAF, THF, rt, 8 h, 98%; (h) 5 M HCl, THF, rt, 7 h, 86%; (i) Swern, DCM, −78 °C to rt, 3 h, 96%; (j) BzCl, py, DCM, rt, 3 h, 98%; (k) $Ac_2O$, py, DCM, rt, 3 h, 95%; (l) morpholine, 60 °C, 6 h, 82%; (m) 10% Pd/C, $H_2$, rt, 7 h, 94%; (n) $Ac_2O$, TEA, DCM, rt, 3 h, 98%; (o) BzCl, TEA, DCM, rt, 3 h, 98%; (p) TosCl, TEA, DCM, rt, 3 h, 98%.

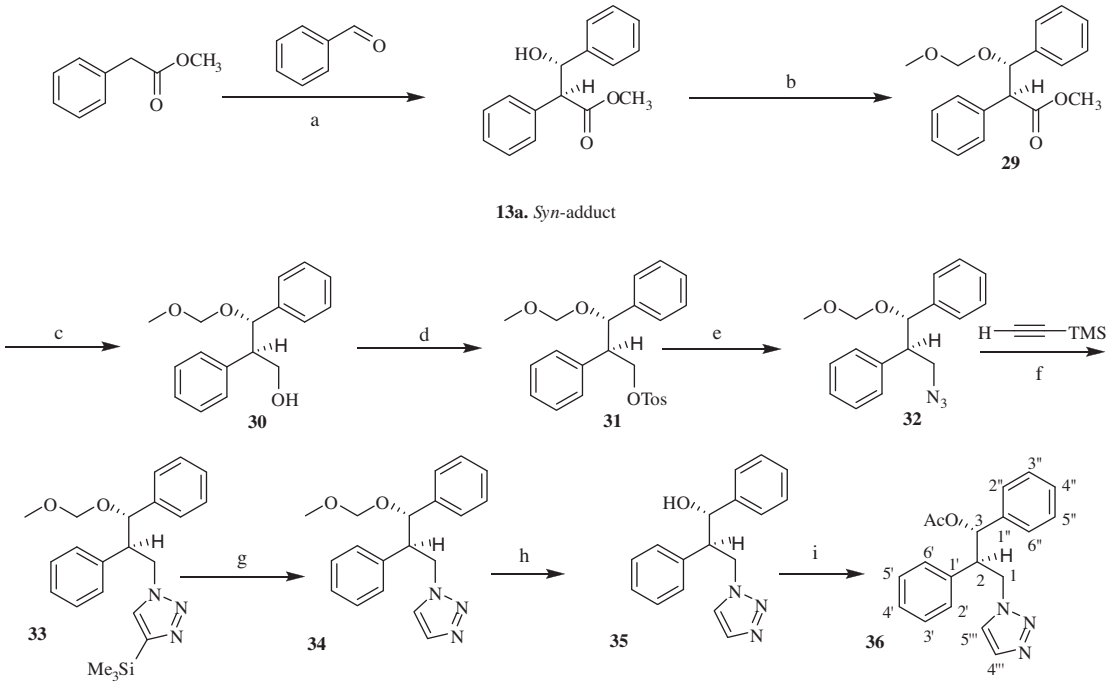
with benzaldehyde yielded a 40:60 mixture of the *syn*- and *anti*-aldol adducts **10a** and **10b**, in 90% isolated yield (Scheme 3).[9j] The aldol adducts were readily separated on silica-gel on a gram scale and the stereochemistry of both adducts proven through X-ray analysis. The adducts were independently reduced to the corresponding 1,3-diols **11a** and **11b**. The relative configuration of **11a** as the *syn*-aldol derivative was proven directly (Fig. 1), while conversion of **11b** to its crystalline benzylidene adduct **12b** (Fig. 2) confirmed its origin from the *anti*-aldol adduct. The slight *anti*-selectivity of this Li-mediated aldol reaction was thus confirmed, in accord with prior studies.[9f,j]

We focused first on conversion of the major *anti*-aldol derivative **13b**, prepared as outlined in Scheme 4, to the desired prototype **9**. Protection of the 3-hydroxy group in **13b** as the MOM ether followed by $LiAlH_4$ reduction of ester **14** gave alcohol **15** in 91% yield. The primary hydroxyl group in **15** was converted to tosylate **16**, which subsequently underwent smooth displacement with sodium azide over 6 h at room temperature in DMF to give azide **17** (83% isolated yield). Under 'Click' chemistry conditions,[10] azide **17** was converted to the TMS-triazole **18** upon reaction with ethynyl trimethylsilane. Desilylation with TBAF at room temperature then gave the free 1,2,3-triazole **19** efficiently. The hydroxy triazole **20** was obtained directly from **19** after hydrolysis with 5 M HCl in THF and subsequently converted via Swern oxidation to the oxo-triazole **21**, and separately to the benzoate **22** and acetate **23**, all in near quantitative yields. Tosylate **16** was also easily displaced with neat morpholine at 60 °C leading to **24**. Reduction of azide **17** with hydrogen over 10% palladium on carbon provided the free amine **25** which was used without further purification in the subsequent conversion to acetamide **26**, benzamide **27** and tosylamide **28**, respectively.

The *anti*-aldol derived derivatives **13–28** were screened for activity against recombinant human aromatase allowing us to identify the triazoles **19**, **22** and **23** as active AI's. We will return to a full discussion on these activities shortly. The initial results allowed us to focus on a more limited selection of *syn*-aldol derived triazoles that were now accessed as outlined in Scheme 5. The *syn*-aldol adduct **13a** was protected as the MOM ether **29**, and converted to azide **32** via a similar reduction, tosylation azido-substitution sequence. Huisgen-cylization gave the TMS-protected triazole **33** which was converted to derivatives **34**, **35** and **36** using the methods established in the *anti*-series.

Compounds **13a–36** were also screened against recombinant human aromatase via kinetic monitoring of the conversion of *O*-dibenzylfluorescein benzyl ester (DBF) substrate to fluorescein by-product.[6n] Fluorometric measurement of emission was made at 535 nm after excitation at 485 nm utilizing ketoconazole as a positive control, as recently reported.[6n] Azide **17** and TMS-triazole **18** proved to be inactive, while hydrolysis of the TMS group produced the active deprotected triazole **19** with $K_i$ 0.79 μM. Cleavage of the MOM group from **19** gave hydroxy triazole **20** which was inactive, while oxidation of **20** to the oxo-triazole **21** resulted in recovered activity ($K_i$ = 1.0 μM). Acylation at C3 was observed to exert a pronounced effect on AI activity. Conversion of **20** to the triazole benzoate **22** ($K_i$ 0.1 μM) and the triazole acetate **23** ($K_i$ 0.06 μM) led to the discovery of potent inhibitors in the *anti*-series. These results were not completely unexpected. Previous studies from our group on cytochrome P450 3A4 inhibitory activities in the natural alkaloid series,[7m,o] as well as synthetic aldol-derived *seco*-analogs[7l,n] revealed the importance of substituents at this position. In moving to the *syn*-aldol series, all new compounds shown in Scheme 5 were screened allowing us to identify the three derivatives **34**, **35** and **36** as potent aromatase inhibitors. The overall SAR data showed that potent inhibitors can be realized in either the *syn*- or *anti*- series, most likely due to conformational flexibility, but that the magnitude is critically dependant on the C3 oxy-substituent. A free triazole is required at the C1 position in accord with the expectation on the role of this substituent as a donor-group (**9**, Scheme 3) binding to the Fe-core of the enzyme.

In order to gauge selectivity, we also screened select active aromatase inhibitors **21**, **22**, **23**, **34**, **35** and **36** against cytochromes P450 3A4, 1A1, and 2D6, results are summarized in Table 1. All compounds proved to be non-inhibitors of CYP3A4 at the initial 10 μM concentration. Compounds **21** and **22** showed moderate activity to CYP1A1, exhibiting $pK_i$(M) values of 5.27 (±0.04) and




**Scheme 5.** Synthesis of functionalized 1,2,3-triazoles in the *syn*-aldol series. Reagents and conditions: (a) LiHMDS, −78 °C to rt, 3 h, 90%; (b) MOMCl, DIPEA, DCM, 0 °C to rt, 8 h, 88%; (c) $LiAlH_4$, THF, 0 °C to rt, 3 h, 90%; (d) TosCl, py, DCM, rt, 5 h, 85%; (e) $NaN_3$, DMF, rt, 6 h, 86%; (f) Cu(I)I, THF, rt, 8 h, 80%; (g) TBAF, THF, rt, 8 h, 95%; (h) 5 M HCl, THF, rt, 7 h, 70%; (i) $Ac_2O$, py, DCM, rt, 3 h, 88%.

**Table 1**
Effect of 1,2,3-triazoles on the catalytic ability of recombinant human aromatase

| Compound | $K_i$ (μM) | $pK_i$[a] (M) |
|---|---|---|
| **17** | na | — |
| **18** | na | — |
| **19** | 0.79 | 6.1 (±0.3) |
| **20** | na | — |
| **21** | 1.00 | 6.0 (±0.3) |
| **22** | 0.10 | 7.0 (±0.5) |
| **23** | 0.06 | 7.2 (±0.3) |
| **24** | na | — |
| **25** | na | — |
| **32** | na | — |
| **33** | na | — |
| **34** | 0.08 | 7.1 (±0.1) |
| **35** | 0.05 | 7.3 (±0.1) |
| **36** | 0.25 | 6.6 (±0.1) |
| Ketoconazole | 0.40 | 6.4 (±0.3) |

[a] Values are means of three experiments, standard deviation is given in parentheses (na = not active at 10 μM).

4.51 (±0.12), respectively. In terms of 2D6 activity, only compounds **19** and **35** showed weak activity, exhibiting $pK_i$(M) values of 2.95 and 3.15, respectively. Both Anastrozole **3** and Letrozole **4** are known to inhibit the CYP3A4 isoenzyme,[11a] responsible for detoxification of the majority of xenobiotics such as drugs and environmental toxins.[11b] The SAR-based results in this study validate our initial hypothesis based on general structure **9** and highlight the potential of this novel triazole aromatase inhibitory pharmacophore towards the discovery of both potent and selective AI's.

In summary, a novel class of 1,2,3-triazole was generated through a concise synthetic strategy involving an aldol reaction of methyl phenylacetate with benzaldehyde. Several triazoles derived from both the *syn*- and *anti*-adducts were shown to be selective inhibitors of the enzyme aromatase, of significance in the therapeutic approach towards breast cancer. The most potent of these triazoles (*anti*-triazole acetate **23**, and *syn*-triazole alcohol **35**) exhibited selective aromatase inhibitory activity with potency as low as 50 nM. Fragment-based refinement of the present inhibitors through functionalization of the aryl-residues in order to elucidate this novel pharmacophore model further and the investigation of in vivo activity in a cell-based model is currently under investigation.

## Acknowledgments

We thank NSERC and McMaster University for financial support of this work.

## Supplementary data

Experimental procedures and characterization data are provided. CCDC files 785411 and 785412 contain the supplementary crystallographic data for compounds **11a** and **12b**. These data can be obtained free of charge from The Cambridge Crystallography Data Centre via www.ccdc.cam.ac.uk/data_requestcif.html.

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2011.10.039.

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