Full Paper

Synthesis and Biological Evaluation of Phenyl Substituted 1*H*-1,2,4-Triazoles as Non-Steroidal Inhibitors of 17β-Hydroxysteroid Dehydrogenase Type 2

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A series of disubstituted-1*H*-1,2,4-triazole derivatives was synthesized with the aim of developing new non-steroidal inhibitors of 17β-hydroxysteroid dehydrogenase type 2 (17βHSD2) – a novel and attractive target for the treatment of osteoporosis. 17βHSD2 catalyzes the oxidation of the highly active estrogen 17β-estradiol (E2) and androgen testosterone (T) into the weak estrone and androstenedione, respectively. Inhibition of this enzyme will locally in the bone lead to an increase in E2 and T levels, two key players in the maintenance of the balance between bone resorption and bone formation. In this study, a new class of 17βHSD2 inhibitors with a 1*H*-1,2,4-triazole scaffold was identified; the three best compounds **8b**, **8f**, and **13a** showed moderate 17βHSD2 inhibitory activity and a good selectivity toward 17βHSD1. They could be a useful tool to map the unexplored enzyme active site.

Keywords: 17βHSD2 / Disubstituted 1*H*-1,2,4-triazoles / Non-steroidal inhibitor / Osteoporosis / Steroidomimetics

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Introduction

17β-Hydroxysteroid dehydrogenases (17βHSDs) catalyze the NAD(P)(H)-dependent interconversion of 17β-hydroxy- and 17-ketosteroids [1]. As both androgens and estrogens display their maximal biological activity in the reduced (17β-hydroxy) form, 17βHSDs play a central role in the regulation of the biological activity of sex steroids. 17βHSD activity is not limited to steroidogenic tissues, it is also found in a number of other tissues. The occurrence of activating and deactivating 17βHSDs is tissue-specific, thus allowing for local adjustment of hormone action. Selective inhibition of enzymes involved in the intracellular adjustment of hormone action is a valuable tool for the treatment of hormone-sensitive diseases as it has the prospect of less side-effects compared to systemic hormonal treatments. This concept was first described for 11βHSDs [2] and has already been successfully applied by our group for several enzymes like aromatase [3–5], CYP17 [6–9], 17βHSD1 [10–18], 5α-reductase [19–23], CYP11B1 [24, 25], and CYP11B2 [26–29].

An intriguing new application for inhibitors interfering with tissue specific modulation of hormone activity may be osteoporosis. This skeletal disease is characterized by low bone mass and deterioration of bone tissue. The disease often affects elderly women and can be linked to a drop of 17β-estradiol (E2) levels after menopause. 17β-Hydroxysteroid dehydrogenase type 2 [30] (17βHSD2) oxidizes E2 into its inactive form estrone (E1, Chart 1) and is expressed in osteoblastic cells which are responsible for bone formation. In addition, androgens are also known to have beneficial effects on bone formation [31, 32]. Testosterone, for example, is also a substrate of 17βHSD2. This enzyme is, therefore, an attractive target for the treatment of osteoporosis. It has been validated by Bagi et al. [33] by using an *in vivo* monkey model. Not to counteract the therapeutic concept, the type 1 enzyme catalyzing the reverse reaction (reduction of E1 to E2, Chart 1) should not be inhibited. Beside the hydroxyphenylnaphthol **A** (Chart 2) described by our group [34, 35], there is only one

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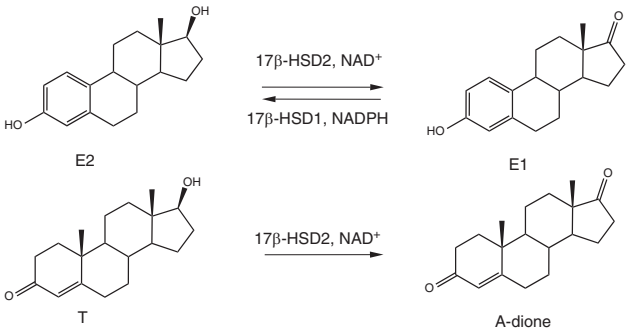


Chart 1. Interconversion of E2 into estrone (E1) and of testosterone (T) into androstenedione (A-dione) by 17**β**HSD2 and 17**β**HSD1.

class of non-steroidal 17βHSD2 inhibitors reported in the literature: the *cis*-pyrrolidinones like the *in vitro* highly active compound **B** (IC_{50} = 50 nM in cell-free assay [36], Chart 2). The latter compound was tested in the monkey model and had shown moderate effects [33]. This underlines the need for the discovery of new, more potent 17βHSD2 inhibitors.

In an earlier study [37], different bis(hydroxyphenyl)substituted heterocycles were evaluated for inhibition of 17βHSD1 and 2. Interestingly, 1*H*-1,2,3-triazole **C** (Chart 2) turned out to be a moderate inhibitor of 17βHSD1 (IC_{50} = 830 nM), showing good selectivity toward 17βHSD2 while the substituted 1*H*-1,2,4-triazole **D** (Chart 2), differing from **C** in the presence of a phenyl group on the triazole moiety and the shift of a nitrogen in the heterocycle, was active on the type 2 enzyme only (44% inhibition at 1 μM). The methylated 1*H*-1,2,4-triazole analogue **E** was slightly less active but still selective toward the type 1 enzyme (21% inhibition at 1 μM). These results caused us to investigate

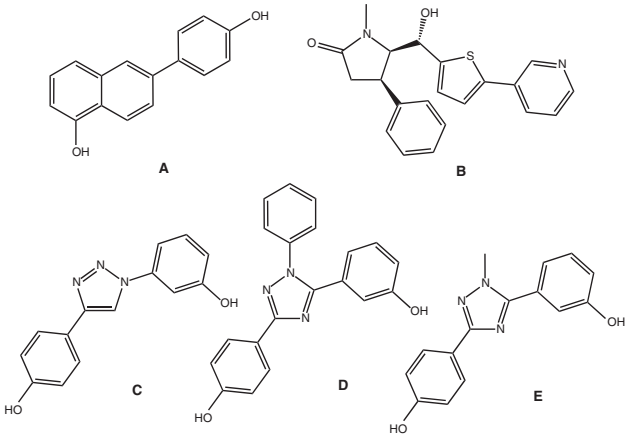


Chart 2. Described inhibitors of 17βHSD2.

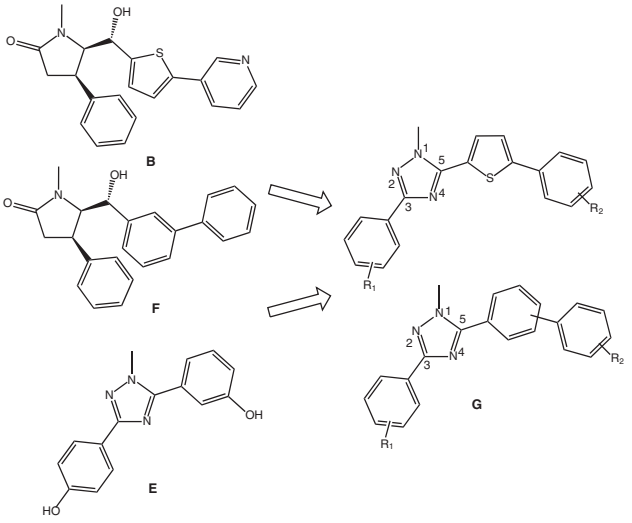


Chart 3. Designed compounds.

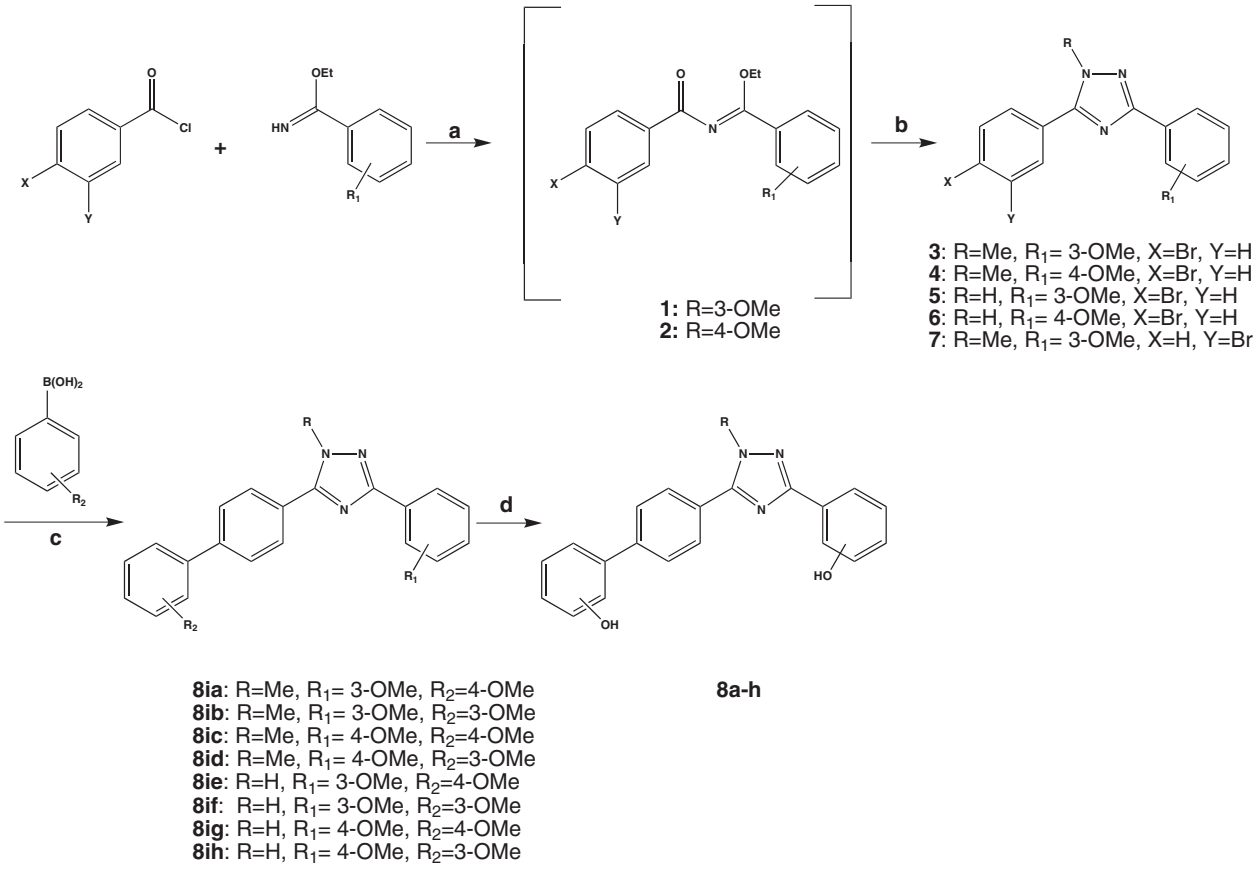
this compound class more thoroughly, trying to improve 17βHSD2 inhibitory activity. As the target enzyme is associated with the ER membrane there is unfortunately no 3D-structure available (neither crystal structure nor homology model has been described to date). Therefore, we followed a ligand-based drug design approach focusing on the two *cis*-pyrrolidinone derivatives **B** and **F** (Chart 3) as the triazole moiety in **D** and **E** is a bioisostere of the amide function present in the pyrrolidinone **B**. It was then hypothesized that the thienopyridyl or the diphenyl moiety present in the *cis*-pyrrolidinones **B** and **F**, respectively, might be important for inhibitory activity as well as the methyl group and should be combined and added to the 1*H*-1,2,4-triazole moiety leading to derivatives **G** (Chart 3).

Based on this hypothesis, in the present study *N*-methyl-1*H*-1,2,4-triazoles bearing an hydroxyphenyl group at C-3 and a biphenyl or aryl-2-thienyl residue at C-5 were designed, synthesized, and evaluated for their 17βHSD2 and 1 inhibitory activities (Chart 3).

Results and discussion

Chemistry

Triazole derivatives **8a–h**, **8ia–8iq**, and **9** bearing substituted phenyl rings at the C-3 position and substituted biphenyl residues at the C-5 position were synthesized according to the route described in Schemes 1 and 2. The 1*H*-1,2,4-triazole moiety was prepared in a two steps reaction: first nucleophilic substitution of the ethyl imino ester to the acyl chloride afforded the *N*-acyliminoester intermediates **1** and **2** (both not isolated). Subsequently nucleophilic addition of



Reagents and conditions: [a] CH_2Cl_2, NEt_3, 30–35 °C, 6 h; [b] for compounds **3**, **4** $MeNHNH_2$ and for compounds **5**, **6** $NH_2NH_2.H_2O$, CH_2Cl_2, 30–40 °C, 4 h; [c] $NaHCO_3$, $Pd(Ph_3)_4$, DMF, microwave irradiation 15 min, 150 °C, 100 W, 15 bar; [d] $BF_3.SM_2$, CH_2Cl_2, rt, 20 h.

Scheme 1. Synthesis of compounds **8a–h**.

hydrazine or methylhydrazine and cyclization led to the brominated 1*H*-1,2,4-triazoles **3–7**. Suzuki coupling between the bromo derivatives **3–7** and the appropriate boronic acid under standard conditions afforded compounds **8ia–8iq**. Ether cleavage using $BF_3.SMe_2$ led to the hydroxylated phenyl derivatives **8a–h** and **9** in 44–74 and 68% yield, respectively.

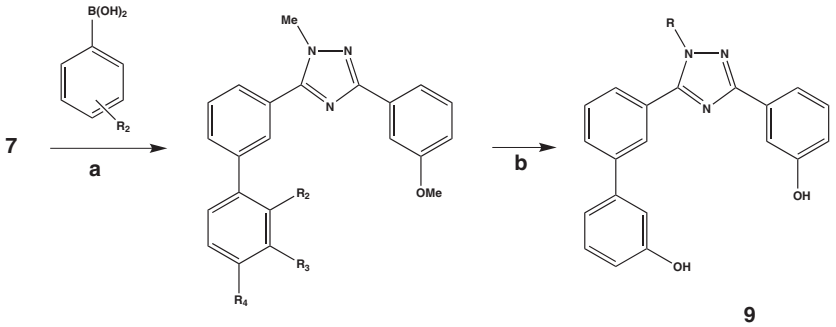
The synthesis of the 1*H*-1,2,4-triazole arylthiophene derivatives **13a–c** was performed following a similar pathway as described for the biphenyl compounds **8ia–ip** in 54–62% yield (Scheme 3) using the brominated thiophene triazole **11** as key intermediate in the cross-coupling reaction. The cleavage of the methoxy groups afforded the final compounds **13a–c** using $BF_3.SMe_2$.

The physical characteristics observed in the ^1H NMR and ^{13}C NMR spectra (including DEPT experiments) and LC-MS spectra of all new prepared compounds are in total agreement with the suggested structures.

Biological evaluation and discussion

The synthesized compounds were tested for inhibitory activity in a cell-free assay using human placental enzymes. For 17βHSD2 the microsomal fraction and for 17βHSD1 the cytosolic fraction were used as described earlier with minor modifications [38]. Results are shown in Table 1 as percentage inhibition measured at a concentration of 1 μM. Compounds showing less than 10% inhibition at 1 μM were considered to be inactive. For the sake of clarity in this manuscript and to be able to distinguish the two hydroxyphenyl moities, they were named A- and B-ring, respectively (Table 1).

The most active compounds **8b**, **8f**, and **13a** show inhibition of the target enzyme of 42, 20, and 30%, respectively (Table 1). It is interesting to notice that all these compounds bear one hydroxy group on each phenyl ring (A and B) while the corresponding methoxy derivatives are all inactive

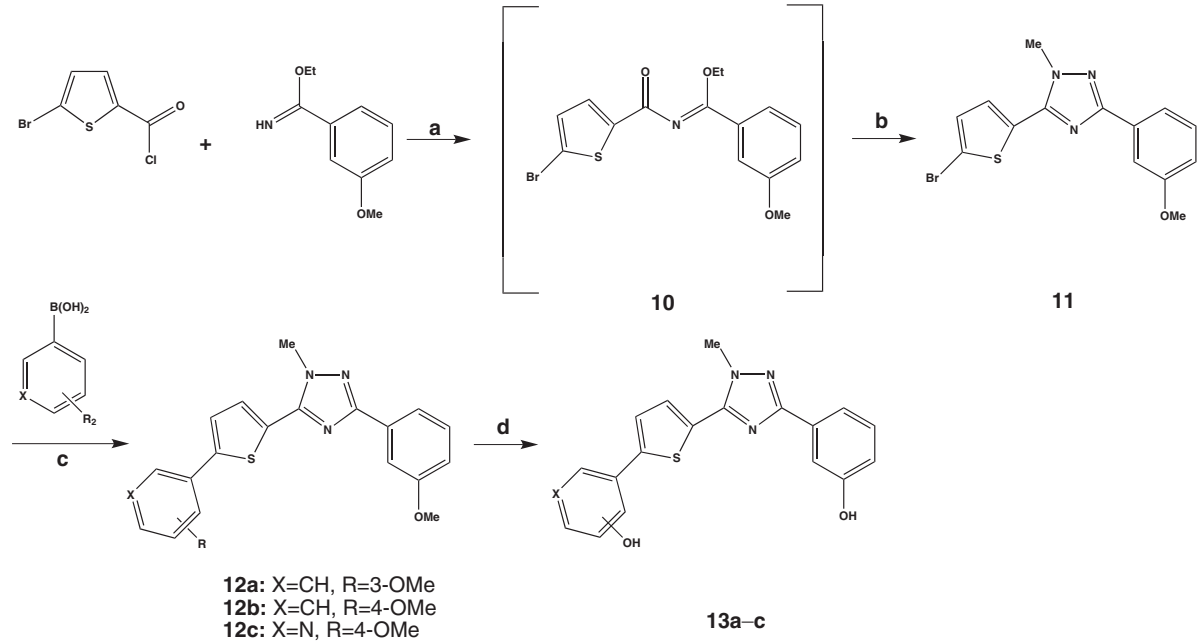


8ii : R_2=H, R_3=OMe, R_4=H
8ij : R_2=H, R_3=OH, R_4=H
8ik : R_2=F, R_3=OMe, R_4=H
8il: R_2=H, R_3=F, R_4=OMe
8im : R_2=H, R_3=NH_2, R_4=H
8in : R_2=H, R_3=H, R_4=OH
8io : R_2=H, R_3=H, R_4=CN
8ip : R_2=Me, R_3=H, R_4=F
8iq : R_2=H, R_3=F, R_4=H

Reagents and conditions: [a] $NaHCO_3$, $Pd(Ph_3)_4$, DMF, microwave irradiation 15 min, 150 °C, 100 W, 15 bar; [b] $BF_3.SM_2$, CH_2Cl_2, rt, 20 h.

Scheme 2. Synthesis of compounds **8ii–iq** and **9**.

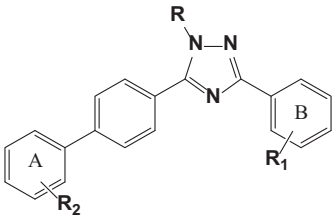
(results not shown). This characteristic has already been observed in the development of 17βHSD2 [10, 34] as well as 17βHSD1 inhibitors [10]. In addition, it is striking that all the active compounds **8b**, **8f**, and **13a** have both OH groups in *meta*-position of the respective aromatic rings. Compound **8d**, with a *meta,para*-substitution pattern for both OH groups shows reduced inhibitory activity compared to the *meta,meta* **8b** although the distance between the two OH groups does



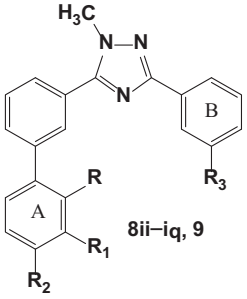
Reagents and conditions: [a] CH_2Cl_2, NEt_3, 30–40 °C, 6 h; [b] $MeNHNH_2$, CH_2Cl_2, 30–40 °C, 4 h; [c] $NaHCO_3$, $Pd(Ph_3)_4$, DMF, microwave irradiation 15 min, 150 °C, 100 W, 15 bar; [d] $BF_3.SM_2$,CH_2Cl_2, rt, 20 h.

Scheme 3. Synthesis of compounds **13a–c**.

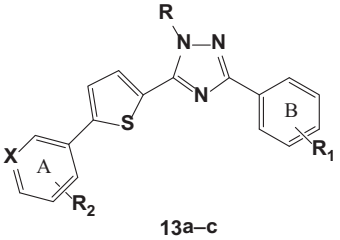
Table 1. Human 17βHSD2 and 17βHSD1 inhibition activity of compounds **8a–h**, **8ii–iq**, **9**, and **13a–c**



8a–h



8ii–iq, 9



13a–c

Compounds	R	R_1	R_2	R_3	X	17βHSD2[a] % Inhibition at 1 μM	17βHSD1[b] % Inhibition at 1 μM
8a	CH_3	3-OH	4-OH			ni	ni
8b	CH_3	3-OH	3-OH			42%, IC_{50} = 1.4 μM[c]	12
8c	CH_3	4-OH	4-OH			ni	ni
8d	CH_3	4-OH	3-OH			14	14
8e	H	3-OH	4-OH			ni	ni
8f	H	3-OH	3-OH			20%, IC_{50} = 4.0 μM[c]	23
8g	H	4-OH	4-OH			ni	ni
8h	H	4-OH	3-OH			ni	27
8ii	H	OCH_3	H	OCH_3		ni	ni
8ij	H	OH	H	OCH_3		ni	ni
8ik	F	OCH_3	H	OCH_3		ni	ni
8il	H	F	OCH_3	OCH_3		ni	ni
8im	H	NH_2	H	OCH_3		ni	ni
8in	H	H	OH	OCH_3		ni	ni
8io	H	H	CN	OCH_3		ni	ni
8ip	CH_3	H	F	OCH_3		ni	ni
8iq	H	F	H	OCH_3		ni	ni
9	H	OH	H	OH		ni	ni
13a	CH_3	3-OH	3-OH		CH	30%, IC_{50} = 2.0 μM[c]	ni
13b	CH_3	3-OH	4-OH		CH	ni	ni
13c	CH_3	3-OH	4-OH		N	ni	ni

[a] Human placenta, microsomal fraction, substrate [^{3}H]-E2 + E2 [500 nM], cofactor NAD^+ [1500 μM].
[b] Human placenta, cytosolic fraction, substrate [^{3}H]-E1 + E1 [500 nM], cofactor NADH [500 μM].
[c] IC_{50}-value (calculated from % inhibition via logit transformation); ni, no inhibition (<10% inhibition at 1 μM).

not vary so much compared to **13a** (14.00 Å in **13a** and 14.81 Å in **8d**). From this it has to be concluded that H-bonding interactions cannot be the main stabilizing force for the compounds, electronic effects might be involved as well as Van der Waals interactions.

Replacement of the central phenyl ring (**8b** and **8f**) by a thiophene (**13a**) seems to have a negligible influence on the biological activity, indicating that the S of the thiophene does not achieve any specific interaction. It should also be noticed that 17βHSD2 inhibitory activity varies with the substitution pattern of the central ring (1,4-phenyl in **8b** being the most active, 2,5-thiophene in **13a** and 1,3-phenyl in **8f** weaker). This difference in activity is certainly linked to the position of the OH-phenyl group which covers a different area of the active site in each case (having the B ring and the triazole moieties fixed). The most favorable conformation has a linear shape as facilitated by the 1,4-phenyl group.

It can also be noticed that the *N*-methyl triazole **8b** has a slightly higher inhibitory activity compared to **8f** without methyl group. This hydrophobic group interacts with a small lipophilic pocket, as hypothesized with the *cis*-pyrrolidinone **B**.

In addition, the overall large size of **8b** and **13a** indicates that the active site of the enzyme must be quite elongated and able to accept big compounds.

Compounds **8ii–8iq** with 1,3-phenyl as central ring with a U-shape were prepared to mimic the conformation of the *cis*-pyrrolidinone **B**. Their inactivity might indicate that either these compounds do not bind in the same way as **B** or that the

flatness and the rigidity of the 1*H*-1,2,4-triazole is detrimental for activity.

Comparing the 1*H*-1,2,3-triazole **C** (inhibitor of 17βHSD1) with the 1*H*-1,2,4-triazole **E** or **8b** (17βHSD2 inhibitor), it is striking that the change in position of one N only within the triazole moiety allows a switch in selectivity. It demonstrates the high differences in both enzyme binding sites.

The 17βHSD2 inhibitory activity of the newly synthesized compound is moderate (40% inhibition at 1 μM for **8b**) but a rather good selectivity is achieved toward 17βHSD1 (12% inhibition at 1 μM for **8b**).

Conclusion

In this study, a series of 21 1*H*-1,2,4-triazole derivatives was synthesized and tested for 17βHSD2 and 17βHSD1 inhibition. Three compounds **8b**, **8f**, and **13a** were identified as moderate 17βHSD2 inhibitors, **8b** being the best identified with an IC_{50} of 1.4 μM. They are selective toward 17βHSD1. They all share an *N*-methyl 1*H*-1,2,4-triazole ring as central core and two *meta,meta*-hydroxyphenyl substituents. These compounds need to be further optimized but they can already be considered as a good tool for the development of further 17βHSD2 inhibitors and for the mapping of the 17βHSD2 active site.

Experimental section

General

Chemical names follow IUPAC nomenclature.

Starting materials were purchased from Aldrich, Acros, Lancaster, Roth, Merck, or Fluka and were used without purification.

Purification was performed on preparative thin layer chromatography (TLC) on 1 mm SIL G-100 UV254 glass plates (Macherey-Nagel, Düren) and reaction progress was monitored by TLC on Alugram SIL G UV254 (Macherey-Nagel). Visualization was accomplished with UV light.

Melting points were measured on a Mettler FP1 melting point apparatus and are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were measured on a Bruker AM500 spectrometer (500 MHz) at 300 K. Chemical shifts are reported in δ (parts per million: ppm), by reference to the hydrogenated residues of deuteriated solvent as internal standard ($CDCl_3$: δ 7.24 ppm (^{1}H NMR) and δ 77 ppm (^{13}C NMR); CD_3OD: δ 3.35 ppm (^{1}H NMR) and δ 49.3 ppm (^{13}C NMR); DMSO-d_6: δ 2.50 ppm (^{1}H NMR), δ 39.5 ppm (^{13}C NMR). Signals are described as s, d, t, dd, and m, for singlet, doublet, triplet, doublet of doublets, and multiplet, respectively. All coupling constants (*J*) are given in Hertz (Hz).

Mass spectra (ESI) were recorded on a TSQ Quantum (Thermo Fisher) instrument using electrospray (ESI) as ionization source.

All microwave irradiation experiments were carried out in a CEM-Discover microwave apparatus.

Compounds **3** [39], **4** [39], and **7** [40] were prepared according to the previously described procedure.

*General procedure for the synthesis of compounds **5**, **6**, and **11** – formation of the 1H-1,2,4-triazole moiety*

A solution of acyl chloride (1 equiv) in 10 mL dichloromethane was added dropwise to a mixture of ethyl imino ester (1 equiv) and anhydrous triethylamine (1 equiv) in 20 mL dichloromethane at rt. The reaction mixture was heated to 30–35°C for 6 h. After cooling to rt, the material was poured into a 3% sodium hydrogenocarbonate solution (25 mL). The layers were separated and the organic layer was washed with water, dried over sodium sulfate, and evaporated to dryness under reduced pressure. The resulting *N*-acylimino esters **1**, **2**, and **10** were not characterized. They were used in the next step without further purification. They were heated to 30–35°C with the hydrazine derivative (2 equiv) in dichloromethane for 4 h. The solvent was removed under reduced pressure. The 1*H*-1,2,4-triazoles were purified by recrystallization using CH_2Cl_2/diethyl ether for compounds **3**, **4**, and **11** and EtOH/petroleum ether for compounds **5** and **6**.

*5-(4-Bromophenyl)-3-(3-methoxyphenyl)-1H-1,2,4-triazole **5***

The title compound was prepared from 4-bromobenzoyl chloride (0.219 g, 1.0 mmol), ethyl 3-methoxybenzimidate (0.179 g, 1.0 mmol), and hydrazine hydrate (0.100 g, 2.0 mmol) according to the procedure described above. The product was crystallized from EtOH (5 mL)/Petroleum ether (1 mL). Yield: 0.180 g (54%). $C_{15}H_{12}BrN_3O$; MW: 330; m.p. 191–193°C (dec). ^{1}H NMR (DMSO-d_6): δ 9.85 (bs, 1H, NH); 8.02 (d, J = 8.5 Hz, 2H); 7.71 (d, J = 8.5 Hz, 2H); 7.67–7.62 (m, 2H); 7.44 (t, J = 7.9 Hz, 1H); 7.05 (m, 1H); 3.84 (s, 3H, OCH_3). ^{13}C NMR (DMSO-d_6): δ 159.6, 157.4, 131.8, 131.3, 130.1, 129.7, 129.0, 127.9, 122.8, 118.4, 115.7, 111.1, 55.2 (OCH_3). MS (ESI): 329–331 $[M+H]^+$.

*5-(4-Bromophenyl)-3-(4-methoxyphenyl)-1H-1,2,4-triazole **6***

The title compound was prepared from 4-bromobenzoyl chloride (0.219 g, 1.0 mmol), ethyl 4-methoxybenzimidate (0.179 g, 1.0 mmol), and hydrazine hydrate (0.100 g, 2.0 mmol) according to the procedure described above. The product was crystallized from EtOH (5 mL)/Petroleum ether (1 mL). Yield: 0.175 g (53%). $C_{15}H_{12}BrN_3O$; MW: 330; m.p. 223–225°C (dec). ^{1}H NMR (DMSO-d_6): δ 14.4 (bs, NH); 8.02 (d, J = 3.9 Hz, 2H); 8.00 (d, J = 4.5 Hz, 2H); 7.70 (d, J = 8.1 Hz, 2H); 7.09 (d, J = 8.5 Hz, 2H); 3.82 (s, 3H, OCH_3). ^{13}C NMR (DMSO-d_6): δ 160.6, 160.5, 131.8, 131.3, 129.0, 127.9, 127.6, 122.5, 114.3, 55.3 (OCH_3). MS (ESI): 329–331 $[M+H]^+$.

*5-(5-Bromo-2-thienyl)-3-(3-methoxyphenyl)-1-methyl-1H-1,2,4-triazole **11***

The title compound was prepared from 5-bromothiophene-2-carbonyl chloride (0.225 g, 1.0 mmol), ethyl 3-methoxybenzimidate (0.179 g, 1.0 mmol), and methyl hydrazine (0.092 g, 2.0 mmol) according to the procedure described above. The product was crystallized from CH_2Cl_2 (5 mL)/Et_2O (1 mL). Yield: 0.302 g (86%). $C_{14}H_{12}BrN_3OS$; MW: 350; m.p. 106–108°C (dec). ^{1}H NMR ($CDCl_3$): δ 7.71–7.69 (m, 1H); 7.65–7.64 (m, 1H); 7.34 (t, J = 7.9 Hz, 1H); 7.26 (d, J = 3.9 Hz, 1H); 7.13 (d, J = 4.0 Hz, 1H); 6.96–6.94 (m, 1H); 4.06 (s, 3H, NCH_3); 3.88 (s, 3H, OCH_3). ^{13}C NMR ($CDCl_3$): δ 161.0, 159.8, 149.0, 131.8, 131.0, 130. 7, 129.6, 128.2, 118.8, 116.2, 115.8, 111.0, 55.4 (OCH_3), 37.1 (NCH_3). MS (ESI): 349–351 $[M+H]^+$.

*General procedure for compounds **8ia–ih**, **8ii–iq** and **12a–c** – Suzuki coupling*

Method A: Boronic acid (0.75 mmol, 1 equiv), 1*H*-1,2,4-triazolylbromide (1 equiv), and tetrakis(triphenylphosphane)palladium(0) (43 mg, 0.0375 mmol, 5 mol %) were suspended in 1.5 mL DMF in a 10 mL septum-capped tube containing a stirring magnet. A solution of $NaHCO_3$ (189 mg, 2.25 mmol, 3 equiv) in 1.5 mL water was added and the vial was sealed with a Teflon cap. The mixture was irradiated with microwaves for 15 min at a temperature of 150°C with an initial irradiation power of 100 W at 15 bar. After the reaction, the vial was cooled to rt, the crude mixture was partitioned between ethyl acetate and water, and the aqueous layer was extracted three times with ethyl acetate. The combined organic layers were dried over $MgSO_4$ and the solvents were removed *in vacuo*. The coupling products were obtained after purification by preparative TLC.

Method B: A mixture of arylbromide (1 equiv), boronic acid derivative (1.2 equiv), cesium carbonat (4 equiv), and tetrakis(triphenylphosphine) palladium (0.03 equiv) in an oxygen-free DME/water (1:1) mixture was stirred at 150°C for 6 h under nitrogen atmosphere. The reaction mixture was cooled to rt. The aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with brine, dried over sodium sulfate, filtered, and concentrated to dryness. The product was purified by preparative TLC.

*5-(4′-Methoxybiphenyl-4-yl)-3-(3-methoxyphenyl)-1-methyl-1H-1,2,4-triazole **8ia***

The title compound was prepared by reaction of 5-(4-bromophenyl)-3-(3-methoxyphenyl)-1-methyl-1*H*-1,2,4-triazole (**3**) (0.344 g, 1.0 mmol) with 4-methoxybenzene boronic acid (0.114 g, 0.75 mmol) according to method A. The product was purified by preparative TLC (CH_2Cl_2/MeOH, 10:0.25); yield: 0.227 g (61%). $C_{23}H_{21}N_3O_2$; MW: 371; m.p. 147–149°C (dec), white powder; ^{1}H NMR (DMSO-d_6): δ 7.90 (d, J = 6.8 Hz, 2H); 7.83 (d, J = 8.4 Hz, 2H); 7.72 (d, J = 8.8 Hz, 2H); 7.65–7.64 (m, 1H); 7.41–7.38 (m, 1H); 7.40 (t, J = 7.9 Hz, 1H); 7.07 (t, J = 8.0 Hz, 2H); 7.02–7.00 (m, 1H); 4.05 (s, 3H, NCH_3); 3.83 (s, 3H, OCH_3); 3.81 (s, 3H, OCH_3). ^{13}C NMR (DMSO-d_6): δ 159.5, 159.5, 159.4, 154.6, 141.2, 132.3, 131.3, 129.9, 129.1, 127.9, 126.4, 125.8, 118.1, 115.0, 114.5, 110.6, 55.2 (OCH_3), 55.1 (OCH_3), 37.2 (NCH_3); MS (ESI): 372 $[M+H]^+$.

*5-(3′-Methoxybiphenyl-4-yl)-3-(3-methoxyphenyl)-1-methyl-1H-1,2,4-triazole **8ib***

The title compound was prepared by reaction of 5-(4-bromophenyl)-3-(3-methoxyphenyl)-1-methyl-1*H*-1,2,4-triazole (**3**) (0.344 g, 1.0 mmol) with 3-methoxybenzene boronic acid (0.114 g, 0.75 mmol) according to method A. The product was purified by preparative TLC (CH_2Cl_2/MeOH, 10:0.25); yield: 0.215 g (58%). $C_{23}H_{21}N_3O_2$; MW: 371; m.p. 123–125°C (dec), white powder. ^{1}H NMR (DMSO-d_6): δ 7.93 (d, J = 8.5 Hz, 2H); 7.88 (d, J = 8.5 Hz, 2H); 7.66–7.65 (m, 1H); 7.59–7.57 (m, 1H); 7.44–7.39 (m, 2H); 7.34–7.29 (m, 2H); 7.02–6.99 (m, 2H); 4.06 (s, 3H, NCH_3); 3.85 (s, 3H, OCH_3); 3.83 (s, 3H, OCH_3). ^{13}C NMR (DMSO-d_6): δ 159.8, 159.5, 154.5, 141.5, 140.6, 132.2, 130.1, 130.1, 129.1, 127.6, 127.1, 126.7, 119.1, 118.1, 115.0, 113.7, 112.3, 110.6, 55.2 (OCH_3), 55.1 (OCH_3), 37.2 (NCH_3). MS (ESI): 372 $[M+H]^+$.

*5-(4′-Methoxybiphenyl-4-yl)-3-(4-methoxyphenyl)-1-methyl-1H-1,2,4-triazole **8ic***

The title compound was prepared by reaction of 5-(4-bromophenyl)-3-(4-methoxyphenyl)-1-methyl-1*H*-1,2,4-triazole (**4**) (0.344 g, 1.0 mmol) with 4-methoxybenzene boronic acid (0.114 g, 0.75 mmol) according to method A. The product was purified by preparative TLC (CH_2Cl_2/MeOH, 10:0.25); yield: 0.200 g (54%). $C_{23}H_{21}N_3O_2$; MW: 371; m.p. 137–139°C (dec), white powder. ^{1}H NMR ($CDCl_3$): δ 8.07 (d, J = 8.8 Hz, 2H); 7.76 (d, J = 8.0 Hz, 2H); 7.68 (d, J = 8.3 Hz, 2H); 7.57 (d, J = 8.6 Hz, 2H); 6.99 (d, J = 8.6 Hz, 2H); 6.95 (d, J = 8.8 Hz, 2H); 4.02 (s, 3H, NCH_3); 3.85 (s, 3H, OCH_3); 3.84 (s, 3H, OCH_3). ^{13}C NMR ($CDCl_3$): δ 161.2, 160.7, 160.0, 155.5, 142.7, 132.7, 130.3, 129.4, 128.5, 128.0, 127.2, 124.0, 114.7, 114.2, 55.6 (OCH_3), 55.5 (OCH_3), 37.2 (NCH_3). MS (ESI): 372 $[M+H]^+$.

*5-(3′-Methoxybiphenyl-4-yl)-3-(4-methoxyphenyl)-1-methyl-1H-1,2,4-triazole **8id***

The title compound was prepared by reaction of 5-(4-bromophenyl)-3-(4-methoxyphenyl)-1-methyl-1*H*-1,2,4-triazole (**4**) (0.344 g, 1.0 mmol) with 3-methoxybenzene boronic acid (0.114 g, 0.75 mmol) according to method A. The product was purified by preparative TLC (CH_2Cl_2/MeOH, 10:0.25); yield: 0.220 g (59%). $C_{23}H_{21}N_3O_2$; MW: 371; m.p. 154–156°C (dec), white powder. ^{1}H NMR ($CDCl_3$): δ 8.09 (d, J = 8.8 Hz, 2H); 7.80 (d, J = 8.3 Hz, 2H); 7.74 (d, J = 8.3 Hz, 2H); 7.40 (t, J = 8.0 Hz, 1H); 7.24–7.17 (m, 2H); 6.97 (d, J = 8.8 Hz, 2H); 6.95 (m, 1H); 4.05 (s, 3H, NCH_3); 3.89 (s, 3H, OCH_3); 3.86 (s, 3H, OCH_3). ^{13}C NMR ($CDCl_3$): δ 161.4, 160.7, 160.33, 155.5, 142.9, 141.8, 130.2, 129.4, 128.0, 127.8, 127.3, 124.1, 119.9, 114.2, 113.5, 113.3, 55.6 (OCH_3), 55.5 (OCH_3), 37.2 (NCH_3). MS (ESI): 372 $[M+H]^+$.

*5-(4′-Methoxybiphenyl-4-yl)-3-(3-methoxyphenyl)-1H-1,2,4-triazole **8ie***

The title compound was prepared by reaction of 5-(4-bromophenyl)-3-(3-methoxyphenyl)-1*H*-1,2,4-triazole (**5**) (0.330 g, 1.0 mmol) with 4-methoxybenzene boronic acid (0.114 g, 0.75 mmol) according to method A. The product was purified by preparative TLC (CH_2Cl_2/MeOH, 10:1); yield: 0.158 g (44%). $C_{22}H_{19}N_3O_2$; MW: 357; m.p. 178–180°C (dec), white powder. ^{1}H NMR (CD_3OD + $CDCl_3$; 2:1): δ 8.08 (d, J = 8.2 Hz, 2H); 7.68 (d, J = 8.2 Hz, 2H); 7.64 (d, J = 6.7 Hz, 2H); 7.58 (d, J = 8.7 Hz, 2H); 7.50–7.45 (m, 1H); 7.39 (t, J = 8.1 Hz, 1H); 7.00–6.98 (m, 2H); 3.88 (s, 3H, OCH_3); 3.83 (s, 3H, OCH_3). ^{13}C NMR (CD_3OD + $CDCl_3$; 2:1): δ 160.1, 159.7, 142.3, 132.5, 129.8, 129.7, 128.6, 127.8, 126.7, 126.6, 126.3, 118.7, 118.6, 115.8, 114.1, 111.4, 54.7 (OCH_3), 54.6 (OCH_3). MS (ESI): 358 $[M+H]^+$.

*5-(3′-Methoxybiphenyl-4-yl)-3-(3-methoxyphenyl)-1H-1,2,4-triazole **8if***

The title compound was prepared by reaction of 5-(4-bromophenyl)-3-(3-methoxyphenyl)-1*H*-1,2,4-triazole (**5**) (0.330 g, 1.0 mmol) with 3-methoxybenzene boronic acid (0.114 g, 0.75 mmol) according to method A. The product was purified by preparative TLC (CH_2Cl_2/MeOH, 10:1); yield: 0.211 g (59%). $C_{22}H_{19}N_3O_2$; MW: 357; m.p. 108–110°C (dec), white powder. ^{1}H NMR (CD_3OD + $CDCl_3$; 2:1): δ 8.10 (d, J = 8.2 Hz, 2H); 7.69 (d, J = 8.3 Hz, 2H); 7.64–7.60 (m, 2H); 7.46–7.36 (m, 1H); 7.31 (t, J = 7.9 Hz, 1H); 7.19–7.14 (m, 2H); 6.99–6.89 (m, 2H); 3.85 (s, 3H, OCH_3); 3.81 (s, 3H, OCH_3). ^{13}C NMR (CD_3OD + $CDCl_3$; 2:1): δ 161.5, 161.5, 143.9, 143.0, 131.4, 131.2, 131.1, 130.1,

129.2, 128.7, 128.2, 127.8, 120.7, 120.1, 117.3, 114.4, 113.9, 112.9, 56.3 (OCH_3), 56.2 (OCH_3). MS (ESI): 358 $[M+H]^+$.

5-(4′-Methoxybiphenyl-4-yl)-3-(4-methoxyphenyl)-1H-1,2,4-triazole ***8ig***

The title compound was prepared by reaction of 5-(4-bromophenyl)-3-(4-methoxyphenyl)-1*H*-1,2,4-triazole (**6**) (0.330 g, 1.0 mmol) with 4-methoxybenzene boronic acid (0.114 g, 0.75 mmol) according to method A. The product was purified by preparative TLC (CH_2Cl_2/MeOH, 10:1); yield: 0.185 g (52%). $C_{22}H_{19}N_3O_2$; MW: 357; m.p. 202–204°C (dec), white powder. ^{1}H NMR (CD_3OD): δ 8.01 (d, J = 7.9 Hz, 2H); 8.00 (d, J = 8.3 Hz, 2H); 7.72 (d, J = 8.0 Hz, 2H); 7.63 (d, J = 8.4 Hz, 2H); 7.07 (d, J = 8.4 Hz, 2H); 7.02 (d, J = 8.6 Hz, 2H); 3.87 (s, 3H, OCH_3); 3.84 (s, 3H, OCH_3). ^{13}C NMR (CD_3OD): δ 161.2, 161.1, 133.8, 133.1, 133.1, 130.0, 129.9, 129.2, 129.1, 128.0, 127.9, 127.6, 118.7, 115.4, 55.9 (OCH_3), 55.8 (OCH_3). MS (ESI): 358 $[M+H]^+$.

5-(3′-Methoxybiphenyl-4-yl)-3-(4-methoxyphenyl)-1H-1,2,4-triazole ***8ih***

The title compound was prepared by reaction of 5-(4-bromophenyl)-3-(4-methoxyphenyl)-1*H*-1,2,4-triazole (**6**) (0.330 g, 1.0 mmol) with 3-methoxybenzene boronic acid (0.114 g, 0.75 mmol) according to method A. The product was purified by preparative TLC (CH_2Cl_2/MeOH, 10:1); yield: 0.171 g (48%). $C_{22}H_{19}N_3O_2$; MW: 357; m.p. 131–133°C (dec), white powder. ^{1}H NMR (CD_3OD + $CDCl_3$; 2:1): δ 8.08–8.02 (m, 2H); 7.96–7.91 (m, 2H); 7.65 (d, J = 8.3 Hz, 2H); 7.45–7.41 (m, 1H); 7.29 (t, J = 7.9 Hz, 1H); 7.17–7.12 (m, 1H); 6.97 (d, J = 8.6 Hz, 2H); 6.87–6.85 (m, 1H); 3.79 (s, 3H, OCH_3); 3.78 (s, 3H, OCH_3). ^{13}C NMR (CD_3OD): δ 162.7, 161.5, 143.7, 143.0, 131.1, 130.0, 129.3, 128.5, 128.1, 127.7, 122.4, 122.3, 120.6, 115.5, 114.3, 113.8, 56.1 (OCH_3), 56.0 (OCH_3). MS (ESI): 358 $[M+H]^+$.

5-(3′-Methoxybiphenyl-3-yl)-3-(3-methoxyphenyl)-1-methyl-1H-1,2,4-triazole ***8ii***

The title compound was prepared by reaction of 5-(3-bromophenyl)-3-(3-methoxyphenyl)-1*H*-1,2,4-triazole (**7**) (0.330 g, 1.0 mmol) with 3-methoxybenzene boronic acid (0.182 g, 1.2 mmol) according to method B. The product was purified by preparative TLC (CH_2Cl_2); yield: 0.250 g (67%). $C_{23}H_{21}N_3O_2$; MW: 371; oily product. ^{1}H NMR ($CDCl_3$): δ 7.95 (s, 1H); 7.77 (d, J = 7.7 Hz, 1H,); 7.73–7.63 (m, 3H); 7.59 (t, J = 7.8 Hz, 1H); 7.40–7.34 (m, 2H); 7.23–7.17 (m, 2); 6.97–6.94 (m, 2H); 4.05 (s, 3H, NCH_3); 3.89 (s, 3H, OCH_3); 3.88 (s, 3H, OCH_3). ^{13}C NMR ($CDCl_3$): δ 161.2, 160.1, 159.9, 155.6, 142.0, 141.7, 132.4, 130.0, 129.7, 129.3, 129.0, 128.6, 127.7, 127.6, 119.8, 118.9, 115.9, 113.2, 113.1, 110.9, 55.4 (OCH_3), 55.4 (OCH_3), 37.0 (NCH_3). MS (ESI): 372 $[M+H]^+$.

3′-[3-(3-Methoxyphenyl)-1-methyl-1H-1,2,4-triazol-5-yl]-biphenyl-3-ol ***8ij***

The title compound was prepared by reaction of 5-(3-bromophenyl)-3-(3-methoxyphenyl)-1*H*-1,2,4-triazole (**7**) (0.330 g, 1.0 mmol) with 3-hydroxybenzene boronic acid (0.166 g, 1.2 mmol) according to method B. The product was purified by preparative TLC (CH_2Cl_2); yield: 0.284 g (79%). $C_{22}H_{19}N_3O_2$; MW: 357; m.p. 180–182°C (dec); white powder. ^{1}H NMR (CD_3COCD_3): 8.50 (bs, 1H, OH); 8.08 (t, J = 1.7 Hz, 1H); 7.85–7.79 (m, 2H); 7.75–7.71 (m, 2H); 7.66 (t, J = 7.8 Hz, 1H); 7.38 (t, J = 7.8 Hz, 1H); 7.33 (t, J = 8.0 Hz, 1H); 7.23–7.21 (m, 2H); 6.99–6.97 (m, 1H); 6.91–6.88 (m, 1H); 4.13 (s, 3H, NCH_3); 3.87 (s, 3H, OCH_3). ^{13}C NMR (CD_3COCD_3): δ 162.2, 162.0, 159.9, 157.1, 143.5, 143.5, 134.9, 132.0, 131.5, 131.2, 130.9, 130.2, 129.5, 129.0, 120.3, 120.2, 116.8, 116.6, 115.8, 113.0, 55.4 (OCH_3), 55.4 (OCH_3), 37.0 (NCH_3). MS (ESI): 358 $[M+H]^+$.

5-(2′-Fluoro-3′-methoxybiphenyl-3-yl)-3-(3-methoxyphenyl)-1-methyl-1H-1,2,4-triazole ***8ik***

The title compound was prepared by reaction of 5-(3-bromophenyl)-3-(3-methoxyphenyl)-1*H*-1,2,4-triazole (**7**) (0.330 g, 1.0 mmol) with 2-fluoro-3-methoxyphenylboronic acid (0.204 g, 1.2 mmol) according to method B. The product was purified by preparative TLC (CH_2Cl_2); yield: 0.266 g (68%). $C_{22}H_{19}N_3O_2$; MW: 389; m.p. 119–121°C (dec); white powder. ^{1}H NMR ($CDCl_3$): 7.80–7.79 (m, 1H); 7.66–7.64 (m, 2H); 7.60–7.56 (m, 2H); 7.94 (t, J = 7.6 Hz, 1H,); 7.75–7.70 (m, 4H); 7.62 (t, J = 7.8 Hz, 1H); 7.24 (t, J = 7.9 Hz, 1H); 7.06–7.03 (m, 1H); 6.96–6.83 (m, 3H); 3.95 (s, 3H, NCH_3); 3.83 (s, 3H, OCH_3); 3.78 (s, 3H, OCH_3). ^{13}C NMR ($CDCl_3$): δ 161.1, 159.9, 155.4, 150.6, 148.6, 148.3, 136.3, 132.3, 130.7, 129.6, 129.4, 129.1, 128.1, 124.2, 124.1, 121.9, 118.8, 115.8, 112.8, 110.8, 56.4 (OCH_3), 55.4 (OCH_3), 37.0 (NCH_3). MS (ESI): 390 $[M+H]^+$.

5-(3′-Fluoro-4′-methoxybiphenyl-3-yl)-3-(3-methoxyphenyl)-1-methyl-1H-1,2,4-triazole ***8il***

The title compound was prepared by reaction of 5-(3-bromophenyl)-3-(3-methoxyphenyl)-1*H*-1,2,4-triazole (**7**) (0.330 g, 1.0 mmol) with 3-fluoro-4-methoxyphenylboronic acid (0.204 g, 1.2 mmol) according to method B. The product was purified by preparative TLC (CH_2Cl_2); yield: 0.278 g (71%). $C_{22}H_{19}N_3O_2$; MW: 389; m.p. 99–101°C (dec); yellow powder. ^{1}H NMR ($CDCl_3$): 8.04 (bs, 1H); 7.85 (d, J = 7.7 Hz, 1H); 7.78 (d, J = 7.7 Hz, 1H); 7.69–7.56 (m, 5H); 7.40 (t, J = 7.9 Hz, 1H); 7.27 (t, J = 7.7 Hz, 1H); 7.00 (d, J = 8.2 Hz, 1H,); 4.05 (s, 3H, NCH_3); 3.90 (s, 3H, OCH_3); 3.83 (s, 3H, OCH_3). ^{13}C NMR ($CDCl_3$): δ 159.5, 159.4, 154.7, 152.7, 150.8, 146.9, 139.2, 132.2, 129.8, 129.4, 128.3, 127.9, 127.4, 126.3, 123.0, 118.1, 114.9, 114.4, 114.2, 110.6, 56.4 (OCH_3), 55.4 (OCH_3), 37.0 (NCH_3). MS (ESI): 390 $[M+H]^+$.

3′-[3-(3-Methoxyphenyl)-1-methyl-1H-1,2,4-triazol-5-yl]-biphenyl-3-amine ***8im***

The title compound was prepared by reaction of 5-(3-bromophenyl)-3-(3-methoxyphenyl)-1*H*-1,2,4-triazole (**7**) (0.330 g, 1.0 mmol) with 3-aminophenylboronic acid (0.164 g, 1.2 mmol) according to method B. The product was purified by preparative TLC (CH_2Cl_2); yield: 0.258 g (72%). $C_{22}H_{20}N_4$; MW: 356; m.p. 142–144°C (dec); yellow powder. ^{1}H NMR (CD_3COCD_3): 8.05 (t, J = 1.7 Hz, 1H); 7.81–7.79 (m, 1H); 7.78–7.74 (m, 2H); 7.72–7.71 (m, 1H); 7.63 (t, J = 7.9 Hz, 1H); 7.38 (t, J = 7.9 Hz, 1H); 7.18 (t, J = 7.8 Hz, 1H); 7.06 (t, J = 2.0 Hz, 1H); 6.99–6.95 (m, 2H); 6.73–6.71 (m, 1H); 4.76 (bs, 2H, NH_2); 4.11 (s, 3H, NCH_3); 3.87 (s, 3H, OCH_3). ^{13}C NMR (CD_3COCD_3): δ 162.2, 161.9, 157.2, 151.0, 144.3, 142.8, 134.9, 131.5, 131.5, 131.0, 130.8, 130.1, 129.1, 129.0, 120.3, 117.4, 116.6, 115.8, 114.8, 113.0, 56.6 (OCH_3), 38.7 (NCH_3). MS (ESI): 357 $[M+H]^+$.

3′-[3-(3-Methoxyphenyl)-1-methyl-1H-1,2,4-triazol-5-yl]-biphenyl-4-ol ***8in***

The title compound was prepared by reaction of 5-(3-bromophenyl)-3-(3-methoxyphenyl)-1*H*-1,2,4-triazole (**7**) (0.330 g, 1.0 mmol) with 4-hydroxybenzene boronic acid (0.166 g, 1.2 mmol) according to method B. The product was purified by preparative TLC (CH_2Cl_2); yield: 0.260 g (73%). $C_{22}H_{19}N_3O_2$; MW: 357; m.p. 211–213°C (dec), white powder. ^{1}H NMR (DMSO-d_6): 9.63 (bs, 1H, OH); 7.98 (t, J = 1.6 Hz, 1H); 7.79–7.76 (m, 1H); 7.74–7.71 (m, 1H); 7.66–

7.57 (m, 5H); 7.40 (t, $J = 8.0$ Hz, 1H); 7.01–6.99 (m, 1H); 6.89 (d, $J = 8.6$ Hz, 2H); 4.06 (s, 3H, NCH_3); 3.83 (s, 3H, OCH_3). ^{13}C NMR (DMSO-d_6): δ 159.5, 157.5, 155.0, 140.8, 132.3, 130.0, 129.9, 129.4, 128.2, 128.0, 127.6, 126.6, 126.1, 118.1, 115.8, 115.0, 110.7, 55.1 (OCH_3), 37.6 (NCH_3). MS (ESI): 358 $[M+H]^+$.

4′-[3-(3-Methoxyphenyl)-1-methyl-1H-1,2,4-triazol-5-yl]-biphenyl-4-carbonitrile ***8io***

The title compound was prepared by reaction of 5-(3-bromophenyl)-3-(3-methoxyphenyl)-1*H*-1,2,4-triazole (**7**) (0.330 g, 1.0 mmol) with 4-cyanobenzene boronic acid (0.176 g, 1.2 mmol) according to method B. The product was purified by preparative TLC (CH_2Cl_2); yield: 0.256 g (69%). $C_{23}H_{18}N_4O$; MW: 366; m.p. 134–136°C (dec), white powder. ^{1}H NMR ($CDCl_3$): 7.99 (t, $J = 1.5$ Hz, 1H); 7.78–7.70 (m, 7H); 7.70 (t, $J = 1.4$ Hz, 1H); 7.65 (t, $J = 7.7$ Hz, 1H); 7.36 (t, $J = 8.0$ Hz, 1H); 6.96 (m, 1H); 4.06 (s, 3H, NCH_3); 3.89 (s, 3H, OCH_3). ^{13}C NMR ($CDCl_3$): 161.2, 159.9, 155.1, 144.5, 140.1, 132.7, 132.1, 129.7, 129.6, 129.0, 128.9, 128.5, 127.9, 127.9, 118.8, 118.7, 115.9, 111.6, 111.0, 55.4 (NCH_3), 37.1 (OCH_3). MS (ESI): 367 $[M+H]^+$.

5-(4′-Fluoro-2′-methylbiphenyl-4-yl)-3-(3-methoxyphenyl)-1-methyl-1H-1,2,4-triazole ***8ip***

The title compound was prepared by reaction of 5-(3-bromophenyl)-3-(3-methoxyphenyl)-1*H*-1,2,4-triazole (**7**) (0.330 g, 1.0 mmol) with 4-fluoro-2-methylbenzene boronic acid (0.184 g, 1.2 mmol) according to method B. The product was purified by preparative TLC (CH_2Cl_2); yield: 0.278 g (74%). $C_{23}H_{20}FN_3O$, MW: 373; m.p. 98–100°C (dec), white powder. ^{1}H NMR ($CDCl_3$): 7.76–7.74 (m, 3H); 7.66 (t, $J = 1.5$ Hz, 1H); 7.57 (t, $J = 7.5$ Hz, 1H); 7.45–7.43 (m, 1H); 7.35 (t, $J = 8.0$ Hz, 1H); 7.24–7.21 (m, 1H); 7.01–6.94 (m, 3H); 4.05 (s, 3H, NCH_3); 3.89 (s, 3H, OCH_3); 2.29 (s, 3H, CH_3). ^{13}C NMR ($CDCl_3$): 163.2, 161.1, 159.9, 155.4, 141.8, 132.3, 131.2, 131.2, 131.0, 129.6, 128.7, 128.1, 117.3, 118.8, 117.0, 116.9, 115.9, 112.8, 112.7, 110.9, 55.4 (NCH_3), 37.6 (OCH_3), 20.6 (CH_3). MS (ESI): 374 $[M+H]^+$.

5-(3′-Fluorobiphenyl-4-yl)-3-(3-methoxyphenyl)-1-methyl-1H-1,2,4-triazole ***8iq***

The title compound was prepared by reaction of 5-(3-bromophenyl)-3-(3-methoxyphenyl)-1*H*-1,2,4-triazole (**7**) (0.330 g, 1.0 mmol) with 3-fluorobenzene boronic acid (0.168 g, 1.2 mmol) according to method B. The product was purified by preparative TLC (CH_2Cl_2); yield: 0.254 g (70%), $C_{22}H_{18}FN_3O$; MW: 359; oily product. ^{1}H NMR ($CDCl_3$): 7.95 (s, 1H); 7.77–7.76 (d, $J = 7.6$ Hz, 1H); 7.72–7.70 (m, 3H); 7.63–7.60 (m, 1H); 7.46–7.41 (m, 2H); 7.38–7.33 (m, 2H); 7.11–7.07 (m, 1H); 6.98–6.95 (m, 1H); 4.06 (s, 3H, NCH_3); 3.90 (s, 3H, OCH_3). ^{13}C NMR ($CDCl_3$): δ 161.2, 159.9, 155.3, 140.8, 132.3 130.5, 130.4, 129.6, 129.4, 128.8, 127.9, 127.7, 122.9, 118.9, 115.9, 114.8, 114.6, 114.2, 114.1, 110.9, 55.4 (OCH_3), 37.0 (NCH_3). MS (ESI): 360 $[M+H]^+$.

3-(3-Methoxyphenyl)-5-[5-(3-methoxyphenyl)-2-thienyl]-1-methyl-1H-1,2,4-triazole ***12a***

The title compound was prepared by reaction of 5-(5-bromo-2-thienyl)-3-(3-methoxyphenyl)-1-methyl-1*H*-1,2,4-triazole (**11**) (0.350 g, 1.0 mmol) with 3-methoxybenzene boronic acid (0.114 g, 0.75 mmol) according to method A. The product was purified by preparative TLC (CH_2Cl_2/MeOH, 10:0.25); yield: 0.248 g (66%). $C_{21}H_{19}N_3O_2S$; MW: 377; m.p. 109–111°C (dec), white powder. ^{1}H NMR ($CDCl_3$): δ 7.75–7.73 (m, 1H); 7.69–7.68 (m, 1H); 7.52 (d, $J = 3.8$ Hz, 1H); 7.73–7.32 (m, 3H); 7.27–7.25 (m, 1H); 7.19–7.18 (m, 1H); 6.97–6.95 (m, 1H); 6.91–6.89 (m, 1H); 4.14 (s, 3H, NCH_3); 3.90 (s, 3H, OCH_3); 3.87 (s, 3H, OCH_3). ^{13}C NMR ($CDCl_3$): δ 160.9, 160.1, 159.8, 149.9, 147.5, 134.6, 132.0, 130.1, 129.6, 129.1, 128.3, 123.9, 118.9, 118.6, 115.9, 114.0, 111.7, 111.0, 55.4 (OCH_3), 55.4 (OCH_3), 37.3 (NCH_3). MS (ESI): 378 $[M+H]^+$.

3-(3-Methoxyphenyl)-5-[5-(4-methoxyphenyl)-2-thienyl]-1-methyl-1H-1,2,4-triazole ***12b***

The title compound was prepared by reaction of 5-(5-bromo-2-thienyl)-3-(3-methoxyphenyl)-1-methyl-1*H*-1,2,4-triazole (**11**) (0.350 g, 1.0 mmol) with 4-methoxybenzene boronic acid (0.114 g, 0.75 mmol) according to method A. The product was purified by preparative TLC (CH_2Cl_2/MeOH, 10:0.25); yield: 0.237 g (63%). $C_{21}H_{19}N_3O_2S$; MW: 377; m.p. 87–89°C (dec), white powder. ^{1}H NMR ($CDCl_3$): δ 7.76–7.74 (m, 1H); 7.70–7.69 (m, 1H); 7.59 (d, $J = 8.7$ Hz, 2H); 7.52 (d, $J = 3.8$ Hz, 1H); 7.36 (t, $J = 7.9$ Hz, 1H); 7.26 (s, 1H); 6.97–695 (m, 3H); 4.14 (s, 3H, NCH_3); 3.91 (s, 3H, OCH_3); 3.86 (s, 3H, OCH_3). ^{13}C NMR ($CDCl_3$): δ 160.8, 159.9, 159.8, 150.0, 147.7, 132.0, 129.6, 129.3, 127.4, 127.1, 126.2, 122.7, 118.9, 115.9, 114.5, 111.0, 55.4 (OCH_3), 55.4 (OCH_3), 37.3 (NCH_3). MS (ESI): 378 $[M+H]^+$.

2-Methoxy-5-{5-[3-(3-methoxyphenyl)-1-methyl-1H-1,2,4-triazol-5-yl]-2-thienyl}pyridine ***12c***

The title compound was prepared by reaction of 5-(5-bromo-2-thienyl)-3-(3-methoxyphenyl)-1-methyl-1*H*-1,2,4-triazole (**11**) (0.350 g, 1.0 mmol) with 2-methoxypyridine boronic acid (0.115 g, 0.75 mmol) according to method A. The product was purified by preparative TLC (CH_2Cl_2/MeOH, 10:0.25); yield: 0.237 mg (56%). $C_{20}H_{18}N_4O_2S$; MW: 378; m.p. 133–135°C (dec), white powder. ^{1}H NMR ($CDCl_3$): δ 8.47 (d, $J = 2.3$ Hz, 1H); 7.80 (m, 1H); 7.73–7.71 (m, 1H); 7.67–7.65 (m, 1H); 7.49 (d, $J = 3.8$ Hz, 1H); 7.34 (t, $J = 7.9$ Hz, 1H); 7.25 (d, $J = 2.3$ Hz, 1H); 6.95–6.93 (m, 1H); 6.79 (d, $J = 8.5$ Hz, 1H); 4.12 (s, 3H, NCH_3); 3.97 (s, 3H, OCH_3); 3.88 (s, 3H, OCH_3). ^{13}C NMR ($CDCl_3$): δ 164.1, 161.0, 159.8, 149.8, 144.2, 144.0, 136.4, 132.0, 129.6, 129.1, 128.2, 123.5, 123.1, 118.9, 115.8, 111.3, 111.0, 55.4 (OCH_3), 53.7 (OCH_3), 37.3 (NCH_3). MS (ESI): 379 $[M+H]^+$.

Ether cleavage – general procedure for compounds ***8a–h****,* ***9****, and* ***13a–c***

To a solution of bis(methoxyphenyl) derivative (1 equiv) in dry dichloromethane at room temperature, borontrifluoride dimethyl sulfide complex (75 equiv) was added dropwise. The reaction mixture was stirred for 20 h at rt. Water was added to quench the reaction and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with brine, dried over sodium sulfate, evaporated to dryness under reduced pressure, and purified by preparative TLC.

4′-[3-(3-Hydroxyphenyl)-1-methyl-1H-1,2,4-triazol-5-yl]-biphenyl-4-ol ***8a***

The title compound was prepared by reaction of 5-(4′-methoxybiphenyl-4-yl)-3-(3-methoxyphenyl)-1-methyl-1*H*-1,2,4-triazole (**8ia**) (0.100 g, 0.269 mmol) according to the general procedure described above. The product was purified by preparative TLC (CH_2Cl_2/MeOH, 10:0.25); yield: 41 mg (44%). $C_{21}H_{17}N_3O_2$; MW: 343. ^{1}H NMR (DMSO-d_6): δ 7.86 (d, $J = 8.3$ Hz, 2H); 7.78 (d, $J = 8.3$ Hz, 2H); 7.59 (d, $J = 8.5$ Hz, 2H); 7.50–7.47 (m, 2H); 7.26 (t, $J = 7.8$ Hz, 1H); 6.90 (d, $J = 8.5$ Hz, 2H); 6.81–6.83 (m, 1H); 4.04 (s, 3H, CH_3). ^{13}C NMR (DMSO-d_6): δ 159.6, 157.8, 157.6, 154.5,

141.6, 132.0, 129.7, 129.5, 129.0, 127.8, 126.0, 125.4, 116.4, 116.1, 115.9, 112.5, 37.1 (NCH_3). MS (ESI): 344 $[M+H]^+$.

4′-[3-(3-Hydroxyphenyl)-1-methyl-1H-1,2,4-triazol-5-yl]-biphenyl-3-ol ***8b***

The title compound was prepared by reaction of 5-(3′-methoxybiphenyl-4-yl)-3-(3-methoxyphenyl)-1-methyl-1*H*-1,2,4-triazole (**8ib**) (0.100 g, 0.269 mmol) according to the general procedure described above. The product was purified by preparative TLC (CH_2Cl_2/MeOH, 10:0.25); yield: 48 mg (52%). $C_{21}H_{17}N_3O_2$; MW: 343. ^{1}H NMR (DMSO-d_6): δ 8.00–8.02 (m, 2H); 7.91–7.80 (m, 2H); 7.50–7.41 (m, 2H); 7.31–7.29 (m, 2H); 7.22–7.12 (m, 2H); 7.00–6.82 (m, 2H); 4.05 (s, 3H, CH_3). ^{13}C NMR (DMSO-d_6): δ 159.7, 157.9, 157.6, 154.4, 141.9, 140.5, 132.1, 130.1, 129.8, 129.1, 126.9, 126.6, 117.5, 116.5, 116.1, 115.0, 113.5, 112.5, 37.2 (NCH_3). MS (ESI): 344 $[M+H]^+$.

4′-[3-(4-Hydroxyphenyl)-1-methyl-1H-1,2,4-triazol-5-yl]-biphenyl-4-ol ***8c***

The title compound was prepared by reaction of 5-(4′-methoxybiphenyl-4-yl)-3-(4-methoxyphenyl)-1-methyl-1*H*-1,2,4-triazole (**8ic**) (0.100 g, 0.269 mmol) according to the general procedure described above. The product was purified by preparative TLC (CH_2Cl_2/MeOH, 10:0.25); yield: 60 mg (64%). $C_{21}H_{17}N_3O_2$; MW: 343. ^{1}H NMR (CD_3OD): δ 7.80 (d, J = 8.6 Hz, 2H); 7.70–7.66 (m, 4H); 7.45 (d, J = 8.5 Hz, 2H); 6.80 (d, J = 8.5 Hz, 2H); 6.77 (d, J = 8.5 Hz, 2H); 3.91 (s, 3H, CH_3). ^{13}C NMR (CD_3OD): δ 162.2, 160.1, 159.0, 156.9, 144.5, 132.3, 130.4, 129.2, 129.0, 127.8, 126.5, 123.2, 116.9, 116.5, 37.3 (NCH_3). MS (ESI): 344 $[M+H]^+$.

4′-[3-(4-Hydroxyphenyl)-1-methyl-1H-1,2,4-triazol-5-yl]-biphenyl-3-ol ***8d***

The title compound was prepared by reaction of 5-(3′-methoxybiphenyl-4-yl)-3-(4-methoxyphenyl)-1-methyl-1*H*-1,2,4-triazole (**8id**) (0.100 g, 0.269 mmol) according to the general procedure described above. The product was purified by preparative TLC (CH_2Cl_2/MeOH, 10:0.25); yield: 63 mg (68%). $C_{21}H_{17}N_3O_2$; MW: 343. ^{1}H NMR (CD_3OD): δ 7.80 (d, J = 8.7 Hz, 2H); 7.73–7.68 (m, 4H); 7.19 (t, J = 7.9 Hz, 1H); 7.07–7.01 (m, 2H); 6.77 (d, J = 7.0 Hz, 2H); 6.74–6.72 (m, 1H); 3.91 (s, 3H, CH_3). ^{13}C NMR (CD_3OD): δ 162.3, 160.1, 159.2, 156.7, 144.6, 142.6, 131.1, 130.4, 129.0, 128.4, 127.6, 123.2, 119.4, 116.5, 116.1, 114.9, 37.3 (NCH_3). MS (ESI): 344 $[M+H]^+$.

4′-[3-(3-Hydroxyphenyl)-1H-1,2,4-triazol-5-yl]biphenyl-4-ol ***8e***

The title compound was prepared by reaction of 5-(4′-methoxybiphenyl-4-yl)-3-(3-methoxyphenyl)-1*H*-1,2,4-triazole (**8ie**) (0.357 g, 1.0 mmol) according to the general procedure described above. The product was purified by preparative TLC (CH_2Cl_2/MeOH, 10:1); yield: 184 mg (56%). $C_{20}H_{15}N_3O_2$; MW: 329. ^{1}H NMR (CD_3OD): δ 8.07 (d, J = 8.4 Hz, 2H); 7.68 (d, J = 8.3 Hz, 2H); 7.53–7.51 (m, 4H); 6.80 (t, J = 8.2 Hz, 1H); 6.92–6.87 (m, 3H). ^{13}C NMR (CD_3OD): δ 160.8, 160.5, 159.2, 158.8, 143.9, 132.7, 131.6, 131.1, 129.1, 128.3, 128.0, 127.7, 118.8, 118.1, 116.9, 114.6. MS (ESI): 330 $[M+H]^+$.

4′-[3-(3-Hydroxyphenyl)-1H-1,2,4-triazol-5-yl]biphenyl-3-ol ***8f***

The title compound was prepared by reaction of 5-(3′-methoxybiphenyl-4-yl)-3-(3-methoxyphenyl)-1*H*-1,2,4-triazole (**8if**) (0.357 g, 1.0 mmol) according to the general procedure described above. The product was purified by preparative TLC (CH_2Cl_2/MeOH, 10:1); yield: 250 mg (76%). $C_{20}H_{15}N_3O_2$; MW: 329. ^{1}H NMR (CD_3OD + CD_3COCD_3, 2:1): δ 8.15 (d, J = 8.4 Hz, 2H); 7.74 (d, J = 8.5 Hz, 2H); 7.57–7.55 (m, 2H); 7.33 (t, J = 8.1 Hz, 1H); 7.28 (d, J = 7.9 Hz, 1H); 7.17–7.12 (m, 2H); 6.93–6.91 (m, 1H); 6.83–6.81 (m, 1H). ^{13}C NMR (CD_3OD + CD_3COCD_3, 2:1): δ 160.5, 160.5, 159.3, 159.2, 143.8, 143.0, 131.6, 131.2, 131.2, 129.7, 128.4, 128.1, 119.3, 118.8, 118.1, 115.9, 114.8, 114.6. MS (ESI): 330 $[M+H]^+$.

4′-[3-(4-Hydroxyphenyl)-1H-1,2,4-triazol-5-yl]biphenyl-4-ol ***8g***

The title compound was prepared by reaction of 5-(4′-methoxybiphenyl-4-yl)-3-(4-methoxyphenyl)-1*H*-1,2,4-triazole (**8ig**) (0.357 g, 1.0 mmol) according to the general procedure described above. The product was purified by preparative TLC (CH_2Cl_2/MeOH, 10:1); yield: 243 mg (74%). $C_{20}H_{15}N_3O_2$; MW: 329. ^{1}H NMR (CD_3OD + CD_3COCD_3, 2:1): δ 8.13 (d, J = 8.2 Hz, 2H); 7.95 (d, J = 8.6 Hz, 2H); 7.69 (d, J = 8.2 Hz, 2H); 7.55 (d, J = 8.6 Hz, 2H); 6.92 (d, J = 8.6 Hz, 2H); 6.89 (d, J = 8.6 Hz, 2H). ^{13}C NMR (CD_3OD + CD_3COCD_3, 2:1): δ 160.1, 160.1, 158.4, 142.9, 132.2, 132.1, 128.8, 128.8, 127.5, 127.2, 117.4, 116.5, 116.4. MS (ESI): 330 $[M+H]^+$.

4′-[3-(4-Hydroxyphenyl)-1H-1,2,4-triazol-5-yl]biphenyl-3-ol ***8h***

The title compound was prepared by reaction of 5-(3′-methoxybiphenyl-4-yl)-3-(4-methoxyphenyl)-1*H*-1,2,4-triazole (**8ih**) (0.357 g, 1.0 mmol) according to the general procedure described above. The product was purified by preparative TLC (CH_2Cl_2/MeOH, 10:1); yield: 214 mg (65%). $C_{20}H_{15}N_3O_2$; MW: 329. ^{1}H NMR (CD_3OD): δ 8.11 (d, J = 8.4 Hz, 2H); 7.89 (d, J = 8.7 Hz, 2H); 7.71 (d, J = 8.4 Hz, 2H); 7.27 (t, J = 7.9 Hz, 1H); 7.15–7.10 (m, 2H); 6.92 (d, J = 8.7 Hz, 2H); 6.81 (dd, J = 2.4 Hz, 1H). ^{13}C NMR (CD_3OD): δ 161.1, 160.0, 159.1, 143.8, 143.0, 131.0, 129.9, 129.3, 128.3, 128.0, 120.8, 119.3, 118.6, 116.9, 115.8, 114.8. MS (ESI): 330 $[M+H]^+$.

3′-[3-(3-Hydroxyphenyl)-1-methyl-1H-1,2,4-triazol-5-yl]-biphenyl-3-ol ***9***

The title compound was prepared by reaction of 5-(3′-methoxybiphenyl-3-yl)-3-(3-methoxyphenyl)-1-methyl-1*H*-1,2,4-triazole (**8ii**) (0.372 g, 1.0 mmol) according to the general procedure described above. The product was purified by preparative TLC (CH_2Cl_2/MeOH, 10:1); yield: 233 mg (68%). $C_{21}H_{17}N_3O_2$; MW: 343; ^{1}H NMR (CD_3COCD_3): δ 8.53 (bs, 1H, OH); 8.42 (bs, 1H, OH); 8.09 (t, J = 1.6 Hz, 1H); 7.86–7.97 (m, 2H); 7.68–7.63 (m, 3H); 7.33 (t, J = 8.1 Hz, 1H); 7.29 (t, J = 7.8 Hz, 1H); 7.23–7.21 (m, 1H); 6.91–6.88 (m, 2H); 4.12 (s, 3H, NCH_3). ^{13}C NMR (CD_3COCD_3): δ 162.3, 159.9, 159.5, 159.4, 157.0, 143.5, 143.5, 134.9, 132.0, 131.5, 131.2, 130.2, 129.4, 129.0, 120.2, 119.2, 117.8, 116.7, 115.8, 114.8, 38.7 (NCH_3).

3-{5-[3-(3-Hydroxyphenyl)-1-methyl-1H-1,2,4-triazol-5-yl]-2-thienyl}phenol ***13a***

The title compound was prepared by reaction of 3-(3-methoxyphenyl)-5-[5-(3-methoxyphenyl)-2-thienyl]-1-methyl-1*H*-1,2,4-triazole (**12a**) (0.377 g, 1.0 mmol) according to the general procedure described above. The product was purified by preparative TLC

(CH_2Cl_2/MeOH, 10:1); yield: 218 mg (62%). $C_{19}H_{15}N_3O_2S$; MW: 349. ^{1}H NMR (CD_3OD): δ 7.45–7.39 (m, 3H); 7.28 (d, J = 3.8 Hz, 1H); 7.16–7.09 (m, 2H); 7.04–7.00 (m, 2H); 6.74 (m, 1H); 6.68 (m, 1H); 3.95 (s, 3H, CH_3). ^{13}C NMR (CD_3OD): δ 161.9, 159.2, 158.8, 151.3, 149.2, 135.8, 133.0, 131.3, 131.1, 130.8, 128.5, 125.1, 118.8, 118.3, 117.6, 116.7, 114.3, 113.7, 37.8 (NCH_3). MS (ESI): 350 $[M+H]^+$.

3-{5-[5-(4-Hydroxyphenyl)-2-thienyl]-1-methyl-1H-1,2,4-triazol-3-yl}phenol ***13b***

The title compound was prepared by reaction of 3-(3-methoxyphenyl)-5-[5-(4-methoxyphenyl)-2-thienyl]-1-methyl-1*H*-1,2,4-triazole (**12b**) (0.377 g, 1.0 mmol) according to the general procedure described above. The product was purified by preparative TLC (CH_2Cl_2/MeOH, 10:1); yield: 189 mg (54%). $C_{19}H_{15}N_3O_2S$; MW: 349; white powder. ^{1}H NMR (CD_3OD): δ 7.48 (d, J = 3.9 Hz, 1H); 7.45–7.39 (m, 4H); 7.22 (d, J = 3.9 Hz, 1H); 7.16 (t, J = 7.9 Hz, 1H); 6.76–6.73 (m, 3H); 3.99 (s, 3H, CH_3). ^{13}C NMR (CD_3OD): δ 161.9, 159.4, 158.9, 151.5, 149.9, 133.0, 131.3, 130.8, 128.4, 127.1, 126.2, 123.6, 118.7, 117.5, 117.0, 114.3, 37.8 (NCH_3). MS (ESI): 350 $[M+H]^+$.

5-{5-[3-(3-Hydroxyphenyl)-1-methyl-1H-1,2,4-triazol-5-yl]-2-thienyl}pyridin-2-ol ***13c***

The title compound was prepared by reaction of 2-methoxy-5-{5-[3-(3-methoxyphenyl)-1-methyl-1*H*-1,2,4-triazol-5-yl]-2-thienyl}-pyridine (**12c**) (0.378 g, 1.0 mmol) according to the general procedure described above. The product was purified by preparative TLC (CH_2Cl_2/MeOH, 10:1); yield: 216 mg (62%). $C_{18}H_{14}N_4O_2S$; MW: 350; white powder. ^{1}H NMR (CD_3OD + CD_3COCD_3, 2:1): δ 8.53 (d, J = 2.0 Hz, 1H); 8.03 (m, 1H); 7.70–7.63 (m, 2H); 7.58–7.54 (m, 1H); 7.52 (d, J = 3.9 Hz, 1H); 7.27 (t, J = 8.1 Hz, 1H); 6.88–6.85 (m, 2H); 3.93 (s, 3H, CH_3). ^{13}C NMR (CD_3OD + CD_3COCD_3, 2:1): δ 165.0, 161.2, 158.5, 150.4, 144.9, 144.3, 137.4, 133.2, 133.1, 132.7, 132.6, 130.5, 130.3, 125.0, 124.1, 118.1, 116.9, 113.7, 111.9, 37.8 (NCH_3). MS (ESI): 351 $[M+H]^+$.

Biological assays

[2,4,6,7-^{3}H]-E2 and [2,4,6,7-^{3}H]-E1 were bought from Perkin-Elmer, Boston. Quickszint Flow 302 scintillator fluid was bought from Zinsser Analytic, Frankfurt. 17βHSD2 and 17βHSD1 were obtained from human placenta according to previously described procedures [38, 41–43]. Fresh human placenta was homogenized and centrifuged. The pellet fraction contains the microsomal 17βHSD2, while 17βHSD1 was obtained after precipitation with ammonium sulfate from the cytosolic fraction.

Inhibition of 17βHSD2

Inhibitory activities were evaluated by a well-established method with minor modifications [41]. Briefly, the enzyme preparation was incubated with NAD^+ (1500 μM) in the presence of potential inhibitors at 37°C in a phosphate buffer (50 mM) supplemented with 20% of glycerol and EDTA 1 mM. Inhibitor stock solutions were prepared in DMSO. Final concentration of DMSO was adjusted to 1% in all samples. The enzymatic reaction was started by addition of a mixture of unlabeled- and [2,4,6,7-^{3}H]-E2 (final concentration: 500 nM, 0.11 μCi). After 20 min at 37°C, the incubation was stopped with $HgCl_2$ and the mixture was extracted with ether. After evaporation, the steroids were dissolved in acetonitrile. E1 and E2 were separated using acetonitrile/water (45:55) as mobile phase in a C18 RP chromatography column (Nucleodur C18 Gravity, 3 μm, Macherey-Nagel) connected to a HPLC system (Agilent 1100 Series, Agilent Technologies, Waldbronn). Detection and quantification of the steroids were performed using a radioflow detector (Berthold Technologies, Bad Wildbad). The conversion rate was calculated according to following equation: %conversion = (%E1/(%E1 + %E2) × 100). Each value was calculated from at least three independent experiments.

Inhibition of 17βHSD1

The 17βHSD1 inhibition assay was performed similarly to the 17βHSD2 procedure. The cytosolic fraction was incubated with NADH (500 μM), test compound and a mixture of unlabeled- and [2,4,6,7-^{3}H]-E1 (final concentration: 500 nM, 0.15 μCi) for 10 min. Further treatment of the samples and HPLC separation was carried out as mentioned above.

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