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5-Phenyl Substituted 1-Methyl-2-pyridones and 4′-Substituted Biphenyl-4-carboxylic Acids. Synthesis and Evaluation as Inhibitors of Steroid-5α-reductase Type 1 and 2

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Abstract—The synthesis of a series of 5-phenyl substituted 1-methyl-2-pyridones (I) and 4′-substituted biphenyl-4-carboxylic acids (II) as novel A–C ring steroidomimetic inhibitors of 5α-reductase (5αR) is described. Compounds **1**–**4** (I) were synthesized by palladium catalyzed cross coupling (Ishikura) reaction between diethyl(3-pyridyl)borane and aryl halides (**1b**–**4b**) followed by α-oxidation with sodium ferrocyanate of the 1-methyl-pyridinium salt. Inhibitors II (**5**–**18**) were obtained either by two successive Friedel–Crafts acylations from biphenyl (**5a**–**10a**) followed by saponification to yield the corresponding carboxylic acids (**5**–**10**) or by Suzuki cross coupling reaction to give the 4′-substituted biphenyl-4-carbaldehydes **11a**–**18a**. The latter compounds were subjected to a Lindgren oxidation to yield compounds **11**–**18**. The compounds were tested for inhibitory activity toward human and rat 5αR1 and 2. The test compounds inhibited 5αR, showing a broad range of inhibitory potencies. The best compound in series I was the *N*-(dicyclohexyl)-4-(1,2-dihydro-1-methyl-2-oxopyrid-5-yl)benzamide **4** exhibiting an IC_{50} value for the human type 2 enzyme of 10 μM. In series II, the most active compound toward human type 2 isozyme was the 4′-(dicyclohexyl)acetyl-4-biphenyl carboxylic acid (**10**; $IC_{50} = 220$ nM). Both series showed only marginal activity toward the human type 1 isozyme. In conclusion, the biphenyl carboxylic acids (II) are more appropriate for 5αR inhibition than the 5-phenyl-1-methyl-2-pyridones (I). Especially the 4′-carbonyl compounds **5**–**10** represent new lead structures for the development of novel human type 2 inhibitors.

Introduction

5α-Reductase (5αR) is a NADPH-dependent, membrane bound enzyme which catalyzes the conversion of testosterone (T) to the more potent androgen dihydrotestosterone (DHT). Two isozymes, named type 1 and 2, have been described with a different tissue distribution pattern and with distinct biochemical and pharmacological properties.[1] Both are able to convert T into DHT. Despite a decrease in plasma testosterone level with aging, the DHT concentration remains at a constant level in the prostate.[2] This is believed to play a crucial role (permissive or/and causative) in benign prostatic hyperplasia (BPH). Searching for a non invasive treatment for BPH, the 5αR appears to be a promising therapeutic target. The first and so far only compound on the market is finasteride, a steroidal type 2 inhibitor.[3] Lots of efforts have been undertaken to develop non steroidal inhibitors[4–8] in order to avoid the side effects reported so far by the use of finasteride[9] and to increase the limited in vivo activity of this compound.

We previously reported that 5-aryl substituted 1-methyl-2-pyridones (I, Chart 1), non steroidal compounds mimicking the steroidal A and C ring, are inhibitors of 5αR.[7] In the class of *N*-substituted piperidine-4-(benzylidene-4-carboxylic acids) — new 5αR inhibitors designed as substrate analogues using molecular modeling — we recently observed that the introduction of hydrophobic and bulky substituents strongly increased the inhibitory activity.[8] This finding encouraged us to introduce some of these substituents into I (**1**–**4**). The biphenyl structure is another steroidal A–C ring mimetic, which has been successfully used by our group for the design of CYP 17 (P450 17) inhibitors.[10] Consequently, we now describe the syntheses of a series of 4′-substituted biphenyl-4-carboxylic acids designated as 5αR inhibitors (II, Chart 1, **5**–**18**). Identical substituents were introduced in II (**13**–**16**) as they have been used in I (**1**–**4**) to compare the two non steroidal skeletons. In addition to the alkylketones **5**–**10** and the

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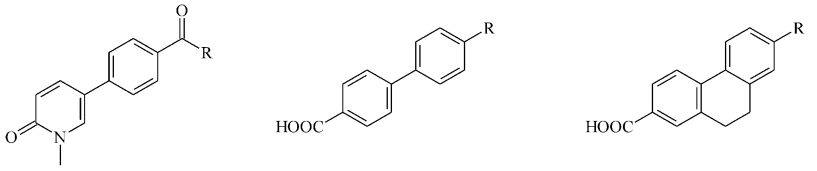


Chart 1. General structures.

amides **11**–**16** two halogenated derivatives were synthesized (**17**, **18**), as the corresponding tricyclic analogues (III, Chart 1) have been reported to be 5αR type 1 inhibitors.[11] In the following, we describe the syntheses of compounds **1**–**18** as well as their evaluation as inhibitors of human and rat 5αR type 1 and 2.

Chemistry

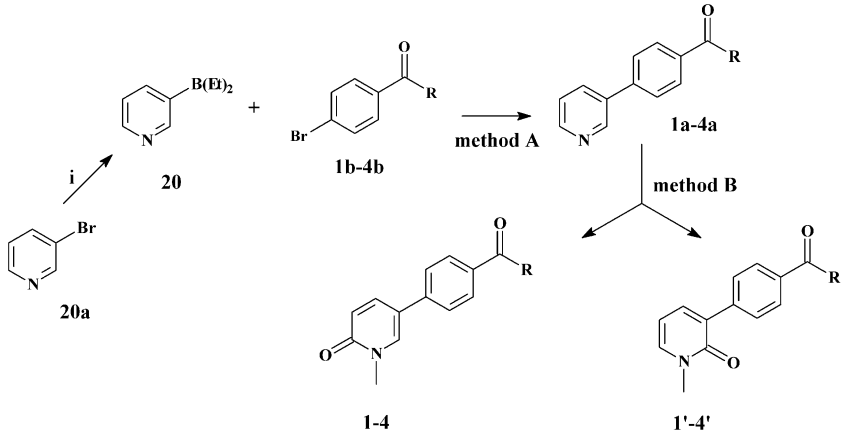
We previously reported on the synthetic strategy of the title compounds **1**–**4** (Scheme 1).[7] Briefly, the first step was the preparation of the diethyl(3-pyridyl)borane **20** which was synthesized from a solution of 3-lithiopyridine and triethylborane as described.[12] The 4-bromobenzoyl chloride, prepared from 4-bromobenzoic acid and thionyl chloride, was reacted with the appropriate amines to give the corresponding *N*-substituted 4-bromobenzamides **1b**–**4b**. The 3-arylpyridines **1a**–**4a** were synthesized by a cross coupling reaction between **20** and **1b**–**4b** using $Pd(Ph_3P)_4$ as a catalyst and KOH as a base (method A).[13] Subsequently compounds **1a**–**4a** were subjected to methylation and $K_3[Fe(CN)_6]$ oxidation (method B). The regioisomers **1**–**4** and **1′**–**4′** obtained were separated by column chromatography.

Two routes **A** and **B** were used for the syntheses of the 4′-substituted biphenyl-4-carboxylic acids **5**–**18** (Scheme 2). Route **A** is based on two successive Friedel–Crafts acylations. In the first one, biphenyl was reacted with the corresponding acid chlorides to yield compounds **5b**–**10b** (method C). Subsequent reaction with oxalylchloride and methanol gave the corresponding 4′-methoxycarbonylbiphenylketones **5a**–**10a** (method D) from which the corresponding carboxylic acids **5**–**10** were obtained by saponification (method E). For route B, a Suzuki cross coupling reaction between 4-formyl-boronic acid and the corresponding *N*-substituted 4-bromobenzamides using $Pd(Ph_3P)_4$ as catalyst[14] was applied (method F). Compounds **17a** and **18a** were prepared as described.[15] The 4′-substituted biphenyl-4-carboxaldehydes **11a**–**18a** were subjected to a Lindgren oxidation using $NaClO_2$ as oxidative agent and 2-methyl-2-butene (**11a**–**16a**)[16] or H_2O_2 (35%; **17a**, **18a**)[17] as a hypochloric acid scavenger to yield the corresponding carboxylic acids **11**–**18** (method G).

Biological Results

The inhibitory activity of compounds **1**–**18** and finasteride as a reference was determined using rat prostate homogenates (pH 6.6, type 1; pH 5.5, type 2) and human prostate homogenate (BPH tissue for type 2) according to the method of Liang et al.,[18] and the DU 145 cell line (for human type 1 enzyme) as described in the literature.[19,20]

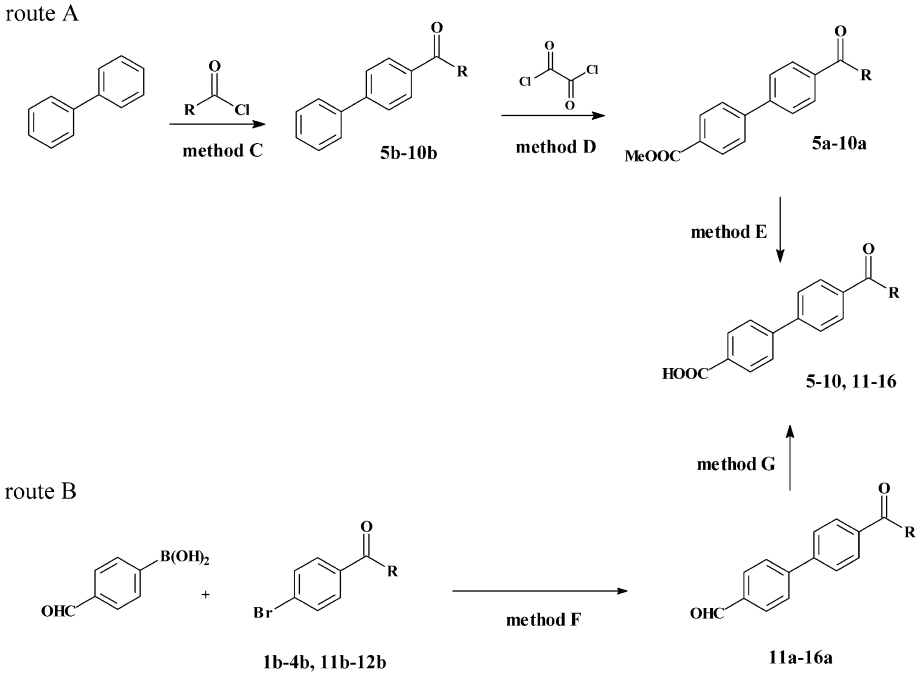
As seen in Table 1, the *N*-methylpyridones **1**–**4** displayed no or only a weak inhibitory activity toward human type 2 isozyme. The most active compound was the dicyclohexyl compound **4** with an IC_{50} value of 10 μM. The highest activity for the human isozymes was displayed by compound **2** for type 1 5αR. Notably, **2** (IC_{50} value 2.6 μM) consists of an analogous 3,5-bis(trifluoromethyl)phenyl amide substituent as does the well



Scheme 1. Synthesis of 5-phenyl and 3-phenyl substituted 1-methyl-2-pyridones **1**–**4** and **1′**–**4′**.

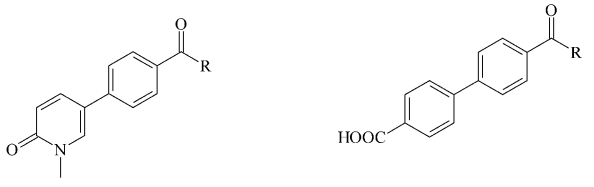
known steroidal inhibitor dutasteride.[21] None of these compounds was able to inhibit the rat type 2 isozyme to a strong extent. Contrary to this, most of them showed a good inhibitory activity toward the rat type 1 isozyme. Except for compound **2**, the inhibitors displayed IC_{50} values in the range of 10 to 1.3 μM for compounds **3** and **4**, respectively. None of the isomers **1′-4′** (Scheme 1) showed inhibitory activity (data not given) which also had been observed with the analogous compounds.[7]

The biphenyl compounds showed a large variety of potencies toward human type 2 isozyme ranging from 11% inhibition at a concentration of 10 μM (**16**) to an IC_{50} value of 220 nM for the most active compound **10** (Table 2). Compounds **9**, **13**, and **15** also showed good inhibition values (IC_{50} values of 0.64, 2.33, and 1.9 μM, respectively). Contrary to the results observed for type 2 isozyme, most of the biphenyl compounds exhibited a poor inhibitory activity versus human type 1 isozyme. The most active compound toward this enzyme was the dicyclohexyl amide **14** exhibiting 44% inhibition. Surprisingly the halogenated compounds **17** and **18** did not show significant inhibition toward human type 1 enzyme (DU 145 cells). Although their tricyclic analogues had



Scheme 2. Synthesis of 4′-substituted biphenyl-4-carboxylic acids **5**–**16**.

Table 1. Inhibition of rat and human 5αR type 1 and 2 in vitro by 5-phenyl-1-methyl-2-pyridones **1**–**4** (I) in comparison to corresponding biphenyl compounds **13**–**16** (II)



I II

R	Class	No.	RVP:[a] (IC_{50}, μM) or % inhibition (10 μM)		Human: (IC_{50}, μM) or % inhibition (10 μM)	
			Type 1[c]	Type 2[c]	BPH[dc]	DU 145[bce]
$N(Phenyl)_2$	**I**	**1**	(3.5)	24	n.i.	37
	II	**13**	(2.44)	23	11	40
NH(3,5-bis(trifluoromethyl)phenyl)	**I**	**2**	19	11	7	(2.6)
	II	**16**	(0.46)	(3)	(2.33)	28
NH(Adamantyl)	**I**	**3**	(10)	23	36	21
	II	**15**	(5.6)	(10)	(1.9)	16
$N(Cyclohexyl)_2$	**I**	**4**	(1.3)	34	(10)	43
	II	**14**	(1.4)	30	(4.7)	44

[a]Enzyme of rat ventral prostate, 200–250 μg protein, substrate [1β, 2β-^{3}H] testosterone 0.21 μM.
[b]Substrate:[^{3}H] androstenedione 5 nM.
[c]Mean value; tests have been run in duplicate. The standard deviation for IC_{50} is 20%, for percent inhibtion is ± 10%.
[d]Enzyme from BPH tissue (type 2), 200–300 μg protein, substrate[1β,2β-^{3}H] testosterone, 0.21 μM.
[e]Prostatic tumor cell line expressing type 1 enzyme.

shown strong activity in CHO cells expressing human isozyme 1.[11] The rat type 2 isozyme was not inhibited strongly by the biphenyl compounds either. The highest activity showed compound **13** exhibiting an IC_{50} value of 3 μM. Interestingly, compounds **13**–**16** inhibited the rat type 1 enzyme stronger than the rat type 2 isozyme. For instance, compound **13** displayed IC_{50} values of 0.46 and 3 μM in rat type 1 and type 2 isozyme, respectively.

Comparing the inhibition values of series I and II compounds with identical substituents, it becomes apparent that the prostatic therapeutic target, the human type 2 enzyme, is inhibited by series II compounds stronger than by **1**–**4** (Table 1).

Discussion and Conclusion

The present paper demonstrates that there is a significant increase in the inhibitory activity profiles of compounds **1**–**4** in comparison with those reported in our previous paper.[7] The most active compound **A** in that series (Chart 2) had shown 61% inhibition at a concentration of 100 μM, whereas the most active compound **4** of this paper displayed an IC_{50} value of 10 μM toward human type 2 isozyme. This result obviously is due to the bulky carboxamide substituents. It supports the hypothesis of the existence of a hydrophobic pocket in the active site of 5αR proposed by others.[22]

Comparing the steroidal A ring mimetics, it becomes apparent that in general the benzoic acid moiety (type II) is superior to the 1-methyl-2-pyridone structure (type I). This is especially true for the human type 2 enzyme. An exception observed for the human type 1 enzyme is compound **2** being a much stronger inhibitor than compound **16**.

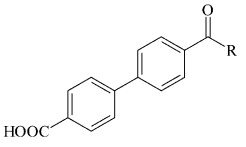
It is striking that the biphenyl compounds are weak inhibitors of the human type 1 enzyme. This might be due to the fact that the benzoic acid derivatives, which under physiological conditions are deprotonated, cannot easily permeate the intact DU 145 cells. To clarify this issue, a parallel artificial membrane permeation assay (PAMPA)[23] was performed. PAMPA mimics the passive diffusion through a cell membrane. Compound **9** showed a high flux rate (41%), even higher than finasteride (32%), indicating that the poor activity is not caused by a low permeation rate. From this, it has to be concluded that the biphenyl-4-carboxylic acids are indeed poor 5αR type 1 inhibitors.

Compounds inhibiting both types of 5αR, so-called dual inhibitors, might be advantageous for the therapy of BPH, since it has been shown that the dual inhibitor dutasteride is more powerful in reducing the DHT plasma concentration than selective type 1 or type 2 inhibitors.[21]

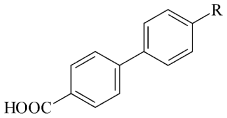
The carboxylic acid groups are essential for activity, as the aldehyde intermediates **13a** and **14a** (Scheme 2) of compounds **13** and **14** did not show any activity at a concentration of 10 μM toward both human isozymes (less than 10% inhibition at a concentration of 10 μM, data not given). Obviously, the carboxylate is required for mimicking the transition state (enolate) formed during the conversion of T to DHT.

In the ketone compounds **5**–**10** of series II, the role of the alkyl substituents was investigated. This study was performed because **MK-386**, an azasteroid bearing a

Table 2. Inhibition of rat and human 5αR type 1 and 2 in vitro by compounds **5**–**18** and finasteride



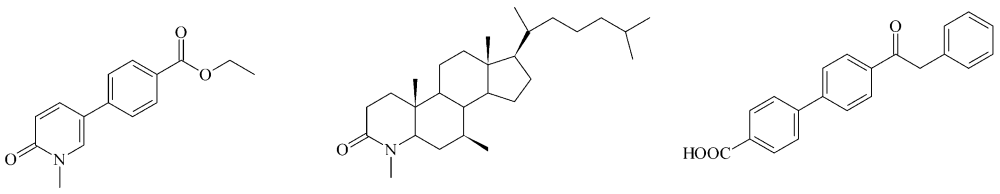
5–16



17,18

R	Route	No.	RVP:[a] (IC_{50}, μM) or % inhibition (10 μM)		Human: (IC_{50}, μM) or % inhibition (10 μM)	
			Type 1[c]	Type 2[c]	BPH[cd]	DU 145[bce]
$(CH_2)_2CH_3$	A	**5**	19	33	(10)	25
$(CH_2)_3CH_3$	A	**6**	24	28	60	35
$CH(CH_3)_2$	A	**7**	15	34	(10)	34
$CH_2CH(CH_3)_2$	A	**8**	22	36	(3.3)	11
Cyclohexyl	A	**9**	31	34	(0.64)	19
$CH(Cyclohexyl)_2$	A	**10**	31	30	(0.22)	27
$N(iPr)_2$	B	**11**	4	10	15	9
$N(iBu)_2$	B	**12**	24	37	(4.0)	16
$N(Phenyl)_2$	B	**13**	(0.46)	(3)	(2.33)	28
$N(Cyclohexyl)_2$	B	**14**	(1.4)	30	(4.7)	44
NH(Adamantyl)	B	**15**	(5.6)	(10)	(1.9)	16
NH(3,5-bis(trifluoromethyl)phenyl)	B	**16**	(2.44)	23	11	40
Br	B	**17**	28	29	65	7
Cl	B	**18**	24	27	65	8
Finasteride			(0.01)	(0.011)	(2–3 nM)	(0.039)

[a–e]See Table 1.



A [7] MK-386 [24] B [25]

Chart 2. General structures.

long alkyl substituent in 17β position (Chart 2), has been described to be a strong inhibitor of the human isozyme 1.[24] Most of these compounds, however, turned out to be weak inhibitors of human type 1 isozyme in spite of a rather good fit obtained by overlaying **MK-386** with compound *6* (minimum energy conformation—Hyperchem program). But they are good inhibitors of the human type 2 isozyme. This is in accordance with the finding of Holt et al. who described compound **B** (Chart 2) to be a strong inhibitor of the human type 2 enzyme.[25] The most active compounds of this series were the cyclohexyl compound **9** and the dicyclohexylmethyl compound **10** showing IC_{50} values of 0.64 and 0.22 μM, respectively. Comparing the ketone compounds **5**–**10** with the amides **11**–**16**, it seems as if the ketone compounds were more active. This originates from the observation that the dicyclohexylmethyl compound **10** is by a factor of 21 more active than the dicyclohexylamide **14** (IC_{50} values of 0.22 and 4.7 μM, respectively). As the most active compounds toward the human type 2 enzyme did not show sufficient activity toward the rat enzyme an in vivo test could not be performed using our rat model.[8]

As shown in the present paper, we have obtained new non steroidal inhibitors of 5αR. In the class of A-C ring steroidomimetics the biphenyl carboxylic acid (series II) is more appropriate for 5αR inhibition than the 5-phenyl-1-methyl-2-pyridone structure (series I). Especially the 4′-carbonyl compounds represent promising new leads for the development of novel human type 2 5αR inhibitors.

Experimental

^{1}H NMR spectra were recorded on a Bruker AM-400 (400 MHz) in DMSO-d_6 or $CDCl_3$. Chemical shifts are reported as δ values (ppm) relative to internal tetramethylsilane (δ 0 ppm). Elemental analyses were performed in the Department of Inorganic Chemistry, University of the Saarland. IR spectra were performed with KBr disks or films as indicated on a Perkin-Elmer 398 infrared spectrometer. Melting points were determined on a Kofler melting point apparatus Thermopan (Reichert) and are uncorrected. Column chromatography was performed on Merck silicagel 60 (40–63 μm) or (50–200 μm). All reactions were followed by thin layer chromatography using Alugram® Silica gel 60. Chemicals and solvents used were commercially available (Lancaster, Fluka, Acros) and were used without further purification.

Diethyl(3-pyridyl)borane (20).[12] A 1 M solution of triethylborane in hexane (21 mL) was added dropwise to a dry diethylether solution (30 mL) of 3-lithiopyridine [prepared from 3-bromopyridine (**20a**, 21 mmol) and *n*-BuLi (21 mmol, 13 mL of 1.6 M solution in hexane)] under a nitrogen atmosphere at −78 °C. The mixture was stirred at the same temperature for 2 h, and at room temperature overnight. Then a solution of iodine (21 mmol) in THF (20 mL) was added slowly at room temperature. After stirring for 2 h, the mixture was diluted with ethyl acetate and washed with 10% $Na_2S_2O_3$ aq. solution and twice with brine. The organic phase was dried over $MgSO_4$. After evaporation the crude compound was purified by chromatography with benzene as eluent to yield **20** (65%) as white crystals, mp 160–161 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.47 (t, 6H, $^3J = 7.5$ Hz, 2-C$\underline{H}_3$), 0.65 (m, 4H, 2-C$\underline{H}_2$–), 7.24 (dd, 1H, $^3J = 7$ Hz, $^3J = 6$ Hz, C_5–H), 7.60 (s, 1$\underline{H}$, C_2–H), 7.71 (ddd, 1H, $^3J = 7$ Hz, $^4J = 1.5$ Hz, $^4J = 1.5$ Hz, C_4–H), 7.98 (d, 1H, $^3J = 6$ Hz, C_6-H). IR (KBr): ν = 3015, 2930, 2900, 2860, 2810, 1600, 1475, 1405, 1260, 1195, 1085, 1045, 1025, 900, 875, 800, 710. Anal. $C_9H_{14}BN\frac{1}{4}H_2O$.

General procedure for the synthesis of 1b–4b, 11b, 12b

4-Bromo-*N*,*N*-diphenylbenzamide (1b). A mixture of 4-bromobenzoic acid (23 g, 0.1 mol), one drop of *N*,*N*-dimethylformamide and thionyl chloride (50 mL) was refluxed for 2 h. After cooling to ambient temperature, $SOCl_2$ was removed by distillation. The crude acid chloride was dissolved in 20 mL of dry CH_2Cl_2 and was added dropwise to a suspension of diphenylamine (18 g, 0.1 mol) and dry triethylamine (40 mL, 0.3 mol) in dry CH_2Cl_2 (170 mL). The solution was stirred for 2 h. The organic phase was washed with water (2×20 mL) and dried over $MgSO_4$. After filtration, the solvent was evaporated in vacuo and the crude product was purified by recrystallization from hexane/ethyl acetate to yield **1b** (18.3 g, 50%) as white crystals, mp 150 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.12 and 7.14 (d, AA′BB′, 4H, $^3J = 8$ Hz, aromat. H), 7.19 (t, 2H, $^3J = 6$ Hz, aromat. H), 7.25–7.36 (m, 8H, aromat. H). IR (KBr): ν = 3450 (br), 3040, 1670, 1590, 1490, 1450, 1395, 1345, 1310, 1180, 1110, 1010, 860, 830, 770, 750, 700. $C_{19}H_{14}NOBr$ (352.23).

4-Bromo-*N*-3,5-bis(trifluoromethyl)phenylbenzamide (2b). Synthesized from 4-bromobenzoic acid and 3,5-bis(trifluoromethyl)aniline. Purified by recrystallization from hexane/ethyl acetate. Yield 55%, white crystals, mp 169 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.64 and 7.74 (d, AA′BB′, 4H, $^3J = 8$ Hz, aromat. H, and 1H, phenyl-H_4),

8.15 (s, 2H, phenyl-$H_{2,}$-H_6), 8.19 (s, 1H, NH). IR (KBr): ν = 3280 (NH), 3100, 1660, 1600, 1560, 1470, 1450, 1380, 1310, 1280, 1230, 1180, 1150, 1110, 1020, 990, 890, 850, 750, 700. $C_{15}H_8NOF_6Br$ (317.13).

4-Bromo-*N*-adamantylbenzamide (3b). Synthesized from 4-bromobenzoic acid and adamantylamine. Purified by recrystallization from hexane/ethyl acetate. Yield 44%, white crystals, mp 160 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.72 (s, 6H, ada. H), 2.11 (s, 9H, ada. H), 5.71 (s, broad, 1H,–NH–), 7.52 and 7.57 (d, AA′BB′, 4H, ^3J = 8 Hz, aromat. H). IR (KBr): ν = 3340 (NH), 2920, 2860, 1650, 1600, 1540, 1490, 1460, 1360, 1310, 1260, 1160, 1070, 1020, 860, 850, 760. $C_{17}H_{20}NOBr$ (334.25).

4-Bromo-*N*,*N*-dicyclohexylbenzamide (4b). Synthesized from 4-bromobenzoic acid and dicylohexylamine and recrystallized from hexane/ethyl acetate. Yield 52%, white crystals, mp 138 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.15–1.78 (m, 20H, cyclohexyl–H), 2.58 and 3.18 (s, broad, 2H,–N(C<u>H</u>)$_2$–), 7.16 and 7.49 (d, AA′BB′, 4H, ^3J = 8 Hz, aromat. H). IR (KBr): ν = 3400 (br), 2960, 2940, 2860, 1640, 1590, 1470, 1440, 1390, 1370, 1320, 1250, 1190, 1130, 1105, 1070, 1020, 1000, 940, 900, 850, 830, 760, 750, 700. $C_{19}H_{26}NOBr$ (364.32).

4-Bromo-*N*,*N*-diisopropylbenzamide (11b).[26] Synthesized from 4-bromobenzoic acid and diisopropylamine. Purified by recrystallization from petrol ether. Yield 64%, mp 72–73 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.43 (s, 12H, –CH(C<u>H</u>$_3$)$_2$), 3.71 (s, 2H, broad,–C<u>H</u>(CH$_3$)$_2$), 7.20 and 7.51 (d, AA′BB′, 4H, ^3J = 8 Hz, aromat. H). $C_{13}H_{18}NOBr$ (284.19).

4-Bromo-*N*,*N*-diisobutylbenzamide (12b). Synthesized from 4-bromobenzoic acid and diisobutylamine. Purified by recrystallization first from petrol ether, then from hexane. Yield 61%, mp 59 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.74 and 0.98 (2s, 12H,–CH(C<u>H</u>$_3$)$_2$), 1.84 and 2.11 (2s, 2H,–C<u>H</u>(CH$_3$)$_2$), 3.07 and 3.34 (2d, 4H, ^3J = 6 Hz,–NC<u>H</u>$_2$–), 7.23 and 7.52 (d, AA′BB′, 4H, ^3J = 8 Hz, aromat. H). $C_{15}H_{22}NOBr$ (312.25).

Method A

***N*,*N*-Diphenyl-4-(3-pyridyl)benzamide (1a).** To a stirred mixture of 4-bromo-*N*,*N*-diphenylbenzamide (**1b**) (10 mmol, 1.2 mol equiv, 3.52 g), and $Pd(Ph_3P)_4$ (500 mg) in THF under nitrogen atmosphere at room temperature, were added tetra-*n*-butylammonium bromide (0.82 mmol, 0.1 mol equiv, 264 mg), powdered KOH (25 mmol, 3 mol equiv, 1.4 g) and diethyl-3-(pyridyl)borane (**20**) (8.2 mmol, 1.2 g). The mixture was heated under reflux for 2 h. After cooling to room temperature the suspension was diluted with ethyl acetate. The combined organic phases were washed with brine and dried over $MgSO_4$. After removal of the solvent, the residue was purified by flash column chromatography (FCC) (hexane/ethyl acetate, 1:1) to give 800 mg (28%) of **1a** as a brown oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.17 and 7.23 (d, AA′BB′, 4H, ^3J = 8 Hz, aromat. H), 7.44–7.58 (m, 10H, aromat. H, and 1H, pyr. C_5–H), 7.99 (d, 1H, ^3J = 8 Hz, pyr. C_4–H), 8.61 (d, 1H, ^{3}J = 5 Hz, pyr. C_6–H), 8.82 (s, 1H, pyr. C_2–H). IR : ν = 3450 (br), 3040, 1670, 1590, 1490, 1450, 1395, 1345, 1310, 1180, 1110, 1010, 860, 830, 770, 750, 700. $C_{24}H_{18}N_2O$ (350.41).

***N*-(3,5-Bis(trifluoromethyl)phenyl)-4-(3-pyridyl)benzamide (2a).** Synthesized from 4-bromo-*N*-3,5-bis(trifluoromethyl)benzamide (**2b**) and diethyl-3-(pyridyl)borane (**20**) and purified by FCC in petrol ether/acetone 9:3. Yield 30%, white solid, mp 226–227 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.44 (dd, 1H, ^3J = 8 Hz, ^3J = 5 Hz, pyr. C_5–H), 7.67 (s, 1H, phenyl-H_4), 7.73 and 8.01 (d, AA′BB′, 4H, ^3J = 8 Hz, aromat. H), 7.93 (d, 1H, ^{3}J = 8 Hz, pyr. C_4–H), 8.22 (s, 2H, phenyl–H_2,–H_6), 8.27 (s, 1H,–NH–), 8.66 (d, 1H, ^3J = 5 Hz, pyr. C_6–H) 8.86 (s, 1H, pyr. C_2–H). IR (KBr): ν = 3320 (NH), 3100, 1660, 1610, 1560, 1470, 1450, 1390, 1280, 1230, 1210, 1180, 1130, 1000, 940, 890, 860, 820, 760, 700. $C_{20}H_{12}N_2OF_6$ (410.32).

***N*-Adamantyl-4-(3-pyridyl)benzamide (3a).** Synthesized from 4-bromo-*N*-adamantylbenzamide (**3b**) and diethyl-3-(pyridyl)borane (**20**) and purified by FCC in petrol ether/acetone 6:4 and recrystallized from hexane/ethyl acetate. Yield 89%, slightly yellow solid, mp 149 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.74 (s, 6H, ada. H), 2.15 (s, 9H, ada. H), 5.85 (s, 1H,–NH–), 7.53 (s, 1H, pyr. C_5-H), 7.63 and 7.83 (d, AA′BB′, 4H, ^3J = 8 Hz, aromat. H) 7.90 (d, 1H, ^3J = 8 Hz, pyr. C_4–H), 8.64 (s, 1H, broad, pyr. C_6–H), 8.87 (s, 1H, broad, pyr. C_2–H). IR (KBr): ν = 3340 (NH), 3040, 2920, 2850, 1660, 1590, 1540, 1510, 1470, 1450, 1360, 1340, 1310, 1260, 1190, 1130, 1030, 1000, 860, 820, 760, 730, 700. $C_{22}H_{24}N_2O$ (332.44).

***N*,*N*-Dicyclohexyl-4-(3-pyridyl)benzamide (4a).** Synthesized from 4-bromo-*N*,*N*-dicyclohexylbenzamide (**4b**) and diethyl(3-pyridyl)borane (**20**) and purified by column chromatography (CC) in petrol ether/acetone 1:1 and recrystallized from hexane/ethyl acetate. Yield 35%, white crystals, mp 167 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.05–1.79 (m, 20H, cyclohexyl-H), 2.61 and 3.16 (s, broad, 2H,–N(C<u>H</u>)$_2$–), 7.39 (s, 1H, pyr. C_5–H) 7.41 and 7.59 (d, AA′BB′, 4H, ^{3}J = 8 Hz, aromat. H), 7.92 (d, 1H, ^3J = 8 Hz, pyr. C_4–H), 8.61 (d, 1H, ^3J = 4 Hz, pyr. C_6–H), 8.87 (s, 1H, pyr. C_2–H). IR (KBr): ν = 3420 (br), 3020, 2940, 2860, 1640, 1450, 1440, 1390, 1370, 1320, 1250, 1190, 1130, 1000, 940, 900, 860, 805, 760, 720, 710. $C_{24}H_{30}N_2O$ (362.51).

Method B

The ^{1}H NMR spectrum of compound **3′** is given as an example. In case of the isomers **1′**, **2′**, **4′** the data corresponding to the (1,2-dihydro-1-methyl-2-oxo-5-pyridyl)benzamide moiety are very similar to that described in **3′**. All the isomers **1′**–**4′** appeared on TLC as a fluorescent UV visible spot.

***N*,*N*-Diphenyl-4-(1,2-dihydro-1-methyl-2-oxo-5-pyridyl)-benzamide (1).** Dimethyl sulfate (2.28 mmol, 288 mg) was slowly added dropwise to 2.28 mmol of *N*,*N*-diphenyl-4-(3-pyridyl)benzamide (**1a**) and heated for 1 h on a

steam bath. The product was oxidized by adding an aqueous solution of $K_3[Fe(CN)_6]$ (5.70 mmol, 1.78 g) in H_2O (5.70 mL) under stirring and cooling. Powdered KOH (18.2 mmol, 1.02 g) was added slowly keeping the temperature at 5–10 °C. After adding CH_2Cl_2 (6 mL), the mixture was stirred for 30 min before additional portions of $K_3[Fe(CN)_6]$ (2.85 mmol, 935 mg) in H_2O (2.85 mL) and powdered KOH (9.12 mmol, 500 mg) were added. The mixture was left overnight. The biphasic mixture was filtered and the layers were separated. The aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, filtered and evaporated to dryness. The brown oily residue was purified by CC in petrol ether/ethyl acetate 1:1 to yield **1** (41%) and **1′** (26%). **1**: slightly yellow powder, mp 200–201 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.60 (s, 3H,–NCH_3), 6.67 (d, 1H, ^3J = 9 Hz, pyr. C_3–H), 7.15 and 7.49 (d, AA′BB′, 4H, ^3J = 8 Hz, aromat. H), 7.17–7.31 (m, 10H, aromat. H), 7.51 (s, 1H, pyr. C_6-H), 7.57 (dd, 1H, ^3J = 9 Hz, ^4J = 2.5 Hz, pyr. C_4–H). IR : ν = 3450 (br), 3060, 1660, 1600, 1540, 1490, 1450, 1400, 1350, 1310, 1190, 1160, 1080, 1010, 860, 830, 770, 700. Anal. $C_{25}H_{20}N_2O_2$ (380.44).

***N*-(3,5-Bis(trifluoromethyl)phenyl)-4-(1,2-dihydro-1-methyl-2-oxo-5-pyridyl)benzamide (2).** Synthesized from *N*-3,5-bis(trifluoromethyl)phenyl-4-(3-pyridyl)benzamide (**2a**). Purified by CC in *n*-hexane/ethyl acetate 1:1. Yield 30%, white crystals, mp 284 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.64 (s, 3H, $-NCH_3$), 6.73 (d, 1H, ^3J = 9 Hz, pyr. C_3–H), 7.46 (s, 1H, phenyl–H_4), 7.52 and 7.66 (d, AA′BB′, 4H, ^3J = 8 Hz, aromat. H), 7.56 (s, 1H, ^4J = 2.5 Hz, pyr. C_6–H), 7.64 (dd, 1H, ^3J = 9 Hz, ^4J = 2.5 Hz, pyr. C_4–H) 8.25 (s, 2H, phenyl–H_2,–H_6), 8.49 (s, 1H, NH). IR (KBr): ν = 3320 (NH), 3100, 1660, 1610, 1560, 1470, 1450, 1390, 1280, 1230, 1210, 1180, 1130, 1000, 940, 890, 860, 820, 760, 700. Anal. $C_{21}H_{14}N_2O_2F_6$ (440.34).

***N*-Adamantyl-4-(1,2-dihydro-1-methyl-2-oxo-5-pyridyl)-benzamide (3).** Synthesized from *N*-adamantyl-4-(3-pyridyl)benzamide (**3a**). Purified by CC in petrol ether/ethyl acetate 1:1 and recrystallized from petrol ether/ethyl acetate. Yield 62%, white crystals, mp 260 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.73 (s, 6H, ada. H), 2.14 (s, 9H, ada. H), 3.64 (s, 3H,–NCH_3), 5.82 (s, 1H,–NH–), 6.69 (d, 1H, ^3J = 9 Hz, pyr. C_3–H), 7.44 and 7.76 (d, AA′BB′, 4H, ^3J = 8 Hz, aromat. H) 7.56 (d, 1H, ^4J = 2.5 Hz, pyr. C_6–H), 7.64 (dd, 1H, ^3J = 9 Hz, ^4J = 2.5 Hz, pyr. C_4–H). IR (KBr): ν = 3350 (NH), 3040, 2905, 2860, 1660, 1600, 1560, 1505, 1510, 1450, 1410, 1360, 1330, 1310, 1250, 1200, 1160, 1090, 1010, 860, 840, 770, 730, 710. Anal. $C_{23}H_{26}N_2O_2$ (362.47).

***N*-Adamantyl-4-(1,2-dihydro-1-methyl-2-oxo-3-pyridyl)-benzamide (3′).** Synthesized from *N*-adamantyl-4-(3-pyridyl)benzamide (**3a**). Yield 26%, colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.73 (s, 6H, ada. H), 2.13 (s, 9H, ada. H), 3.62 (s, 3H, –NCH_3), 5.86 (s, 1H, –NH–), 6.27 (t, 1H, ^3J = 7 Hz, pyr. C_5–H), 7.34 (dd, 1H, ^3J = 7 Hz, ^4J = 2 Hz, pyr. C_4–H), 7.52 (dd, 1H, ^3J = 7 Hz, ^4J = 2 Hz, pyr. C_6–H), 7.72 and 7.75 (d, AA′BB′, 4H, ^3J = 8 Hz, aromat. H).

***N*,*N*-Dicyclohexyl-4-(1,2-dihydro-1-methyl-2-oxo-5-pyridyl)benzamide (4).** Synthesized from *N*,*N*-dicyclohexyl-4-(3-pyridyl)benzamide (**4a**). Purified by FCC in hexane/ethyl acetate 1:9 and recrystallized form hexane/ethyl acetate. Yield 51%, white crystals, mp 232 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.10–1.78 (m, 20H, cyclohexyl–H), 2.61 and 3.20 (s, broad, 2H,–N($C\underline{H}$)$_2$–), 3.64 (s, 3H,–NCH_3), 6.69 (d, 1H, ^3J = 9 Hz, pyr. C_3–H), 7.34 and 7.41 (d, AA′BB′, 4H, ^3J = 8 Hz, aromat. H), 7.54 (d, 1H, ^4J = 2.5 Hz, pyr. C_6–H), 7.65 (dd, 1H, ^3J = 9 Hz, ^4J = 2.5 Hz, pyr. C_4–H). IR (KBr): ν = 3420 (br), 2940, 2860, 1670, 1620, 1540, 1470, 1440, 1370, 1320, 1300, 1260, 1190, 1170, 1130, 1000, 940, 900, 830, 770, 710. Anal. $C_{25}H_{32}N_2O_2$ (392.54).

Route A: method C

4-Biphenylyldicyclohexylmethylketone (10b). Under anhydrous conditions, a stirred mixture of biphenyl (6.50 g, 0.028 mol), carbon disulfide (150 mL), and finely powdered anhydrous aluminum chloride (4.13 g, 0.031 mol) was treated with dicyclohexylacetylchloride (7.00 g, 0.028 mol). The reaction mixture was refluxed for 4 h. After cooling to ambient temperature the carbon disulfide was removed by distillation under reduced pressure and the residue was decomposed by carefully pouring onto a mixture of ice and dilute hydrochloric acid. The solid was filtered off, dried and purified by FCC in hexane/CH_2Cl_2 6:1 to yield 3.40 g (33%) of **10b** as a white solid, mp 140 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.86–1.91 (m, 22H, cyclohexyl–H), 3.34 (m, 1H, ^3J = 7 Hz,–COCH–), 7.38 (t, 1H, ^3J = 7 Hz, aromat. H), 7.46 (t, 2H, ^3J = 7 Hz, aromat. H), 7.62 (d, 2H, ^3J = 8 Hz, aromat. H), 7.66 and 8.03 (d, AA′BB′, 4H, ^3J = 8 Hz, aromat. H). IR (KBr): ν = 1680 (CO stretch). $C_{26}H_{32}O$ (360.54).

4-Biphenylyl-*n*-propylketone (5b). Synthesized from biphenyl and butanoyl chloride. Yield 58%, white solid, mp 95 °C, (lit. 94 °C).[27] ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.02 (t, 3H, ^3J = 7 Hz,–$CH_2CH_2C\underline{H}_3$), 1.80 (sextett, 2H, ^3J = 7 Hz,–$CH_2C\underline{H}_2CH_3$), 2.97 (t, 2H, ^3J = 7 Hz,–$C\underline{H}_2CH_2CH_3$), 7.39 (t, 1H, ^3J = 7 Hz, aromat. H), 7.46 (t, 2H, ^3J = 7 Hz, aromat. H), 7.62 (d, 2H, ^3J = 7 Hz, aromat. H), 7.67 and 8.03 (d, AA′BB′, 4H, ^3J = 8 Hz, aromat. H). IR (KBr): ν = 1690 (CO stretch). $C_{16}H_{16}O$ (224.30).

4-Biphenylyl-*n*-butylketone (6b). Synthesized from biphenyl and pentanoyl chloride. Yield 61%, white solid, mp 73 °C, (lit. 76–78 °C).[27] ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.97 (t, 3H, ^3J = 7 Hz,–$CH_2CH_2CH_2C\underline{H}_3$), 1.43 (sextett, 2H, ^3J = 7 Hz,–$CH_2CH_2C\underline{H}_2CH_3$), 1.74 (quintett, 2H, ^3J = 7 Hz,–$CH_2C\underline{H}_2CH_2CH_3$), 2.99 (t, 2H, ^3J = 7 Hz,–$C\underline{H}_2CH_2CH_2CH_3$), 7.39 (t, 1H, ^3J = 7 Hz, aromat. H), 7.47 (t, 2H, ^3J = 7 Hz, aromat. H), 7.62 (d, 2H, ^3J = 7 Hz, aromat. H), 7.68 and 8.03 (d, AA′BB′, 4H, ^3J = 8 Hz, aromat. H). IR (KBr): ν = 1670 (CO stretch). $C_{17}H_{18}O$ (238.33).

4-Biphenylylisopropylketone (7b). Synthesized from biphenyl and isobutyryl chloride. Yield 54%, white powder, mp 49–50 °C. (lit. 62 °C).[27] ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.24 (d, 6H, ^3J = 7 Hz, –CH($C\underline{H}_3$)$_2$), 3.58

(septett, 1H, $^3J=7$ Hz, –CH(CH$_3$)$_2$), 7.39 (t, 1H, $^3J=7$ Hz, aromat. H), 7.46 (t, 2H, $^3J=7$ Hz, aromat. H), 7.62 (d, 2H, $^3J=7$ Hz, aromat. H), 7.68 and 8.03 (d, AA′BB′, 4H, $^3J=8$ Hz, aromat. H). IR (KBr): ν = 1640 (CO stretch). $C_{16}H_{16}O$ (224.30).

4-Biphenylylisobutylketone (8b). Synthesized from biphenyl and 3-methylbutyryl chloride. Yield 65%, white powder, mp 73 °C, (lit. 74–76.5 °C).[27] ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.01 (d, 6H, $^3J=7$ Hz,–CH(CH$_3$)$_2$), 2.32 (septett, 1H, $^3J=7$ Hz,–CH(CH$_3$)$_2$), 2.86 (d, 2H, $^3J=7$ Hz,–COCH$_2$–), 7.39 (t, 1H, $^3J=7$ Hz, aromat. H), 7.47 (t, 2H, $^3J=7$ Hz, aromat. H), 7.62 (d, 2H, $^3J=7$ Hz, aromat. H), 7.67 and 8.02 (d, AA′BB′, 4H, $^3J=8$ Hz, aromat. H). IR (KBr): ν = 1670 (CO stretch). $C_{17}H_{18}O$ (238.33).

4-Biphenylylcyclohexylketone (9b). Synthesized from biphenyl and cyclohexyl carboxylic acid chloride. Yield 52%, white crystals, mp 86 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.27–1.93 (m, 10H, cylohexyl–H), 3.29 (m, 1H,–COCH–), 7.40 (t, 1H, $^3J=8$ Hz, aromat. H), 7.47 (t, 2H, $^3J=8$ Hz, aromat. H), 7.62 (d, 2H, $^3J=8$ Hz, aromat. H), 7.68 and 8.02 (d, AA′BB′, 4H, $^3J=8$ Hz, aromat. H). IR (KBr): ν = 1680 (CO stretch). $C_{19}H_{20}O$ (264.36).

Method D

4′-Butanoylbiphenyl-4-carboxylic acid methyl ester (5a). In an ice bath, anhydrous aluminum chloride (4.00 g, 30.0 mmol) was added in one portion to a mixture of 4-biphenylyl-*n*-propylketone **5b** (2.20 g, 9.90 mmol), and oxalylchloride (1.70 mL, 2 equiv, 20.0 mmol) in 40 mL of anhydrous dichloromethane. The mixture was stirred for 45 min at 4–10 °C, then poured carefully onto 50 g of ice. The solution was extracted several times with ethyl acetate. The organic layer was washed with brine and dried over $MgSO_4$. After removal of the solvent the residue was dissolved in dry dichloromethane and added dropwise to a solution of dry methanol (10 mL) in dry dichloromethane. An exothermic reaction occurs. The black mixture was stirred for 1 h, diluted with CH_2Cl_2 and washed with water. The combined organic phases were dried over $MgSO_4$ and evaporated. The residue was purified by FCC in hexane/ethyl acetate 9:1 to yield the title compound **5a** (18%), mp 158 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.95 (t, 3H, $^3J=7$ Hz,–(CH$_2$)$_2$CH$_3$), 1.63 (sextett, 2H, $^3J=7$ Hz,–CH$_2$CH$_2$CH$_3$), 3.04 (t, 2H, $^3J=7$ Hz,–CH$_2$CH$_2$CH$_3$), 3.96 (s, 3H, $COOCH_3$), 7.86 (2×overlapp. d, 4H, $^3J=8$ Hz, aromat. H), 7.90 and 8.03 (d, AA′BB′, 4H, $^3J=8$ Hz, aromat. H). $C_{18}H_{18}O_3$ (282.34).

4′-Pentanoylbiphenyl-4-carboxylic acid methyl ester (6a). Synthesized from 4-biphenylyl-*n*-butylketone (**6b**) and oxalylchloride. Purified by FCC in hexane/ethyl acetate 9:1. Yield 20%, white solid, mp 150 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.97 (t, 3H, $^3J=7$ Hz, –(CH$_2$)$_3$CH$_3$), 1.44 (sextett, 2H, $^3J=7$ Hz, –CH$_2$CH$_2$CH$_2$CH$_3$), 1.75 (quintett, 2H, $^3J=7$ Hz, –CH$_2$CH$_2$CH$_2$CH$_3$), 3.00 (t, 2H, $^3J=7$ Hz, –CH$_2$CH$_2$CH$_2$CH$_3$), 3.95 (s, 3H, $COOCH_3$), 7.70 (2×overlapp., d, 4H, $^3J=8$ Hz, aromat. H), 8.05 and 8.13 (d, AA′BB′, 4H, $^3J=8$ Hz, aromat. H). $C_{19}H_{20}O_3$ (296.36).

4′-Isobutanoylbiphenyl-4-carboxylic acid methyl ester (7a). Synthesized from 4-biphenylylisopropylketone (**7b**) and oxalylchloride. Purified by FCC in hexane/ethyl acetate 9:1. Yield 53%, white solid, mp 101 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.25 (d, 6H, $^3J=7$ Hz, –CH(CH$_3$)$_2$), 3.59 (septett, 1H, $^3J=7$ Hz,–CH(CH$_3$)$_2$), 3.95 (s, 3H, $COOCH_3$), 7.70 (2×overlapp., d, 4H, $^3J=8$ Hz, aromat. H), 8.05 and 8.13 (d, AA′BB′, 4H, $^3J=8$ Hz, aromat. H). $C_{18}H_{18}O_3$ (282.34).

4′-(3-Methylbutanoyl)biphenyl-4-carboxylic acid methyl ester (8a). Synthesized from 4-biphenylyl-(3-methylpropyl)ketone (**8b**) and oxalylchloride. Purified by FCC in hexane/ethyl acetate 9:1. Yield 12%, slightly yellow solid, mp 121 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.02 (d, 6H, $^3J=7$ Hz,–CH(CH$_3$)$_2$), 2.32 (septett, 1H, $^3J=7$ Hz,–CH(CH$_3$)$_2$), 2.86 (d, 2H, $^3J=7$ Hz,–COCH$_2$–), 3.95 (s, 3H, $COOCH_3$), 7.69 (2×overlapp., d, 4H, $^3J=8$ Hz, aromat. H), 8.04 and 8.13 (d, AA′BB′, 4H, $^3J=8$ Hz, aromat. H). $C_{19}H_{20}O_3$ (296.36).

4′-Cyclohexanoylbiphenyl-4-carboxylic acid methyl ester (9a). Synthesized from 4-biphenylylcyclohexylketone (**9b**) and oxalylchloride. Purified by FCC in hexane/ethyl acetate 9:1. Yield 54%, white crystals, mp 119 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.27–1.93 (m, 10H, cylohexyl–H), 3.29 (m, 1H,–COCH–), 3.95 (s, 3H,–$COOCH_3$), 7.70 (2×overlapp., d, 4H, $^3J=8$ Hz, aromat. H), 8.03 and 8.13 (d, AA′BB′, 4H, $^3J=8$ Hz, aromat. H). $C_{21}H_{22}O_3$ (322.40).

4′-Dicyclohexylacetylbiphenyl-4-carboxylic acid methyl ester (10a). Synthesized from 4-biphenylyldicyclohexylmethylketone (**10b**) and oxalylchloride. Purified by FCC in hexane/diethyl ether 8.5:1. Yield 50%, white crystals, mp 149 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.88–1.80 (m, 22H, cyclohexyl–H), 3.33 (t, 1H, $^3J=7$ Hz,–COCH–), 3.95 (s, 3H,–$COOCH_3$), 7.69 and 8.05 (d, AA′BB′, 4H, $^3J=8$ Hz, aromat. H), overlapped with 7.69 and 8.13 (d, AA′BB′, 4H, $^3J=8$ Hz, aromat. H). $C_{28}H_{34}O_3$ (418.57).

Method E

4′-Butanoylbiphenyl-4-carboxylic acid (5). A mixture of 4′-butanoylbiphenyl-4-carboxylic acid methyl ester **5a** (500 mg, 1.77 mmol) and potassium carbonate (3.45 mmol, 485 mg) in methanol/water 9:1 (33 mL) was refluxed for 3 h, then stirred at room temperature overnight. The reaction was acidified with 1 N hydrochloric acid and was extracted with CH_2Cl_2 (3×30 mL). The combined organic phases were washed with water and dried over $MgSO_4$. The solvent was removed in vacuo and the residue recrystallized from hexane/ethyl acetate to yield 350 mg (73%) of **5** as white crystals. mp 221 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 0.95 (t, 3H, $^3J=7$ Hz,–CH$_2$CH$_2$CH$_3$), 1.66 (sextett, 2H, $^3J=7$ Hz,–CH$_2$CH$_2$CH$_3$), 3.04 (t, 2H, $^3J=7$ Hz,–CH$_2$CH$_2$CH$_3$), 7.87 and 7.88 (d, AA′BB′, 4H, $^3J=8$ Hz, aromat. H), 8.06 (2×overlapp., d, 4H, $^3J=8$ Hz, aromat. H), 13.03 (s, 1H, COOH). IR (KBr): ν = 2960, 2840, 1680, 1610, 1430, 1400, 1300, 1220, 1130, 1000, 900, 830, 780, 750. Anal. $C_{17}H_{16}O_3$ (268.31).

4′-Pentanoylbiphenyl-4-carboxylic acid (6). Synthesized from 4′-pentanoylbiphenyl-4-carboxylic acid methyl ester (**6a**). Purified by two recrystallizations from hexane/ethyl acetate. Yield 53%, white solid, mp 202–203 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 0.91 (t, 3H, ^3J = 7 Hz,–$CH_2CH_2CH_2C\underline{H}_3$), 1.36 (sextett, 2H, ^3J = 7 Hz,–$CH_2CH_2C\underline{H}_2CH_3$), 1.62 (quintett, 2H, ^3J = 7 Hz,–$CH_2C\underline{H}_2CH_2CH_3$), 3.05 (t, 2H, ^3J = 7 Hz,-$C\underline{H}_2CH_2CH_2CH_3$), 7.88 and 7.87 (d, AA′BB′, 4H, ^3J = 8 Hz, aromat. H), 8.06 (2×overlapp., d, 4H, ^3J = 8 Hz, aromat. H), 13.03 (s, 1H, COOH). IR (KBr): ν = 2980, 2860, 1680, 1610, 1440, 1420, 1300, 1240, 1130, 1000, 900, 830, 780, 750. Anal. $C_{18}H_{18}O_3$ (282.34).

4′-Isobutanoylbiphenyl-4-carboxylic acid (7). Synthesized from 4′-isobutanoylbiphenyl-4-carboxylic acid methyl ester (**7a**). Purified by two recrystallizations from hexane/ethyl acetate. Yield 62%, white solid, mp 234–235 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.24 (d, 6H, ^3J = 7 Hz,–$CH(C\underline{H}_3)_2$), 3.71 (septett, 1H, ^3J = 7 Hz,–$C\underline{H}(CH_3)_2$), 7.81 (2×overlapp., d, 4H, ^3J = 8 Hz, aromat. H), 8.05 and 8.10 (d, AA′BB′, 4H, ^3J = 8 Hz, aromat. H), 13.04 (s, 1H, COOH). IR (KBr): ν = 2980, 2880, 1680, 1610, 1430, 1300, 1230, 1160, 1000, 980, 850, 750. Anal. $C_{17}H_{16}O_3$ (268.31).

4′-(3-Methylbutanoyl)biphenyl-4-carboxylic acid (8). Synthesized from 4′-(3-methylbutanoyl)biphenyl-4-carboxylic acid methyl ester (**8a**). Purified by two recrystallizations from hexane/ethyl acetate. Yield 60%, white solid, mp 230–231 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 0.96 (d, 6H, ^3J = 7 Hz,–$CH(C\underline{H}_3)_2$), 2.18 (septett, 1H, ^3J = 7 Hz,–$C\underline{H}(CH_3)_2$), 2.93 (d, 2H, ^3J = 7 Hz,–$COCH_2$–), 7.88 and 7.89 (d, AA′BB′, 4H, ^3J = 8 Hz, aromat. H), 8.05 and 8.07 (d, AA′BB′, 4H, ^3J = 8 Hz, aromat. H), 13.03 (s, 1H, COOH). IR (KBr): ν = 2960 (br), 1680, 1610, 1430, 1400, 1370, 1300, 1240, 1180, 1130, 1000, 950, 850, 820, 780. Anal. $C_{18}H_{18}O_3$ (282.34).

4′-Cyclohexanoylbiphenyl-4-carboxylic acid (9). Synthesized from 4′-cyclohexanoylbiphenyl-4-carboxylic acid methyl ester (**9a**). Purified by two recrystallizations from hexane/ethyl acetate. Yield 54%, white crystals, mp 250 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.16–1.84 (m, 10H, cylohexyl-H), 3.45 (m, 1H,–COCH–), 7.88 and 7.89 (d, AA′BB′, 4H, ^3J = 8 Hz, aromat. H), 8.06 and 8.07 (d, AA′BB′, 4H, ^3J = 8 Hz, aromat. H), 13.02 (s, 1H, COOH). IR (KBr): ν = 2940, 2860, 1680, 1610, 1430, 1400, 1300, 1250, 1220, 1170, 1130, 1000, 980, 950, 850, 770, 750. Anal. $C_{20}H_{20}O_3$ (308.37).

4′-Dicyclohexylacetylbiphenyl-4-carboxylic acid (10). Synthesized from 4′-dicyclohexylacetylbiphenyl-4-carboxylic acid methyl ester (**10a**). Purified by two recrystallisations from hexane/ethyl acetate. Yield 56%, white crystals, mp 231–232 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 0.82–1.80 (m, 22H, cylohexyl–H), 3.48 (t, 1H, ^3J = 7 Hz,–COCH–), 7.87 and 7.87 (d, AA′BB′, 4H, ^3J = 8 Hz, aromat. H), 8.06 and 8.09 (d, AA′BB′, 4H, ^3J = 8 Hz, aromat. H), 13.03 (s, 1H, COOH). IR (KBr): ν = 2920, 2840, 1680, 1610, 1450, 1430, 1280, 1250, 1200, 1130, 1000, 940, 840, 770, 760. Anal. $C_{27}H_{32}O_3$ (404.55).

Route B: method F

Compounds **17a** and **18a** were prepared according to the literature.[15]

***N,N*-Diisopropyl-4-(4-formylphenyl)benzamide (11a).** Under nitrogen aqueous potassium carbonate (646 μL of a 2 M solution) was added to a stirred solution of 4-bromo-*N*,*N*-diisopropylbenzamide (**11b**) (7.07 mmol, 2.00 g) and tetrakis(triphenylphosphine)palladium (200 mg) in 20 mL anhydrous toluene. After this a solution of 4-formylphenyl boronic acid (1.00 g, 6.67 mmol) in methanol (10 mL) was dropped into the reaction mixture, which was stirred at 85 °C for 4 h and then left at room temperature overnight. The phases were separated and the organic phase was washed with 5% aqueous HCl and saturated aqueous sodium hydrogen carbonate and dried over $MgSO_4$. The solvent was evaporated under reduced pressure to give a brown solid which was recrystallized from hexane/chloroform to yield the title compound **11a** (1.00 g, 48%), mp 184 °C. ^{1}H NMR (400 MHz, $CDCl_3$) : δ 1.25 (s, broad, 12H,–$CH(C\underline{H}_3)_2$), 3.70 (s, broad, 2H,–$C\underline{H}(CH_3)_2$), 7.42 and 7.65 (d, AA′BB′, 4H, ^3J = 8 Hz, aromat. H), 7.75 and 7.96 (d, AA′BB′, 4H, ^3J = 8 Hz, aromat. H), 10.06 (s, 1H, CHO). IR (KBr): ν = 2960, 2940, 1700, 1640, 1600, 1440, 1370, 1350, 1210, 1170, 1040, 1000, 840, 820, 770. $C_{20}H_{23}NO_2$ (309.41).

***N,N*-Diisobutyl-4-(4-formylphenyl)benzamide (12a).** Synthesized from 4-bromo-*N*,*N*-diisobutylbenzamide (**12b**) and 4-formylphenylboronic acid. Yield 53%, white crystals, mp 151 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.77 and 1.01 (2s, 12H,–$CH(C\underline{H}_3)_2$), 1.89 and 2.14 (2s, broad, 2H,–$C\underline{H}(CH_3)_2$), 3.15 and 3.38 (2s, 4H,–$NC\underline{H}_2$–), 7.46 and 7.65 (d, AA′BB′, 4H, ^3J = 8 Hz, aromat. H), 7.77 and 7.96 (d, AA′BB′, 4H, ^3J = 8 Hz, aromat. H), 10.07 (s, 1H, CHO). IR (KBr): ν = 2960, 2880, 1700, 1640, 1600, 1470, 1380, 1320, 1220, 1170, 1100, 1000, 840, 820, 760. $C_{22}H_{27}NO_2$ (337.46).

***N,N*-Diphenyl-4-(4-formylphenyl)benzamide (13a).** Synthesized from 4-bromo-*N*,*N*-diphenylbenzamide (**1b**) and 4-formylphenylboronic acid. Yield 14%, white crystals, mp 180–181 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.17–7.33 (m, 10H, aromat. H), 7.49 and 7.57 (d, AA′BB′, 4H, ^3J = 8 Hz, aromat. H), 7.69 and 7.92 (d, AA′BB′, 4H, ^3J = 8 Hz, aromat. H), 10.04 (s, 1H, CHO). IR (KBr): ν = 3050, 2820, 1700, 1650, 1600, 1490, 1320, 1300, 1210, 1170, 1110, 1000, 850, 770, 700. $C_{26}H_{19}NO_2$ (377.44).

***N,N*-Dicyclohexyl-4-(4-formylphenyl)benzamide (14a).** Synthesized from 4-bromo-*N*,*N*-dicyclohexylbenzamide (**4b**) and 4-formylphenylboronic acid. Yield 38%, white crystals, mp 235–236 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.09 and 1.79 (m, 20H, cyclohexyl-H), 2.62 and 3.18 (2s, broad, 2H,–$NC\underline{H}_2$–), 7.41 and 7.65 (d, AA′BB′, 4H, ^3J = 8 Hz, aromat. H), 7.78 and 7.97 (d, AA′BB′, 4H, ^3J = 8 Hz, aromat. H), 10.07 (s, 1H, CHO). IR (KBr): ν = 2940, 2840, 1700, 1630, 1450, 1370, 1320, 1220, 1130, 1000, 940, 900, 840, 830, 770. $C_{26}H_{31}NO_2$ (389.53).

***N*-Adamantyl-4-(4-formylphenyl)benzamide (15a).** Synthesized from 4-bromo-*N*-adamantylbenzamide (**3b**) and 4-formylphenylboronic acid. Yield 37%, white crystals, mp 182–183 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.74 (s, 6H, ada. H), 2.15 (s, 9H, ada. H), 5.83 (s, 1H,–NH–), 7.67 and 7.76 (d, AA′BB′, 4H, $^3J = 8$ Hz, aromat. H), 7.82 and 7.97 (d, AA′BB′, 4H, $^3J = 8$ Hz, aromat. H), 10.07 (s, 1H, CHO). IR (KBr): ν = 3400 (NH), 2940, 2840, 1700, 1620, 1450, 1350, 1320, 1200, 1130, 1000, 940, 840, 830, 700. $C_{24}H_{25}NO_2$ (359.47).

***N*-(3,5-Bis(trifluoromethyl)phenyl)-4-(4-formylphenyl)-benzamide (16a).** Synthesized from 4-bromo-*N*-3,5-bis(trifluoromethyl)benzamide (**2b**) and 4-formylphenylboronic acid. Yield 44%, white crystals, mp 209 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.67 (s, 1H, phenyl–H_4), 7.79 and 7.80 (d, AA′BB′, 4H, $^3J = 8$ Hz, aromat. H), 8.0 and 8.01 (d, AA′BB′, 4H, $^3J = 8$ Hz, aromat. H), 8.17 (s, 1H,–NH–), 8.22 (s, 2H, phenyl–H_2,–H_6), 10.09 (s, 1H, CHO). IR (KBr): ν = 3380 (NH), 2920, 2860, 1680, 1610, 1550, 1470, 1440, 1390, 1280, 1170, 1140, 1000, 900, 830, 770, 700. $C_{22}H_{13}NO_2F_6$ (437.34).

Method G

Compounds were prepared following the procedure described in the literature.[16,17] For substances **17** and **18** THF was used as a solvent instead of acetonitrile. Compounds were recrystallized twice from hexane/ethyl acetate.

***N*,*N*-Diisopropyl-4-(4-carboxyphenyl)benzamide (11).** Synthesized from *N*,*N*-diisopropyl-4-(4-formylphenyl)benzamide (**11a**). Yield 48%, white crystals, mp 270–271 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.29 (s, broad, 12H,–CH(C$\underline{H}_3$)$_2$), 3.66 (s, 2H,–C$\underline{H}$(CH$_3$)$_2$), 7.38 and 7.77 (d, AA′BB′, 4H, $^3J = 8$ Hz, aromat. H), 7.82 and 8.02 (d, AA′BB′, 4H, $^3J = 8$ Hz, aromat. H), 12.93 (s, 1H, COOH). IR (KBr): ν = 2920 (br), 2860, 1680, 1640, 1610, 1430, 1360, 1310, 1180, 1140, 1000, 900, 840, 750. Anal. $C_{20}H_{23}NO_3$ (325.41).

***N*,*N*-Diisobutyl-4-(4-carboxyphenyl)benzamide (12).** Synthesized from *N*,*N*-diisobutyl-4-(4-formylphenyl)-benzamide (**12a**). Yield 45%, white crystals, mp 179 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 0.69 and 0.94 (2s, 12H,–CH(C$\underline{H}_3$)$_2$), 1.83 and 2.07 (2s, 2H,–C$\underline{H}$(CH$_3$)$_2$), 3.01 and 3.12 (2s, 4H,–NC$\underline{H}_2$-), 7.43 and 7.80 (d, AA′BB′, 4H, $^3J = 8$ Hz, aromat. H), 7.84 and 8.03 (d, AA′BB′, 4H, $^3J = 8$ Hz, aromat. H), 12.97 (s, 1H, COOH). IR (KBr): ν = 2980 (br), 1700, 1640, 1610, 1470, 1430, 1280, 1100, 1010, 930, 840, 760. Anal. $C_{22}H_{27}NO_3$ (353.46).

***N*,*N*-Diphenyl-4-(4-carboxyphenyl)benzamide (13).** Synthesized from *N*,*N*-diphenyl-4-(4-formylphenyl)-benzamide (**13a**). Yield 31%, white crystals, mp 266–267 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.20–7.37 (m, 10H, aromat. H), 7.53 and 7.63 (d, AA′BB′, 4H, $^3J = 8$ Hz, aromat. H), 7.77 and 7.99 (d, AA′BB′, 4H, $^3J = 8$ Hz, aromat. H), 12.97 (s, 1H, COOH). IR (KBr): ν = 3000 (br), 1680, 1650, 1600, 1490, 1410, 1340, 1280, 1180, 1100, 1000, 850, 760, 700. Anal. $C_{26}H_{19}NO_3$ (393.44).

***N*,*N*-Dicyclohexyl-4-(4-carboxyphenyl)benzamide (14).** Synthesized from *N*,*N*-dicyclohexyl-4-(4-formylphenyl)-benzamide (**14a**). Yield 42%, white crystals, mp 266 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.09 and 1.98 (m, 22H, cyclohexyl–H), 7.38 and 7.79 (d, AA′BB′, 4H, $^3J = 8$ Hz, aromat. H), 7.84 and 8.03 (d, AA′BB′, 4H, $^3J = 8$ Hz, aromat. H), 12.98 (s, 1H, COOH). IR (KBr): ν = 2920, 2860, 1680, 1640, 1610, 1430, 1360, 1310, 1180, 1140, 1000, 900, 840, 750. Anal. $C_{26}H_{31}NO_3$ (405.53).

***N*-Adamantyl-4-(4-carboxyphenyl)benzamide (15).** Synthesized from *N*-adamantyl-4-(4-formylphenyl)-benzamide (**15a**). Yield 42%, white crystals, mp > 300 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.66 (s, 6H, ada. H), 2.06 (s, 9H, ada. H), 7.65 (s, 1H,–NH–), 7.79 and 7.84 (d, AA′BB′, 4H, $^3J = 8$ Hz, aromat. H), 7.89 and 8.03 (d, AA′BB′, 4H, $^3J = 8$ Hz, aromat. H), 12.97 (s, 1H, COOH). IR (KBr): ν = 3400 (NH), 2910, 2860, 1690, 1660, 1610, 1510, 1430, 1300, 1100, 1000, 950, 850, 750. Anal. $C_{24}H_{25}NO_3$ (375.47).

***N*-(3,5-Bis(trifluoromethyl)phenyl)-4-(4-carboxyphenyl)-benzamide (16).** Synthesized from *N*-(3,5-bis(trifluoromethyl)phenyl)-4-(4-formylphenyl)benzamide (**16a**). Yield 30%, white crystals, mp > 300 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.83 (s, 1H, phenyl–H_4), 7.91 and 7.96 (d, AA′BB′, 4H, $^3J = 8$ Hz, aromat. H), 8.07 and 8.14 (d, AA′BB′, 4H, $^3J = 8$ Hz, aromat. H), 8.56 (s, 2H, phenyl–H_2,–H_6), 10.91 (s, 1H,–NH–), 13.02 (s, 1H, COOH). IR (KBr): ν = 3450 (NH), 2940 (br), 1680, 1610, 1550, 1450, 1380, 1270, 1250, 1180, 1140, 1000, 940, 890, 850, 750, 700. Anal. $C_{22}H_{13}NO_3F_6$ (453.34).

4′-Bromobiphenyl-4-carboxylic acid (17). Synthesized from 4′-bromobiphenyl-4-carbaldehyde (**18a**). Yield 37%, white crystals, mp 292–293 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.56 and 7.76 (d, AA′BB′, 4H, $^3J = 8$ Hz, aromat. H), 7.80 and 8.02 (d, AA′BB′, 4H, $^3J = 8$ Hz, aromat. H), 12.99 (s, 1H, COOH). IR (KBr): ν = 2950 (br), 1670, 1610, 1480, 1430, 1300, 1200, 1100, 1080, 1000, 930, 870, 820, 770. Anal. $C_{13}H_9O_2Br$ (277.11).

4′-Chlorobiphenyl-4-carboxylic acid (18). Synthesized from 4′-chlorobiphenyl-4-carbaldehyde (**19a**). Yield 42%, white crystals, mp 293–294 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.55 and 7.76 (d, AA′BB′, 4H, $^3J = 8$ Hz, aromat. H), 7.80 and 8.03 (d, AA′BB′, 4H, $^3J = 8$ Hz, aromat. H), 13.01 (s, 1H, COOH). IR (KBr): ν = 2990 (br), 1670, 1610, 1480, 1430, 1330, 1300, 1100, 1000, 830, 770. Anal. $C_{13}H_9O_2Cl$ (232.66).

Enzyme inhibition test

Reagents. [1,2-^{3}H]Androstenedione (4-androstene-3,17-dione, AD), and [1,2-^{3}H]testosterone (17β-hydroxy-4-androstene-3-one, T) were purchased from DuPont, Bad Homburg, Germany.

Preparation of tissue. Rat prostatic enzyme was prepared according to the method of Liang et al.[18] with slight modifications.[8] Male rats were sacrificed and prostates were taken within 5 min and put in ice cold

0.9% NaCl solution. All the following operations were performed at 0–4 °C. The prostates were dissected free from fat and connective tissue, cut into pieces and weighed. Per 1 g of tissue, 3 mL of 20 mM phosphate buffer pH 6.5 containing 0.32 mM sucrose and 1 mM DTT were added. The tissue was homogenized by ten 10-s strokes at 20,500 rpm of an ultraturax (IKA) in 60-s intervals, filtered through cheesecloth and centrifuged for 60 min at 105,000*g*. The pellet obtained was resuspended in phosphate buffer. The centrifugation was repeated, the final pellet resuspended in a minimum volume of phosphate buffer and stored in 300 μL portions at −70 °C. The 105,000-g pellet contains nuclei, mitochondria and microsomes and is referred to as the enzyme preparation. The protein content was determined and was in the range of 15–25 mg/mL. Human prostatic tissue from BPH patients was processed in the same way using citrate buffer pH 5.5.

Incubation procedure. The assay was performed as described[18] with modifications.[8] All values were run in duplicate. The incubation was carried out for 30 min at 37 °C in a total volume of 250 μL. In the case of rat enzyme preparation phosphate buffer (40 mM, pH 6.6) and in the case of human enzyme preparation citrate buffer (40 mM, pH 5.5) was used. The incubation mixture contained approximately 250 μg rat protein (125 μg human protein), 200 μM NADPH (human enzyme: 100 μM NADPH), 0.21 μM T including 45 nCi [1,2-^{3}H]-T, and 2% DMSO with or without test compound (100 μM). The reaction was started by adding the prostatic enzyme preparation and stopped by addition of 50 μL NaOH (10 M). The steroids were extracted using 500 μL of diethylether. The mixture was shaken for 10 min and centrifuged 10 min at 4000 rpm. The water layer was frozen and the ether layer was decanted in fresh tubes and evaporated to dryness.

Human type 1 inhibition: DU 145-assay[20]. Intact human prostatic carcinoma DU 145 cells were used as the source of type 1 5α-reductase.[19] The inhibitory potencies of the compounds were determined by monitoring the conversion of the tritiated substrate androstenedione (5 nM) to androstanedione during an incubation period of 6 h. A day before the experiment, DU 145 cells were seeded in a 24-multiwell-plate at a density of 180,000 cells/well and allowed to become adherent overnight. Compounds to be tested were dissolved in DMSO and 5 μL of each were added to the cells in a final volume of 0.5 mL complete medium. Inhibitors are first screened at concentrations of 10 μM in an initial test and in case of exceeding 80% inhibition, three concentrations were choosen for measurement of IC_{50} values. As control of conversion (typically about 35% under these conditions) served a triplicate of wells without inhibitors and as positive control for inhibition finasteride (80, 60, 40, 20 nM) was used. After the 6 h incubation period in 5% CO_2 at 37 °C, the medium samples were extracted twice with 1 mL diethylether and the steroids were separated by HPLC. Results are expressed as amount of formed androstanedione as percentage of control values.

HPLC procedure. The procedure was carried out[8] similar to the method of Cook et al.[28] The steroids were dissolved in 50 μL methanol and 25 μL injected into the computer-controlled HPLC system, which was checked before using labelled reference controls. Radioactivity was measured using a Berthold LB 506C monitor. Using methanol/water (55:45, w/w) for T and DHT, with a flow of 0.4 ml/min and an additive flow of 1.0 mL for scintillator, base-line-separation of T and DHT was achieved within 20 min. For the steroids androstenedione and dihydroandrostenedione methanol/water (50:50, w/w) was used.

Calculation procedure. The amount of DHT formed was calculated (% DHT). The zero value was subtracted from the control (cv) and inhibition (iv) value (cv_{corr} and iv_{corr}).

Inhibition (I) was calculated using the following equation:%

$$\%I = (1 - iv_{corr}/cv_{corr})100$$

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