6860 *J. Med. Chem.* **2009,** *52,* 6860–6870
DOI: 10.1021/jm901120h

Journal of Medicinal Chemistry Article

1,1′-Disubstituted Ferrocenes as Molecular Hinges in Mono- and Bivalent Dopamine Receptor Ligands

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Received July 28, 2009

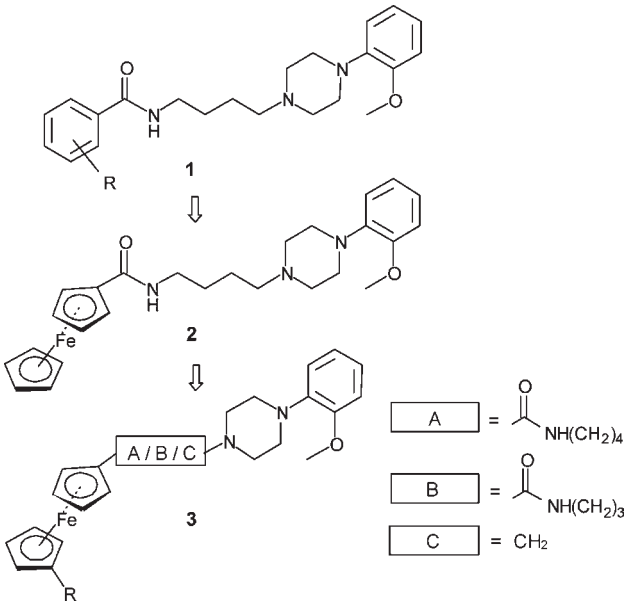
On the basis of previous work on dopaminergic partial agonists of type **1** and **2**, disubstituted ferrocenes are presented as valuable arene bioisosteres. Because substituents at the distal cyclopentadienyl ring are able to adjust the relative disposition that is required for ligand binding, disubstituted ferrocenes can act as molecular hinges. Taking advantage of click chemistry, the regioselective construction and functionalization of the target molecules is reported. Thus triazole derived appendages were used for the fine-tuning of biological activity and for the attachment of linker units generating bivalent GPCR ligands. Receptor binding was evaluated by radioligand displacement experiments, revealing superaffinity with sub- to single-digit nanomolar K_i values for particular test compounds. As a neutral antagonist at the dopamine receptors D3 and D4 and a potent partial agonist at the D2 subtype (intrinsic activity = 57%, EC_{50} = 2.5 nM), the bifunctional ferrocene **10b** revealed a novel and unique activity profile.

Introduction

Bioisosteric replacement is an efficient concept for lead optimization, significantly extending the chemical space of bioactive ligands.[1] Evaluating atypical bioactive arene surrogates, metallocene-based compounds were reported, including the novel chemotherapeutic agent ferroquine.[2,3] Starting from dopamine D3 receptor selective lead structures of type **1** and heterocyclic analogues thereof,[4,5] we have recently shown that metallocene-derived benzamide bioisosteres of type **2** can serve as highly potent G-protein coupled receptor (GPCR[a]) ligands preferentially interacting with the subtypes of the dopamine D2 receptor family, the serotonergic 5-HT_{1A} and the adrenergic α_1 receptor (Chart 1).[6]

The biological activity of benzamides of type **1** can be tuned by the introduction of substituents into ortho-, meta-, and para-positions of the aromatic system.[7−10] As an extension of our studies on GPCR ligands of type **2**, we envisaged to discover the ferrocene derived bifunctional analogues **3**. According to earlier studies of arene carboxamides, we anticipated a putative control of subtype selectivity by a careful selection of the spacer that links the ferrocene moiety and the phenylpiperazine substructure.[11,12] Thus, linker units of type A, B, and C should be employed. Bioisosteric displacement of the arene moiety and beneficial substituents of the lead compound **1** by a conformational flexible, 1,1′-disubstituted ferrocenyl subunit should lead to novel mono- and bivalent scaffolds when the substituents at the distal cyclopentadienyl rings should be able to adopt the relative disposition that is required for ligand binding and thus act as molecular hinges (Chart 2). The enhanced conformational flexibility of the ferrocene derivatives could accelerate lead optimization.

Chart 1. General Approach



Taking advantage of click chemistry, we herein report on the construction of disubstituted ferrocenes when triazole derived appendages were used as affinity generating groups and for the attachment of linker units generating monovalent and the corresponding bivalent GPCR ligands (Chart 2).[13−15] Receptor binding was evaluated by radioligand displacement experiments, revealing superaffinity with subnanomolar K_i values for some of the ferrocene derived test compounds. Finally, intrinsic activity was investigated in vitro.

Results and Discussion

Chemical Synthesis. Our initial investigations were directed to the elaboration of a practical synthesis of the

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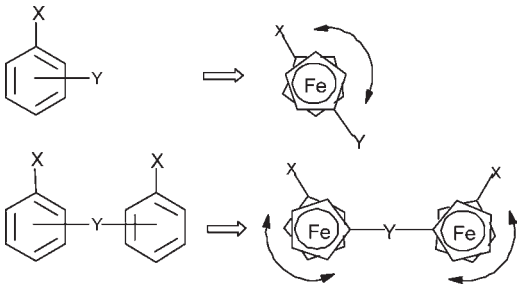
[a] Abbreviations: GPCR, G-protein coupled receptor; CHO, Chinese hamster ovary; HR-EIMS, high resolution electron ionization mass spectrometry; EI-MS, electron ionization mass spectrometry, APCI-MS, atmospheric pressure chemical ionization mass spectrometry, ESI-MS, electrospray ionization mass spectrometry.

 Published on Web 10/06/2009

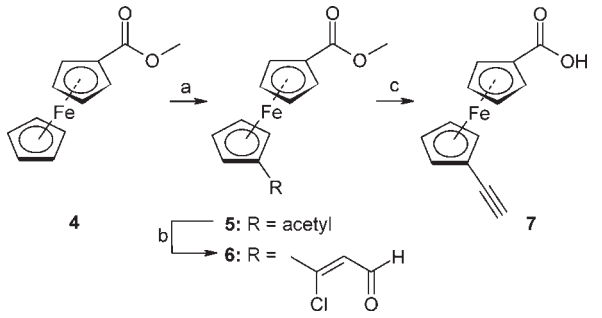
Chart 2. Conformational Flexibility of the Ferrocene Moiety Can Be Exploited to Efficiently Generate Monovalent and Bivalent GPCR Ligands



1′-ethynylferrocene-1-carboxylic acid **7**, which should serve as a key intermediate for the synthesis of bioactive carboxamides of type **3**. On the basis of a recently described preparation of 1′-ethynylferrocene-1-carbaldehyde,[16] we intended to work out a reaction sequence involving Friedel–Crafts acylation followed by a Vilsmeier type formylation and a final elimination step. In detail, methyl ferrocene carboxylate (**4**)[17] was reacted with acetyl chloride in the presence of aluminum chloride to afford the acylation product **5** almost quantitatively (Scheme 1). Subsequent activation of DMF with phosphorus oxychloride and treatment of the resulting Vilsmeier reagent with the ferrocene **5** led to formation of the chloroacrolein derivative **6**. Elimination was initiated by subsequent heating in dioxane and sodium hydroxide, leading to the bifunctional ethynylferrocene **7** in 57% overall yield.

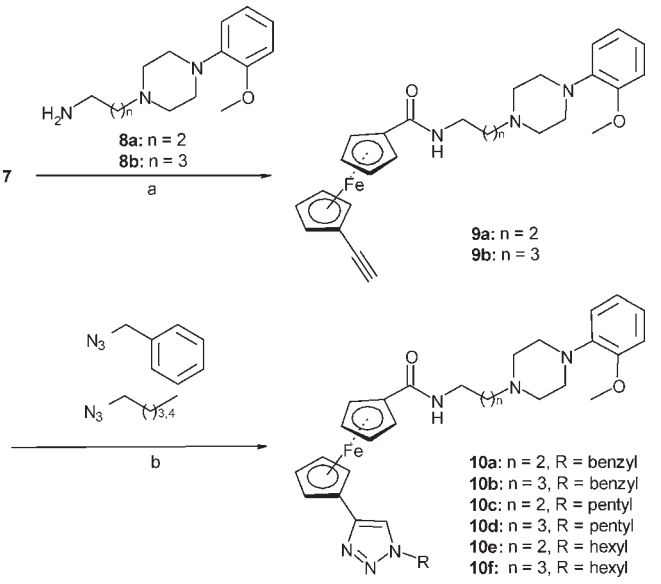
The orthogonal reactivity of the ferrocene derived building block **7** was used for a selective functionalization. Upon activation with TBTU and addition of the aminopropyl and aminobutyl substituted phenylpiperazines **8a** and **8b**,[9] respectively, the carboxamides **9a**,**b** could be prepared when complete conversion was observed (Scheme 2). Choosing 1,2,3-triazole derivatives as affinity generating appendages, the advantages of click chemistry should be exploited. Following slightly modified recently described protocols for the $CuSO_4$/sodium ascorbate promoted variant of copper(I)-catalyzed azide–alkyne cycloaddition (CuAAC),[18] benzylazide[19] as well as pentyl- and hexylazide[20] were reacted with the ferrocenylethynes **9a**,**b** to give rise to the target compounds **10a**–**f** in excellent yield. According to our computational docking and mutagenesis studies on classical arene carboxamides, the triazole substituent should direct to the entrance of the binding pocket and thus should be in a highly

Scheme 1[a]



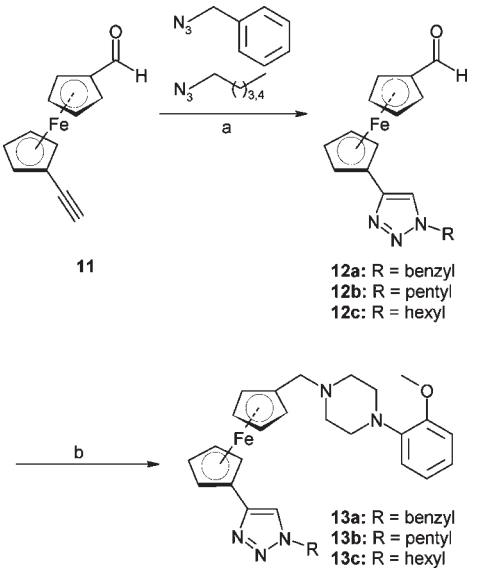
[a] Reagents and conditions: (a) acetyl chloride, $AlCl_3$, CH_2Cl_2, 0 °C, 4 h (99%); (b) $POCl_3$, DMF, 0 °C (15 min) to RT (2 h) (71%); (c) (1) dry dioxane, reflux, 5 min; (2) 0.5 N NaOH, reflux, 25 min (81%).

Scheme 2[a]



[a] Reagents and conditions: (a) TBTU, DIPEA, DMF, CH_2Cl_2, **8a**,**b**, 0 °C to RT, 4 h (96–99%); (b) sodium ascorbate, $CuSO_4$, H_2O:^{t}BuOH: CH_2Cl_2 2:1:1, RT, 16 h (72–98%).

Scheme 3[a]

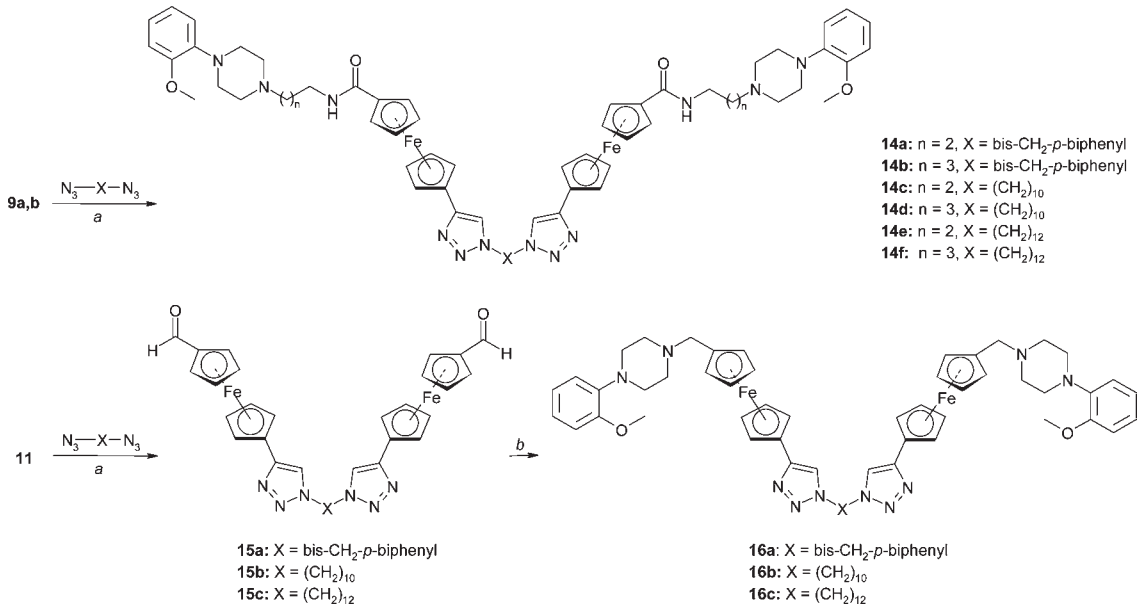


[a] Reagents and conditions: (a) sodium ascorbate, $CuSO_4$, H_2O:^{t}BuOH: CH_2Cl_2 2:1:1, RT, 16 h (72–94%); (b) 2-methoxyphenylpiperazine, $Na(OAc)_3BH$, CH_2Cl_2, RT, 16 h (75–99%).

critical region. Further modifications, however, will be done within future studies for the optimization of the respective dimeric ligands when this moiety will determine the linker length and thus will be highly crucial.

Benzyl piperazines and heterocyclic analogues thereof have been described as dopamine D4 receptor antagonists and partial agonists.[21–23] To approach to metallocene derived analogues, triazolyl substituted ferrocene carbaldehydes should be prepared and coupled to *ortho*-methoxyphenyl piperazine via reductive amination. Again, orthogonal functionalization was envisaged renouncing the use of protecting groups. Thus, triazole formation was done by reacting benzyl-, pentyl-, and hexylazide with the ethynyl substituted building block **11** (Scheme 3).[16] The synthetic

Scheme 4[a]



[a] Reagents and conditions: (a) sodium ascorbate, $CuSO_4$, H_2O:^{t}BuOH:CH_2Cl_2 2:1:1, RT, 16 h (61−99%); (b) 2-methoxyphenylpiperazine, $Na(OAc)_3BH$, CH_2Cl_2, RT, 16 h (48−84%).

intermediates **12a**−**c** were reductively aminated with *ortho*-methoxyphenylpiperazine, resulting in formation of the test compounds **13a**−**c**.

Taking advantage of the high impact and efficiency of click chemistry, copper promoted 1,3-dipolar cycloaddition should be used for the construction of dimeric dopamine receptor ligands that putatively act as bivalent receptor modulators (Scheme 4).[24] According to previous investigations on bivalent ligands containing μ-opioid agonist and type 2 cholecystokinin antagonist receptor pharmacophores,[25] spacers with 16−18 atoms were chosen in conformationally flexible and rigidized form. For the synthesis of bivalent carboxamides of type **14a**−**f**, the monomeric ethynyl substituted precursors **9a**,**b** were coupled with aliphatic diazides and biphenyl derivatives[26] to afford the reaction products **14a**−**f** in good to excellent yield (61−99%). For a preparation of the respective methylene bridged analogues **16a**−**c**, the building block **11** was reacted with the diazides mentioned above. Reductive amination of the thus formed intermediates **15a**−**c** furnished the dimeric final products **16a**−**c** in 48−84% yield.

Receptor Binding. Radioligand binding assays were employed to analyze affinity and selectivity profiles of the monomeric target compounds **10a**−**f** and **13a**−**c** and its dimeric congeners **14a**−**f** and **16a**−**c**. The K_i values of the test compounds were compared to the properties of the lead structure **2** and the reference agent quinpirole,[27] which is known to activate D2, D3, and D4 receptors. The binding data were generated by measuring their ability to compete with [^{3}H]spiperone for the cloned human dopamine receptor subtypes $D2_{long}$, $D2_{short}$,[28] D3,[29] and D4.4[30] stably expressed in Chinese hamster ovary cells (CHO).[31] D1 receptor affinities were determined utilizing porcine striatal membranes and the D1 selective radioligand [^{3}H]SCH 23390.[31]

The characterization of the test compounds was initiated by investigating the ferrocenylcarboxamides **10b**,**d**,**f** incorporating a butylene spacer and thus displaying the highest degree of similarity with the lead compounds of type **1** and **2**. In fact, the binding data depicted in Table 1 clearly indicate that the benzyl, pentyl, and hexyl substituted triazole units significantly extending the volume of the ferrocene moiety are tolerated by the binding sites of the D2 receptor family. Significant radioligand displacement was observed, leading to K_i values in the nanomolar range. Whereas D4 preference was determined for our core structure **2**, the substituted derivatives **10b**,**d**,**f** revealed superaffinity at D3 resulting in K_i values of 0.34, 1.3, and 0.63 nM, respectively. Competition experiments at $D2_{long}$, $D2_{short}$, and D4.4 led to K_i values between 3.7 and 25 nM, indicating only moderately lower target recognition than for D3. Compared to the aminobutyl substituted ferrocenylcarboxamides **10b**,**d**,**f**, the aminopropyl analogues **10a**,**c**,**e** displayed lower affinity toward $D2_{long}$, $D2_{short}$, and D3 but comparable D4 binding, resulting in a significant D4 preference. On the other hand, only weak to moderate D1 affinity was observed for all test compounds. Because of the observation that the lead compounds of type **1** reveal serotonergic and adrenergic properties,[32] all ferrocene derived test compounds were investigated for their potency to displace [^{3}H]WAY100635, [^{3}H]ketanserin, and [^{3}H]prazosin. Employing porcine α_1, 5-HT_{1A} and 5-HT_2 receptors, **10b** displayed substantial affinity with K_i values in the nanomolar range (α_1: K_i = 2.5 nM, 5-HT_{1A}: K_i = 14 nM, 5-HT_2: K_i = 260 nM; data for all test compounds, see Supporting Information).

Because benzyl piperazines and heterocyclic analogues thereof have been described as dopamine D4 receptor ligands,[21−23] significant D4 recognition was expected for the ferrocene derived analogues **13a**−**c**. Surprisingly, the displacement studies gave disappointing K_i values (82−130 nM) for D4 and weak preference for D2, indicating that a successful bioisosteric replacement was not possible in this case. This might be due to different binding modes of the ferrocene entity depending on the lengths of the spacer units.

Over the past decade, evidence has accumulated to suggest that GPCRs may function as dimers or large oligomers.[33] Very recently, communication between protomers of

Table 1. Receptor Binding Data for the Monomeric Ferrocene Compounds **2**, **10a−f**, and **13a−c** and the Reference Quinpirole Employing Porcine D1 Receptor and the Human Subtypes $D2_{long}$, $D2_{short}$, D3, and D4.4 Receptors

			K_i values (nM) ± SD[a]				
				[^{3}H]spiperone			
compd	*n*	R	[^{3}H]SCH 23390 D_1	$hD2_{long}$	$hD2_{short}$	hD3	hD4.4
2			1900 ± 250	110 ± 10	78 ± 1.5	6.5 ± 0.54[b]	0.52 ± 0.086[b]
10a	2	benzyl	780 ± 300	140 ± 91	170 ± 14	73 ± 36	2.8 ± 0.14
10b	3	benzyl	370 ± 7.1	3.7 ± 0.21	4.0 ± 0.50	0.34 ± 0.064	5.4 ± 0.071
10c	2	pentyl	690 ± 200	44 ± 14	100 ± 0	58 ± 23	4.6 ± 0.14
10d	3	pentyl	1200 ± 210	25 ± 7.8	15 ± 7.4	1.3 ± 0.35	16 ± 5.0
10e	2	hexyl	510 ± 260	33 ± 8.5	81 ± 0.71	43 ± 21	3.5 ± 0.21
10f	3	hexyl	240 ± 71	4.7 ± 0.85	4.4 ± 1.1	0.63 ± 0.042	5.4 ± 1.7
13a		benzyl	260 ± 85	25 ± 12	49 ± 2.8	370 ± 7.1	82 ± 23
13b		pentyl	250 ± 35	32 ± 5.7	49 ± 9.9	260 ± 57	87 ± 19
13c		hexyl	360 ± 19[b]	39 ± 9.9[b]	70 ± 8.1[b]	390 ± 110[b]	130 ± 13[b]
quinpirole			72000 ± 0	950 ± 340[b]	870 ± 0	49 ± 8.6[b]	16 ± 4.7[b]

[a] Derived from two individual experiments each done in triplicate. [b] K_i values ± SEM derived from 3−6 experiments each done in triplicate

Chart 3. Structure and Mode of a Mono- (Black) and a Bivalent Ligand Binding (Black and Grey)

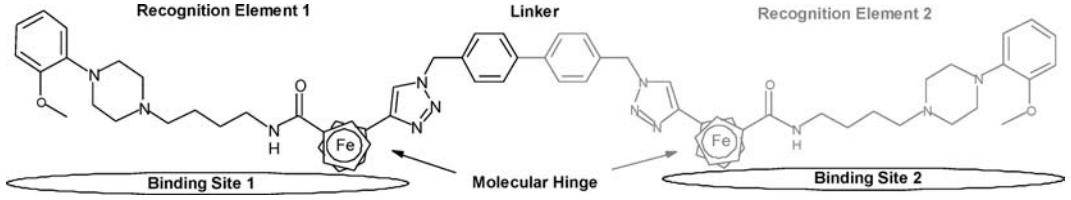


Table 2. Receptor Binding Data for the Dimeric Ferrocene Compounds **14a−f**, **16a−c**, and the Benzamide Analogues **17**,**18** Employing Porcine D1 Receptor and the Human Subtypes $D2_{long}$, $D2_{short}$, D3, and D4.4 receptors

			K_i values (nM) ± SD[a]				
				[^{3}H]spiperone			
compd	*n*	R	[^{3}H]SCH 23390 D_1	$hD2_{long}$	$hD2_{short}$	hD3	hD4.4
14a	2	bis-CH_2-*p*-biphenyl	100 ± 52	76 ± 62	54 ± 32	22 ± 16	27 ± 6.4
14b	3	bis-CH_2-*p*-biphenyl	87 ± 19	15 ± 4.2	14 ± 3.5	1.1 ± 0.21	22 ± 6.4
14c	2	$(CH_2)_{10}$	210 ± 64	45 ± 13	43 ± 17	9.0 ± 2.8	30 ± 0.71
14d	3	$(CH_2)_{10}$	430 ± 99	54 ± 18	55 ± 15	8.4 ± 2.3	63 ± 25
14e	2	$(CH_2)_{12}$	130 ± 7.1	64 ± 22	33 ± 21	7.0 ± 4.2	35 ± 13
14f	3	$(CH_2)_{12}$	1100 ± 0	240 ± 28	170 ± 21	14 ± 7.2	58 ± 1.4
16a		bis-CH_2-*p*-biphenyl	20000 ± 2100	64 ± 41	48 ± 46	300 ± 92	480 ± 200
16b		$(CH_2)_{10}$	400 ± 14	65 ± 4.2	33 ± 11	86 ± 13	190 ± 21
16c		$(CH_2)_{12}$	2000 ± 860[b]	64 ± 30	100 ± 46[b]	110 ± 70	360 ± 85[b]
17	3		3400 ± 1300	15000 ± 6200[b]	10000 ± 2100[b]	230 ± 86[b]	3400 ± 710
18	3		9500 ± 6400	2000 ± 140	770 ± 200	70 ± 57	850 ± 640

[a] Derived from two individual experiments each done in triplicate. [b] K_i values ± SEM derived from 3−4 experiments each done in triplicate

dopamine D2 receptors has been proved to modulate GPCR activation.[34]

In the course of our investigations of bivalent GPCR ligands putatively binding two binding sites of interacting receptor oligomers, we tried to evaluate the scope of our click chemistry based strategy (Chart 3).

Dopamine receptor binding studies of the dimeric ferrocenylcarboxamides **14a−f** and its methylene analogues **16a−c** clearly revealed significant GPCR recognition with K_i values between 1.1 and 480 nm at the D2-like subtypes (Table 2).

As observed for the monomers, combination of a butylene spacer and a benzyltriazolyl substituent was superior for dopamine receptor binding. Thus, a binding pattern was observed for the dimer **14b**, which closely resembles the affinity profile of the respective monomer **10b** when the affinities to $D2_{long}$, $D2_{short}$, D3, and D4 proved to be only three- to 4-fold lower. Comparing the excellent binding data of **14b** (K_i = 15, 14, 1.1, and 22 nM for $D2_{short}$, $D2_{long}$, D3, and D4, respectively) with those of the meta- and para-substituted benzamides as reference dimers **17** and **18** (Chart 4) with poor dopamine receptor binding clearly displayed a highly beneficial effect of the ferrocene-based molecular hinge that obviously allows the conformationally restricted bis-methyl-*p*-biphenyl linker to adopt an optimal orientation.

Functional Experiments. Evaluation of the binding data indicating particular high D2, D3, and D4 affinity for test compound **10b** (FAUC 552) suggested further in vitro studies. As a measure of functional activity, ligand efficacy of the ferrocenylcarboxamide **10b** was determined by a mitogenesis assay measuring the rate of [^{3}H]thymidine

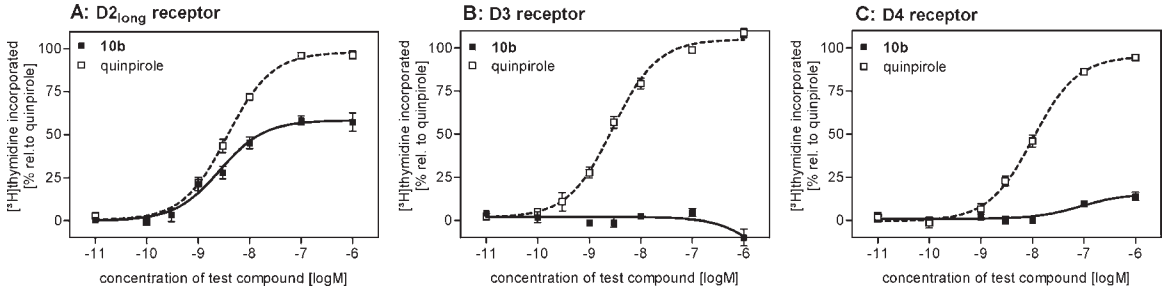
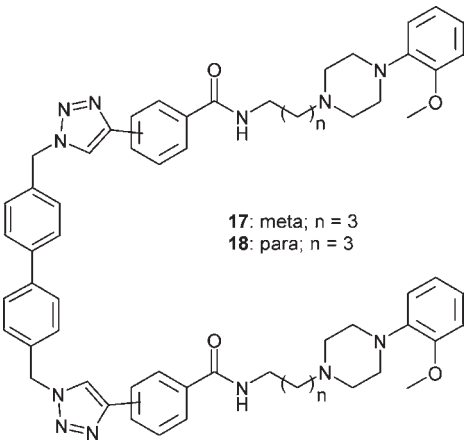


Figure 1. Measurement of [^{3}H]thymidine incorporation as an assay for functional activity of the test compound **10b** at the dopamine receptor subtypes $D2_{long}$ (A), D3 (B), and D4 (C) in comparison to the effect of the reference quinpirole.

Chart 4. Structures of the Reference Dimers **17** and **18**



incorporation into growing CHO10001 cells and a CHO dhfr$^-$ cell line stably expressing the human $D2_{long}$, D4.2, and D3 receptor, respectively (Figure 1).[29,35,36]

Interestingly, test compound **10b** displayed to act as a partial agonist at $D2_{long}$ with an intrinsic activity of 57% and an EC_{50} value of 2.6 nM (Figure 1A), which is very similar to the K_i value of the binding experiments (3.7 nM). This effect could be reversed by the neutral antagonist haloperidol in a concentration dependent manner (see Supporting Information). On the other hand, the ferrocene **10b** did not show any ligand efficacy at the D3 subtype. Because the reference compounds of type **1** and **2** are known as D3 partial agonists, the neutral antagonist properties of **10b** are obviously due to the steric demand of the benzyltriazolyl substituent (Figure 1B). Measuring the rate of [^{3}H]thymidine incorporation at D4 indicated only a very low effect (<20%) at high concentration of **10b** (Figure 1C). Thus the bifunctional ferrocene **10b** revealed a particularly interesting activity profile, with neutral antagonist properties for D3 and D4 behaving as a potent partial agonist at the D2 subtype.

In conclusion, 1,1′-disubstituted ferrocenes can serve as valuable arene bioisosteres when click chemistry allowed a regioselective construction and functionalization as well as the formation of GPCR binding dimers. Receptor recognition was evaluated by radioligand displacement experiments revealing superaffinity with sub- and single-digit nanomolar K_i values for some of the ferrocene derived test compounds. Aiming to better treat schizophrenia in future, the bifunctional ferrocene **10b** revealed a particularly interesting activity profile when neutral antagonist properties for D3 and D4 combined with a potent partial agonist behavior at the D2 subtype (intrinsic activity = 57%, EC_{50} = 2.5 nM) could potentially lead to an atypical neuroleptic profile.

Experimental Section

Chemistry. Dry solvents and reagents were of commercial quality and were used as purchased. MS were run on a JEOL JMS-GC Mate II spectrometer by EI (70 eV) with solid inlet or a Bruker Esquire 2000 by APC or ES ionization. HR-EIMS were run on a JEOL JMS-GC Mate II using peak-matching ($M/\Delta M > 5000$). NMR spectra were obtained on a Bruker Avance 360 or a Bruker Avance 600 spectrometer relative to TMS in the solvents indicated (J value in Hz). Melting points were determined with a MEL-TEMP II melting point apparatus (Laboratory Devices, USA) in open capillaries and given uncorrected. IR spectra were performed on a Jasco FT/IR 410 spectrometer. Purification by flash chromatography was performed using Silica Gel 60; TLC analyses were performed using Merck 60 F254 aluminum sheets and analyzed by UV light (254 nm). Analytical HPLC was performed on Agilent 1100 HPLC systems employing a VWL detector. The purity of all test compounds and key intermediates was determined to be >95%. As a column, a ZORBAX ECLIPSE XDB-C8 (4.6 mm × 150 mm, 5 μm) was used. HPLC purity was measured using several elution systems. System A, eluent: methanol/water/0.1 N formic acid, 10% methanol for 3 min to 100% methanol in 15 min, 100% for 6 min; flow rate, 0.5 mL/min; λ, 254 nm. System B, eluent: methanol/water/0.1 N formic acid, 30% methanol for 1 min to 100% methanol in 11 min, 100% for 4 min; flow rate, 0.5 mL/min; λ, 254 nm. System C, eluent: methanol/water/0.1 N trifluoroacetic acid, 10−100% methanol in 21 min, 100% for 3 min; flow rate, 1.0 mL/min; λ, 254 nm. System D, eluent: acetonitrile/water/0.1 N trifluoroacetic acid, 10% acetonitrile for 2 min to 50% acetonitrile in 13 min to 100% acetonitrile in 9 min, 100% for 1 min; flow rate, 1.0 mL/min; λ, 254 nm.

Methyl 1′-Acetylferrocene-1-carboxylate (5). Acetyl chloride (1.32 mL, 18.5 mmol) was added at 0 °C to a suspension of anhydrous aluminum chloride (2.46 g, 18.5 mmol) in CH_2Cl_2 (12 mL) and stirred for 15 min. The mixture was then added at 0 °C to a solution of methyl ferrocene-1-carboxylate (**4**, 1.50 g, 6.15 mmol) in CH_2Cl_2 (23 mL) over a period of 15 min upon stirring under nitrogen atmosphere. To prevent light induced degradation, the flask was covered with aluminum foil during the reaction. After 4 h, the reaction mixture was poured into ice water and the resulting precipitate was solubilized by addition of concentrated HCl. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give **5** as an orange solid (1.75 g, 99% yield); mp 99−101 °C. IR 1712, 1666, 1465, 1281, 1146, 671 cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.38 (s, 3 H), 3.83 (s, 3 H), 4.42 (m, 2 H), 4.51 (m, 2 H), 4.78 (m, 2 H), 4.82 (m, 2 H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 27.53, 51.71, 70.94, 71.59, 72.62, 72.99, 73.45, 80.51, 170.67, 201.23. EI-MS calcd m/z for $C_{14}H_{14}FeO_3$: 286.1, found 286 (M^+).

Methyl 1′-(1-Chloro-3-oxoprop-1-enyl)ferrocene-1-carboxylate (6). $POCl_3$ (1.42 mL, 15.5 mmol) was added dropwise to anhydrous DMF (1.42 mL) at 0 °C. After stirring for 15 min, the

resulting Vilsmeier reagent was added to an ice-cold mixture of **5** (1.64 g, 5.73 mmol) and anhydrous DMF (1 mL) over a period of 15 min. The reaction mixture was warmed to room temperature and stirred for 2 h. The Vilsmeier complex was quenched with sodium acetate trihydrate (6.60 g, 48.7 mmol). Saturated aqueous $NaHCO_3$ was added until the aqueous phase was neutralized. Extraction with CH_2Cl_2, drying ($MgSO_4$), and evaporation gave the crude product, which was purified by flash chromatography (*n*-hexane:ethylacetate 6:1) to yield **6** as a red oil (1.36 g, 71% yield): IR 1716, 1666, 1601, 1465, 1281, 1138, 833 cm^{-1}. ^1H NMR (360 MHz, $CDCl_3$) δ 3.79 (s, 3 H), 4.44 (m, 2 H), 4.56 (m, 2 H), 4.75 (m, 2 H), 4.84 (m, 2 H), 6.35 (d, 1 H, J = 7.04 Hz), 10.10 (d, 1 H, J = 7.04 Hz). ^{13}C NMR: (90 MHz, $CDCl_3$) δ 51.75, 69.98, 72.45, 73.43, 73.90, 81.55, 121.45, 152.97, 170.20, 190.62. EI-MS calcd m/z for $C_{15}H_{13}ClFeO_3$: 332.6, found 332 (M^+).

1′-Ethynylferrocene-1-carboxylic Acid (7). A solution of **6** (1.36 g, 4.09 mmol) in anhydrous dioxane (26 mL) was heated at reflux temperature for 5 min and subsequently treated with a boiling solution of 0.5 N NaOH (49.2 mL). The reaction mixture was refluxed for 25 min and subsequently cooled by addition of ice water. Neutralization with diluted HCl was followed by extraction with CH_2Cl_2. The organic layer was dried (Na_2SO_4), and the solvent was removed by reduced pressure. The residue was purified by flash chromatography (*n*-hexane:Et_2O 1:1) to give **7** as a red−orange solid (846 mg, 81% yield); mp 144−145 °C. IR 2110, 1674, 1477, 1296, 1165, 1029, 829, 744 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$) δ 2.80 (s, 1 H), 4.29 (m, 2 H), 4.45 (m, 2 H), 4.50 (m, 2 H), 4.52 (m, 2 H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 66.41, 70.72, 71.87, 72.11, 73.25, 73.96, 74.92, 80.18, 176.65. HPLC system A (245 nm) purity 96% (t_R = 20.5 min). EI-MS calcd m/z for $C_{13}H_{10}FeO_2$: 254.1, found 254 (M^+).

1′-Ethynyl-*N*-{3-[4-(2-methoxyphenyl)piperazin-1-yl]propyl}-ferrocene-1-carboxamide (9a). DIPEA (0.52 mL, 3.2 mmol) was added to a solution of **7** (0.20 g, 0.79 mmol) in anhydrous CH_2Cl_2 (65 mL). The solution was cooled to 0 °C, and subsequently TBTU (0.31 g, 0.97 mmol) in anhydrous DMF (16 mL) was added. After stirring for 15 min, **8a** (0.35 g, 1.4 mmol) in anhydrous CH_2Cl_2 (82 mL) was added dropwise. The reaction mixture was warmed to room temperature and stirred for 4 h. The reaction was quenched with saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2. The combined organic layers were dried (Na_2SO_4) and evaporated. The residue was purified by flash chromatography (CH_2Cl_2:MeOH 98:2) to give **9a** as an orange solid (0.38 g, 99% yield); mp 156−158 °C. IR 3290, 2939, 2816, 2110, 1635, 1539, 1500, 1454, 1300, 1242, 1030, 749 cm^{-1}. ^1H NMR (360 MHz, $CDCl_3$) δ 1.83 (m, 2 H), 2.63 (br t, 2 H, J = 6.36 Hz), 2.69−2.84 (m, 5 H), 3.18 (m, 4 H), 3.52 (dt, 2 H, J_1 = 5.98 Hz, J_2 = 5.98 Hz), 3.87 (s, 3 H), 4.24 (m, 2 H), 4.36 (m, 2 H), 4.45 (m, 2 H), 4.71 (m, 2 H), 6.84−7.07 (m, 4 H), 7.12 (m, 1 H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 25.35, 39.49, 50.54, 53.64, 55.41, 57.68, 65.20, 70.15, 70.52, 72.24, 73.26, 74.62, 78.07, 81.58, 111.29, 118.23, 121.04, 123.15, 141.02, 152.31, 169.28. HPLC system A (245 nm) purity 98% (t_R = 16.3 min). APCI-MS calcd m/z for $C_{27}H_{31}FeN_3O_2$: 485.4, found 486 $(M + H)^+$.

1′-Ethynyl-*N*-{4-[4-(2-methoxyphenyl)piperazin-1-yl]butyl}-ferrocene-1-carboxamide (9b). Compound **9b** was prepared according to the protocol of **9a** using a solution of **7** (0.20 g, 0.79 mmol) in anhydrous CH_2Cl_2 (65 mL) as well as DIPEA (0.52 mL, 3.2 mmol) and TBTU (0.31 g, 0.97 mmol) in anhydrous DMF (16 mL) and **8b** (0.37 g, 1.4 mmol) in anhydrous CH_2Cl_2 (82 mL) to give **9b** as a brown oil (0.38 g, 96% yield): IR 3298, 2939, 2819, 2110, 1631, 1539, 1500, 1450, 1300, 1242, 1026, 795, 752 cm^{-1}. ^1H NMR (360 MHz, $CDCl_3$) δ 1.62−1.76 (m, 4 H), 2.58 (m, 2 H), 2.78 (m, 4 H), 2.82 (s, 1 H), 3.15 (m, 4 H), 3.44 (dt, 2 H, J_1 = 6.28 Hz, J_2 = 6.19 Hz), 3.86 (s, 3 H), 4.26 (m, 2 H), 4.38 (m, 2 H), 4.44 (m, 2 H), 4.65 (m, 2 H), 6.16 (m, 1 H), 6.83−7.05 (m, 4 H). ^{13}C NMR (90 MHz, $CDCl_3$) δ 23.89, 27.69, 39.33, 50.18, 53.43, 55.40, 58.04, 64.98, 70.50, 72.12, 73.48, 74.72, 77.89, 81.75, 111.30, 118.34, 121.06, 123.17, 140.98, 152.30, 169.44. HPLC system A (245 nm) purity 98% (t_R = 16.2 min). APCI-MS calcd m/z for $C_{28}H_{33}FeN_3O_2$: 499.4, found 500 $(M + H)^+$.

1′-(1-Benzyl-1*H*-1,2,3-triazole-4-yl)-*N*-{3-[4-(2-methoxyphenyl)piperazin-1-yl]propyl}ferrocene-1-carboxamide (10a). A suspension of **9a** (26 mg, 54 μmol), benzyl azide (21 mg, 0.16 mmol), sodium ascorbate (2.2 mg, 11 μmol), and copper sulfate pentahydrate (0.7 mg, 2.8 μmol) in H_2O (1 mL), ^{t}BuOH (0.5 mL), and CH_2Cl_2 (0.5 mL) was stirred at room temperature overnight. The reaction was quenched with saturated aqueous $NaHCO_3$, extracted with CH_2Cl_2, dried (Na_2SO_4), and evaporated. The residue was purified by flash chromatography (CH_2Cl_2:MeOH 98:2−95:5) to give **10a** as an orange solid (32 mg, 96% yield); mp 102−105 °C. IR 3325, 2939, 2819, 1635, 1539, 1500, 1454, 1300, 1242, 1026, 752 cm^{-1}. ^1H NMR (360 MHz, $CDCl_3$) δ 1.79 (m, 2 H), 2.59 (br t, 2 H, J = 6.58 Hz), 2.74 (m, 4 H), 3.16 (m, 4 H), 3.28 (dt, 2 H, J_1 = 6.13 Hz, J_2 = 6.02 Hz), 3.87 (s, 3 H), 4.25 (m, 2 H), 4.31 (m, 2 H), 4.53 (m, 2 H), 4.60 (m, 2 H), 5.53 (s, 2 H), 6.84−6.90 (m, 1 H), 6.91−6.98 (m, 2 H), 6.99−7.05 (m, 1 H), 7.29−7.44 (m, 5 H), 7.48 (s, 1 H), 7.55 (m, 1 H). ^{13}C NMR (90 MHz, $CDCl_3$) δ 25.42, 39.17, 50.55, 53.57, 54.14, 55.40, 57.45, 68.62, 69.76, 69.98, 70.85, 76.88, 78.75, 111.30, 118.25, 120.07, 121.07, 123.01, 128.11, 128.74, 129.13, 134.70, 141.22, 145.48, 152.34, 169.12. HPLC system D (245 nm) purity > 99% (t_R = 15.8 min). HR-EIMS calcd m/z for $C_{34}H_{38}FeN_6O_2$: 618.2406, found 618.2408.

1′-(1-Benzyl-1*H*-1,2,3-triazole-4-yl)-*N*-{4-[4-(2-methoxyphenyl)piperazin-1-yl]butyl}ferrocene-1-carboxamide (10b). Compound **10b** was prepared according to the protocol of **10a** using a suspension of **9b** (25.5 mg, 51.1 μmol), benzylazide (20.4 mg, 0.153 mmol), sodium ascorbate (2.0 mg, 10.1 μmol), and copper sulfate pentahydrate (0.7 mg, 2.80 μmol) in H_2O (1 mL), ^{t}BuOH (0.5 mL), and CH_2Cl_2 (0.5 mL) to give **10b** as an orange solid (27.0 mg, 83% yield); mp 98−101 °C. IR 3317, 2939, 2819, 1635, 1539, 1500, 1454, 1300, 1242, 1026, 752 cm^{-1}. ^1H NMR: (360 MHz, $CDCl_3$) δ 1.62−1.76 (m, 4 H), 2.51 (m, 2 H), 2.71 (m, 4 H), 3.12 (m, 4 H), 3.32 (m, 2 H), 3.85 (s, 3 H), 4.26 (m, 2 H), 4.33 (m, 2 H), 4.45 (m, 2 H), 4.54 (m, 2 H), 5.54 (s, 2 H), 6.82−6.87 (m, 1 H), 6.88−6.95 (m, 2 H), 6.96−7.02 (m, 1 H), 7.15 (m, 1 H), 7.28−7.45 (m, 6 H). ^{13}C NMR (90 MHz, $CDCl_3$) δ 24.26, 27.66, 39.41, 50.44, 53.41, 54.21, 55.38, 58.27, 69.18, 69.79, 70.44, 70.68, 76.46, 78.77, 111.25, 118.28, 119.99, 121.02, 122.94, 128.09, 128.82, 129.18, 134.59, 141.28, 145.95, 152.30, 169.72. HPLC system D (245 nm) purity 98% (t_R = 15.7 min). HR-EIMS calcd m/z for $C_{35}H_{40}FeN_6O_2$: 632.2562, found 632.2558.

***N*-{3-[4-(2-Methoxyphenyl)piperazin-1-yl]propyl}-1′-(1-pentyl-1*H*-1,2,3-triazole-4-yl)ferrocene-1-carboxamide (10c).** Sodium azide (1.73 g, 26.6 mmol) was added to a solution of 1-bromopentane (830 μL, 6.65 mmol) in CH_3CN (9 mL) and H_2O (1 mL) and heated at reflux temperature overnight. The reaction was quenched with saturated aqueous $NaHCO_3$, extracted with *n*-hexane, dried (Na_2SO_4), and evaporated to 3.1 mL to obtain a concentration of 1-azidopentane of 2.15 mmol/mL.

Compound **10c** was prepared according to the protocol of **10a** using a suspension of **9a** (26.2 mg, 54.0 μmol), a 2.15 M solution of 1-azidopentane in *n*-hexane (75.3 μL, 0.162 mmol), sodium ascorbate (2.10 mg, 10.8 μmol), and copper sulfate pentahydrate (0.7 mg, 2.80 μmol) in H_2O (1 mL), ^{t}BuOH (0.5 mL), and CH_2Cl_2 (0.5 mL). Purification by flash chromatography (CH_2Cl_2:MeOH 98:2−97:3) gave **10c** as an orange solid (24.6 mg, 76% yield); mp 108−111 °C. IR 3309, 2931, 2819, 1635, 1539, 1500, 1450, 1300, 1242, 1026, 748 cm^{-1}. ^1H NMR (360 MHz, $CDCl_3$) δ 0.92 (t, 3 H, J = 6.93 Hz), 1.30−1.44 (m, 4 H), 1.81 (m, 2 H), 1.94 (m, 2 H), 2.59 (br t, 2 H, J = 6.47 Hz), 2.73 (m, 4 H), 3.16 (m, 4 H), 3.32 (dt, 2 H, J_1 = 6.21 Hz, J_2 = 6.07 Hz), 3.87 (s, 3 H), 4.26 (m, 2 H), 4.30−4.38 (m, 4 H), 4.53 (m, 2 H), 4.63 (m, 2 H), 6.84−7.05 (m, 4 H), 7.55 (s, 1 H), 7.57 (m, 1 H). ^{13}C NMR (90 MHz, $CDCl_3$) δ 13.87, 22.12, 25.44, 28.68, 29.98, 39.27, 50.36, 50.60, 53.59, 55.40, 57.52, 68.67, 69.69, 70.02, 70.80, 77.24, 78.77, 111.30, 118.23, 119.97,

121.06, 123.00, 141.26, 144.96, 152.35, 169.17. HPLC system A (245 nm) purity 97% (t_R = 17.5 min); system D (245 nm) purity >99% (t_R = 16.6 min). HR-EIMS calcd m/z for $C_{32}H_{42}FeN_6O_2$: 598.2719, found 598.2719.

***N*-{4-[4-(2-Methoxyphenyl)piperazin-1-yl]butyl}-1′-(1-pentyl-1*H*-1,2,3-triazole-4-yl)ferrocene-1-carboxamide (10d).** Compound **10d** was prepared according to the protocol of **10a** using a suspension of **9b** (19.5 mg, 39.0 μmol), a 2.15 M solution of 1-azidopentane in *n*-hexane (54.0 μL, 0.117 mmol), sodium ascorbate (1.50 mg, 7.57 μmol), and copper sulfate pentahydrate (0.5 mg, 1.95 μmol) in H_2O (1 mL), ^{t}BuOH (0.5 mL) and CH_2Cl_2 (0.5 mL) to give **10d** as a red−orange solid (19.5 mg, 81% yield); mp 82−85 °C. IR 3324, 2934, 2816, 1635, 1540, 1500, 1451, 1297, 1241, 1026, 750 cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.92 (t, 3 H, J = 6.99 Hz), 1.32−1.42 (m, 4 H), 1.62−1.72 (m, 4 H), 1.95 (m, 2 H), 2.50 (br t, 2 H, J = 6.61 Hz), 2.70 (m, 4 H), 3.12 (m, 4 H), 3.34 (dt, 2 H, J_1 = 6.04 Hz, J_2 = 5.95 Hz), 3.86 (s, 3 H), 4.28 (m, 2 H), 4.33−4.39 (m, 4 H), 4.45 (m, 2 H), 4.57 (m, 2 H), 6.83−6.88 (m, 1 H), 6.89−6.96 (m, 2 H), 6.97−7.02 (m, 1 H), 7.20 (m, 1 H), 7.51 (s, 1 H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 13.88, 22.12, 24.29, 27.66, 28.67, 29.99, 39.42, 50.42, 50.47, 53.41, 55.36, 58.28, 69.20, 69.73, 70.46, 70.64, 76.68, 78.76, 111.20, 118.26, 119.90, 121.00, 122.94, 141.27, 145.38 152.29, 169.76. HPLC system B (245 nm) purity 96% (t_R = 8.5 min); system D (245 nm) purity >99% (t_R = 16.4 min). HR-EIMS calcd m/z for $C_{33}H_{44}FeN_6O_2$: 612.2875, found 612.2875.

1′-(1-Hexyl-1*H*-1,2,3-triazole-4-yl)-*N*-{3-[4-(2-methoxyphenyl)piperazin-1-yl]propyl}ferrocene-1-carboxamide (10e). Sodium azide (793 mg, 12.2 mmol) was added to a solution of 1-bromohexane (0.430 mL, 3.05 mmol) in CH_3CN (9 mL) and H_2O (1 mL) and heated at reflux temperature overnight. The reaction was quenched with saturated aqueous $NaHCO_3$, extracted with *n*-hexane, dried (Na_2SO_4), and evaporated to 7.80 mL to obtain a concentration of 1-azidohexane of 0.391 mmol/mL.

Compound **10e** was prepared according to the protocol of **10a** using a suspension of **9a** (23.1 mg, 47.6 μmol), a 0.391 M solution of 1-azidohexane in *n*-hexane (366 μL, 0.143 mmol), sodium ascorbate (1.90 mg, 9.60 μmol), and copper sulfate pentahydrate (0.6 mg, 2.40 μmol) in H_2O (1 mL), ^{t}BuOH (0.5 mL) and CH_2Cl_2 (0.5 mL) to give **10e** as an orange solid (28.6 mg, 98% yield); mp 87−89 °C. IR 3336, 2931, 2819, 1635, 1539, 1500, 1450, 1300, 1242, 1026, 795, 748 cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.89 (t, 3 H, J = 6.99 Hz), 1.28−1.40 (m, 6 H), 1.81 (m, 2 H), 1.94 (m, 2 H), 2.59 (br t, 2 H, J=6.61 Hz), 2.74 (m, 4 H), 3.16 (m, 4 H), 3.32 (dt, 2 H, J_1 = 6.29 Hz, J_2 = 6.14 Hz), 3.87 (s, 3 H), 4.26 (m, 2 H), 4.33 (m, 2 H), 4.35 (t, 2 H, J = 7.37 Hz), 4.53 (m, 2 H), 4.63 (m, 2 H), 6.85−6.89 (m, 1 H), 6.91−6.97 (m, 2 H), 6.99−7.04 (m, 1 H), 7.55 (s, 1 H), 7.60 (m, 1 H). ^{13}C NMR (90 MHz, $CDCl_3$) δ 13.90, 22.39, 25.39, 26.19, 30.21, 31.13, 39.21, 50.34, 50.54, 53.54, 55.36, 57.47, 68.63, 69.65, 69.99, 70.77, 77.08, 78.71, 111.26, 118.19, 119.92, 121.01, 122.96, 141.21, 144.92, 152.30, 169.14. HPLC system C (245 nm) purity 99% (t_R = 18.3 min); system D (245 nm) purity >99% (t_R = 17.8 min). HR-EIMS calcd m/z for $C_{33}H_{44}FeN_6O_2$: 612.2875, found 612.2875.

1′-(1-Hexyl-1*H*-1,2,3-triazole-4-yl)-*N*-{4-[4-(2-methoxyphenyl)piperazin-1-yl]butyl}ferrocene-1-carboxamide (10f). Compound **10f** was prepared according to the protocol of **10a** using a suspension of **9b** (25.2 mg, 50.5 μmol), a 0.391 M solution of 1-azidohexane in *n*-hexane (390 μL, 0.152 mmol), sodium ascorbate (2.0 mg, 10.1 μmol), and copper sulfate pentahydrate (0.6 mg, 2.40 μmol) in H_2O (1 mL), ^{t}BuOH (0.5 mL) and CH_2Cl_2 (0.5 mL) to give **10f** as an orange solid (23.0 mg, 72% yield); mp 68−72 °C. IR 3317, 2931, 1635, 1539, 1500, 1454, 1300, 1242, 1026, 667 cm^{-1}. ^{1}H NMR (360 MHz, $CDCl_3$) δ 0.89 (t, 3 H, J = 7.15 Hz), 1.28−1.45 (m, 6 H), 1.61−1.76 (m, 4 H) 1.94 (m, 2 H), 2.52 (br t, 2 H, J = 7.04 Hz), 2.71 (m, 4 H), 3.14 (m, 4 H), 3.34 (dt, 2 H, J_1 = 6.28 Hz, J_2 = 6.13 Hz), 3.86 (s, 3 H), 4.27 (m, 2 H), 4.31−4.39 (m, 4 H), 4.46 (m, 2 H), 4.57 (m, 2 H), 6.81−7.03 (m, 4 H), 7.18 (m, 1 H), 7.51 (s, 1 H). ^{13}C NMR (90 MHz, $CDCl_3$) δ 13.94, 22.43, 24.24, 26.22, 27.65, 30.25, 31.16, 39.41, 50.44, 53.41, 55.38, 58.26, 69.19, 69.74, 70.46, 70.66, 78.76, 111.27, 118.28, 119.90, 121.03, 122.95, 141.28, 145.39, 152.31, 169.76. HPLC system A (245 nm) purity 98% (t_R = 18.0 min); system D (245 nm) purity >99% (t_R = 17.7 min). HR-EIMS calcd m/z for $C_{34}H_{46}FeN_6O_2$: 626.3032, found 626.3038.

1′-(1-Benzyl-1*H*-1,2,3-triazole-4-yl)ferrocene-1-carbaldehyde (12a). A suspension of 1′-ethynylferrocene-1-carbaldehyde (**11**, 66.4 mg, 0.279 mmol), benzylazide (111 mg, 0.837 mmol), sodium ascorbate (11.1 mg, 56.0 μmol), and copper sulfate pentahydrate (3.50 mg, 14.0 μmol) in H_2O (4 mL), ^{t}BuOH (2 mL), and CH_2Cl_2 (2 mL) was stirred at room temperature overnight. Afterward, the reaction was quenched with saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2. The combined organic layers were dried (Na_2SO_4), and the solvent was removed under reduced pressure. The residue was purified by flash chromatography (*n*-hexane:Et_2O 1:1) to give **12a** as an orange solid (97.9 mg, 94% yield); mp 128−131 °C. IR 3113, 2924, 1678, 1454, 1246, 1045, 825, 721 cm^{-1}. ^{1}H NMR (360 MHz, $CDCl_3$) δ 4.36 (m, 2 H), 4.50 (m, 2 H), 4.66 (m, 2 H), 4.79 (m, 2 H), 5.55 (s, 2 H), 7.28−7.33 (m, 2 H), 7.35−7.45 (m, 4 H), 9.70 (s, 1 H). ^{13}C NMR (90 MHz, $CDCl_3$,) δ 54.19, 68.00, 70.03, 70.96, 74.53, 77.71, 79.97, 119.52, 128.00, 128.77, 129.15, 134.71, 145.10, 193.57. HPLC system A (245 nm) purity 96% (t_R = 18.9 min). APCI-MS calcd m/z for $C_{20}H_{17}FeN_3O$: 371.2, found 372 $(M + H)^+$.

1′-(1-Pentyl-1*H*-1,2,3-triazole-4-yl)ferrocene-1-carbaldehyde (12b). Compound **12b** was prepared according to the protocol of **12a** using a suspension of **11** (63.2 mg, 0.265 mmol), a 2.15 M solution of 1-azidopentane in *n*-hexane (372 μL, 800 μmol), sodium ascorbate (10.5 mg, 53.0 μmol), and copper sulfate pentahydrate (3.3 mg, 13.2 μmol) in H_2O (4 mL), ^{t}BuOH (2 mL), and CH_2Cl_2 (2 mL) to give **12b** as an orange brown solid (87.5 mg, 93% yield); mp 68−70 °C. IR 3498, 3120, 2954, 2931, 1682, 1454, 1246, 1049, 825, 744 cm^{-1}. ^{1}H NMR (360 MHz, $CDCl_3$) δ 0.92 (t, 3 H, J = 6.93 Hz), 1.30−1.42 (m, 4 H), 1.95 (m, 2 H), 4.33−4.40 (m, 4 H), 4.53 (m, 2 H), 4.67 (m, 2 H), 4.83 (m, 2 H), 7.47 (s, 1 H), 9.71 (s, 1 H). ^{13}C NMR (90 MHz, $CDCl_3$) δ 13.87, 22.10, 28.63, 29.95, 50.40, 68.02, 69.97, 71.00, 74.48, 77.99, 80.00, 119.42, 144.48, 193.57. HPLC system A (245 nm) purity 99% (t_R = 19.7 min). APCI-MS calcd m/z for $C_{18}H_{21}FeN_3O$: 351.2, found 352 $(M + H)^+$.

1′-(1-Hexyl-1*H*-1,2,3-triazole-4-yl)ferrocene-1-carbaldehyde (12c). Compound **12c** was prepared according to the protocol of **12a** using a suspension of **11** (34.5 mg, 145 μmol), a 0.391 M solution of 1-azidohexane in *n*-hexane (111 μL, 0.435 mmol), sodium ascorbate (5.80 mg, 29.3 μmol), and copper sulfate pentahydrate (1.8 mg, 7.21 μmol) in H_2O (2 mL), ^{t}BuOH (1 mL), and CH_2Cl_2 (1 mL) to give **12c** as an orange−brown solid (38.3 mg, 72% yield); mp 79−80 °C. IR 3118, 2927, 2856, 1682, 1456, 1244, 1047, 822, 742 cm^{-1}. ^{1}H NMR (360 MHz, $CDCl_3$) δ 0.89 (t, 3 H, J = 7.04 Hz), 1.27−1.41 (m, 6 H), 1.95 (m, 2 H), 4.33−4.40 (m, 4 H), 4.53 (m, 2 H), 4.67 (m, 2 H), 4.83 (m, 2 H), 7.46 (s, 1 H), 9.71 (s, 1 H). ^{13}C NMR (150 MHz, $CDCl_3$,) δ 13.96, 22.45, 26.18, 30.24, 31.18, 50.42, 68.03, 69.99, 71.02, 74.50, 77.96, 79.98, 119.42, 144.49, 193.63. HPLC system A (245 nm) purity 99% (t_R = 20.5 min). APCI-MS calcd m/z for $C_{19}H_{23}FeN_3O$: 365.3 found 366 $(M + H)^+$.

1-{[1′-(1-Benzyl-1*H*-1,2,3-triazole-4-yl)ferrocene-1-yl]methyl}-4-(2-methoxyphenyl)piperazine (13a). A solution of **12a** (21.1 mg, 56.8 μmol), 1-(2-methoxyphenyl)piperazine (16.4 mg, 85.2 μmol), and $Na(OAc)_3BH$ (25.3 mg, 114 μmol) in anhydrous CH_2Cl_2 (13 mL) was stirred at room temperature overnight. The reaction mixture was quenched with saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2. The combined organic layers were dried (Na_2SO_4) and evaporated. The residue was purified

by flash chromatography (CH_2Cl_2:MeOH 98:2) to give **13a** as a yellow−orange solid (27.3 mg, 87% yield); mp 121−125 °C. IR 2939, 2816, 1500, 1454, 1238, 1026, 752 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$) δ 2.50 (m, 4 H), 3.01 (m, 4 H), 3.16 (s, 2 H), 3.84 (s, 3 H), 4.03 (m, 2 H), 4.07 (m, 2 H), 4.25 (m, 2 H), 4.65 (m, 2 H), 5.54 (s, 2 H), 6.81−6.85 (m, 1 H), 6.86−6.91 (m, 2 H), 6.94−7.00 (m, 1 H), 7.28−7.32 (m, 2 H), 7.34−7.42 (m, 4 H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 50.39, 52.70, 54.10, 55.33, 57.59, 66.98, 69.17, 69.65, 71.79, 75.75, 82.97, 111.15, 118.21, 118.66, 120.97, 122.83, 127.96, 128.71, 129.16, 134.93, 141.35, 146.73, 152.24. HPLC system A (245 nm) purity 98% (t_R = 16.5 min); system D (245 nm) purity > 99% (t_R = 16.7 min). HR-EIMS calcd m/z for $C_{31}H_{33}FeN_5O$: 547.2035, found 547.2035.

1-(2-Methoxyphenyl)-4-{[1′-(1-pentyl-1*H*-1,2,3-triazole-4-yl)ferrocene-1-yl]methyl}piperazine (13b). Compound **13b** was prepared according to the protocol of **13a** using a solution of **12b** (20.4 mg, 58.1 μmol), 1-(2-methoxyphenyl)piperazine (16.8 mg, 87.2 μmol), and $Na(OAc)_3BH$ (25.7 mg, 116 μmol) in CH_2Cl_2 (13 mL) to give **13b** as an orange−brown solid (30.4 mg, 99% yield); mp 92−94 °C. IR 2931, 2816, 1500, 1454, 1238, 1025, 748 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$,) δ 0.92 (t, 3 H, J = 6.99 Hz), 1.30−1.43 (m, 4 H), 1.94 (m, 2 H), 2.55 (m, 4 H), 3.02 (m, 4 H), 3.23 (s, 2 H), 3.83 (s, 3 H), 4.05 (m, 2 H), 4.10 (m, 2 H), 4.27 (m, 2 H), 4.35 (t, 2 H, J = 7.18 Hz), 4.68 (m, 2 H), 6.81−6.84 (m, 1 H), 6.86−6.90 (m, 2 H), 6.94−6.99 (m, 1 H), 7.44 (s, 1 H). ^{13}C NMR (150 MHz, $CDCl_3$,) δ 13.90, 22.12, 28.66, 30.08, 50.29, 50.38, 52.74, 55.32, 57.65, 66.98, 69.14, 69.69, 71.80, 76.01, 82.97, 111.14, 118.21, 118.58, 120.96, 122.84, 141.32, 146.10, 152.24. HPLC system A (245 nm) purity 97% (t_R = 16.9 min); system D (245 nm) purity > 99% (t_R = 17.5 min). HR-EIMS calcd m/z for $C_{29}H_{37}FeN_5O$: 527.2348, found 527.2348.

1-{[1′-(1-Hexyl-1*H*-1,2,3-triazole-4-yl)ferrocene-1-yl]methyl}-4-(2-methoxyphenyl)piperazine (13c). Compound **13c** was prepared according to the protocol of **13a** using a solution of **12c** (29.2 mg, 80.0 μmol), 1-(2-methoxyphenyl)piperazine (23.1 mg, 120 μmol), and $Na(OAc)_3BH$ (35.5 mg, 160 μmol) in CH_2Cl_2 (19 mL). Purification by flash chromatography (CH_2Cl_2:MeOH 98:2−95:5) gave **13c** as a yellow−orange solid (32.7 mg, 75% yield); mp 91−93 °C. IR 2931, 2816, 1500, 1454, 1238, 1026, 748 cm^{-1}. ^1H NMR (360 MHz, $CDCl_3$) δ 0.89 (t, 3 H, J = 7.15 Hz), 1.21−1.42 (m, 6 H), 1.93 (m, 2 H), 2.56 (m, 4 H), 3.02 (m, 4 H), 3.24 (s, 2 H), 3.83 (s, 3 H), 4.05 (m, 2 H), 4.10 (m, 2 H), 4.27 (m, 2 H), 4.35 (t, 2 H, J = 7.27 Hz), 4.68 (m, 2 H), 6.80−6.84 (m, 1 H), 6.86−6.90 (m, 2 H), 6.92−7.00 (m, 1 H), 7.44 (s, 1 H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 13.96, 22.45, 26.20, 30.34, 31.17, 50.30, 50.35, 52.70, 55.32, 57.62, 66.98, 69.14, 69.72, 71.80, 76.00, 82.82, 111.13, 118.21, 118.58, 120.96, 122.86, 141.29, 146.09, 152.23. HPLC system A (245 nm) purity 99% (t_R = 18.0 min); system D (245 nm) purity > 99% (t_R = 18.7 min). HR-EIMS calcd m/z for $C_{30}H_{39}FeN_5O$: 541.2504, found 541.2505.

1′,1″-[Biphenyl-4,4′-diylbis(methylene-1*H*-1,2,3-triazole-1,4-diyl)]bis(*N*-{3-[4-(2-methoxyphenyl)piperazin-1-yl]propyl}ferrocene-1-carboxamide) (14a). A suspension of **9a** (36 mg, 75 μmol), 4,4′-bis(azidomethyl)biphenyl (6.7 mg, 25 μmol), sodium ascorbate (1.0 mg, 5.0 μmol), and copper sulfate pentahydrate (0.3 mg, 1.2 μmol) in H_2O (2 mL), ^{t}BuOH (1 mL), and CH_2Cl_2 (1 mL) was stirred at room temperature overnight. The reaction was quenched with saturated aqueous $NaHCO_3$, extracted with CH_2Cl_2, dried (Na_2SO_4), and evaporated. The residue was purified by flash chromatography (CH_2Cl_2:MeOH 95:5−9:1) to give **14a** as an orange solid (27 mg, 88% yield); mp 147−148 °C. IR 3328, 2943, 2823, 1635, 1539, 1500, 1450, 1300, 1242, 1026, 752 cm^{-1}. ^1H NMR (360 MHz, $CDCl_3$) δ 1.80 (m, 4 H), 2.61 (br t, 4 H, J = 6.58 Hz), 2.76 (m, 8 H), 3.17 (m, 8 H), 3.28 (dt, 4 H, J_1 = 5.98 Hz, J_2 = 5.85 Hz), 3.86 (s, 6 H), 4.25 (m, 4 H), 4.31 (m, 4 H), 4.55 (m, 4H), 4.61 (m, 4 H), 5.57 (s, 4 H), 6.84−6.89 (m, 2 H), 6.90−6.96 (m, 4 H), 6.98−7.04 (m, 2 H), 7.36−7.42 (m, 4 H), 7.51−7.62 (m, 8 H). ^{13}C NMR (90 MHz, $CDCl_3$) δ 25.28, 39.15, 50.44, 50.54, 53.79, 55.41, 57.43, 68.59, 69.78, 69.97, 70.88, 76.86, 78.73, 111.33, 118.26, 120.17, 121.07, 123.09, 127.77, 128.66, 134.11, 140.73, 141.12, 145.54, 152.33, 169.10. HPLC system A (245 nm) purity 95% (t_R = 16.7 min); system D (245 nm) purity 98% (t_R = 17.4 min). APCI-MS calcd m/z for $C_{68}H_{74}Fe_2N_{12}O_4$: 1235.1 found 1236 $(M + H)^+$.

1′,1″-[Biphenyl-4,4′-diylbis(methylene-1*H*-1,2,3-triazole-1,4-diyl)]bis(*N*-{4-[4-(2-methoxyphenyl)piperazin-1-yl]butyl}ferrocene-1-carboxamide) (14b). Compound **14b** was prepared according to the protocol of **14a** using a suspension of **9b** (39 mg, 78 μmol), 4,4′-bis(azidomethyl)biphenyl (6.9 mg, 26 μmol), sodium ascorbate (1.0 mg, 5.0 μmol), and copper sulfate pentahydrate (0.3 mg, 1.2 μmol) in H_2O (2 mL), ^{t}BuOH (1 mL), and CH_2Cl_2 (1 mL) to give **14b** as an orange solid (32 mg, 96% yield); mp 147−150 °C. IR 3402, 2939, 2819, 1631, 1539, 1500, 1450, 1300, 1242, 1026, 752 cm^{-1}. ^1H NMR (360 MHz, $CDCl_3$) δ 1.61−1.76 (m, 8 H), 2.53 (m, 4 H), 2.73 (m, 8 H), 3.13 (m, 8 H), 3.32 (m, 4 H), 3.84 (s, 6 H), 4.26 (m, 4 H), 4.33 (m, 4 H), 4.47 (m, 4 H), 4.55 (m, 4 H), 5.58 (s, 4 H), 6.81−7.04 (m, 8 H), 7.11 (m, 2 H), 7.34−7.44 (m, 4 H), 7.49 (s, 2 H), 7.55−7.67 (m, 4 H). ^{13}C NMR (150 MHz, $CDCl_3$,) δ 24.07, 27.57, 39.30, 50.29, 53.34, 53.83, 55.37, 58.17, 69.12, 69.83, 70.40, 70.74, 76.44, 78.72, 111.23, 118.29, 120.09, 121.02, 123.05, 127.80, 128.64, 134.02, 140.72, 141.12, 145.98, 152.27, 169.71. HPLC system C (245 nm) purity 95% (t_R = 18.0 min); system D (245 nm) purity 97% (t_R = 17.1 min). APCI-MS calcd m/z for $C_{70}H_{78}Fe_2N_{12}O_4$: 1263.1, found 1264 $(M + H)^+$.

1′,1″-[Decane-1,10-diylbis(1*H*-1,2,3-triazole-1,4-diyl)]bis(*N*-{3-[4-(2-methoxyphenyl)piperazin-1-yl]propyl}ferrocene-1-carboxamide) (14c). Compound **14c** was prepared according to the protocol of **14a** using a suspension of **9a** (38 mg, 78 μmol), 1,10-diazidodecane (5.9 mg, 26 μmol), sodium ascorbate (1.0 mg, 5.0 μmol), and copper sulfate pentahydrate (0.3 mg, 1.2 μmol) in H_2O (2 mL), ^{t}BuOH (1 mL), and CH_2Cl_2 (1 mL). Purification by flash chromatography (CH_2Cl_2:MeOH 98:2−9:1) gave **14c** as an orange−brown solid (21 mg, 69% yield); mp 61−62 °C. IR 3313, 2931, 2819, 1635, 1539, 1500, 1454, 1242, 1026, 910, 733 cm^{-1}. ^1H NMR (360 MHz, $CDCl_3$) δ 1.20−1.41 (m, 12 H), 1.82 (m, 4 H), 1.92 (m, 4 H), 2.61 (br t, 4 H, J = 6.47 Hz), 2.76 (m, 8 H), 3.17 (m, 8 H), 3.32 (dt, 4 H, J_1 = 6.06 Hz, J_2 = 5.96 Hz), 3.86 (s, 6 H), 4.26 (m, 4 H), 4.30−4.37 (m, 8 H), 4.53 (m, 4 H), 4.63 (m, 4 H), 6.84−6.89 (m, 2 H), 6.90−6.98 (m, 4 H), 6.99−7.05 (m, 2 H), 7.55 (s, 2 H), 7.58 (m, 2 H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 25.30, 26.50, 28.93, 29.23, 30.26, 39.17, 50.34, 50.46, 53.53, 55.40, 57.45, 68.63, 69.72, 70.01, 70.85, 77.09, 78.67, 111.25, 118.23, 119.99, 121.04, 123.06, 141.11, 144.95, 152.30, 169.19. HPLC system C (245 nm) purity 96% (t_R = 18.7 min). APCI-MS calcd m/z for $C_{64}H_{82}Fe_2N_{12}O_4$: 1195.1, found 1196 $(M + H)^+$.

1′,1″-[Decane-1,10-diylbis(1*H*-1,2,3-triazole-1,4-diyl)]bis(*N*-{4-[4-(2-methoxyphenyl)piperazin-1-yl]butyl}ferrocene-1-carboxamide) (14d). Compound **14d** was prepared according to the protocol of **14a** using a suspension of **9b** (39 mg, 78 μmol), 1,10-diazidodecane (5.9 mg, 26 μmol), sodium ascorbate (1.0 mg, 5.0 μmol), and copper sulfate pentahydrate (0.3 mg, 1.2 μmol) in H_2O (2 mL), ^{t}BuOH (1 mL), and CH_2Cl_2 (1 mL). Purification by flash chromatography (CH_2Cl_2:MeOH 98:2−9:1) gave **14d** as an orange solid (20 mg, 61% yield); mp 63−64 °C. IR 3332, 2931, 2819, 1635, 1539, 1500, 1454, 1242, 1026, 752 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$) δ 1.18−1.39 (m, 12 H), 1.63−1.73 (m, 8 H), 1.92 (m, 4 H), 2.52 (m, 4 H), 2.73 (m, 8 H), 3.13 (m, 8 H), 3.33 (m, 4 H), 3.85 (s, 6 H), 4.27 (m, 4 H), 4.30−4.37 (m, 8 H), 4.45 (m, 4 H), 4.57 (m, 4 H), 6.83−6.87 (m, 2 H), 6.89−6.96 (m, 4 H), 6.97−7.02 (m, 2 H), 7.16 (m, 2 H), 7.51 (s, 2 H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 24.15, 26.50, 27.62, 28.94, 29.24, 30.27, 39.36, 50.36, 50.39, 53.38, 55.38, 58.22, 69.15, 69.77, 70.43, 70.71, 76.68, 78.71, 111.22, 118.27, 119.92, 121.02, 123.01, 141.17, 145.38, 152.27, 169.75. HPLC system A (245 nm) purity 96% (t_R = 17.2 min); system D (245 nm) purity 96% (t_R = 17.7 min). APCI-MS calcd m/z for $C_{66}H_{86}Fe_2N_{12}O_4$: 1223.2 found 1224 $(M + H)^+$.

1,1′′-[Dodecane-1,12-diylbis(1*H*-1,2,3-triazole-1,4-diyl)]bis-(*N*-{3-[4-(2-methoxyphenyl)piperazin-1-yl]propyl}ferrocene-1-carboxamide) (14e). Compound **14e** was prepared according to the protocol of **14a** using a suspension of **9a** (58 mg, 0.12 mmol), 1,12-diazidododecane (9.9 mg, 39 μmol), sodium ascorbate (1.5 mg, 7.8 μmol), and copper sulfate pentahydrate (0.5 mg, 2.0 μmol) in H_2O (2 mL), ^{t}BuOH (1 mL), and CH_2Cl_2 (1 mL) to give **14e** as an orange solid (42 mg, 87% yield); mp 116−118 °C. IR 3332, 2927, 1635, 1539, 1500, 1454, 1242, 1026, 752 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$) δ 1.21−1.40 (m, 16 H), 1.81 (m, 4 H), 1.92 (m, 4 H), 2.59 (br t, 4 H, J = 6.42 Hz), 2.74 (m, 8 H), 3.16 (m, 8 H), 3.32 (dt, 4 H, J_1 = 5.92 Hz, J_2 = 5.76 Hz), 3.87 (s, 6 H), 4.26 (m, 4 H), 4.30−4.36 (m, 8 H), 4.53 (m, 4 H), 4.62 (m, 4 H), 6.85−6.90 (m, 2 H), 6.92−6.97 (m, 4 H), 6.99−7.04 (m, 2 H), 7.55 (s, 2 H), 7.59 (m, 2 H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 25.37, 26.53, 28.99, 29.35, 29.41, 30.28, 39.25, 50.36, 50.56, 53.56, 55.38, 57.51, 68.63, 69.70, 70.01, 70.82, 77.09, 78.71, 111.24, 118.20, 119.98, 121.03, 123.02, 141.19, 144.93, 152.30, 169.17. HPLC system D (245 nm) purity >99% (t_R = 19.2 min). APCI-MS calcd m/z for $C_{66}H_{86}Fe_2N_{12}O_4$: 1223.2 found 1224 $(M + H)^+$.

1,1′′-[Dodecane-1,12-diylbis(1*H*-1,2,3-triazole-1,4-diyl)]bis-(*N*-{4-[4-(2-methoxyphenyl)piperazin-1-yl]butyl}ferrocene-1-carboxamide) (14f). Compound **14f** was prepared according to the protocol of **14a** using a suspension of **9b** (72.4 mg, 145 μmol), 1,12-diazidododecane (12.2 mg, 48.3 μmol), sodium ascorbate (1.90 mg, 9.60 μmol), and copper sulfate pentahydrate (0.6 mg, 2.40 μmol) in H_2O (2 mL), ^{t}BuOH (1 mL), and CH_2Cl_2 (1 mL) to give **14f** as an orange solid (59.9 mg, 99% yield); mp 141−143 °C. IR 3317, 2931, 1635, 1539, 1500, 1454, 1300, 1242, 1026, 752 cm^{-1}. ^1H NMR (360 MHz, $CDCl_3$) δ 1.17−1.45 (m, 16 H), 1.60−1.78 (m, 8 H), 1.92 (m, 4 H), 2.51 (m, 4 H), 2.70 (m, 8 H), 3.12 (m, 8 H), 3.34 (m, 4 H), 3.85 (s, 6 H), 4.27 (m, 4 H), 4.30−4.39 (m, 8 H), 4.45 (m, 4 H), 4.57 (m, 4 H), 6.82−7.03 (m, 8 H), 7.14 (m, 2 H), 7.51 (s, 2 H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 24.25, 26.54, 27.66, 29.00, 29.37, 29.43, 30.29, 39.40, 50.43, 53.40, 55.37, 58.26, 69.17, 69.76, 70.45, 70.69, 76.69, 78.73, 111.21, 118.25, 119.91, 121.00, 122.97, 141.24, 145.38, 152.28, 169.75. HPLC system D (245 nm) purity 99% (t_R = 19.1 min). APCI-MS calcd m/z for $C_{68}H_{90}Fe_2N_{12}O_4$: 1251.2, found 1252 $(M + H)^+$.

1,1′′-[Biphenyl-4,4′-diylbis(methylene-1*H*-1,2,3-triazole-1,4-diyl)]diferrocene-1-carbaldehyde (15a). A suspension of 1′-ethynylferrocene-1-carbaldehyde (**11**, 58.3 mg, 245 μmol), 4,4′-bis-(azidomethyl)biphenyl (21.6 mg, 81.7 μmol), sodium ascorbate (3.20 mg, 16.2 μmol), and copper sulfate pentahydrate (1.0 mg, 4.00 μmol) in H_2O (4 mL), ^{t}BuOH (2 mL), and CH_2Cl_2 (2 mL) was stirred at room temperature overnight. Afterward, the reaction was quenched with saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2. The combined organic layers were dried (Na_2SO_4) and the solvent was removed under reduced pressure. The residue was purified by flash chromatography (CH_2Cl_2:MeOH 98:2) to give **15a** as a brown solid (60.2 mg, 99% yield); mp > 200 °C (decomposition). IR 3120, 1678, 1454, 1246, 1045, 822, 760 cm^{-1}. ^1H NMR (360 MHz, C_6D_6/CD_3CN) δ 4.20 (m, 4 H), 4.30 (m, 4 H), 4.56 (m, 4H), 4.77 (m, 4 H), 5.37 (s, 4 H), 7.26−7.32 (m, 4 H), 7.43−7.54 (m, 6 H), 9.69 (s, 2 H). ^{13}C NMR (90 MHz, C_6D_6/CD_3CN) δ 53.35, 68.11, 70.10, 70.96, 74.45, 78.51, 80.72, 120.47, 135.32, 140.52, 144.99, 150.90, 170.47, 192.99. APCI-MS calcd m/z for $C_{40}H_{32}Fe_2N_6O_2$: 740.4, found 741 $(M + H)^+$.

1,1′′-[Decane-1,10-diylbis(1*H*-1,2,3-triazole-1,4-diyl)]diferrocene-1-carbaldehyde (15b). Compound **15b** was prepared according to the protocol of **15a** using a suspension of **11** (45.2 mg, 190 μmol), 1,10-diazidodecane (14.2 mg, 63.3 μmol), sodium ascorbate (2.50 mg, 12.6 μmol), and copper sulfate pentahydrate (0.8 mg, 3.20 μmol) in H_2O (2 mL), ^{t}BuOH (1 mL), and CH_2Cl_2 (1 mL) to give **15b** as an orange−brown solid (43.5 mg, 98% yield); mp 153−156 °C. IR 3116, 2924, 2854 1678, 1454, 1246, 1038, 822, 744 cm^{-1}. ^1H NMR (360 MHz, $CDCl_3$) δ 1.20−1.42 (m, 12 H), 1.93 (m, 4 H), 4.35 (t, 4 H J = 7.27 Hz), 4.38 (m, 4 H), 4.53 (m, 4 H), 4.66 (m, 4 H), 4.82 (m, 4 H), 7.46 (s, 2 H), 9.70 (s, 2 H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 26.40, 28.86, 29.17, 30.19, 50.34, 67.98, 69.95, 70.97, 74.45, 77.93, 79.95, 119.42, 144.45, 193.56. HPLC system A (245 nm) purity 96% (t_R = 20.8 min). APCI-MS calcd m/z for $C_{36}H_{40}Fe_2N_6O_2$: 700.4, found 701 $(M + H)^+$.

1′,1′′-[Dodecane-1,12-diylbis(1*H*-1,2,3-triazole-1,4-diyl)]diferrocene-1-carbaldehyde (15c). Compound **15c** was prepared according to the protocol of **15a** using a suspension of **11** (31.0 mg, 130 μmol), 1,12-diazidododecane (10.9 mg, 43.2 μmol), sodium ascorbate (1.70 mg, 8.58 μmol), and copper sulfate pentahydrate (0.6 mg, 2.40 μmol) in H_2O (2 mL), ^{t}BuOH (1 mL), and CH_2Cl_2 (1 mL) to give **15c** as an orange solid (30.0 mg, 95% yield); mp 112−114 °C. IR 3116, 2927, 2854 1678, 1454, 1242, 1045, 825, 744 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$) δ 1.20−1.40 (m, 16 H), 1.93 (m, 4 H), 4.35 (t, 4 H, J = 7.37 Hz), 4.38 (m, 4 H), 4.53 (m, 4 H), 4.67 (m, 4 H), 4.83 (m, 4 H), 7.47 (s, 2 H), 9.71 (s, 2 H). ^{13}C NMR (90 MHz, $CDCl_3$) δ 26.46, 28.94, 29.32, 29.37, 30.23, 50.40, 68.02, 69.98, 71.00, 74.48, 77.96, 79.98, 119.43, 144.46, 193.57. APCI-MS calcd m/z for $C_{38}H_{44}Fe_2N_6O_2$: 728.5 found 729 $(M + H)^+$.

1,1′-[Biphenyl-4,4′-diylbis(methylene-1*H*-1,2,3-triazole-1,4-diylferrocene-1,1′-diylmethylene)]bis[4-(2-methoxyphenyl)piperazine] (16a). A solution of **15a** (20 mg, 27 μmol), 1-(2-methoxyphenyl)piperazine (16 mg, 83 μmol), and $Na(OAc)_3BH$ (24 mg, 0.11 mmol) in anhydrous CH_2Cl_2 (6 mL) was stirred at room temperature overnight. The reaction mixture was quenched with saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2. The combined organic layers were dried (Na_2SO_4) and evaporated. The residue was purified by flash chromatography (CH_2Cl_2:MeOH 98:2−95:5) to give **16a** as an orange solid (21.9 mg, 74% yield); mp 238−240 °C (decomposition). IR 2925, 1591, 1498, 1450, 1240, 1024, 910, 802, 733, 663 cm^{-1}. ^1H NMR (360 MHz, $CDCl_3$ + 0.5% HCOOH) δ 2.80 (m, 4 H), 3.05 (m, 4 H), 3.18−3.41 (m, 8 H), 3.64 (s, 4 H), 3.80 (s, 6 H), 4.23 (m, 8 H), 4.32 (m, 4 H), 4.73 (m, 4 H), 5.60 (s, 4 H), 6.75−6.96 (m, 6 H), 6.99−7.09 (m, 2 H), 7.37−7.47 (m, 4 H), 7.51−7.66 (m, 6 H). ^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm): 49.28, 51.72, 53.77, 55.34, 56.71, 67.16, 69.35, 70.18, 72.14, 76.02, 79.77, 111.18, 118.37, 119.07, 121.01, 123.32, 127.76, 128.62, 134.33, 140.55, 140.58, 146.39, 152.15. HPLC system A (245 nm) purity 95% (t_R = 16.4 min). APCI-MS calcd m/z for $C_{62}H_{64}Fe_2N_{10}O_2$: 1092.9, found 1094 $(M + H)^+$.

1,1′-[Decane-1,10-diylbis(1*H*-1,2,3-triazole-1,4-diylferrocene-1,1′-diylmethylene)]bis[4-(2-methoxyphenyl)piperazine] (16b). Compound **16b** was prepared according to the protocol of **16a** using a solution of **15b** (20.3 mg, 29.0 μmol), 1-(2-methoxyphenyl)piperazine (16.7 mg, 87.0 μmol), and $Na(OAc)_3BH$ (25.7 mg, 116 μmol) in CH_2Cl_2 (7 mL). Purification by flash chromatography (CH_2Cl_2:MeOH 98:2) gave **16b** as an orange−brown solid (14.8 mg, 48% yield); mp 148−151 °C. IR 2931, 2819, 1500, 1454, 1238, 1026, 748 cm^{-1}. ^1H NMR (360 MHz, $CDCl_3$) δ 1.20−1.41 (m, 12 H), 1.91 (m, 4 H), 2.56 (m, 8 H), 3.03 (m, 8 H), 3.24 (s, 4 H), 3.82 (s, 6 H), 4.05 (m, 4 H), 4.10 (m, 4 H), 4.27 (m, 4 H), 4.33 (t, 4 H, J = 7.27 Hz), 4.68 (m, 4 H), 6.80−6.85 (m, 2 H), 6.86−6.92 (m, 4 H), 6.93−7.01 (m, 2 H), 7.45 (s, 2 H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 26.47, 28.91, 29.23, 30.33, 50.26, 50.31, 52.68, 55.33, 57.61, 66.99, 69.17, 69.76, 71.82, 76.02, 82.70, 111.15, 118.21, 118.62, 120.97, 122.89, 141.25, 146.07, 152.23. HPLC system A (245 nm) purity 96% (t_R = 17.0 min). APCI-MS calcd m/z for $C_{58}H_{72}Fe_2N_{10}O_2$: 1053.0, found 1054 $(M + H)^+$.

1,1′-[Dodecane-1,12-diylbis(1*H*-1,2,3-triazole-1,4-diylferrocene-1,1′-diylmethylene)]bis[4-(2-methoxyphenyl)piperazine] (16c). Compound **16c** was prepared according to the protocol of **16a** using a solution of **15c** (23.4 mg, 32.1 μmol), 1-(2-methoxyphenyl)piperazine (18.5 mg, 96.3 μmol), and $Na(OAc)_3BH$ (28.4 mg, 128 μmol) in CH_2Cl_2 (7 mL) to give **16c** as a yellow−orange oil (29.4 mg, 84% yield). IR 2927, 2854, 1593, 1500, 1454, 1242, 1026, 752 cm^{-1}. ^1H NMR (360 MHz, $CDCl_3$ + 0.5% HCOOH) δ 1.18−1.40 (m, 16 H), 1.93 (m, 4 H), 3.03 (m, 8 H), 3.22 (m, 8 H),

3.67 (s, 4 H), 3.82 (s, 6 H), 4.20 (m, 4 H), 4.24 (m, 4 H), 4.32 (m, 4 H), 4.33 (t, 4 H, $J = 7.38$ Hz), 4.75 (m, 4 H), 6.81−6.96 (m, 6 H), 6.98−7.06 (m, 2 H), 7.59 (s, 2 H). ^{13}C NMR (150 MHz, $CDCl_3$ + 0.5% HCOOH) δ 26.51, 28.98, 29.36, 29.42, 30.32, 47.81, 50.42, 50.56, 55.40, 55.66, 67.34, 69.51, 70.97, 72.47, 75.32, 76.76, 111.24, 118.66, 119.52, 121.14, 124.03, 139.43, 145.07, 152.03. HPLC system A (245 nm) purity 97% ($t_R = 17.8$ min). APCI-MS calcd m/z for $C_{60}H_{76}Fe_2N_{10}O_2$: 1081.0, found 1082 $(M + H)^+$.

Dopamine Receptor Binding Studies. Receptor binding studies were carried out as described.[31] In brief, the dopamine D1 receptor assay was done with porcine striatal membranes at a final protein concentration of 40 μg/assay tube and the radioligand [^{3}H]SCH 23390 at 0.3 nM (K_d = 0.41−0.58 nM). Competition experiments with human $D2_{long}$, $D2_{short}$,[28] D3,[29] and D4.4[30] receptors were run with preparations of membranes from CHO cells stably expressing the corresponding receptor and [^{3}H]spiperone at a final concentration of 0.1−0.2 nM. The assays were carried out at a protein concentration of 5−20 μg/assay tube and K_d values of 0.07−0.15, 0.05−0.13, 0.11−0.19, and 0.17−0.35 nM for the $D2_{long}$, $D2_{short}$, D3, and D4.4 receptors, respectively. Protein concentration was established by the method of Lowry using bovine serum albumin as standard.[37]

Data Analysis. The resulting competition curves of the receptor binding experiments were analyzed by nonlinear regression using the algorithms in PRISM 3.0 (GraphPad Software, San Diego, CA). The data were initially fit using a sigmoid model to provide an IC_{50} value, representing the concentration corresponding to 50% of maximal inhibition. IC_{50} values were transformed to K_i values according to the equation of Cheng and Prusoff.[38] In the fact of two individual measurements K_i was calculated as mean value in nM with the standard deviation (SD), while analyzing more than two single values the standard error of mean (SEM) was calculated as manner of confidence.

Mitogenesis Experiments. Determination of the intrinsic activity of the representative compound was carried out by measuring the incorporation of [^{3}H]thymidine into growing cells after stimulation with the test compound as described in the literature.[4,36] For this assay, D3 expressing CHO dhfr$^-$ cells as well as $D2_{long}$ and D4.2 expressing CHO100001 cells have been incubated with 0.02 μCi [^{3}H]thymidine per well (specific activity 25 μCi/mmol). Dose−response curves of 6−10 experiments have been normalized and pooled to get a mean curve from which the EC_{50} value and the maximum intrinsic activity of each compound could be compared to the effects of the full agonist quinpirole.

Acknowledgment. This work was supported by the Deutsche Forschungsgemeinschaft (DFG: Gm 13/8).

Supporting Information Available: Synthesis of compounds **17**−**20**, analytical data (^{1}H NMR, ^{13}C NMR, LC-MS, or HPLC spectra), receptor binding data employing porcine 5-HT_{1A}, 5-HT_2, and α_1 receptors of all target compounds and further mitogenesis experiments with **10b** at $D2_{long}$, and reference agents. This material is available free of charge via the Internet at http://pubs.acs.org.

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