Copper-catalyzed amination of (bromophenyl)ethanolamine for a concise synthesis of aniline-containing analogues of NMDA NR2B antagonist ifenprodil†

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An operationally simple and concise synthesis of anilinoethanolamines, as NMDA NR2B receptor antagonist ifenprodil analogues, was developed *via* a copper-catalyzed amination of the corresponding bromoarene. Coupling was achieved with linear primary alkylamines, α,ω-diamines, hexanolamine and benzophenone imine, as well as with aqueous ammonia, in good yields using CuI and *N*,*N*-diethylsalicylamide, 2,4-pentadione or 2-acetylcyclohexanone as catalytic systems. Amination with ethylene diamine was efficient even in the absence of an additive ligand, whereas no reaction occurred with ethanolamine whatever the conditions used. The anilinoethanolamines were evaluated as NR2B receptor antagonists in a functional inhibition assay. Aminoethylanilines displayed inhibition effects close to that of ifenprodil.

Introduction

The *N*-methyl-D-aspartate (NMDA) receptor is a ligand-gated cationic channel that plays a critical role in a wide range of physiological and pathological processes in the central nervous system, including memory, learning and cognition, as well as neurotoxicity associated to stroke and neurodegenerative (Alzheimer's and Parkinson's) diseases.[1] The structure of the NMDA receptor has been elucidated in great detail as a heterotetrameric complex made up of a combination of two major subunits, termed NR1 and NR2, based on the amino acid sequence identity. Eight splice variants of the NR1 subunit (a–h) as well as four variants of the NR2 subunit (A–D) have been characterized. It is clear that the pharmacological and functional properties of the NMDA receptor are highly dependent on the NR2 isoforms (mainly NR2A or NR2B) that are present in the receptor. At present, the NR2B sub-type NMDA receptor represents an essential molecular target for the understanding of cerebral pathologies and the development of new therapies.

Ifenprodil, from the phenylethanolamine class of compounds, has remained the antagonist of reference of NR2B receptors (Fig. 1).[2] It was clearly demonstrated that ifenprodil potency at NR2B was due to the key structural elements incorporating a phenolic aromatic ring connected to a benzylamine moiety *via* a linker of adequate length.[3] The stereochemistry of the ethanolamine linker was not found to be very crucial for the NR2B subunit binding. Ifenprodil was usually used in the *erythro* (*R***S** or "unlike") racemic form; the *threo* (*R***R** or "like") relative configuration was suggested to be important for NR2B receptor selectivity.[2,4]

In recent years, extensive effort has been made to develop ifenprodil-like molecules as pharmacotherapeutic agents and molecular tools in the study of NMDA receptors'

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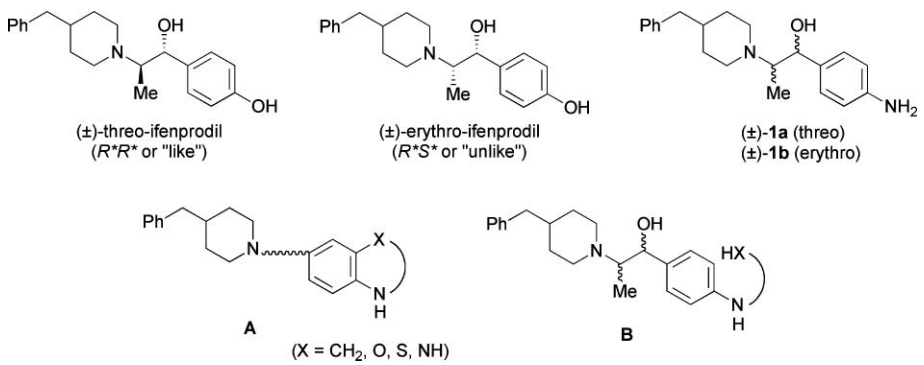
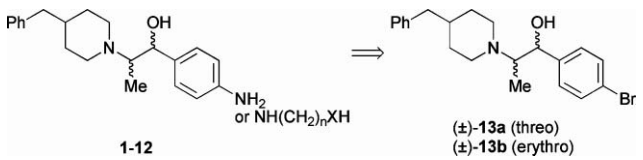


Fig. 1 Diastereoisomers of ifenprodil and anilines **1**, and general structure of analogues **A** and target molecules **B**.

physiopathology.[5] From the structure–activity relationship studies, the replacement of phenol by a nitrogen-bearing aryl moiety was identified as one of the structural requirements for improving the pharmacological profile of this class of NR2B ligands. Anilines **1** were proposed as potential probes to investigate the NR2B receptor active binding site,[6] and several heterocyclic derivatives of general formula **A** were found to display potent NR2B antagonistic activity[5] (Fig. 1). With the aim of developing selective NR2B receptor imaging agents, we focused on ifenprodil-based inhibitors possessing a functional group as an attachment point for a contrastophore. In this context, we considered the aniline-containing analogues **B** as valuable candidates (Fig. 1), and we designed anilines **1–12** bearing a linear alkyl chain of varied length (from two to twelve carbon atoms), eventually functionalized with a reactive function (hydroxyl or amine) for bioconjugation (Scheme 1). Therefore, we required an operationally simple and general protocol to access to such products.



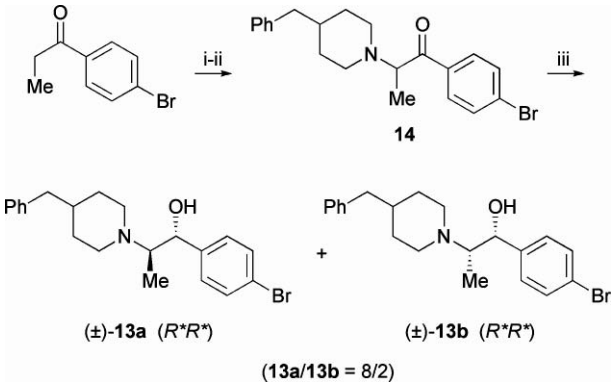
Scheme 1 Strategy for the synthesis of anilines **1–12** through transition metal-catalyzed amination reaction from aryl bromides **13**.

A synthetic scheme based on the reported preparations of anilines **1**, involving either a low yielding (17%) Friedel–Crafts reaction from acetanilide[6] or thiophenylation of a *para*-nitrophenylpropanaminodiol intermediate[7] as key steps, could not be regarded as an efficient and straightforward approach to *N*-substituted anilines **2–12**. For the last few years, transition metal-catalyzed amination of aryl halides broke through in the field of aminoarene synthesis.[8–10] This approach, investigated mainly on model compounds, has proven to be very efficacious and attractive due to the mild reaction conditions and the broad functional group tolerance. On the other hand, arylation of linear polyamines has remained less explored,[9d] and extension to provide access to primary anilines[11] from ammonia sources may represent a real challenge. Herein, we disclose our efforts towards the application of the amination methodology to the synthesis of anilinoethanolamines **1–12**, as well as our results for the evaluation of their NR2B receptor inhibition activity (Scheme 1).

Results and discussion

Synthesis of aryl bromide precursors 13a and 13b

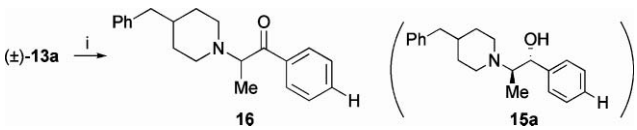
The aryl halides we chose as precursors were the (±)-(*R***R**)- and (±)-(*R***S**)-(bromophenyl)ethanolamines **13a** and **13b**, readily achieved starting from commercially available 4′-bromopropiophenone (Scheme 2).[12] Preparation occurred according to a three-step synthesis involving bromination, substitution with benzylpiperidine, then reduction. The use of sodium borohydride[2a] as the reducing agent led to a mixture of the easily separable (*R***R**) and (*R***S**) diastereoisomers in 80 : 20 ratio. Bromoarenes **13a** and **13b** were obtained in 63 and 15% overall yields respectively.



Scheme 2 Synthesis of aryl bromides **13a** and **13b**: (i) Br_2, CCl_4, rt, 1.5 h (99%); (ii) 4-benzylpiperidine, Et_3N, EtOH, 80 °C, 24 h (82%); (iii) $NaBH_4$, EtOH, rt, 24h (**13a**: 78%; **13b**: 19%).

Coupling with primary monoamines

Amination of aryl bromide **13a**, using *n*-propyl- and *n*-hexylamine as model primary amines, was first attempted under palladium catalysis[9e] (data not reported). Whatever the palladium source [Pd_2dba_3, $PdCl_2$(dppf), 1–5 mol%], the ligand (dppf, PPh_3, 2–10 mol%) or the base (tBuONa, 1–3 equiv.), the reactions carried out in refluxing dioxane or toluene always led to numerous unidentified degradation products. Although the formation of the hydrogenated analogue **15a** (Scheme 3) could be detected by mass spectra analyses of the crude products, it was clear from the ^{1}H NMR spectra that the main transformations occurred on the ethanolamine linker. These observations led us to examine the stability of the phenylethanolamine **13a** under palladium-catalyzed amination conditions (Table 1). Bromoarene **13a** was found unchanged after refluxing in dioxane with tBuONa (entry 1), whereas it was converted into phenone **16** in 65% yield when palladium catalyst [$PdCl_2$(dppf), with or without extra dppf]



Scheme 3 Conversion of aryl bromide **13a** into phenone **16**: (i) tBuONa (2 equiv.), $PdCl_2$(dppf) (2 mol%), dppf (0 or 4 mol%), dioxane, 110 °C, 18 h (65% isolated yield).

Table 1 Stability of bromoarene **13a**[a]

Entry	Base	Catalyst	Solvent	Bromoarene **13a** recovered (%)[b]
1	tBuONa	—	Dioxane	98
2	tBuONa	$PdCl_2$(dppf)[c]	Dioxane	<10[f]
3	tBuONa	$PdCl_2$(dppf)[c]/dppf[d]	Dioxane	<10[f]
4	tBuONa	CuI[e]	DMF	97
5	K_3PO_4	—	DMF	98
6	K_3PO_4	CuI[e]	DMF	97
7	K_3PO_4	$PdCl_2$(dppf)[c]	Dioxane	<10[g]

[a] Bromoarene **13a** (1 equiv.), base (2 equiv.), 110 °C in dioxane, or 90 °C in DMF, 18 h reaction time. [b] Isolated yield. [c] 2 mol%. [d] 4 mol%. [e] 20 mol%. [f] Formation of phenone **16** (65% isolated yield) and alcohol **15** (5% isolated yield). [g] Formation of phenone **16** (55% isolated yield) and alcohol **15** (30% isolated yield).

was added (Table 1, entries 2 and 3). Both the oxidation of the benzylic alcohol and the reduction of the bromophenyl moiety occurred under these conditions (Scheme 3). Palladium-catalyzed oxidation of the alcohol, which was proposed as resulting from a deprotonation of palladium-coordinated alcohol followed by a β-hydride elimination, usually needed a co-oxidant.[13] In the formation of phenone **16** under anaerobic conditions and in the absence of an added oxidant reagent, we can suspect that the aryl bromide moiety played such an oxidant role.[13a,14] As a remark, the palladium-induced oxidation of **13a** to phenone **16** also occurred using K_3PO_4 as the base, but to a lesser extent (entry 7). Attempts to carry out palladium-catalyzed amination from bromophenone **14** and *O*-protected bromoarene **13a** also failed (data not shown).

So, we turned to copper-mediated amination. As oxidation of benzylic alcohol could also occur under copper catalysis,[13c,15] we examined as preliminary experiments the stability of the starting ethanolamine **13a** under usual coupling conditions involving K_3PO_4 (2 equiv.) as base and CuI (20 mol%) as copper source in DMF at 90 °C (Table 1). Under nitrogen or air atmospheres, no conversion of **13a** was observed by reaction with K_3PO_4 alone (entry 5), or with CuI (entry 6). Ethanolamine **13a** was also found to be stable in tBuONa–CuI-containing medium (entry 4). In the absence of an additional ligand, aryl bromide **13a** was also inert in copper-catalyzed amination using *n*-propyl- and *n*-hexylamine (data not shown). These data prompted us to screen for appropriate ligands. Among the attractive, structurally simple, commercially available ligands we tested,[16] only *N*,*N*-diethylsalicylamide[10c], **L1**, and 2-acetylcyclohexanone,[10a] **L2**, were found to be efficient (Table 2). For the CuI–**L1** catalyst, coupling was low at 90 °C, whatever the amounts used (entries 1 and 4). At 130 °C, anilines **2a** and **3a** were obtained in 50% yield using at least 40 mol% of both CuI and **L1** (entries 2 and 5). By using the CuI–**L2** catalyst, yields for anilines **2a** and **3a** reached 50–53% under milder conditions, *i.e.* at 90 °C with 10 and 20 mol% of CuI and ligand, respectively (entries 3 and 6). The replacement of K_3PO_4 by Cs_2CO_3 led to yields that did not exceed 25%, and no coupling occurred at rt (data not shown). In all assays, no trace of oxidation product was detected. The only side products obtained, besides anilines, were the starting aryl bromide **13a**, recovered as the major by-product, and the hydrogenated analogue **15a**, formed in less than 10% yields.

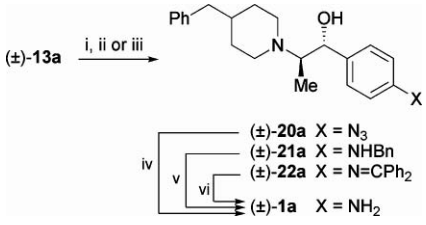
Given these results, we examined amination with functionalized aliphatic amines, using either CuI–**L1** (40/50 mol%) at 130 °C or CuI–**L2** (10/20 mol%) at 90 °C as reaction conditions. Coupling was achieved in 51% yield with hexanolamine according to the CuI–**L2**-based method (entry 11). Surprisingly, it did not exceed 15% yield with ethanolamine, whatever the protocol used (entries 7–10). Starting from *N*-Boc monoprotected hexyldiamine, no coupling product was formed under either conditions (entries 12 and 13).

Coupling with α,ω-diamines

Coupling was studied starting from unprotected α,ω-diamines for the synthesis of aminoanilines **7a–12a**. Whatever the length of the alkyl chain of the diamine (from 2 to 12 carbon atoms), the monoamination of bromoarene **13a** occurred in about 52–86% yields (Table 2). No traces of bis-coupling product were detected. Using the CuI–**L1** combination (requiring a temperature of 130 °C) and DMF as the solvent, formylation of the second amine function also took place, leading to the corresponding formamidoanilines **17a–19a** as major compounds (entries 14, 18 and 21). The desired aminoanilines **9a–12a** were obtained as the sole coupling products by carrying out amination in DMSO (entries 22, 28, 30 and 33). Using the CuI–**L2** catalyst that allowed reactions at a lower temperature (90 °C), coupling in DMF proceeded without formylation, leading exclusively to aminoanilines **7a–12a** in high yields (entries 15, 19, 23, 29, 31 and 34). Amination was found to be strongly dependent on the nature of the solvent, and the yields of aminoaniline **9a** decreased by changing the solvent according to the order DMF > dioxane > DMSO ≫ toluene (entry 23 compared to entries 26, 24 and 25 respectively). Extension of the reaction time from 24 to 48 h did not allow an improvement in coupling efficiency (data not shown). Contrary to ethanolamine, 1,2-ethylenediamine was found to be very reactive, even when using a very low amount of CuI and no additional ligand (entries 15–17 compared to entries 8–10). Ethylenediamine probably acted both as nucleophile and as ligand. None of the other α,ω-diamines used, possessing a longer alkyl chain, could display such a dual role (entries 20, 27 and 32).

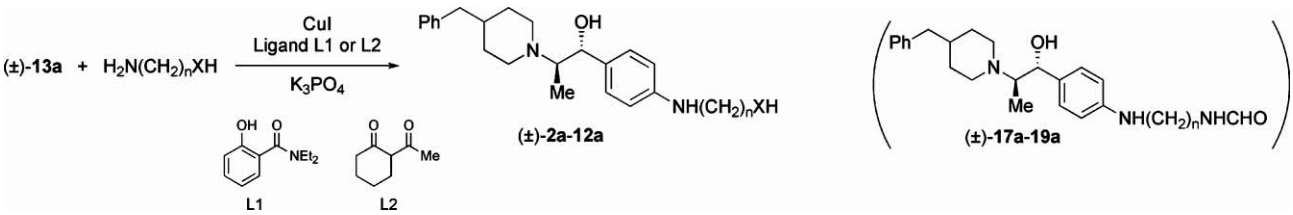
Synthesis of aniline 1a

We extended the copper-catalyzed coupling approach to the preparation of primary aniline **1a**, using the optimal catalyst CuI–**L2** in DMF, and several ammonia surrogates or aqueous ammonia (Scheme 4). First, coupling was achieved with sodium azide,[17] and was followed by reduction with lithium aluminium hydride. Both the intermediate azide **20a** and aniline **1a** were formed in very poor yields (10 and 30%, respectively). All attempts to increase yields by changing the reaction conditions (reagent amounts, reaction time, temperature, solvent and nature of the ligand) failed (data not reported). Amination performed with benzylamine[10] led to the corresponding aniline **21a** in yields that did not exceed 26%, even by increasing the amounts of CuI and **L2** to 40 and 50 mol%, respectively, and by using benzylamine in excess (5 equiv.). After catalytic hydrogenation, aniline **1a** was obtained in only 9% yield from bromoarene **13a**. Coupling with benzophenone imine[18] afforded imine **22a** in 80% yield using CuI–**L2** catalyst at 40/50 mol%. Imine **22a** was then converted to aniline **1a** by treatment with hydroxylamine in 72% yield (58% overall yield from bromoarene **13a**). Finally, amination using



Scheme 4 Synthesis of aniline **1a**: (i) NaN_3, $BnNH_2$ or $HN{=}CPh_2$ (5 equiv.), CuI (40 mol%), **L2** (50 mol%), K_3PO_4 (2 equiv.), DMF, 90 °C, 48 h (**20a**: 10%, **21a**: 26%, **22a**: 80%); (ii) 28% aqueous NH_3 (5 equiv.), CuI (10 mol%), **L2** (60 mol%), K_3PO_4 or Cs_2CO_3 (2 equiv.), DMF, 90 °C, 18 h (**1a**: 28% or 43%); (iii) 28% aqueous NH_3 (5 equiv.), CuI (10 mol%), 2,4-pentadione (60 mol%), Cs_2CO_3 (2 equiv.), DMF, 90 °C, 18 h (**1a**: 65%); (iv) $LiAlH_4$, THF, rt, 24 h (30%); (v) H_2 (50 bar), Pd/C, THF, 60 °C, 72 h (35%); (vi) $NH_2OH{\cdot}HCl$, CH_3CO_2Na, MeOH, rt, 24 h (72%).

Table 2 Copper-catalyzed amination of bromoarene **13a**[a]



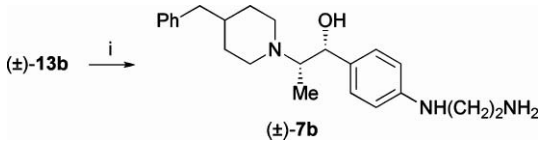
	$H_2N(CH_2)_nXH$								
Entry	X	*n*	equiv	CuI (mol%)	Ligand (mol%)	Solvent	*T*/°C	Aniline	Yield (%)[b]
1	CH_2	2	1.5	40	**L1** (30)	DMF	90 or 130	**2a**	<5[c]
2			1.5	10	**L1** (50)	DMF	130	**2a**	50
3			1.5	10	**L2** (20)	DMF	90	**2a**	53
4	CH_2	5	1.2	40	**L1** (40)	DMF	90	**3a**	10
5			1.5	40	**L1** (40)	DMF	130	**3a**	50
6			1.5	10	**L2** (20)	DMF	90	**3a**	50
7	O	2	2	40	**L1** (40)	DMF	130	**4a**	5[d]
8			2	10	**L2** (20)	DMF	90	**4a**	5[d]
9			2	20	—	DMF	90	**4a**	<5[c]
10			5	20	—	DMF	90	**4a**	15[c]
11	O	6	2	40	**L1** (40)	DMF	130	**5a**	51
12	NBoc	6	2	40	**L1** (40)	DMF	130	**6a**	—[e]
13			2	10	**L2** (20)	DMF	90	**6a**	—[e]
14	NH	2	5	40	**L1** (50)	DMF	130	**7a**	35[f]
15			5	10	**L2** (20)	DMF	90	**7a**	68
16			5	40	—	DMF	90	**7a**	86
17			5	10	—	DMF	90	**7a**	84
18	NH	4	5	10	**L1** (50)	DMF	130	**8a**	15[g]
19			5	40	**L2** (20)	DMF	90	**8a**	61
20			5	10	—	DMF	90	**8a**	—
21	NH	6	5	40	**L1** (50)	DMF	130	**9a**	8[h]
22			5	40	**L1** (50)	DMSO	130	**9a**	42
23			5	10	**L2** (20)	DMF	90	**9a**	62
24			5	10	**L2** (20)	DMSO	90	**9a**	45
25			5	10	**L2** (20)	Toluene	90	**9a**	10
26			5	10	**L2** (20)	Dioxane	90	**9a**	56
27			5	10	—	DMF	90	**9a**	—
28	NH	8	5	40	**L1** (50)	DMSO	130	**10a**	54
29			5	10	**L2** (20)	DMF	90	**10a**	58
30	NH	10	5	40	**L1** (50)	DMSO	130	**11a**	53
31			5	10	**L2** (20)	DMF	90	**11a**	57
32			5	10	—	DMF	90	**11a**	—
33	NH	12	5	40	**L1** (50)	DMSO	130	**12a**	52
34			5	10	**L2** (20)	DMF	90	**12a**	55

[a] Bromoarene (**13a**) (1 equiv.), K_3PO_4 (2 equiv.), 24 h reaction time. [b] Isolated yields. [c] ArBr (**13a**) recovered. [d] Low conversion and difficult purification. [e] Unidentified products. [f] Isolation of the corresponding formamidoaniline **15a** in 38% yield. [g] Isolation of the corresponding formamidoaniline **16a** in 41% yield. [h] Isolation of the corresponding formamidoaniline **17a** in 30% yield.

aqueous ammonia and CuI–**L2** catalyst at 10/60 mol% succeeded in 28% yield. The yield of aniline **1a** increased to 43% by changing K_3PO_4 for Cs_2CO_3, and reached 65% under the recently reported conditions[11g] using 2,4-pentadione instead of **L2**.[19] The latter coupling was revealed as a very efficient synthesis of aniline **1a** compared to those reported.[6,7] The sequence with benzophenone imine could represent an attractive alternative in the case of ammonia-sensitive substrates.

It is noteworthy that the amination reaction occurred, in all cases, without any epimerization. The stereochemistry of the anilines **1a–12a** and **17a–19a** was unchanged compared to that of bromoarene **13a**. The *erythro* (*R***S** or "unlike") aniline **7b**

could be obtained in the same manner, starting from the *erythro* diastereoisomer of bromoarene **13b** (Scheme 5).



Scheme 5 Synthesis of (±)-(*R**,*S**)-aniline **7b**: (i) $H_2N(CH_2)_2NH_2$ (5 equiv.), CuI (10 mol%), K_3PO_4 (2 equiv.), DMF, 90 °C, 24 h (82%).

NMDA NR2B receptor inhibition studies

The antagonistic efficiency for the NR2B subunit of ifenprodil (*threo* and *erythro* isomers taken separately as reference compounds)[2a] and anilines **1a–5a**, **7a–12a** and **7b** (used in their ammonium hydrochloride form or as neutral anilines) was evaluated through the monitoring of the intracellular calcium concentration under videomicroscopy in HEK-293 cells transfected with the cDNA encoding for NR1-1A and NR2B. As NMDA receptors are calcium-permeable ion channels and critical for glutamatergic synaptic transmission,[20] we measured calcium influx induced by the application of NMDA (at 100 µM for 30 s) in the presence of increasing concentrations of potential antagonists. HEK cells, successfully transfected with NR1/NR2B-GFP subunits, display a green fluorescence. In these GFP positive HEK cells, the application of NMDA induced a rapid and sustained increase in $[Ca^{2+}]_i$ (determined as 100% value). Following a 5 min rinse with HBBSS, *erythro*-, *threo*-ifenprodil and its analogues **1a–5a**, **7a–12a** and **7b** (used at 10 µM in HBBSS) were applied for 1 min before and during NMDA application. The results are presented in Fig. 2. Incubation with *erythro*-ifenprodil reduced with a dose–response relationship the amplitude of NMDA-induced $[Ca^{2+}]_i$, with a maximum effect corresponding to 11.16 ± 1.87% ($p < 0.0001$) of NMDA-induced $[Ca^{2+}]_i$. Close values were obtained with *threo*-ifenprodil (21.53 ± 1.48%; $p < 0.0001$), showing that the stereochemistry had no significant influence on the functional NR2B subunit binding. We did not observe a significant difference between the non-substituted aniline **1a** (18.60 ± 3.46%; $p < 0.0001$) and each diastereoisomer of ifenprodil. These results confirmed that the replacement of the phenol by the primary aniline ring had not modified the NR2B receptor inhibition properties. Within the *N*-substituted anilines, both the nature and the length of the substituent were crucial to retain receptor binding properties. Alkyl groups were detrimental (>90% NMDA response found for *N*-propyl- and hexylanilines **2a** and **3a**), as well as hydroxy and aminoalkyl long chains to a slightly lesser extent (>68% NMDA response for hydroxy and aminoalkylanilines **5a**, **9–12a** at 6, 8, 10 and 12 carbon atoms). Hydroxyethyl, aminoethyl and aminobutylanilines **4a** (44.46 ± 3.44%; $p < 0.001$), **7a** (39.03 ± 3.97%; $p < 0.001$) and **8a** (47.71 ± 2.21%; $p < 0.001$), respectively, reduced NMDA responses with high magnitude. Both the *threo* and *erythro* aminoethylanilines, **7a** (39.03 ± 3.97%; $p < 0.001$) and **7b** (35.69 ± 3.64%; $p < 0.001$), were found to be potent NR2B receptor inhibitors, with NMDA responses close to those of aniline **1a** and ifenprodil.

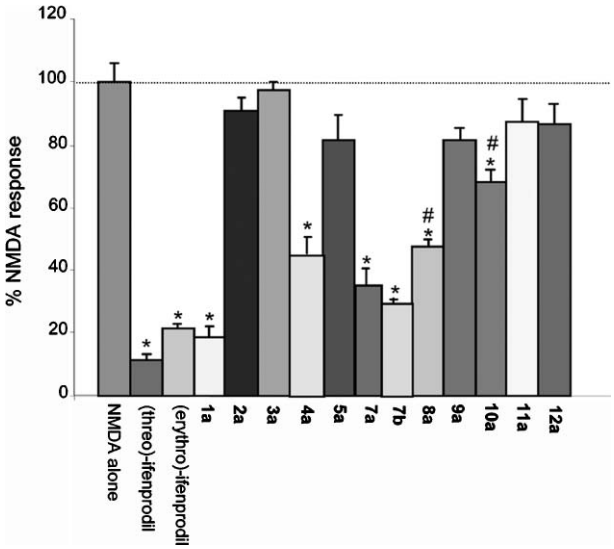


Fig. 2 Effect of ifenprodil analogues on NMDA-induced calcium influx. Histograms represent quantification of the calcium influx during 2 min from the beginning of 100 µM NMDA application (30 s) from three independent experiments ± s.e.m. ($n = 3$). Responses to the compounds' application were normalized to NMDA 100 µM mean value. * indicates significantly different from the NMDA alone; # indicates significantly different from *erythro*-ifenprodil and NMDA alone.

Conclusion

In summary, we have shown that the copper-mediated amination with alkylamines, hexanolamine, alkyldiamines, benzophenone imine and aqueous ammonia could be efficiently applied to the easily prepared bromoarene **13** and constituted an efficient, operationally simple route to anilinoethanolamines **1–12**. We found that this coupling reaction was very ligand-sensitive, except with ethylene diamine, and some unexpected failures (notably with ethanolamine) were encountered. This work complemented the scope of the copper-catalyzed amination methodology and illustrated once more the beneficial impact of this approach compared with the pallado-catalyzed version. The aminoethylanilines **7** were found to be active in an NR2B receptor inhibition functional assay, and could be exploited for imaging agents elaboration. Further applications of the amination reaction for the synthesis of new generations of aniline analogues as potent NR2B antagonists are under way, and will be reported in due course.

Experimental

General synthesis methods

All reactions were performed under anhydrous conditions and an atmosphere of nitrogen. All reagents were purchased from Acros Organics, Fluka or Sigma-Aldrich and were used as commercially supplied. Anhydrous *N*,*N*-dimethylformamide (DMF) was distilled from calcium hydride under nitrogen prior to use. Flash column chromatography was carried out on silica gel (Merck Kieselgel 60 F_{254}, 40–63 µm). Analytical thin layer chromatography (TLC) was performed on Merck aluminium-backed plates precoated with silica (0.2 mm, 60 F_{254}), which were visualized by quenching of ultraviolet fluorescence ($\lambda = 254$ and 366 nm). Melting points were determined on a Barnstead Electrothermal

IA 9100 Mp apparatus and are uncorrected. Infrared spectra were recorded on a Thermo Nicolet 350 FT-IR ATR spectrometer. Only selected absorbances are reported (ν in cm^{-1}). ^1H NMR spectra were recorded at either 250 or 400 MHz on Brucker DPX 250 or DPX 400. Chemical shifts (δ) are quoted in parts per million (ppm) and referenced to tetramethylsilane (TMS). Coupling constants (J) are given in Hz and reported to the nearest 0.5 Hz. Coupling patterns are abbreviated as follows: s (singlet), d (doublet), t (triplet), q (quadruplet), qt (quintuplet), sex (sextuplet), m (multiplet). ^{13}C NMR spectra were recorded at 62.9 or 100.6 MHz on Brucker DPX 250 or DPX 400. Chemical shifts (δ) are quoted in parts per million (ppm) and referenced to tetramethylsilane (TMS). MS and high resolution mass spectra (HRMS) were recorded using a Waters Q-TOF micro spectrometer by electrospray ionisation (ESI). Relative intensities are given in brackets. Elemental analyses were performed on a ThermoQuest analyser CHNS and were given within ± 0.4% of the calculated values. Syntheses of bromoarenes **13a** and **13b**, aniline **21a** and imine **22a**, and biological experimental procedures are given in the ESI.†

General procedure for copper-catalyzed amination reactions

Method A. CuI (0.4 equiv.), *N*,*N*-diethylsalicylamide (**L1**, 0.4 equiv.), aryl bromide **13a** or **13b** (1 equiv.) and potassium triphosphate (2 equiv.) were added to a screw-capped tube with a Teflon-lined septum. The tube was then evacuated and backfilled with nitrogen. Amine (1.4–2 equiv.), aminoalcohol (2–5 equiv.) or diamine (5 equiv.) and dry DMF (0.5 mL for 1.0 mmol of aryl bromide **13**) were added by syringe at rt. The reaction mixture was stirred at 130 °C for 24 h, then allowed to reach rt. Dichloromethane, water and NH_4OH (respectively 10, 10 and 1 mL for 0.5 mL of DMF) were added. After extraction with dichloromethane, the combined organic layers were washed with brine and dried over $MgSO_4$. The solvent was removed *in vacuo*, and the crude residue was purified by flash column chromatography on silica gel to afford the desired product.

Method B. CuI (0.1 equiv.), 2-acetylcyclohexanone (**L2**, 0.2 equiv.), aryl bromide **13a** or **13b** (1 equiv.) and potassium triphosphate (2 equiv.) were added to a screw-capped tube with a Teflon-lined septum. The tube was then evacuated and backfilled with nitrogen. Amine (1.4 or 2 equiv.) or diamine (5 equiv.) and dry DMF (0.5 mL for 1.0 mmol of aryl bromide **13**) were added by syringe at rt. The reaction mixture was stirred at 90 °C for 24 h, then allowed to reach rt. Dichloromethane, water and NH_4OH (respectively 10, 10 and 1 mL for 0.5 mL of DMF) were added. After extraction with dichloromethane, the combined organic layers were washed with brine and dried over $MgSO_4$. The solvent was removed *in vacuo* and the residue was purified by flash column chromatography on silica gel to afford the desired product.

(*1R**,*2R**)-2-(4-Benzylpiperidin-1-yl)-1-(4-propylaminophenyl)propan-1-ol 2a

Obtained from aryl bromide **13a** (106 mg, 273 µmol) and propylamine (32 mg, 546 µmol) as a yellow solid (50 mg, 50%) according to method A. Mp 80 °C. R_f 0.12 (ethyl acetate–heptanes 50 : 50). ^1H NMR ($CDCl_3$, 400 MHz) δ 7.33-7.28 (m, 2H), 7.22-7.14 (m, 5H), 6.59 (d, J = 8.8 Hz, 2H), 4.14 (d, J = 9.6 Hz, 1H), 3.09 (t, J = 7.2 Hz, 2H), 2.88-2.82 (m, 1H), 2.72-2.65 (m, 1H), 2.58 (d, J = 7.2 Hz, 2H), 2.60-2.48 (m, 2H), 2.11-2.05 (m, 1H), 1.73-1.69 (m, 2H), 1.67 (sext, J = 7.2 Hz, 2H), 1.61-1.53 (m, 1H), 1.48-1.38 (m, 1H), 1.32-1.26 (m, 3H), 1.01 (t, J = 7.2 Hz, 3H), 0.73 (d, J = 6.8 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 148.5, 141.1, 130.9, 129.5, 128.7, 128.6, 126.2, 112.9, 74.3, 67.0, 46.3, 44.8, 43.6, 38.7, 33.4, 33.0, 23.1, 12.0, 8.3. IR (cm^{-1}) 3342, 2955, 2927, 2873, 1614, 1522, 1453, 1289, 1148, 1082, 1016, 815, 741, 697, 543. ESI^+/MS/MS m/z (%) 367.4 ([M + H]$^+$, 55), 349.4 (100). ESI^+/HRMS calcd for $C_{24}H_{35}N_2O$ 367.2749; found 367.2732.

The ammonium salt of piperidine **2a** was obtained as a white solid after stirring in diethyl ether (5 mL) with HCl in diethyl ether (1 M, 2 mL) for 30 min. Anal. calcd for $C_{24}H_{34}N_2O$·1.1HCl, C, 70.89, H, 8.70, N, 6.89; found C, 70.91, H, 9.08, N, 6.63.

(*1R**,*2R**)-2-(4-Benzylpiperidin-1-yl)-1-(6-hexylaminophenyl)propan-1-ol 3a

Obtained from aryl bromide **13a** (113 mg, 290 µmol) and hexylamine (41 mg, 406 µL) as an orange oil (60 mg, 50%) according to method A or B. R_f 0.18 (ethyl acetate–heptanes 50 : 50). ^1H NMR ($CDCl_3$, 400 MHz) δ 7.33-7.28 (m, 2H), 7.22-7.14 (m, 5H), 6.58 (d, J = 8.8 Hz, 2H), 4.14 (d, J = 9.6 Hz, 1H), 3.10 (t, J = 7.2 Hz, 2H), 2.88-2.82 (m, 1H), 2.72-2.65 (m, 1H), 2.58 (d, J = 7.2 Hz, 2H), 2.60-2.48 (m, 2H), 2.11-2.05 (m, 1H), 1.73-1.69 (m, 2H), 1.68-1.50 (m, 3H), 1.49-1.25 (m, 10H), 0.91 (m, 3H), 0.73 (d, J = 6.8 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 148.6, 141.0, 132.6, 129.5, 128.7, 128.6, 126.2, 112.9, 74.4, 68.4, 44.8, 44.5, 43.6, 38.7, 33.4, 32.9, 32.0, 30.0, 27.3, 26.0, 23.1, 14.5, 8.3. IR (cm^{-1}) 2923, 1600, 1448, 1380, 1291, 1233, 1179, 1119, 1070, 1019, 747, 701, 591, 552. ESI^+/MS/MS m/z (%) 409.5 ([M + H]$^+$, 60), 391.5 (100). ESI^+/HRMS calcd for $C_{27}H_{41}N_2O$ 409.3219; found 409.3199.

The ammonium salt of piperidine **3a** was obtained as a white solid after stirring in diethyl ether (5 mL) with HCl in diethyl ether (1 M, 2 mL) for 30 min. Anal. calcd for $C_{27}H_{40}N_2O$·1.8HCl, C, 68.12, H, 9.23; found, C, 68.53, H, 9.57.

(*1R**,*2R**)-6-{4-[2-(4-Benzylpiperidin-1-yl)-1-hydroxypropyl]phenylamino}ethan-1-ol 4a

Obtained from aryl bromide **13a** (195 mg, 502 µmol) and ethanolamine (75 mg, 2.51 mmol) as a yellow oil (27 mg, yield 15%) according to method A. R_f 0.80 (dichloromethane–methanol 90 : 10). ^1H NMR ($CDCl_3$, 400 MHz) δ 7.23-7.05 (m, 7H), 6.51 (d, J = 8.4 Hz, 2H), 4.04 (d, J = 9.6 Hz, 1H), 3.70 (t, J = 5.2 Hz, 2H), 3.16 (t, J = 5.2 Hz, 2H), 2.75-2.70 (m, 1H), 2.62-2.59 (m, 1H), 2.51-2.40 (m, 4H), 1.64-1.61 (m, 2H), 1.48-1.45 (m, 1H), 1.35-1.31 (m, 1H), 1.22-1.21 (m, 1H), 0.64 (d, J = 6.4 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 147.8, 140.4, 131.0, 129.1, 128.4, 128.2, 125.8, 113.0, 66.5, 61.2, 52.8, 46.2, 44.4, 43.2, 38.3, 32.9, 32.5, 29.7. IR (cm^{-1}) 3353, 2916, 1615, 1522, 1054, 734, 699. ESI^+/MS/MS m/z (%) 369.3 ([M + H]$^+$, 75), 351.3 (100). ESI^+/HRMS calcd for $C_{23}H_{33}N_2O_2$ 369.2542; found 369.2548.

The ammonium salt of piperidine **4a** was obtained as a yellow solid after stirring in THF (2 mL) with HCl in diethyl ether (2M, 1 mL) for 1 h. Anal. calcd for $C_{27}H_{40}N_2O_2$·2HCl·2.5 H_2O·0.5 Et_2O, C, 57.35, H, 8.47, N, 5.35; found, C, 56.91, H, 8.83, N, 5.79.

(*1R*,2R)-6-{4-[2-(4-Benzylpiperidin-1-yl)-1-hydroxypropyl]phenylamino}hexan-1-ol 5a**

Obtained from aryl bromide **13a** (125 mg, 320 μmol) and 6-aminohexan-1-ol (75 mg, 640 μmol) as a brown oil (70 mg, yield 51%) according to method A. R_f 0.80 (dichloromethane–methanol 90 : 10). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.32-7.15 (m, 7H), 6.58 (d, J = 8.8 Hz, 2H), 4.15 (d, J = 9.6 Hz, 1H), 3.66 (t, J = 7.0 Hz, 2H), 3.12 (t, J = 7.0 Hz, 2H), 2.88-2.83 (m, 1H), 2.81-2.62 (m, 2H), 2.58 (d, J = 6.8 Hz, 2H), 2.58-2.51 (m, 2H), 2.16-2.11 (m, 1H), 1.75-1.71 (m, 2H), 1.64-1.55 (m, 5H), 1.44-1.39 (m, 9H), 0.75 (d, J = 6.4 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 152.2, 139.6, 129.7, 129.5, 128.7, 128.6, 126.3, 113.0, 74.3, 66.9, 63.3, 53.8, 46.5, 44.7, 44.4, 33.2, 33.1, 32.2, 29.9, 27.3, 26.0, 8.2. IR (cm^{-1}) 2958, 2926, 2858, 1727, 1456, 1271, 1122, 1071, 744, 703. ESI$^+$/MS/MS m/z (%) 425.4 ([M + H]$^+$, 53), 407.4 (100). ESI$^+$/HRMS calcd for $C_{27}H_{41}N_2O_2$ 425.3168; found 425.3188.

The ammonium salt of piperidine **5a** was obtained as a white solid after stirring in diethyl ether (5 mL) with HCl in diethyl ether (1M, 2 mL) for 30 min. Anal. calcd for $C_{27}H_{40}N_2O_2$·HCl, C, 70.33, H, 8.96, N, 6.07; found, C, 70.83, H, 9.18, N, 6.61.

(*1R*,2R)-*N*-(2-{4-[2-(4-Benzylpiperidin-1-yl)-1-hydroxypropyl]phenylamino}ethyl) formamide 15a**

Obtained from aryl bromide **13a** (107 mg, 270 μmol) and 1,2-ethylenediamine (97 mg, 1.62 mmol) as an orange oil (60 mg, 60%) according to method A. R_f 0.60 (dichloromethane–methanol–NH_4OH 95 : 5 : 0.5). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.12 (s, 1H), 7.32-7.24 (m, 2H), 7.23-7.14 (m, 5H), 6.58 (d, J = 8.8 Hz, 2H), 6.40 (bs, 3H), 4.13 (d, J = 9.6 Hz, 1H), 3.52-3.48 (m, 2H), 3.27 (t, J = 7.2 Hz, 2H), 2.88-2.82 (m, 1H), 2.75-2.71 (m, 1H), 2.62-2.54 (m, 4H), 2.14-2.10 (m, 1H), 1.75-1.71 (m, 2H), 1.71-1.51 (m, 1H), 1.49-1.38 (m, 1H), 1.38-1.22 (m, 1H), 0.74 (d, J = 6.8 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 162.4, 147.9, 141.0, 131.3, 129.5, 128.9, 128.6, 126.3, 113.1, 74.3, 66.8, 53.1, 44.9, 44.1, 43.6, 38.6, 38.1, 33.3, 32.8, 8.4. IR (cm^{-1}) 3274, 2926, 2850, 1669, 1614, 1525, 1334, 1139, 1018, 817, 744, 695, 546. ESI$^+$/MS/MS m/z (%) 396.4 ([M + H]$^+$, 25), 378.4 (100). ESI$^+$/HRMS calcd for $C_{24}H_{34}N_3O_2$ 396.2651; found 396.2641. Anal. calcd for $C_{24}H_{33}N_3O_2$·0.7H_2O, C, 70.63, H, 8.50, N, 10.30; found, C, 70.21, H, 8.65, N, 10.85.

(*1R*,2R)-1-[4-(4-Aminoethylamino)phenyl]-2-(4-benzylpiperidin-1-yl)propan-1-ol 7a**

Obtained from aryl bromide **13a** (141 mg, 360 μmol) and 1,2-ethylenediamine (159 mg, 1.80 mmol) as an orange oil (99 mg, 70%) according method B. R_f 0.17 (dichloromethane–methanol–NH_4OH 95 : 5 : 0.5). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.33-7.28 (m, 2H), 7.23-7.10 (m, 5H), 6.59 (d, J = 8.8 Hz, 2H), 4.10 (d, J = 9.6 Hz, 1H), 3.13-3.09 (m, 2H), 2.92-2.80 (m, 2H), 2.76-2.71 (m, 1H), 2.66-2.49 (m, 1H), 2.56-2.43 (m, 4H), 2.12-1.98 (m, 1H), 1.73-1.63 (m, 2H), 1.58-1.46 (m, 1H), 1.39-1.23 (m, 1H), 0.69 (d, J = 6.8 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 148.0, 140.7, 130.8, 129.1, 128.6, 128.4, 128.2, 125.8, 112.8, 73.9, 66.6, 52.8, 46.6, 44.4, 43.6, 43.2, 41.2, 38.3, 33.1, 32.7, 32.6, 7.9. IR (cm^{-1}) 2961, 2926, 1727, 1443, 1274, 1139, 1076, 1058, 931, 745, 699. ESI$^+$/MS/MS m/z (%) 368.3 ([M + H]$^+$, 92), 350.3 (100). ESI$^+$/HRMS calcd for $C_{23}H_{34}N_3O$ 368.2702; found 368.2704.

(*1R*,2S)-1-[4-(4-Aminoethylamino)phenyl]-2-(4-benzylpiperidin-1-yl)propan-1-ol 7b**

Obtained from aryl bromide **13b** (100 mg, 250 μmol) and 1,2-ethylenediamine (75 mg, 1.25 mmol) as an orange oil (77 mg, 87%) according to method B. R_f 0.34 (dichloromethane–methanol–NH_4OH 90 : 10 : 0.1). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.31-7.28 (m, 2H), 7.21-7.08 (m, 5H), 6.58 (d, J = 8.8 Hz, 2H), 4.70 (d, J = 4.4 Hz, 1H), 3.21-3.06 (m, 2H), 3.05-2.94 (m, 1H), 2.92-2.83 (m, 2H), 2.76-2.69 (m, 1H), 2.65-2.58 (m, 1H), 2.56-2.43 (m, 2H), 2.29-2.15 (m, 1H), 2.07-1.93 (m, 1H), 1.71-1.35 (m, 3H), 1.33-1.01 (m, 2H), 0.69 (d, J = 6.8 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 147.3, 140.7, 131.2, 129.2, 129.1, 128.2, 127.0, 125.8, 112.5, 72.3, 64.6, 52.6, 49.4, 46.6, 46.5, 43.7, 43.2, 41.1, 38.1, 32.6, 10.1. IR (cm^{-1}) 2961, 2926, 1727, 1443, 1274, 1139, 1076, 1058, 931, 745, 699. ESI$^+$/MS/MS m/z (%) 368.3 ([M + H]$^+$, 90), 350.3 (100). ESI$^+$/HRMS calcd for $C_{23}H_{34}N_3O$ 368.2702; found 368.2704.

(*1R*,2R)-*N*-(4-{4-[2-(4-Benzylpiperidin-1-yl)-1-hydroxypropyl]phenylamino}butyl) formamide 16a**

Obtained from aryl bromide **13a** (141 mg, 360 μmol) and 1,4-butanediamine (190 mg, 2.16 mmol) as an orange oil (58 mg, 41%) according to method A. R_f 0.38 (dichloromethane–methanol–NH_4OH 95 : 5 : 0.5). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.10 (s, 1H), 7.32-7.28 (m, 2H), 7.22-7.14 (m, 5H), 6.57 (d, J = 8.8 Hz, 2H), 6.05 (bs, 3H), 4.13 (d, J = 9.6 Hz, 1H), 3.40-3.22 (m, 2H), 3.14-3.11 (m, 2H), 2.88-2.82 (m, 1H), 2.73-2.68 (m, 1H), 2.62-2.54 (m, 4H), 2.14-2.10 (m, 1H), 1.75-1.68 (m, 2H), 1.68-1.51 (m, 5H), 1.49-1.38 (m, 1H), 1.38-1.22 (m, 1H), 0.74 (d, J = 6.8 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 161.8, 148.3, 141.0, 131.0, 129.5, 128.8, 128.6, 126.2, 113.1, 74.3, 66.9, 53.0, 50.0, 43.7, 43.6, 38.7, 38.3, 33.4, 32.9, 27.6, 27.1, 8.3. IR (cm^{-1}) 3309, 2927, 2848, 1661, 1614, 1522, 1382, 1321, 1140, 1045, 822, 744, 699, 545. ESI$^+$/MS/MS m/z (%) 424.4 ([M + H]$^+$, 35), 406.4 (100). ESI$^+$/HRMS calcd for $C_{26}H_{38}N_3O_2$ 424.2964; found 424.2944. Anal. calcd for $C_{26}H_{37}N_3O_2$·H_2O, C, 70.71, H, 8.90, N, 9.52; found, C, 70.60, H, 9.01, N, 9.70.

(*1R*,2R)-1-[4-(4-Aminobutylamino)phenyl]-2-(4-benzylpiperidin-1-yl)propan-1-ol 8a**

Obtained from aryl bromide **13a** (141 mg, 360 μmol) and 1,4-butanediamine (190 mg, 2.16 mmol) as an orange oil (86 mg, 61%) according to method B. R_f 0.17 (dichloromethane–methanol–NH_4OH 95 : 5 : 0.5). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.32-7.28 (m, 2H), 7.22-7.10 (m, 5H), 6.58 (d, J = 8.8 Hz, 2H), 4.18 (bs, 4H), 4.13 (d, J = 9.6 Hz, 1H), 3.04 (t, J = 7.2 Hz, 2H), 2.92-2.80 (m, 2H), 2.72-2.65 (m, 1H), 2.64-2.48 (m, 2H), 2.56 (d, J = 7.2 Hz, 2H), 2.12-2.04 (m, 1H), 1.75-1.51 (m, 8H), 1.49-1.22 (m, 2H), 0.70 (d, J = 6.8 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 148.6, 140.9, 130.2, 129.5, 128.7, 128.6, 126.3, 113.1, 74.2, 66.8, 53.0, 45.0, 43.7, 43.5, 40.5, 38.4, 33.0, 32.6, 26.8, 26.7, 8.5. IR (cm^{-1}) 2964, 2922, 1725, 1445, 1270, 1137, 1071, 1053, 939, 741, 697. ESI$^+$/MS/MS m/z (%) 396.4 ([M + H]$^+$, 65), 378.3 (100). ESI$^+$/HRMS calcd for $C_{25}H_{38}N_3O$ 396.3015; found 396.3003.

The ammonium salt of piperidine **8a** was obtained as a white solid after stirring in diethyl ether (5 mL) with HCl in diethyl ether (1M, 2 mL) for 30 min. Anal. calcd for $C_{25}H_{38}N_3O$·2.8HCl, C, 60.21, H, 8.25, N, 8.43; found, C, 60.55, H, 8.64, N, 8.81.

(*1R*,2R)-*N*-(6-{4-[2-(4-Benzylpiperidin-1-yl)-1-hydroxypropyl]phenylamino}hexyl) formamide 17a**

Obtained from aryl bromide **13a** (110 mg, 280 μmol) and 1,6-hexanediamine (195 mg, 1.68 mmol) as an orange oil (35 mg, 30%) according to method A. R_f 0.23 (dichloromethane–methanol–NH_4OH 95 : 5 : 0.5). ^1H NMR ($CDCl_3$, 400 MHz) δ 8.16 (s, 1H), 7.32-7.28 (m, 2H), 7.21-7.14 (m, 5H), 6.58 (d, J = 8.8 Hz, 2H), 5.70 (bs, 3H), 4.13 (d, J = 9.6 Hz, 1H), 3.35-3.27 (m, 2H), 3.11 (t, J = 7.2 Hz, 2H), 2.88-2.82 (m, 1H), 2.72-2.66 (m, 1H), 2.61-2.48 (m, 2H), 2.57 (d, J = 7.2 Hz, 2H), 2.12-2.06 (m, 1H), 1.75-1.48 (m, 7H), 1.47-1.27 (m, 6H), 0.72 (d, J = 6.8 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 161.6, 148.5, 141.1, 130.9, 129.5, 128.8, 128.6, 126.2, 113.0, 74.3, 66.9, 53.0, 48.0, 44.8, 44.3, 38.7, 38.4, 33.4, 33.0, 29.9, 29.8, 27.1, 27.0, 8.31. IR (cm^{-1}) 3309, 2927, 2854, 1663, 1614, 1522, 1382, 1320, 1142, 1045, 1020, 822, 699, 545. ESI^+/MS/MS m/z (%) = 340.3 ([M + H]$^+$, 32), 322.2 (100). ESI^+/HRMS calcd for $C_{28}H_{42}N_3O_2$ 452.3277; found 452.3264. Anal. calcd for $C_{28}H_{41}N_3O_2 \cdot 0.4H_2O$, C, 73.29, H, 9.18, N, 9.16; found, C, 73.18, H, 9.58, N, 9.63.

(*1R*,2R)-1-[4-(6-Aminohexylamino)phenyl]-2-(4-benzylpiperidin-1-yl)propan-1-ol 9a**

Obtained from aryl bromide **13a** (110 mg, 280 μmol) and 1,6-hexanediamine (195 mg, 1.68 mmol) as an orange oil (80 mg, 62%) according to method B. R_f 0.05 (dichloromethane–methanol–NH_4OH 95 : 5 : 0.5). ^1H NMR ($CDCl_3$, 400 MHz) δ 7.30-7.14 (m, 7H), 6.58 (d, J = 8.8 Hz, 2H), 4.13 (d, J = 9.6 Hz, 1H), 3.10 (t, J = 7.0 Hz, 2H), 3.00 (bs, 4H), 2.88-2.82 (m, 1H), 2.73 (t, J = 7.0 Hz, 2H), 2.72-2.65 (m, 1H), 2.57 (d, J = 6.8 Hz, 2H), 2.60-2.51 (m, 2H), 2.12-2.06 (m, 1H), 1.75-1.22 (m, 13H), 0.73 (d, J = 6.4 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 148.5, 141.0, 130.8, 129.5, 128.7, 128.6, 126.2, 112.9, 74.3, 66.9, 53.2, 44.8, 44.3, 43.6, 41.9, 38.7, 33.4, 32.9, 32.5, 29.8, 27.2, 26.9, 8.3. IR (cm^{-1}) 2963, 2921, 1724, 1444, 1269, 1070, 1052, 939, 741, 697. ESI^+/MS/MS m/z (%) 424.4 ([M + H]$^+$, 68), 406.4 (100). ESI^+/HRMS calcd for $C_{27}H_{42}N_3O$ 424.3328; found 424.3315.

The ammonium salt of piperidine **9a** was obtained as a white solid after stirring in diethyl ether (5 mL) with HCl in diethyl ether (1 M, 2 mL) for 30 min. Anal. calcd for $C_{27}H_{41}N_3O \cdot 3HCl$, C, 70.18, H, 9.60, N, 9.09; found, C, 70.63, H, 10.11, N, 9.78.

(*1R*,2R)-1-[4-(8-Aminooctylamino)phenyl]-2-(4-benzylpiperidin-1-yl)propan-1-ol 10a**

Obtained from aryl bromide **13a** (103 mg, 264 μmol) and 1,8-octanediamine (228 mg, 1.58 mmol) as an orange oil (70 mg, 58%) according to method B. R_f 0.04 (dichloromethane–methanol–NH_4OH 95 : 5 : 0.5). ^1H NMR ($CDCl_3$, 400 MHz) δ 7.32-7.14 (m, 7H), 6.57 (d, J = 8.8 Hz, 2H), 4.13 (d, J = 9.6 Hz, 1H), 3.50 (bs, 4H), 3.10 (t, J = 7.0 Hz, 2H), 2.88-2.82 (m, 1H), 2.71-2.67 (m, 3H), 2.60-2.48 (m, 4H), 2.12-2.06 (m, 1H), 1.73-1.71 (m, 2H), 1.71-1.27 (m, 15H), 0.72 (d, J = 6.4 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 148.6, 141.1, 130.8, 129.5, 128.7, 128.6, 126.2, 112.9, 74.3, 66.9, 53.2, 44.8, 44.5, 43.6, 42.1, 38.7, 33.4, 33.0, 29.9, 29.8, 29.7, 27.5, 27.2, 8.3. IR (cm^{-1}) 2958, 2926, 2857, 1724, 1462, 1271, 1123, 1073, 743. ESI^+/MS/MS m/z (%) 452.8 ([M + H]$^+$, 32), 434.8 (100). ESI^+/HRMS calcd for $C_{29}H_{46}N_3O$ 452.3641; found 452.3652.

Ammonium salt of piperidine **10a** was obtained as a white solid after stirring in diethyl ether (5 mL) with HCl in diethyl ether (1 M, 2 mL) for 30 min. Anal. calcd for $C_{29}H_{45}N_3O \cdot 2.9HCl$, C, 62.49, H, 8.66; found, C, 62.77, H, 8.79.

(*1R*,2R)-1-[4-(10-Aminodecylamino)phenyl]-2-(4-benzylpiperidin-1-yl)propan-1-ol 11a**

Obtained from aryl bromide **13a** (100 mg, 257 μmol) and 1,10-decanediamine (266 mg, 1.54 mmol) as a yellow oil (70 mg, yield 57%) according to method B. R_f 0.04 (dichloromethane–methanol–NH_4OH 95 : 5 : 0.5). ^1H NMR ($CDCl_3$, 400 MHz) δ 7.30-7.12 (m, 7H), 6.56 (d, J = 8.8 Hz, 2H), 4.11 (d, J = 9.6 Hz, 1H), 3.08 (t, J = 7.0 Hz, 2H), 3.06 (bs, 4H), 2.83-2.80 (m, 1H), 2.68 (t, J = 7.0 Hz, 2H), 2.58-2.50 (m, 5H), 2.12-2.06 (m, 1H), 1.71-1.68 (m, 2H), 1.61-1.18 (m, 19H), 0.71 (d, J = 6.4 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 148.6, 141.1, 130.7, 129.5, 128.7, 128.6, 126.2, 112.9, 74.3, 66.9, 50.6, 44.8, 44.5, 43.6, 42.3, 38.7, 33.5, 33.4, 33.0, 30.0, 29.9, 29.8, 27.5, 27.2, 8.3. IR (cm^{-1}) 2925, 2854, 1598, 1495, 1454, 1392, 1271, 1050, 1020, 746, 702, 592, 556. ESI^+/MS/MS m/z (%) 480.8 ([M + H]$^+$, 25), 462.8 (100). ESI^+/HRMS calcd for $C_{31}H_{50}N_3O$ 480.3954; found 480.3974.

The ammonium salt of piperidine **11a** was obtained as a white solid after stirring in diethyl ether (5 mL) with HCl in diethyl ether (1 M, 2 mL) for 30 min. Anal. calcd for $C_{31}H_{49}N_3O \cdot 3HCl \cdot 1.8H_2O$, C, 60.28, H, 9.42, N, 6.59; found, C, 60.12, H, 9.39, N, 6.49.

(*1R*,2R)-1-[4-(12-Aminododecylamino)phenyl]-2-(4-benzylpiperidin-1-yl)propan-1-ol 12a**

Obtained from aryl bromide **13a** (100 mg, 257 μmol) and 1,12-dodecanediamine (309 mg, 1.54 mmol) as a yellow oil (69 mg, 55%) according to method B. R_f 0.04 (dichloromethane–methanol–NH_4OH 95 : 5 : 0.5). ^1H NMR ($CDCl_3$, 400 MHz) δ 7.32-7.13 (m, 7H), 6.57 (d, J = 8.8 Hz, 2H), 4.12 (d, J = 9.6 Hz, 1H), 3.70 (bs, 4H), 3.08 (t, J = 7.0 Hz, 2H), 2.83-2.80 (m, 1H), 2.73 (t, J = 7.0 Hz, 2H), 2.72-2.67 (m, 1H), 2.58-2.50 (m, 4H), 2.12-2.06 (m, 1H), 1.72-1.28 (m, 25H), 0.72 (d, J = 6.4 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 148.6, 141.1, 130.8, 129.5, 128.7, 128.6, 126.2, 112.9, 74.3, 66.9, 53.2, 44.8, 44.5, 43.6, 42.2, 38.7, 36.2, 33.5, 33.0, 32.9, 30.0, 29.8, 29.7, 27.6, 27.2, 26.5, 24.5, 8.3. IR (cm^{-1}) 2923, 2852, 1725, 1598, 1455, 1384, 1272, 1071, 743, 701. ESI^+/MS/MS m/z (%) 508.9 ([M + H]$^+$, 36), 490.9 (100). ESI^+/HRMS calcd for $C_{33}H_{54}N_3O$ 508.4267; found 508.4265.

The ammonium salt of piperidine **12a** was obtained as a white solid after stirring in diethyl ether (5 mL) with HCl in diethyl ether (1 M, 2 mL) for 30 min. Anal. calcd for $C_{33}H_{53}N_3O \cdot 3HCl \cdot H_2O$ C, 62.40, H, 9.20; found, C, 62.55, H, 9.77.

(*1R*,2R)-1-(4-Aminophenyl)-2-(4-benzylpiperidin-1-yl)propan-1-ol 1a**

Obtained as a clear yellow solid (65 mg, yield 65%) from aryl bromide **13a** (120 mg, 0.31 mmol), CuI (5.8 mg, 31 μmol), 2,4-pentadione (18 mg, 0.186 mmol), aqueous ammonia (28%, 95 μL, 1.55 mmol) and Cs_2CO_3 (202 mg, 0.62 mmol) in DMF (600 μL) at 90 °C for 18 h according to method B. Mp 128 °C. R_f 0.2 (ethyl acetate). ^1H NMR ($CDCl_3$, 250 MHz) δ 7.90-7.13 (m, 7H), 6.62 (d, J = 8.3 Hz, 2H), 4.09 (d, J = 9.8 Hz, 1H), 2.83-2.79 (m, 1H), 2.63-2.53 (m, 1H), 2.51-2.43 (m, 4H), 2.06-2.00 (m, 1H),

1.70-1.65 (m, 2H), 1.63-1.23 (m, 3H), 0.69 (d, J = 6.7 Hz, 3H). ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 145.9, 140.6, 132.0, 129.1, 128.8, 128.4, 125.8, 114.9, 73.9, 66.6, 53.5, 44.4, 43.2, 38.3, 33.0, 32.5, 7.9. IR (cm^{-1}) 3332, 2958, 2922, 2890, 1610, 1518, 1443, 1238, 1148, 1094, 1069, 840, 740, 697, 538. ESI$^+$/MS/MS m/z (%) 325.5 ([M + H]$^+$, 43), 307.5 (100). ESI$^+$/HRMS calcd for $C_{21}H_{29}N_2O$ 325.2280; found 325.2289.

The ammonium salt of aniline **1a** was obtained as a white solid after stirring in diethyl ether (5 mL) with HCl in diethyl ether (1 M, 2 mL) for 30 min. Anal. calcd for $C_{21}H_{28}N_2O{\cdot}2.5HCl$, C, 60.69, H, 7.40, N, 6.74; found, C, 60.77, H, 7.72, N, 6.99.

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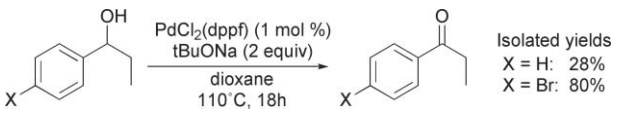

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