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Original article

Synthesis and biological evaluation of novel delta (δ) opioid receptor ligands with diazatricyclodecane skeletons

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2,7-Diazatricyclo[4.4.0.0^{3,8}]decane
Binding assays
Antinociceptive activity

ABSTRACT

Considering the interesting pharmacological profile of the delta (δ) selective opioid agonist compound SNC-80, conformationally constrained analogs containing two diazatricyclodecane ring systems in place of dimethylpiperazine core motif were synthesized.

The compounds showed subnanomolar or low nanomolar δ opioid receptor binding affinity. Depending upon the substituents on the diazatricyclodecane ring, these compounds displayed varying selectivity for δ opioid receptor over μ and κ receptors.

Amongst the novel compounds, **1Aa** showed the more interesting biological profile, with higher δ affinity and selectivity compared to SNC-80. The δ receptor agonist profile and antinociceptive activity of **1Aa** were confirmed using *ex-vivo* (isolated mouse vas deferens) and *in vivo* (tail flick) assays.

1. Introduction

The delta (δ) receptor is an opioid receptor (δ OR) that is broadly expressed in both the central nervous system and peripheral tissues and organs [1].

Although the biology and function of δ receptors are not completely understood [2], modulation of δ receptors in pre-clinical animal models has shown promising efficacy in conditions such as analgesia, addiction, Parkinson's disease, Alzheimer's disease, and seizure disorders [3–5]. Moreover, peripheral δ-opioid receptors seem to be involved in cancer [6], cardioprotection [7,8], gastrointestinal disorders [9], and weight loss [10].

The δ selective opioid ligands thus represent for pharmaceutical industry and academia attractive candidates for a broad range of pharmacological applications.

Several small-molecule ligands with high affinity and selectivity for δ receptors have been recently reported [11,12]. Examples of those compounds are typified by agonists such as SNC-80, TAN-67, and ADL-5859 (Fig. 1) [13–15] and antagonists such as CP-646,777, naltrindole, and naltriben [16–20].

Amongst the considerable number of reported δ opioid ligands [11,12], SNC-80 displayed an interesting pharmacological profile, with good binding affinity to δ receptor (nanomolar range) and remarkable δ selectivity relative to μ [13,21]. δ opioid mediated activity of this reference compound was successfully ascertained by *in vivo* assays [22–26]. Pre-clinical studies showed in particular SNC-80 efficacy towards acute pain [27], hypertension [28], Parkinson's disease [4,24], anxiety [22,29], depression [22], motor dysfunction and neuronal injury after spinal cord ischemia [30]. This unique biopharmacological profile makes it an attractive lead compound in the search for novel δ opioid receptor ligands.

In this context, our research has been focused on the design of conformationally restricted analogs of SNC-80 in which the

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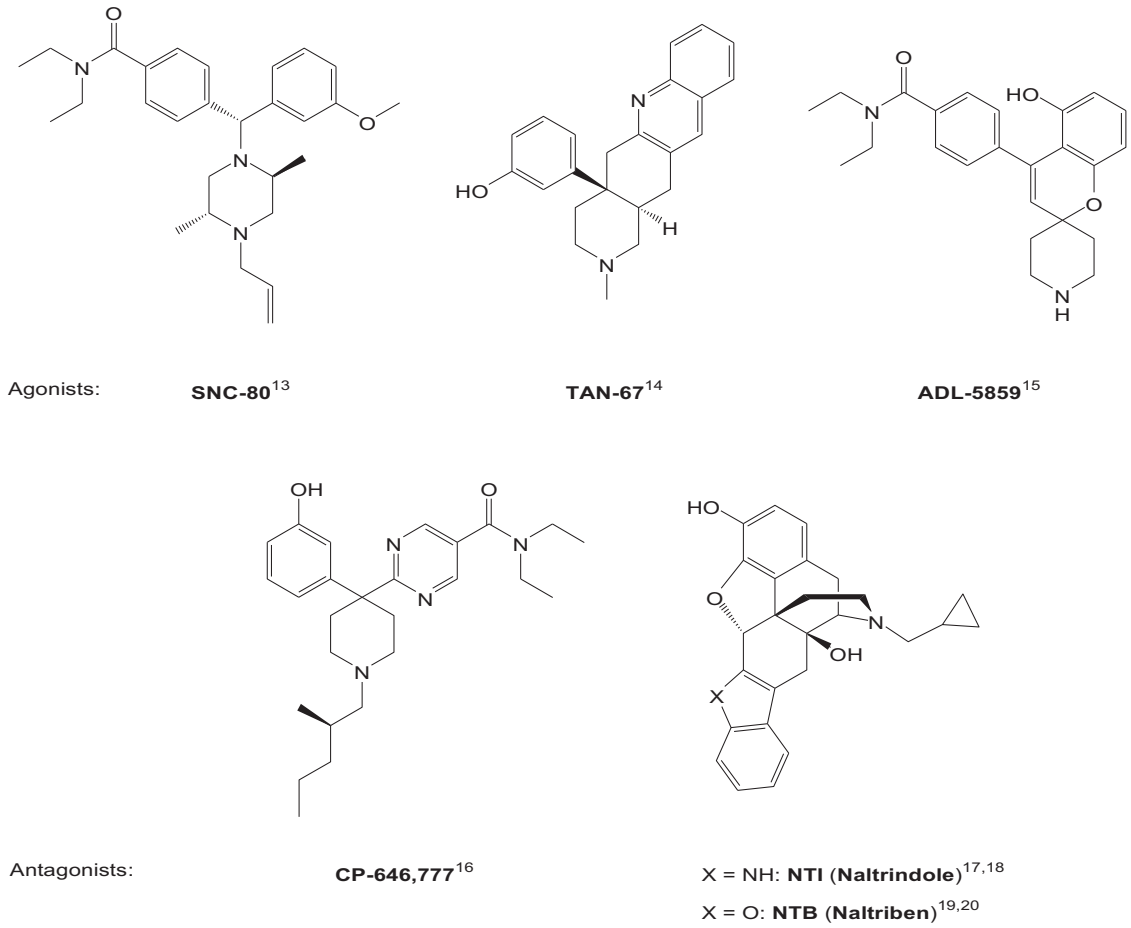


Fig. 1. Structures of δ opioid receptor ligands.

dimethylpiperazine core motif was incorporated into diazatricyclodecane ring systems of type **1** and **2** (Fig. 2).

In this paper, we present the synthesis and preliminary pharmacological characterization of 9-disubstitutedbenzhydryl-10-allyl-9,10-diazatricyclo[4.2.1.1^{2,5}]decane derivatives **1Aa**–**f**, **1Ba**–**f** and of 2-disubstitutedbenzhydryl-7-allyl-2,7-diazatricyclo [4.4.0.0^{3,8}]decane derivatives **2Aa**, **2Ac**, **2Ad** and **2Ba**, **2Bc** and **2Bd** (see Table 1). In this first stage of the research, the compounds have been obtained without the introduction of specific steps aimed to the separation of potential stereoisomers. The novel compounds exhibited good affinity to delta receptors relative to the other opioid receptor subtypes μ and κ. Moreover, interesting profiles were highlighted by *ex vivo* and *in vivo* assays.

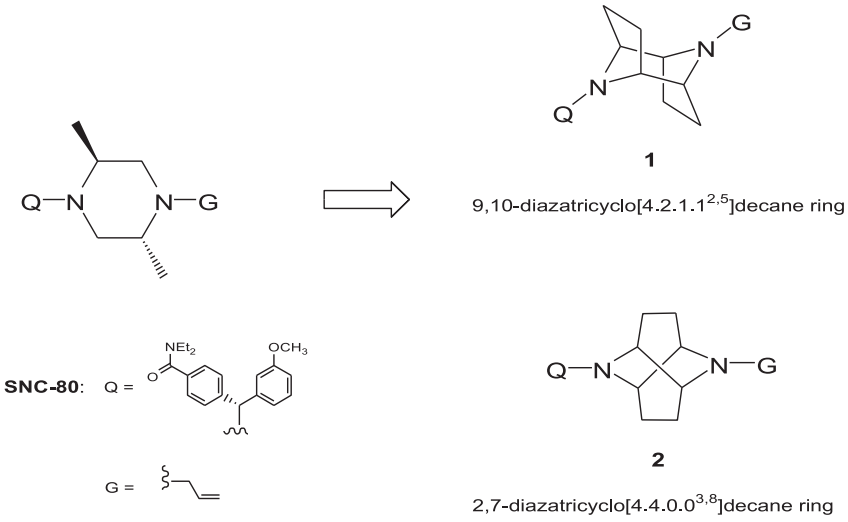
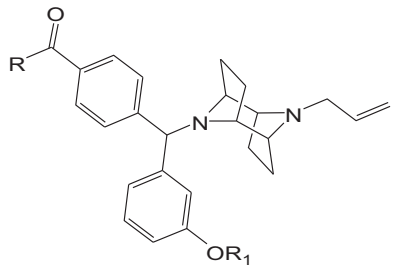
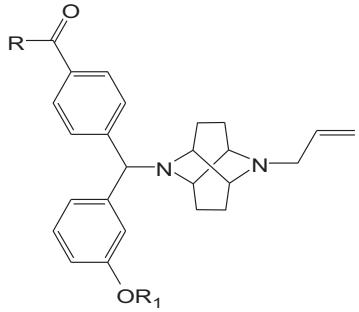


Fig. 2. Process of rational drug design based on conformational restriction strategy.

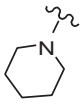
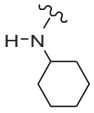
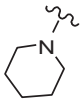
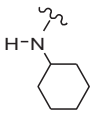
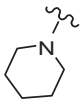
Table 1
Binding affinities of benzhydryl derivatives **1Aa**, **1Ac**–**e**, **1Ba**–**e**, **2Aa**, **2Ad**, **2Ba**, **2Bc**, **2Bd** and SNC-80 for opioid receptors[a,b] (values expressed as Ki).



1A,B[c]

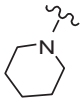


2A,B[c]

Compd	R	R_1	Ki (nM)			Selectivity	
			δ	μ	κ	μ/δ	κ/δ
1Aa		$-CH_3$	0.203 ± 0.032	1633 ± 186	600 ± 29	8044	2956
1Ac		$-CH_3$	1 ± 0.041	585 ± 101	1000 ± 100	585	1000
1Ad		$-CH_3$	1.03 ± 0.111	650 ± 96.4	706 ± 101	631	685
1Ae		$-CH_3$	45 ± 3.8	2000 ± 289	300 ± 58	44	6.7
1Ba		$-H$	0.23 ± 0.03	20 ± 0.5	4.8 ± 0.9	87	21
1Bb		$-H$	0.900 ± 0.1	173.3 ± 14.5	683 ± 9	193	759
1Bc		$-H$	0.208 ± 0.02	23.7 ± 2	4.7 ± 0.4	114	23
1Bd		$-H$	1.3 ± 0.13	160 ± 15.3	56 ± 8	123	43
1Be		$-H$	0.833 ± 0.203	36.7 ± 1.7	3.6 ± 0.5	44	4.3
2Aa		$-CH_3$	0.633 ± 0.033	533.3 ± 33.4	1267 ± 67	842	2002
2Ad		$-CH_3$	22 ± 4.012	293.3 ± 52.13	4750 ± 250	13	216

(*continued on next page*)

Table 1 (*continued*)

Compd	R	R_1	Ki (nM)			Selectivity	
			δ	μ	κ	μ/δ	κ/δ
2Ba		–H	0.267 ± 0.033	61.6 ± 13.3	n.d.	231	–
2Bc		–H	0.700 ± 0.087	63.25 ± 11.9	n.d	90	–
2Bd		–H	2.5 ± 0.2	170.0 ± 10.01	n.d.	68	–
SNC-80			0.71 ± 0.06	2383 ± 142	2750 ± 250	3356	3873

[c]All compounds were prepared as racemates. n.d.: not determined value.
[a] Binding assays were carried out in triplicate.
[b] [^{3}H-ADPE], [^{3}H-DAMGO] and [^{3}H-U-69,593] were used for the δ, μ and κ receptor binding studies, respectively (see Experimental section for full descriptions of the assays).

In order to well compare proposed compounds with SNC-80, hereafter, it is our intention to separate the enantiomers or diastereoisomers which constitute, respectively, the racemic or diastereomeric mixtures of the presented products. The separation of the stereoisomers of defined leads and their structural characterization could allow us to evaluate the stereochemical configuration of enantiomers related to the best receptor profiles. Moreover, this could allow us to study in deep the relevance of the stereochemistry on the biological activity of the compounds. However, this deepening goes beyond the scope of this first paper which is aimed to preliminary investigate the pharmacological profile of novel delta opioid receptor agonists based on conformationally constrained compounds containing diazatricyclodecane skeletons. Thus, to further support our research concerning this novel class of delta opioid agonists, the separation of the stereoisomers of defined leads and their structural characterization will be the subject of a future investigation. Finally, further studies will be performed in the future to complete the pre-clinical evaluations (i.e. affinity profiles to various receptors, toxicological data, pharmaco-kinetic studies) of each enantiomer or diastereoisomer of identified lead compounds.

2. Chemistry

The general strategy for preparation of the benzhydryl-diazatricyclodecane opioids **1A**,**B** and **2A**,**B** was to synthesize the chloro-benzhydryl moiety and then to attach the functionalized diazatricyclodecane cores (Scheme 1).

The synthesis of **6a**–**f** commenced with the conversion of 4-(3-methoxybenzoyl)benzoic acid (**3**) [13] into the corresponding amides **4a**–**f** using the appropriate amines. Reduction of ketoamides **4** with sodium borohydride in diluted ethanol at room temperature for 2 h afforded the corresponding alcohols **5a**–**f**. Treatment of **5a**–**f** with 37% HCl provided the corresponding benzhydryl chlorides **6a**–**f** in good yields. Alkylation of 9-benzyl-9,10-diazatricyclo [4.2.1.1^{2,5}]decane [31] and 2-benzyl-2,7-diazatricyclo[4.4.0.0^{3,8}] decane [31] with the appropriate chloride **6**, in the presence of anhydrous potassium carbonate in refluxing acetonitrile, afforded benzyl-benzyhdryl-diazatricyclodecanes **7a**–**f** and **8a**, **c**, **d** in moderate to good yields. These intermediates were next subjected to debenzylation by treatment with H_2 on Pd/C to provide **9a**–**f** and **10a**, **c**, **d**. Target ligands **1Aa**–**f** and **2Aa**, **2Ac** and **2Ad** were isolated by alkylation with allyl bromide, whereas completion of compound **1Ba**–**f** and **2Ba**, **2Bc** and **2Bd** was achieved in two steps by using alkylation followed by methyl deprotection using BBr_3.

3. Biology

The binding affinities of the prepared benzhydryl derivatives **1** and **2** for the μ, δ, and κ opioid receptors were determined on brain membranes according to a procedure based on that previously described by Gillan and Kosterlitz [32].

Intrinsic activity of the novel compounds characterized by the more favorable binding profiles was investigated through isolated organ assays (mouse vas deferens). In fact, it has been ascertained that delta opioid receptor agonists are able to reduce the electrically induced contractions of the musculature of the mouse vas deferens [21]. Moreover, it has been shown that delta antagonist derivatives are able to block or reduce the inhibition of the electrically evoked contraction amplitude of the vas deferens induced by delta agonists, with parallel dextral shifts in delta receptor agonist log concentration–response curves in electrically stimulated tissues.

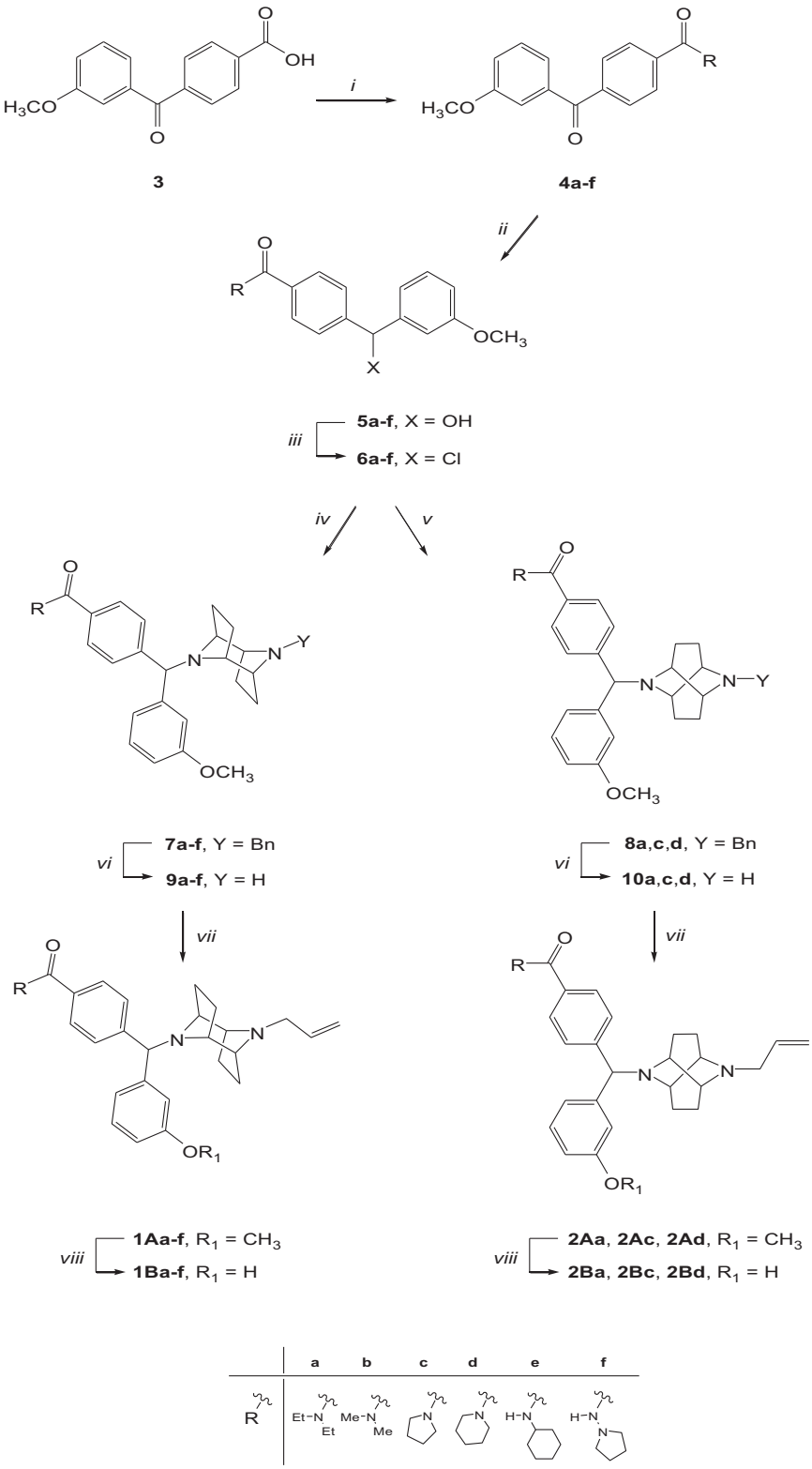
To evaluate the potential therapeutic activity of the novel compounds, antinociceptive effect of a selected derivative amongst those synthesized was assayed in animal model of acute pain (tail flick test).

4. Results and discussion

4.1. Radioligand binding assays

Affinities for δ, μ, and κ opioid receptors from mouse brain membranes were computed by displacement of [^{3}H-DPDPE], [^{3}H-DAMGO] and [^{3}H-U-69,593], respectively, in equilibrium binding assays (Table 1). Independent of the used diazatricyclodecane core, most of the compounds exhibited subnanomolar/low nanomolar affinity [Ki (δ) = 0.20–2.5 nM] except compounds **1Ae** and **2Ad** [Ki (δ) = 45 and 22 nM, respectively]; μ-opioid receptor affinities fall within the 20–2000 nM range. Except **1Ba**, **1Bc** and **1Be**, the other ligands listed in Table 1 showed no significant κ-opioid receptor affinity.

Compound **1Aa**, the best of this series with a δ opioid receptor affinity of 0.203 nM and 8044-fold and 2956-fold lower affinity for μ and κ, respectively, serves as a convenient benchmark for all



Scheme 1. Reagents and conditions: (i) a) $SOCl_2$, toluene, 110 °C, 3 h, b) RH, $CHCl_3$, r.t., 4 h; (ii) $NaBH_4$, EtOH/H_2O, r.t., 2 h; (iii) 37% HCl, $CHCl_3$, r.t., 12 h; (iv) 9-benzyl-9,10-diazatricyclo[4.2.1.1^{2,5}]decane [31], K_2CO_3, CH_3CN, 80 °C, 72 h; (v) 2-benzyl-2,7-diazatricyclo[4.4.0.0^{3,8}]decane [31], K_2CO_3, CH_3CN, 80 °C, 72 h; (vi) 3 atm H_2, 10% Pd/C, EtOH, 60 °C, 6 h; (vii) allyl bromide, K_2CO_3, acetone, 56 °C, 12 h; (viii) BBr_3, CH_2Cl_2, 0 °C, 1.5 h.

others in terms of presenting structure-binding affinity relationships.

Examination of δ receptor affinities of those compounds with diethylcarbamoyl moiety being replaced by various types of carbamoyl moieties (**1Ac**–**1Ae**) reveals a great impact on δ receptor binding affinity. Compound **1Ac** and **1Ad** had a pyrrolidine and a piperidine ring replacements of the diethylamine moiety as compared to **1Aa**. Both maintained high δ receptor affinities and relatively low μ and κ receptor affinities. The piperidine derivative **1Ad** exhibited higher δ to μ selectivity (631-fold) than did

pyrrolidine derivative **1Ac** (585-fold). Compound **1Ae** has a cyclohexylamine in the carbamoyl moiety and its Ki value indicated that it had much lower affinity for δ receptor as compared to **1Aa** and no significant affinity for μ (Ki > 1000 nM) and κ (Ki > 300 nM) receptors.

Compound **1Ba**–**1Be** have a phenol OH group in place of the methoxy moiety. Their δ receptor affinities were similar to that of **1Aa** but their μ receptor affinities were increased when compared to that of **1Aa**. The diethylamide **1Ba** as well as the cyclohexylamide **1Be** displayed significant binding affinities at μ and κ receptors.

Replacement of the 9,10-diazatricyclo[4.2.1.1^{2,5}]decane unit with a 2,7-diazatricyclo[4.4.0.0^{3,8}]decane ring system resulted in ligands, compounds **2Aa**, **2Ac**, **2Ad**, **2Ba**, **2Bc** and **2Bd**, that had interesting but unpredictable effects on δ binding affinity and subtype selectivity.

Compound **2Aa** with a similar pattern of substitution to **1Aa** had 3-fold lower affinity than **1Aa** for the δ opioid receptor. Similarly, the methoxy isomer **2Ad** displayed 21-fold lower affinity compared to **1Ad**. Compounds **2Ba**, **2Bc** and **2Bd** have a phenol OH group replacement of the methoxy group. The diethylamide compound **2Ba** had the highest δ receptor affinity among the three phenol OH analogs, with a δ receptor affinity that is comparable to that of **1Aa**. All three compounds, **2Ba**, **2Bc**, and **2Bd**, had higher μ receptor affinities as compared to **1Aa**.

4.2. Isolated organs (mouse vas deferens)

In conformity with previously reported data [21], SNC-80 showed δ agonist profile by inhibiting mouse vas deferens contraction in isolated organ assays (Fig. 3). This effect was counteracted by the δ selective antagonist Naltrindole (NTI). Selective action of the reference compound through the δ receptor was further confirmed by the inefficacy of the μ selective antagonist D-Phe-Cys-Tyr-D-Trp-Arg-Thr-Pen-Thr-NH_2 (CTAP) to affect SNC-80 activity.

Based on a balance of binding properties, **1Aa** and **1Ba** were selected as key compounds for isolated organ assays. The first one was in fact the more affine and selective compound for δ receptors (Ki = 0.203 nM; Ki μ/Ki δ = 8044), with an improved profile relative to the reference compound SNC-80. Compound **1Ba** displayed affinity at δ receptor comparable to **1Aa** but with much higher affinity at the μ receptor (Ki = 20 nM).

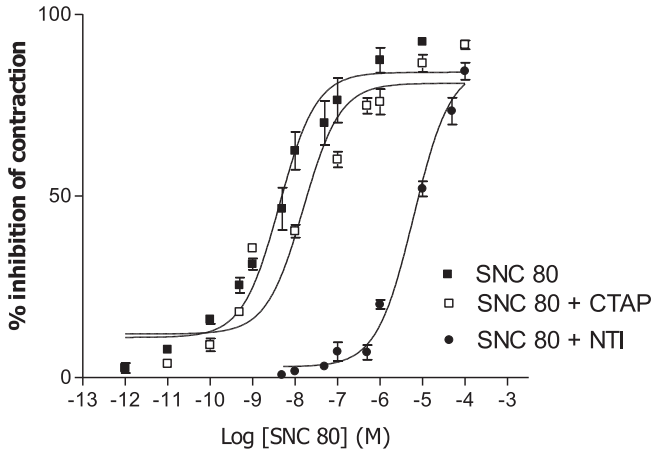


Fig. 3. Concentration–response curves for SNC-80 on the amplitude of twitch contractions elicited by electrical field stimulation of the mouse vas deferens obtained in the absence and in presence of NTI (50 nM) and CTAP (100 nM). Assays were performed as described under Materials and Methods. Each curve represents the mean values ± S.E.M. of 10 experiments. Responses are expressed as a percentage of the amplitude of the twitch response measured before the first addition of SNC-80.

Similar to SNC-80, compound **1Aa** showed δ agonist behavior in inhibiting electrically evoked contractions of mouse vas deferens. Moreover, **1Aa** action was antagonized by Naltrindole, but not by CTAP (Fig. 4).

Isolated organ assay results concerning derivative **1Ba** reflected the determined opioid affinity profile of the compound. As for SNC-80 and **1Aa**, δ agonist activity was ascertained by the capability of **1Ba** to counteract the electrically evoked contractions on mouse vas deferens (Fig. 5). The effect of **1Ba** on mouse vas deferens contractions was antagonized by the selective δ antagonist Naltrindole. However, the action of the novel compound was also partially counteracted by the μ selective antagonist CTAP. These results agree with the ascertained presence of μ receptors in the mouse vas deferens and with the good affinity (Ki = 20 nM) of **1Ba** for the same opioid sub-receptors.

4.3. In vivo assays: tail flick (acute pain model)

Administration of the compound **1Aa** (5 mg/kg, i.p.) induced a significant increase of % MPE in the test of tail-flick after 30 min from drug injection ($P < 0.05$). No significant differences vs. vehicle treated mice were observed after 60 and 120 min from drug administration ($P > 0.05$) (Fig. 6).

Tail-flick test analyses suggest that compound **1Aa** may be able to stimulate delta opioid receptors causing a rapid, but significant, analgesic effects. To date, the possibility that selective δ opioid agonists may induce analgesia in absence of μ receptor stimulation is still debated [21,33,34], partially explaining the moderate analgesic effect induced by the compound **1Aa** relative to that detected with morphine.

5. Conclusions

In conclusion, we report here a novel family of δ-selective opioid receptor agonists containing the 9-disubstitutedbenzhydryl-10-allyl-9,10-diazatricyclo[4.2.1.1^{2,5}]decane (compounds **1A**,**B**) and the 2-disubstitutedbenzhydryl-7-allyl-2,7-diazatricyclo[4.4.0.0^{3,8}]decane (compounds **2A**,**B**) core structures as conformationally restricted analogs of the reference delta selective agonist SNC-80.

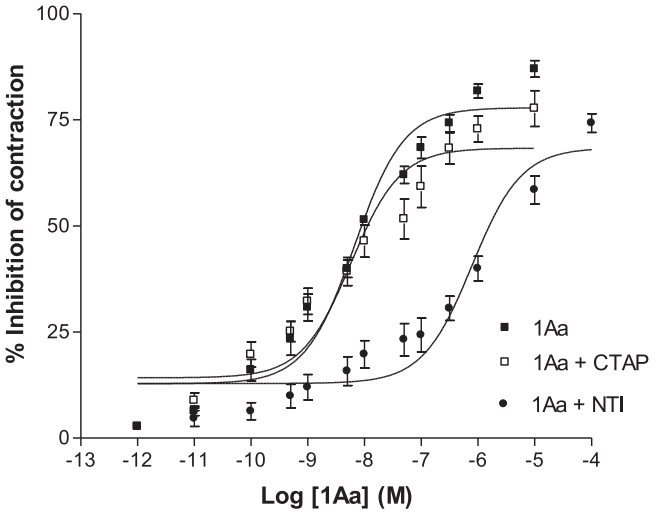


Fig. 4. Concentration–response curves for **1Aa** on the amplitude of twitch contractions elicited by electrical field stimulation of the mouse vas deferens obtained in the absence and in presence of NTI (50 nM) and CTAP (100 nM). Assays were performed as described under Materials and Methods. Each curve represents the mean values ± S.E.M. of 10 experiments. Responses are expressed as a percentage of the amplitude of the twitch response measured before the first addition of **1Aa**.

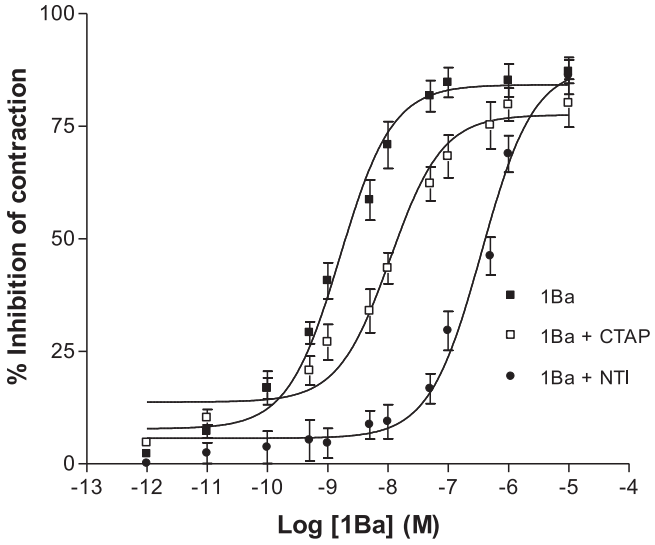


Fig. 5. Concentration–response curves for **1Ba** on the amplitude of twitch contractions elicited by electrical field stimulation of the mouse vas deferens obtained in the absence and in presence of NTI (50 nM) and CTAP (100 nM). Assays were performed as described under Materials and Methods. Each curve represents the mean values ± S.E.M. of 10 experiments. Responses are expressed as a percentage of the amplitude of the twitch response measured before the first addition of **1Ba**.

Although all the novel compounds were prepared and evaluated as racemic mixtures, the biological profile of the evaluated compounds provides support for the design strategies implemented in the present study. In fact, all of the diazatricyclodecanes displayed higher affinity for binding at the δ sites than at μ or κ sites. Amongst the novel compounds, **1Aa** displayed the best binding profile, with δ Ki values 3-fold lower than that of the reference compound SNC-80, and Ki μ/Ki δ value of 8044 (more than twice the corresponding value determined for SNC-80).

As a potential lead compound, **1Aa** was evaluated in *ex vivo* and *in vivo* assays and was found to display δ selective agonist activity in the isolated organ assay (mouse vas deferens) and antinociceptive activity in acute pain animal model (tail flick test).

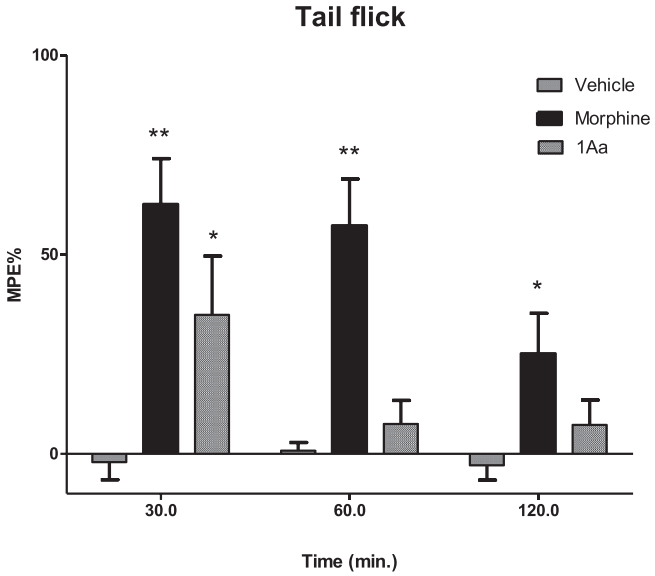


Fig. 6. Histogram showing the effects induced by vehicle, morphine and **1Aa** (dosages 5 mg/kg, i.p.) in the tail-flick test. Each bar represents mean values ± S.E.M. of % MPE obtained from 6 to 10 mice at different time points after drug injection. Statistical analyses have been carried out using Two-Way ANOVA, followed by Newman–Keuls post-hoc test (*,**$P < 0.05$ and $P < 0.01$ vs. vehicle treated mice).

Based on these profiles, **1Aa** appears to be a promising candidate to investigate further for the development of new drugs for the treatment of δ opioid receptor mediated pathologies.

To confirm and validate the adopted synthetic strategies in the development of novel δ selective agents, the separation and the characterization of the enantiomers in the racemic mixtures will be carried out in the future in order to identify the component with the best profile.

6. Experimental protocols

6.1. Chemistry. General informations

Melting points were obtained on an Electrothermal IA 9100 digital melting point apparatus or on a Kopfler melting point apparatus and are uncorrected.

Thin layer chromatography (TLC) was performed with Polygram® SIL N-HR/HV_{254} precoated plastic sheets (0.2 mm).

Flash chromatography (FC) was performed using Merck silica gel 60 (230–400 mesh ASTM).

IR spectra were recorded as thin films (for oils) or nujol mulls (for solids) on NaCl plates with a Jasco FT/IR 460 plus spectrophotometer and are expressed in ν (cm^{-1}).

All NMR spectra were taken on a Varian XL-200 NMR spectrometer with ^1H and ^{13}C being observed at 200 and 50 MHz respectively. Chemical shifts for ^1H and spectra were reported in δ or ppm downfield from TMS [$(CH_3)_4Si$]. Multiplicities are recorded as s (singlet), br s (broad singlet), d (doublet), t (triplet), dd (double doublet), dt (double triplet), q (quartet), m (multiplet).

Elemental analyses were performed by Laboratorio di Microanalisi, Dipartimento di Chimica e Farmacia, Università di Sassari, Italy, and are within ±0.4% of the calculated values.

All reactions involving air or moisture-sensitive compounds were performed under argon atmosphere.

Unless otherwise specified, all materials, solvents, and reagents were obtained from commercial suppliers.

6.2. General procedure I: preparation of compounds ***4a–f***

A solution of 4-(3-methoxybenzoyl)benzoic acid **3** [13] (2.24 g, 8.74 mmol) and of $SOCl_2$ (5 mL, 68.92 mmol) in 5 mL of toluene was allowed to stir at reflux for 3 h under N_2. The volatiles were removed under reduced pressure. The remaining $SOCl_2$ was coevaporated with toluene (3 × 5 mL). The acid chloride was dissolved in 10 mL of $CHCl_3$, and the resulting solution was added dropwise to a stirred solution of the appropriate amine or hydrazine (1.5 eq) in $CHCl_3$ (13 mL). The biphasic reaction mixture was allowed to stir at room temperature for 4 h. The organic layer was separated, washed with water (2 × 15 mL), and dried (Na_2SO_4). The solvent was evaporated under reduced pressure, and the residue was purified by flash chromatography to afford the desired amide **4a–f**.

6.2.1. *4-(3-Methoxybenzoyl)-N,N-diethylbenzamide (**4a**)*

General procedure I was used to convert diethylamine into the title product. Yield 98%; R_f 0.44 (petroleum ether/ethyl acetate 1:1); IR (nujol): 1650, 1690; ^1H NMR ($CDCl_3$) δ 1.00–1.38 (m, 6H), 3.20–3.38 (m, 2H), 3.50–3.70 (m, 2H), 3.86 (s, 3H), 7.10–7.40 (m, 4H), 7.48 (d, 2H, $J = 8.4$ Hz), 7.84 (d, 2H, $J = 8.4$ Hz). Anal. calcd for $C_{19}H_{21}NO_3$: C, 73.29; H, 6.80; N, 4.50. Found: C, 73.08; H, 6.79; N, 4.49.

6.2.2. *4-(3-Methoxybenzoyl)-N,N-dimethylbenzamide (**4b**)*

General procedure I was used to convert dimethylamine into the title product. Yield 99%; R_f 0.23 (petroleum ether/ethyl acetate 1:1); IR (nujol): 1680, 1690; ^1H NMR ($CDCl_3$) δ 2.90–3.05 (m, 3H), 3.10–

3.20 (m, 3H), 3.86 (s, 3H), 6.87–7.60 (m, 6H), 7.80–7.95 (m, 2H). Anal. calcd for $C_{17}H_{17}NO_3$: C, 72.07; H, 6.05; N, 4.94. Found: C, 71.93; H, 6.03; N, 4.93.

*6.2.3. (3-Methoxyphenyl)-[4-(pyrrolidine-1-carbonyl)phenyl] methanone (**4c**)*

General procedure I was used to convert pyrrolidine into the title product. Yield 98%; R_f 0.20 (petroleum ether/ethyl acetate 1:1); IR (nujol): 1690, 1700; ^{1}H NMR ($CDCl_3$) δ 1.90–2.10 (m, 4H), 3.40–3.50 (m, 2H), 3.60–3.75 (m, 2H), 3.86 (s, 3H), 7.10–7.45 (m, 4H), 7.61 (dd, 2H, J = 1.6 and 6.6 Hz), 7.83 (dd, 2H, J = 2.0 and 6.6 Hz). Anal. calcd for $C_{19}H_{19}NO_3$: C, 73.77; H, 6.19; N, 4.53. Found: C, 73.59; H, 6.17; N, 4.52.

*6.2.4. (3-Methoxyphenyl)-[4-(piperidine-1-carbonyl)phenyl] methanone (**4d**)*

General procedure I was used to convert piperidine into the title product. Yield 91%; R_f 0.45 (petroleum ether/ethyl acetate 1:1); IR (nujol): 1680, 1690; ^{1}H NMR ($CDCl_3$) δ 1.48–1.90 (m, 6H), 3.30–3.40 (m, 2H), 3.70–3.80 (m, 2H), 3.86 (s, 3H), 7.10–7.55 (m, 6H), 7.80–7.90 (m, 2H). Anal. calcd for $C_{20}H_{21}NO_3$: C, 74.28; H, 6.55; N, 4.33. Found: C, 74.21; H, 6.54; N, 4.32.

*6.2.5. 4-(3-Methoxybenzoyl)-N-cyclohexylbenzamide (**4e**)*

General procedure I was used to convert cyclohexylamine into the title product. Yield 95%; R_f 0.42 (petroleum ether/ethyl acetate 7:3); IR (nujol): 1680, 1690, 3100; ^{1}H NMR ($CDCl_3$) δ 1.00–1.95 (m, 8H), 2.00–2.20 (m, 2H), 3.85 (s, 3H), 3.90–4.10 (m, 1H), 6.05–6.15 (m, 1H), 7.10–7.40 (m, 8H). Anal. calcd for $C_{21}H_{23}NO_3$: C, 74.75; H, 6.87; N, 4.15. Found: C, 74.68; H, 6.85; N, 4.14.

*6.2.6. 4-(3-Methoxybenzoyl)-N-pyrrolidin-1-yl-benzamide (**4f**)*

General procedure I was used to convert 1-aminopyrrolidine into the title product. Yield 50%; R_f 0.20 (petroleum ether/ethyl acetate 2:8); IR (nujol): 1680, 1700, 3300; ^{1}H NMR ($CDCl_3$) δ 1.90–2.00 (m, 4H), 3.00–3.20 (m, 4H), 3.86 (s, 3H), 6.86 (s, 1H), 7.15 (d, 1H, J = 6.0 Hz), 7.30–7.43 (m, 3H), 7.80–7.87 (m, 4H). Anal. calcd for $C_{19}H_{20}N_2O_3$: C, 70.35; H, 6.21; N, 8.64. Found: C, 70.24; H, 6.20; N, 8.62.

*6.3. General procedure II: preparation of compounds **5a**–**f***

To a solution of the appropriate benzophenone **4a**–**f** (16.58 mmol) in 56 mL of 3:1 ethanol/water mixture was added portionwise $NaBH_4$ (6.0 eq). The reaction mixture was allowed to stir at room temperature for 2 h. The volatiles were evaporated under reduced pressure, and the pH of the solution was adjusted to 5 by dropwise addition of 1 M HCl solution. The obtained solid was filtered and air dried to afford the pure product **5a**–**f**.

*6.3.1. 4-[Hydroxy-(3-methoxyphenyl)methyl]-N,N-diethylbenzamide (**5a**)*

General procedure II was used to convert **4a** into the title product. Yield 99%; R_f 0.16 (petroleum ether/ethyl acetate 1:1); IR (nujol): 1680, 3300; ^{1}H NMR ($CDCl_3$) δ 1.00–1.35 (m, 6H), 2.39 (s, 1H), 3.10–3.18 (m, 2H), 3.20–3.30 (m, 2H), 3.79 (s, 3H), 5.82 (d, 1H, J = 3.2 Hz), 6.75–7.00 (m, 3H), 7.24 (d, 2H, J = 8.2 Hz), 7.25–7.38 (m, 1H), 7.41 (d, 2H, J = 8.2 Hz). Anal. calcd for $C_{19}H_{23}NO_3$: C, 72.82; H, 7.40; N, 4.47. Found: C, 72.67; H, 7.41; N, 4.46.

*6.3.2. 4-[Hydroxy-(3-methoxyphenyl)methyl]-N,N-dimethylbenzamide (**5b**)*

General procedure II was used to convert **4b** into the title product. Yield 99%; R_f 0.35 ($CHCl_3$/CH_3OH 95:5); IR (nujol): 1690, 3300; ^{1}H NMR ($CDCl_3$) δ 2.58 (bs, 1H), 2.90–3.20 (m, 6H), 3.78 (s, 3H), 5.81 (s, 1H), 6.75–6.95 (m, 3H), 7.10–7.50 (m, 5H). Anal. calcd for $C_{17}H_{19}NO_3$: C, 71.56; H, 6.71; N, 4.91. Found: C, 71.49; H, 6.70; N, 4.90.

*6.3.3. {4-[Hydroxy(3-methoxyphenyl)methyl]phenyl}(pyrrolidin-1-yl)methanone (**5c**)*

General procedure II was used to convert **4c** into the title product. Yield 99%; R_f 0.31 ($CHCl_3$/CH_3OH 95:5); IR (nujol): 1680, 3300; ^{1}H NMR ($CDCl_3$) δ 1.75–2.00 (m, 4H), 2.62 (d, 1H, J = 3.4 Hz), 3.40 (t, 2H, J = 6.2 Hz), 3.62 (t, 2H, J = 6.2 Hz), 3.78 (s, 3H), 5.81 (d, 1H, J = 3.0 Hz), 6.78–7.00 (m, 3H), 7.10–7.50 (m, 5H). Anal. calcd for $C_{19}H_{21}NO_3$: C, 73.29; H, 6.80; N, 4.50. Found: C, 73.20; H, 6.79; N, 4.49.

*6.3.4. {4-[Hydroxy(3-methoxyphenyl)methyl]phenyl}(piperidin-1-yl)methanone (**5d**)*

General procedure II was used to convert **4d** into the title product. Yield 99%; R_f 0.45 ($CHCl_3$/CH_3OH 95:5); IR (nujol): 1690, 3300; ^{1}H NMR ($CDCl_3$) δ 1.40–1.75 (m, 6H), 2.85 (bs, 1H), 3.25–3.40 (m, 2H), 3.60–3.75 (m, 2H), 3.78 (s, 3H), 5.78 (s, 1H), 6.78–7.00 (m, 3H), 7.20–7.45 (m, 5H). Anal. calcd for $C_{20}H_{23}NO_3$: C, 73.82; H, 7.12; N, 4.30. Found: C, 73.77; H, 7.10; N, 4.29.

*6.3.5. 4-[Hydroxy-(3-methoxyphenyl)methyl]-N-cyclohexylbenzamide (**5e**)*

General procedure II was used to convert **4e** into the title product. Yield 85%; R_f 0.30 ($CHCl_3$/CH_3OH 9:1); IR (nujol): 1690, 3100, 3300; ^{1}H NMR ($CDCl_3$) δ 1.00–2.10 (m, 11H), 3.78 (s, 3H), 3.80–4.05 (m, 1H), 5.83 (s, 1H), 5.96–6.00 (m, 1H), 6.78–6.95 (m, 2H), 7.20–7.30 (m, 2H), 7.43 (d, 2H, J = 8.2 Hz), 7.70 (d, 2H, J = 8.2 Hz). Anal. calcd for $C_{21}H_{25}NO_3$: C, 74.31; H, 7.42; N, 4.13. Found: C, 74.22; H, 7.41; N, 4.11.

*6.3.6. 4-[Hydroxy-(3-methoxyphenyl)methyl]-N-pyrrolidin-1-yl-benzamide (**5f**)*

General procedure II was used to convert **4f** into the title product. Yield 99%; R_f 0.50 ($CHCl_3$/CH_3OH 9:1); IR (nujol): 1670, 3100, 3300; ^{1}H NMR ($CDCl_3$) δ 1.90–2.00 (m, 5H), 2.85–3.10 (m, 4H), 3.77 (s, 3H), 5.82 (s, 1H), 6.75 (s, 1H), 7.20–7.55 (m, 4H), 7.66 (d, 2H, J = 8.0 Hz), 7.68 (d, 2H, J = 8.0 Hz). Anal. calcd for $C_{19}H_{22}N_2O_3$: C, 69.92; H, 6.79; N, 8.58. Found: C, 69.90; H, 6.77; N, 8.56.

*6.4. General procedure III: preparation of compounds **6a**–**f***

A solution of the appropriate alcohol **5a**–**f** (37.38 mmol) in 50 mL of $CHCl_3$ was added dropwise to 150 mL of 37% HCl. The biphasic reaction mixture was allowed to stir at room temperature overnight. The organic layer was separated, washed with water (2 × 25 mL), dried, and evaporated under reduced pressure to give pure product **6a**–**f**.

*6.4.1. 4-[Chloro-(3-methoxyphenyl)methyl]-N,N-diethylbenzamide (**6a**)*

General procedure III was used to convert **5a** into the title product. Yield 95%; R_f 0.33 (petroleum ether/ethyl acetate 4:6); IR (nujol): 1680; ^{1}H NMR ($CDCl_3$) δ 1.00–1.78 (m, 6H), 3.08–3.38 (m, 2H), 3.40–3.60 (m, 2H), 3.80 (s, 3H), 6.09 (s, 1H), 6.80–7.00 (m, 4H), 7.35 (d, 2H, J = 8.4 Hz), 7.44 (d, 2H, J = 8.4 Hz). Anal. calcd for $C_{19}H_{22}ClNO_2$: C, 68.77; H, 6.68; N, 4.22. Found: C, 68.61; H, 6.67; N, 4.21.

*6.4.2. 4-[Chloro-(3-methoxyphenyl)methyl]-N,N-dimethylbenzamide (**6b**)*

General procedure III was used to convert **5b** into the title product. Yield 99%; R_f 0.35 (petroleum ether/ethyl acetate 4:6); IR

(nujol): 1690; ^{1}H NMR ($CDCl_3$) δ 2.90–3.20 (m, 6H), 3.79 (s, 3H), 6.53 (s, 1H), 6.70–7.60 (m, 8H). Anal. calcd for $C_{17}H_{18}ClNO_2$: C, 67.21; H, 5.97; N, 4.61. Found: C, 67.15; H, 5.95; N, 4.61.

*6.4.3. {4-[Chloro(3-methoxyphenyl)methyl]phenyl}(pyrrolidin-1-yl)methanone (**6c**)*

General procedure III was used to convert **5c** into the title product. Yield 99%; R_f 0.21 (petroleum ether/ethyl acetate 8:2); IR (nujol): 1680; ^{1}H NMR ($CDCl_3$) δ 1.90–2.00 (m, 4H), 3.42 (t, 2H, J = 6.4 Hz), 3.64 (t, 2H, J = 6.4 Hz), 3.79 (s, 3H), 6.09 (s, 1H), 6.90–7.00 (m, 3H), 7.20–7.60 (m, 5H). Anal. calcd for $C_{19}H_{20}ClNO_2$: C, 69.19; H, 6.11; N, 4.25. Found: C, 69.07; H, 6.09; N, 4.24.

*6.4.4. {4-[Chloro(3-methoxyphenyl)methyl]phenyl}(piperidin-1-yl)methanone (**6d**)*

General procedure III was used to convert **5d** into the title product. Yield 99%; R_f 0.50 (petroleum ether/ethyl acetate 8:2); IR (nujol): 1690; ^{1}H NMR ($CDCl_3$) δ 1.40–1.80 (m, 6H), 3.30–3.45 (m, 2H), 3.60–3.78 (m, 2H), 3.80 (s, 3H), 6.09 (s, 1H), 6.80–7.00 (m, 3H), 7.20–7.50 (m, 5H). Anal. calcd for $C_{20}H_{22}ClNO_2$: C, 69.86; H, 6.45; N, 4.07. Found: C, 69.70; H, 6.44; N, 4.06.

*6.4.5. 4-[Chloro-(3-methoxyphenyl)methyl]-N-cyclohexylbenzamide (**6e**)*

General procedure III was used to convert **5e** into the title product. Yield 97%; R_f 0.31 (petroleum ether/ethyl acetate 8:2); IR (nujol): 1690, 3100; ^{1}H NMR ($CDCl_3$) δ 1.00–1.80 (m, 8H), 1.95–2.10 (m, 2H), 3.78 (s, 3H), 3.85–4.05 (m, 1H), 5.90–6.00 (m, 1H), 6.09 (s, 1H), 6.80–7.00 (m, 3H), 7.20–7.30 (m, 1H), 7.46 (d, 2H, J = 8.4 Hz), 7.72 (d, 2H, J = 8.4 Hz). Anal. calcd for $C_{21}H_{24}ClNO_2$: C, 70.48; H, 6.76; N, 3.91. Found: C, 70.27; H, 6.74; N, 3.90.

*6.4.6. 4-[Chloro-(3-methoxyphenyl)methyl]-N-pyrrolidin-1-yl-benzamide (**6f**)*

General procedure III was used to convert **5f** into the title product. Yield 95%; R_f 0.50 ($CHCl_3$/CH_3OH 9:1); IR (nujol): 1680, 3300; ^{1}H NMR ($CDCl_3$) δ 1.70–2.10 (m, 4H), 2.90–3.15 (m, 4H), 3.79 (s, 3H), 6.09 (s, 1H), 6.75 (s, 1H), 6.77–7.00 (m, 2H), 7.20–7.35 (m, 2H), 7.69 (d, 2H, J = 8.0 Hz), 7.71 (d, 2H, J = 8.0 Hz). Anal. calcd for $C_{19}H_{21}ClN_2O_2$: C, 66.18; H, 6.14; N, 8.12. Found: C, 66.04; H, 6.13; N, 8.10.

*6.5. General procedure IV: preparation of compounds **7a**–**f** and **8a**, **c**, **d***

A mixture of the appropriate chloride **6a**–**f** (1.5 eq), 9-benzyl-9,10-diazatricyclo[4.2.1.1^{2,5}]decane [31] or 2-benzyl-2,7-diazatricyclo[4.4.0.0^{3,8}]decane [31] (0.5 g, 2.19 mmol), and anhydrous K_2CO_3 (3 eq) in 20 mL of anhydrous acetonitrile was allowed to stir at reflux for 72 h, under Ar. The solution was filtered, and the volatiles were evaporated under reduced pressure. The residue was purified by flash chromatography to afford the desired compounds **7a**–**f** and **8a**, **c**, **d**.

*6.5.1. 4-[(10-Benzyl-9,10-diazatricyclo[4.2.1.1^{2,5}]dec-9-yl)-(3-methoxyphenyl)methyl]-N,N-diethylbenzamide (**7a**)*

General procedure IV was used to convert 9-benzyl-9,10-diazatricyclo[4.2.1.1^{2,5}]decane and **6a** into the title product. Yield 52%; R_f 0.40 (petroleum ether/ethyl acetate 7:3); IR (nujol): 1680; ^{1}H NMR ($CDCl_3$) δ 1.00–1.30 (m, 6H), 1.60–2.20 (m, 8H), 2.75–2.85 (m, 4H), 3.20–3.36 (m, 2H), 3.37 (s, 2H), 3.40–3.60 (m, 2H), 3.80 (s, 3H), 4.28 (s, 1H), 6.70–6.80 (m, 1H), 7.00–7.40 (m, 10H), 7.55 (d, 2H, J = 8.4 Hz). Anal. calcd for $C_{34}H_{41}N_3O_2$: C, 77.98; H, 7.89; N, 8.02. Found: C, 77.71; H, 7.87; N, 8.00.

*6.5.2. 4-[(10-Benzyl-9,10-diazatricyclo[4.2.1.1^{2,5}]dec-9-yl)-(3-methoxyphenyl)methyl]-N,N-dimethylbenzamide (**7b**)*

General procedure IV was used to convert 9-benzyl-9,10-diazatricyclo[4.2.1.1^{2,5}]decane and **6b** into the title product. Yield 50%; R_f 0.45 (petroleum ether/ethyl acetate 1:1); IR (nujol): 1700; ^{1}H NMR ($CDCl_3$) δ 1.60–2.30 (m, 8H), 2.70–2.85 (m, 4H), 2.90–3.15 (m, 6H), 3.36 (s, 2H), 3.79 (s, 3H), 4.29 (s, 1H), 6.65–6.75 (m, 1H), 7.10–7.40 (m, 10H), 7.55 (d, 2H, J = 8.4 Hz). Anal. calcd for $C_{32}H_{37}N_3O_2$: C, 77.54; H, 7.52; N, 8.48. Found: C, 77.37; H, 7.50; N, 8.49.

*6.5.3. {4-[(10-Benzyl-9,10-diazatricyclo[4.2.1.1^{2,5}]dec-9-yl)-(3-methoxyphenyl)methyl]phenyl}pyrrolidin-1-yl-methanone (**7c**)*

General procedure IV was used to convert 9-benzyl-9,10-diazatricyclo[4.2.1.1^{2,5}]decane and **6c** into the title product. Yield 44%; R_f 0.42 (petroleum ether/ethyl acetate 1:1); IR (nujol): 1680; ^{1}H NMR ($CDCl_3$) δ 1.50–2.25 (m, 12H), 2.70–2.90 (m, 4H), 3.30–3.45 (m, 4H), 3.55–3.65 (m, 2H), 3.79 (s, 3H), 4.29 (s, 1H), 6.65–6.75 (m, 1H), 7.00–7.50 (m, 10H), 7.55 (d, 2H, J = 8.4 Hz). Anal. calcd for $C_{34}H_{39}N_3O_2$: C, 78.28; H, 7.54; N, 8.05. Found: C, 78.22; H, 7.55; N, 8.04.

*6.5.4. {4-[(10-Benzyl-9,10-diazatricyclo[4.2.1.1^{2,5}]dec-9-yl)-(3-methoxyphenyl)methyl]phenyl}piperidin-1-yl-methanone (**7d**)*

General procedure IV was used to convert 9-benzyl-9,10-diazatricyclo[4.2.1.1^{2,5}]decane and **6d** into the title product. Yield 85%; R_f 0.27 (petroleum ether/ethyl acetate 7:3); IR (nujol): 1650; ^{1}H NMR ($CDCl_3$) δ 1.40–1.85 (m, 10H), 1.90–2.00 (m, 2H), 2.15–2.25 (m, 2H), 2.70–2.85 (m, 4H), 3.20–3.35 (m, 2H), 3.36 (s, 2H), 3.60–3.75 (m, 2H), 3.79 (s, 3H), 4.28 (s, 1H), 6.65–6.75 (m, 1H), 7.05–7.40 (m, 10H), 7.55 (d, 2H, J = 8.0 Hz). Anal. calcd for $C_{35}H_{41}N_3O_2$: C, 78.47; H, 7.71; N, 7.84. Found: C, 78.35; H, 7.69; N, 7.81.

*6.5.5. 4-[(10-Benzyl-9,10-diazatricyclo[4.2.1.1^{2,5}]dec-9-yl)-(3-methoxyphenyl)methyl]-N-cyclohexylbenzamide (**7e**)*

General procedure IV was used to convert 9-benzyl-9,10-diazatricyclo[4.2.1.1^{2,5}]decane and **6e** into the title product. Yield 42%; R_f 0.45 (petroleum ether/ethyl acetate 8:2); IR (nujol): 1720, 3100; ^{1}H NMR ($CDCl_3$) δ 1.00–1.55 (m, 5H), 1.58–1.85 (m, 6H), 1.90–2.10 (m, 4H), 2.15–2.25 (m, 2H), 2.70–2.90 (m, 4H), 3.36 (s, 2H), 3.78 (s, 3H), 4.31 (s, 1H), 5.85 (d, 2H, J = 7.4 Hz), 6.65–6.75 (m, 1H), 7.00–7.40 (m, 8H), 7.55–7.65 (m, 4H), 8.10 (d, 1H, J = 7.2 Hz). Anal. calcd for $C_{36}H_{43}N_3O_2$: C, 78.65; H, 7.88; N, 7.64. Found: C, 78.59; H, 7.87; N, 7.63.

*6.5.6. 4-[(10-Benzyl-9,10-diazatricyclo[4.2.1.1^{2,5}]dec-9-yl)-(3-methoxyphenyl)methyl]-N-pyrrolidin-1-yl-benzamide (**7f**)*

General procedure IV was used to convert 9-benzyl-9,10-diazatricyclo[4.2.1.1^{2,5}]decane and **6f** into the title product. Yield 87%; R_f 0.39 (petroleum ether/ethyl acetate 2:8); IR (nujol): 1680, 3100; ^{1}H NMR ($CDCl_3$) δ 1.20–2.00 (m, 8H), 2.10–2.40 (m, 4H), 2.70–2.90 (m, 4H), 2.95–3.05 (m, 4H), 3.36 (s, 2H), 3.76 (s, 3H), 4.15 (s, 1H), 5.85 (s, 1H), 6.70–7.70 (m, 11H), 8.00–8.20 (m, 2H). Anal. calcd for $C_{34}H_{40}N_4O_2$: C, 76.09; H, 7.51; N, 10.44. Found: C, 75.98; H, 7.50; N, 10.41.

*6.5.7. 4-[(7-Benzyl-2,7-diazatricyclo[4.4.0.0^{3,8}]dec-2-yl)-(3-methoxyphenyl)methyl]-N,N-diethylbenzamide (**8a**)*

General procedure IV was used to convert 2-benzyl-2,7-diazatricyclo[4.4.0.0^{3,8}]decane and **6a** into the title product. Yield 65%; R_f 0.21 (petroleum ether/ethyl acetate 1:1); IR (nujol): 1680; ^{1}H NMR ($CDCl_3$) δ 1.00–1.95 (m, 14H), 2.70–2.90 (m, 4H), 3.15–3.35 (m, 2H), 3.40–3.60 (m, 2H), 3.78 (s, 3H), 3.80–4.00 (m, 2H), 5.07 (s, 1H), 6.65–6.75 (m, 1H), 7.00–7.40 (m, 10H), 7.52 (d, 2H, J = 8.2 Hz).

Anal. calcd for $C_{34}H_{41}N_3O_2$: C, 77.98; H, 7.89; N, 8.02. Found: C, 77.80; H, 7.88; N, 8.00.

*6.5.8. {4-[(7-Benzyl-2,7-diazatricyclo[4.4.0.0^{3,8}]dec-2-yl)-(3-methoxyphenyl)methyl]phenyl}pyrrolidin-1-yl-methanone (**8c**)*

General procedure IV was used to convert 2-benzyl-2,7-diazatricyclo[4.4.0.0^{3,8}]decane and **6c** into the title product. Yield 44%; R_f 0.20 (petroleum ether/ethyl acetate 1:1); IR (nujol): 1680; ^{1}H NMR ($CDCl_3$) δ 1.40–2.00 (m, 12H), 2.75–3.10 (m, 4H), 3.30–3.50 (m, 2H), 3.55–3.75 (m, 2H), 3.78 (s, 3H), 4.00–4.20 (m, 2H), 5.07 (s, 1H), 6.90–7.60 (m, 13H). Anal. calcd for $C_{34}H_{39}N_3O_2$: C, 78.28; H, 7.54; N, 8.05. Found: C, 78.20; H, 7.53; N, 8.03.

*6.5.9. {4-[(7-Benzyl-2,7-diazatricyclo[4.4.0.0^{3,8}]dec-2-yl)-(3-methoxyphenyl)methyl]phenyl}piperidin-1-yl-methanone (**8d**)*

General procedure IV was used to convert 2-benzyl-2,7-diazatricyclo[4.4.0.0^{3,8}]decane and **6d** into the title product. Yield 90%; R_f 0.36 (petroleum ether/ethyl acetate 6:4); IR (nujol): 1680; ^{1}H NMR ($CDCl_3$) δ 1.30–2.10 (m, 14H), 2.75–2.90 (m, 4H), 3.20–3.45 (m, 2H), 3.55–3.75 (m, 2H), 3.77 (s, 3H), 3.79 (s, 2H), 5.10 (s, 1H), 6.65–7.40 (m, 11H), 8.00–8.20 (m, 2H). Anal. calcd for $C_{35}H_{41}N_3O_2$: C, 78.47; H, 7.71; N, 7.84. Found: C, 78.40; H, 7.70; N, 7.82.

*6.6. General procedure V: preparation of compounds **9a**–**f** and **10a**, **c**, **d***

A solution of the appropriate benzyl diazatricyclodecane **7** or **8** (0.38 mmol) in 5 mL of ethanol was hydrogenated over 10% Pd/C (0.1 eq) in a Parr shaker under a hydrogen pressure of 3 atm at 60 °C for 6 h. The mixture was filtered through Celite and the catalyst washed with several portions of ethanol. The solution was evaporated to afford the pure product **9a**–**f** or **10a**, **c**, **d**.

*6.6.1. 4-[(9,10-Diazatricyclo[4.2.1.1^{2,5}]dec-9-yl)-(3-methoxyphenyl)methyl]-N,N-diethylbenzamide (**9a**)*

General procedure V was used to convert **7a** into the title product. Yield 99%; R_f 0.40 ($CHCl_3$/CH_3OH 9:1); IR (nujol): 1630, 3200; ^{1}H NMR ($CDCl_3$) δ 1.00–1.45 (m, 6H), 1.90–2.43 (m, 10H), 2.90–3.10 (m, 2H), 3.10–3.30 (m, 2H), 3.40–3.60 (m, 2H), 3.66 (bs, 1H), 3.79 (s, 3H), 4.26 (s, 1H), 6.75–6.80 (m, 1H), 7.03–7.38 (m, 5H), 7.60 (d, 2H, J = 8.0 Hz). Anal. calcd for $C_{27}H_{35}N_3O_2$: C, 74.79; H, 8.14; N, 9.69. Found: C, 74.61; H, 8.12; N, 9.67.

*6.6.2. 4-[(9,10-Diazatricyclo[4.2.1.1^{2,5}]dec-9-yl)-(3-methoxyphenyl)methyl]-N,N-dimethylbenzamide (**9b**)*

General procedure V was used to convert **7b** into the title product. Yield 99%; R_f 0.35 ($CHCl_3$/CH_3OH 9:1); IR (nujol): 1620, 3100; ^{1}H NMR ($CDCl_3$) δ 2.00–2.50 (m, 10H), 2.90–3.10 (m, 9H), 3.78 (s, 3H), 4.34 (s, 1H), 6.70–6.85 (m, 1H), 7.00–7.60 (m, 7H). Anal. calcd for $C_{25}H_{31}N_3O_2$: C, 74.04; H, 7.70; N, 10.36. Found: C, 73.88; H, 7.68; N, 10.33.

*6.6.3. {4-[(9,10-Diazatricyclo[4.2.1.1^{2,5}]dec-9-yl)-(3-methoxyphenyl)methyl]phenyl}pyrrolidin-1-yl-methanone (**9c**)*

General procedure V was used to convert **7c** into the title product. Yield 99%; R_f 0.23 ($CHCl_3$/CH_3OH 9:1); IR (nujol): 1650, 3300; ^{1}H NMR ($CDCl_3$) δ 1.80–2.10 (m, 11H), 2.30–2.40 (m, 2H), 2.80–3.00 (m, 2H), 3.30–3.45 (m, 4H), 3.55–3.70 (m, 2H), 3.79 (s, 3H), 4.29 (s, 1H), 6.70–6.80 (m, 1H), 7.00–7.30 (m, 3H), 7.43 (d, 2H, J = 8.0 Hz), 7.53 (d, 2H, J = 8.0 Hz). Anal. calcd for $C_{27}H_{33}N_3O_2$: C, 75.14; H, 7.71; N, 9.74. Found: C, 75.02; H, 7.70; N, 9.72.

*6.6.4. {4-[(9,10-Diazatricyclo[4.2.1.1^{2,5}]dec-9-yl)-(3-methoxyphenyl)methyl]phenyl}piperidin-1-yl-methanone (**9d**)*

General procedure V was used to convert **7d** into the title product. Yield 99%; R_f 0.40 ($CHCl_3$/CH_3OH 9:1); IR (nujol): 1680, 3100; ^{1}H NMR ($CDCl_3$) δ 1.40–1.90 (m, 13H), 2.20–2.40 (m, 2H), 2.75–2.95 (m, 2H), 3.06 (s, 2H), 3.22–3.45 (m, 2H), 3.60–3.75 (m, 2H), 3.80 (s, 3H), 4.22 (s, 1H), 6.70–6.80 (m, 1H), 7.00–7.40 (m, 5H), 7.55 (d, 2H, J = 8.0 Hz). Anal. calcd for $C_{28}H_{35}N_3O_2$: C, 75.47; H, 7.92; N, 9.43. Found: C, 75.23; H, 7.90; N, 9.42.

*6.6.5. 4-[(9,10-Diazatricyclo[4.2.1.1^{2,5}]dec-9-yl)-(3-methoxyphenyl)methyl]-N-cyclohexylbenzamide (**9e**)*

General procedure V was used to convert **7e** into the title product. Yield 80%; R_f 0.32 ($CHCl_3$/CH_3OH 9:1); IR (nujol): 1680, 3100, 3300; ^{1}H NMR ($CDCl_3$) δ 1.05–1.45 (m, 6H), 1.50–2.00 (m, 6H), 2.00–2.35 (m, 7H), 2.40–2.55 (m, 2H), 3.60–3.77 (m, 3H), 3.78 (s, 3H), 4.33 (s, 1H), 6.74 (d, 1H, J = 6.8 Hz), 7.08 (d, 1H, J = 11.6 Hz), 7.10–7.25 (m, 3H), 7.57 (d, 2H, J = 8.0 Hz), 7.75 (d, 2H, J = 8.0 Hz). Anal. calcd for $C_{29}H_{37}N_3O_2$: C, 75.78; H, 8.11; N, 9.14. Found: C, 75.70; H, 8.09; N, 9.13.

*6.6.6. 4-[(9,10-Diazatricyclo[4.2.1.1^{2,5}]dec-9-yl)-(3-methoxyphenyl)methyl]-N-pyrrolidin-1-yl-benzamide (**9f**)*

General procedure V was used to convert **7f** into the title product. Yield 75%; R_f 0.27 ($CHCl_3$/CH_3OH 8:2); IR (nujol): 1680, 3200; ^{1}H NMR ($CDCl_3$) δ 1.20–1.90 (m, 8H), 1.92–2.30 (m, 8H), 2.95–3.00 (m, 1H), 3.05–3.20 (m, 4H), 3.76 (s, 3H), 3.98 (s, 1H), 4.80 (bs, 1H), 6.65–6.80 (m, 2H), 7.00–7.30 (m, 4H), 7.90–8.05 (m, 2H). Anal. calcd for $C_{27}H_{34}N_4O_2$: C, 72.62; H, 7.67; N, 12.55. Found: C, 72.48; H, 7.66; N, 12.53.

*6.6.7. 4-[(2,7-Diazatricyclo[4.4.0.0^{3,8}]dec-2-yl)-(3-methoxyphenyl)methyl]-N,N-diethylbenzamide (**10a**)*

General procedure V was used to convert **8a** into the title product. Yield 90%; R_f 0.27 ($CHCl_3$/CH_3OH 9:1); IR (nujol): 1670, 3100; ^{1}H NMR ($CDCl_3$) δ 1.00–1.40 (m, 6H), 1.90–2.50 (m, 10H), 2.90–3.00 (m, 2H), 3.10–3.30 (m, 2H), 3.40–3.60 (m, 3H), 3.96 (s, 3H), 4.95 (s, 1H), 6.65–6.85 (m, 1H), 7.00–7.40 (m, 5H), 7.48 (d, 2H, J = 6.0 Hz). Anal. calcd for $C_{27}H_{35}N_3O_2$: C, 74.79; H, 8.14; N, 9.69. Found: C, 74.70; H, 8.13; N, 9.67.

*6.6.8. {4-[(2,7-Diazatricyclo[4.4.0.0^{3,8}]dec-2-yl)-(3-methoxyphenyl)methyl]phenyl}pyrrolidin-1-yl-methanone (**10c**)*

General procedure V was used to convert **8c** into the title product. Yield 90%; R_f 0.27 ($CHCl_3$/CH_3OH 9:1); IR (nujol): 1680, 3100; ^{1}H NMR ($CDCl_3$) δ 1.10–2.20 (m, 11H), 2.25–2.35 (m, 2H), 2.95–3.05 (m, 2H), 3.30–3.40 (m, 3H), 3.55–3.75 (m, 3H), 3.78 (s, 3H), 4.96 (s, 1H), 7.00–7.09 (m, 2H), 7.15–7.30 (m, 2H), 7.40–7.55 (m, 4H). Anal. calcd for $C_{27}H_{33}N_3O_2$: C, 75.14; H, 7.71; N, 9.74. Found: C, 74.97; H, 7.70; N, 9.73.

*6.6.9. {4-[(2,7-Diazatricyclo[4.4.0.0^{3,8}]dec-2-yl)-(3-methoxyphenyl)methyl]phenyl}piperidin-1-yl-methanone (**10d**)*

General procedure V was used to convert **8d** into the title product. Yield 99%; R_f 0.40 ($CHCl_3$/CH_3OH 9:1); IR (nujol): 1680, 3100; ^{1}H NMR ($CDCl_3$) δ 1.40–2.10 (m, 13H), 2.15–2.30 (m, 1H), 2.80–3.00 (m, 2H), 3.15–3.45 (m, 2H), 3.50–3.75 (m, 2H), 3.78 (s, 3H), 5.00–5.25 (m, 3H), 5.70–5.90 (m, 1H), 6.65–7.40 (m, 6H), 7.95–8.15 (m, 2H). Anal. calcd for $C_{28}H_{35}N_3O_2$: C, 75.47; H, 7.92; N, 9.43. Found: C, 75.35; H, 7.91; N, 9.40.

*6.7. General procedure VI: preparation of compounds **1Aa**–**f** and **2Aa**, **c**, **d***

A mixture of the appropriate diazatricyclodecane **9** or **10** (0.98 mmol), allyl bromide (1.5 eq), and anhydrous K_2CO_3 (3 eq) in acetone (25 mL) was stirred at reflux overnight. The inorganic salt was filtered off, and the solvent was then evaporated to give pure product **1A** or **2A**.

*6.7.1. 4-[(10-Allyl-9,10-diazatricyclo[4.2.1.1^{2,5}]dec-9-yl)-(3-methoxyphenyl)methyl]-N,N-diethylbenzamide (**1Aa**)*

General procedure VI was used to convert **9a** into the title product. Yield 96%; R_f 0.27 (petroleum ether/ethyl acetate 1:1); mp 99–101 °C; IR (nujol): 1680; ^{1}H NMR ($CDCl_3$) δ 1.00–1.30 (m, 6H), 1.50–2.20 (m, 8H), 2.70–2.90 (m, 6H), 3.20–3.35 (m, 2H), 3.40–3.55 (m, 2H), 3.80 (s, 3H), 4.28 (s, 1H), 4.98–5.15 (m, 2H), 5.70–5.90 (m, 1H), 6.65–6.80 (m, 1H), 7.00–7.20 (m, 5H), 7.54 (d, 2H, J = 8.0 Hz); ^{13}C NMR ($CDCl_3$) δ 12.9, 14.2, 25.5× 2, 25.6, 25.7, 39.1, 43.2, 55.2, 55.7, 63.2, 63.3, 65.1, 65.3, 69.7, 112.0, 113.5, 115.6, 120.3, 126.5× 2, 127.8× 2, 129.3, 135.7, 137.4, 145.0, 145.2, 159.5, 171.2. Anal. calcd for $C_{30}H_{39}N_3O_2$: C, 76.07; H, 8.30; N, 8.87. Found: C, 75.88; H, 8.28; N, 8.84.

*6.7.2. 4-[(10-Allyl-9,10-diazatricyclo[4.2.1.1^{2,5}]dec-9-yl)-(3-methoxyphenyl)methyl]-N,N-dimethylbenzamide (**1Ab**)*

General procedure VI was used to convert **9b** into the title product. Yield 88%; R_f 0.41 (petroleum ether/ethyl acetate 1:1); mp 100–103 °C; IR (nujol): 1670; ^{1}H NMR ($CDCl_3$) δ 1.50–2.10 (m, 8H), 2.70–3.10 (m, 12H), 3.79 (s, 3H), 4.29 (s, 1H), 4.95–5.15 (m, 2H), 5.70–5.95 (m, 1H), 6.60–6.68 (m, 1H), 7.00–7.40 (m, 5H), 7.56 (d, 2H, J = 7.4 Hz); ^{13}C NMR ($CDCl_3$) δ 25.5× 2, 25.6× 2, 29.6, 35.3, 39.6, 55.1, 55.6, 63.2, 65.2, 65.3, 69.6, 112.0, 113.4, 115.7, 120.2, 127.2, 127.3, 127.7, 128.7, 129.3, 134.7, 137.2, 145.1, 145.4, 159.5, 171.5. Anal. calcd for $C_{28}H_{35}N_3O_2$: C, 75.47; H, 7.92; N, 9.43. Found: C, 75.30; H, 7.91; N, 9.41.

*6.7.3. {4-[(10-Allyl-9,10-diazatricyclo[4.2.1.1^{2,5}]dec-9-yl)-(3-methoxyphenyl)methyl]phenyl}-pyrrolidin-1-yl-methanone (**1Ac**)*

General procedure VI was used to convert **9c** into the title product. Yield 94%; R_f 0.17 (petroleum ether/ethyl acetate 1:1); mp 46–48 °C; IR (nujol): 1680; ^{1}H NMR ($CDCl_3$) δ 1.60–2.30 (m, 12H), 2.70–2.95 (m, 6H), 3.30–3.45 (m, 2H), 3.50–3.70 (m, 2H), 3.79 (s, 3H), 4.28 (s, 1H), 4.95–5.15 (m, 2H), 5.70–5.95 (m, 1H), 6.65–6.75 (m, 1H), 7.00–7.15 (m, 3H), 7.41 (d, 2H, J = 8.0 Hz), 7.55 (d, 2H, J = 8.0 Hz); ^{13}C NMR ($CDCl_3$) δ 24.4, 25.5× 2, 25.6× 2, 26.3, 46.1, 49.6, 55.1, 55.7, 63.2× 2, 65.2, 66.6, 69.7, 112.0, 113.5, 115.6, 120.3, 127.2× 2, 127.6× 2, 129.3, 135.7, 137.5, 145.1, 145.7, 159.5, 169.5. Anal. calcd for $C_{30}H_{37}N_3O_2$: C, 76.40; H, 7.91; N, 8.91. Found: C, 76.24; H, 7.89; N, 8.89.

*6.7.4. {4-[(10-Allyl-9,10-diazatricyclo[4.2.1.1^{2,5}]dec-9-yl)-(3-methoxyphenyl)methyl]phenyl}-piperidin-1-yl-methanone (**1Ad**)*

General procedure VI was used to convert **9d** into the title product. Yield 99%; R_f 0.40 (petroleum ether/ethyl acetate 4:6); mp 134–136 °C; IR (nujol): 1650; ^{1}H NMR ($CDCl_3$) δ 1.40–1.90 (m, 10H), 1.91–2.00 (m, 2H), 2.10–2.25 (m, 2H), 2.70–2.95 (m, 6H), 3.20–3.45 (m, 2H), 3.55–3.75 (m, 2H), 3.80 (s, 3H), 4.28 (s, 1H), 5.00–5.20 (m, 2H), 5.70–5.90 (m, 1H), 6.70–6.80 (m, 1H), 7.00–7.40 (m, 5H), 7.55 (d, 2H, J = 8.0 Hz); ^{13}C NMR ($CDCl_3$) δ 19.1, 24.5, 25.6× 2, 25.7× 2, 29.2, 30.9, 53.8, 55.2, 55.7, 63.2, 63.3, 65.2, 65.3, 69.7, 112.0, 113.5, 115.6, 120.3, 127.0, 127.8, 128.8, 129.3, 130.9, 134.9, 137.4, 145.2, 145.3, 159.5, 170.2. Anal. calcd for $C_{31}H_{39}N_3O_2$: C, 76.67; H, 8.09; N, 8.65. Found: C, 76.51; H, 8.06; N, 8.64.

*6.7.5. 4-[(10-Allyl-9,10-diazatricyclo[4.2.1.1^{2,5}]dec-9-yl)-(3-methoxyphenyl)methyl]-N-cyclohexylbenzamide (**1Ae**)*

General procedure VI was used to convert **9e** into the title product. Yield 99%; R_f 0.31 (petroleum ether/ethyl acetate 8:2); mp 58–60 °C; IR (nujol): 1680, 3100; ^{1}H NMR ($CDCl_3$) δ 1.10–1.80 (m, 14H), 1.85–2.10 (m, 4H), 2.15–2.20 (m, 2H), 2.70–2.95 (m, 5H), 3.78 (s, 3H), 4.31 (s, 1H), 5.00–5.20 (m, 2H), 5.70–5.95 (m, 2H), 6.65–6.75 (m, 1H), 7.00–7.25 (m, 3H), 7.50–7.70 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 24.8× 2, 25.5× 2, 25.6, 25.7× 2, 33.2× 2, 48.5, 55.1, 55.7, 63.2, 63.3, 65.2, 65.3, 69.6, 112.1, 113.4, 115.6, 120.2, 126.9× 2, 127.9× 2, 129.4, 133.7, 137.4, 144.9, 147.4, 159.6, 166.5. Anal. calcd for $C_{32}H_{41}N_3O_2$: C, 76.92; H, 8.27; N, 8.41. Found: C, 76.77; H, 8.25; N, 8.40.

*6.7.6. 4-[(10-Allyl-9,10-diazatricyclo[4.2.1.1^{2,5}]dec-9-yl)-(3-methoxyphenyl)methyl]-N-pyrrolidin-1-yl-benzamide (**1Af**)*

General procedure VI was used to convert **9f** into the title product. Yield 80%; R_f 0.35 ($CHCl_3$/CH_3OH 95:5); mp 70–72 °C; IR (nujol): 1680, 3200; ^{1}H NMR ($CDCl_3$) δ 1.20–1.80 (m, 8H), 2.00–2.55 (m, 8H), 3.40–3.60 (m, 2H), 3.75 (s, 3H), 3.95 (s, 1H), 4.25–4.40 (m, 2H), 4.60 (d, 2H, J = 6.8 Hz), 5.40–5.55 (m, 2H), 5.95–6.15 (m, 1H), 6.65–6.80 (m, 2H), 7.10–7.25 (m, 4H), 7.89 (d, 2H, J = 8.0 Hz), 8.02 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 10.8, 13.9, 19.1, 21.6, 23.6, 28.8, 29.6, 30.2, 38.6, 41.7, 55.0, 63.7, 64.2, 68.0, 71.7, 111.3, 114.5, 121.2, 124.5, 127.7, 127.8, 128.3, 128.6, 128.7, 129.2, 130.8, 142.3, 142.9, 159.5, 169.6. Anal. calcd for $C_{30}H_{38}N_4O_2$: C, 74.04; H, 7.87; N, 11.51. Found: C, 73.93; H, 7.86; N, 11.48.

*6.7.7. 4-[(7-Allyl-2,7-diazatricyclo[4.4.0.0^{3,8}]dec-2-yl)-(3-methoxyphenyl)methyl]-N,N-diethylbenzamide (**2Aa**)*

General procedure VI was used to convert **10a** into the title product. Yield 80%; R_f 0.22 (CH_2Cl_2/Acetone 1:1); mp 217–220 °C (hydrochloride); IR (nujol): 1680; ^{1}H NMR ($CDCl_3$) δ 1.00–1.95 (m, 16H), 2.77–2.89 (m, 2H), 3.15–3.30 (m, 2H), 3.32–3.40 (m, 2H), 3.40–3.60 (m, 2H), 3.79 (s, 3H), 5.00–5.25 (m, 3H), 5.70–5.90 (m, 1H), 6.65–6.75 (m, 1H), 7.00–7.30 (m, 5H), 7.53 (dd, 2H, J = 2.0 and 8.0 Hz); ^{13}C NMR ($CDCl_3$) δ 12.8, 14.2, 22.1× 2, 22.4× 2, 29.7, 39.2, 43.3, 53.7, 55.1, 55.3, 56.0× 2, 70.3, 111.7, 112.6, 113.4, 113.5, 119.9, 120.3, 126.4, 126.5, 126.6, 127.2, 127.4, 127.8, 129.2, 129.3, 159.5. Anal. calcd for $C_{30}H_{39}N_3O_2$: C, 76.07; H, 8.30; N, 8.87. Found: C, 75.84; H, 8.28; N, 8.85.

*6.7.8. {4-[(7-Allyl-2,7-diazatricyclo[4.4.0.0^{3,8}]dec-2-yl)-(3-methoxyphenyl)methyl]phenyl}pyrrolidin-1-yl-methanone (**2Ac**)*

General procedure VI was used to convert **10c** into the title product. Yield 99%; R_f 0.25 (CH_2Cl_2/Acetone 1:1); mp 126–128 °C; IR (nujol): 1680; ^{1}H NMR ($CDCl_3$) δ 1.10–2.00 (m, 12H), 2.70–3.00 (m, 4H), 3.20–3.50 (m, 4H), 3.50–3.70 (m, 2H), 3.77 (s, 3H), 5.00–5.25 (m, 3H), 5.70–5.90 (m, 1H), 6.65–6.80 (m, 1H), 7.00–7.35 (m, 3H), 7.40 (d, 2H, J = 8.0 Hz), 7.53 (d, 2H, J = 8.0 Hz); ^{13}C NMR ($CDCl_3$) δ 19.0, 22.0× 2, 22.3× 2, 24.3, 26.2, 46.0, 49.5, 53.4, 53.6, 55.0, 55.2, 55.9, 70.2, 111.7, 112.1, 113.2, 113.4, 115.5, 119.7, 120.1, 127.1× 2, 127.2, 127.5, 129.2, 137.5, 159.5, 169.5. Anal. calcd for $C_{30}H_{37}N_3O_2$: C, 76.40; H, 7.91; N, 8.91. Found: C, 76.28; H, 7.88; N, 8.90.

*6.7.9. {4-[(7-Allyl-2,7-diazatricyclo[4.4.0.0^{3,8}]dec-2-yl)-(3-methoxyphenyl)methyl]phenyl}piperidin-1-yl-methanone (**2Ad**)*

General procedure VI was used to convert **10d** into the title product. Yield 90%; R_f 0.27 (petroleum ether/ethyl acetate 7:3); mp 94–96 °C (hydrochloride); IR (nujol): 1680; ^{1}H NMR ($CDCl_3$) δ 1.15–2.00 (m, 18H), 2.75–2.85 (m, 2H), 3.20–3.40 (m, 2H), 3.60–3.75 (m, 2H), 3.78 (s, 3H), 5.00–5.25 (m, 3H), 5.70–5.90 (m, 1H), 6.65–7.40 (m, 6H), 7.95–8.15 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 9.9, 13.0, 18.1× 2, 21.8, 22.6, 26.6, 27.8, 28.5, 28.8, 29.2, 37.6, 54.2, 66.8, 70.5, 111.9, 118.0, 125.9, 126.0, 127.6× 2, 127.7, 128.9, 129.2, 129.9× 2, 131.2, 131.3, 166.3, 166.4. Anal. calcd for $C_{31}H_{39}N_3O_2$: C, 76.67; H, 8.09; N, 8.65. Found: C, 76.56; H, 8.08; N, 8.64.

*6.8. General procedure VII: preparation of compounds **1Ba–f** and **2Ba, c, d***

To a solution of the appropriate methoxy derivative **1A** or **2A** (0.50 mmol) in CH_2Cl_2 (10 mL), cooled in an ice bath, BBr_3 (2 eq) was added dropwise, and the mixture was stirred at 0 °C for 1.5 h. The cold bath was removed, the reaction was quenched with 1%

KOH, and the mixture extracted with dichloromethane. The extract was dried (Na_2SO_4) and concentrated to give pure product **1B** or **2B**.

*6.8.1. 4-[(10-Allyl-9,10-diazatricyclo[4.2.1.1^{2,5}]dec-9-yl)-(3-hydroxyphenyl)methyl]-N,N-diethylbenzamide (**1Ba**)*

General procedure VII was used to convert **1Aa** into the title product. Yield 99%; R_f 0.25 (petroleum ether/ethyl acetate 3:7); mp 112–115 °C (CH_3CN/water); IR (nujol): 1680, 3400; ^{1}H NMR ($CDCl_3$) δ 1.00–1.35 (m, 6H), 1.60–2.30 (m, 8H), 2.70–3.10 (m, 6H), 3.20–3.35 (m, 2H), 3.45–3.75 (m, 2H), 4.26 (s, 1H), 5.30–5.50 (m, 2H), 6.40–6.60 (m, 2H), 6.65–6.75 (m, 1H), 6.90–7.40 (m, 5H), 7.51 (d, 2H, J = 8.0 Hz); ^{13}C NMR ($CDCl_3$) δ 12.8, 14.2, 24.6× 2, 25.0, 29.7, 39.5, 43.5, 54.9, 61.2× 2, 67.2, 67.5, 68.3, 114.5, 115.1, 118.9, 124.9, 126.8, 127.8, 129.9, 136.3, 142.5, 143.2, 157.3, 171.1. Anal. calcd for $C_{29}H_{37}N_3O_2$: C, 75.78; H, 8.11; N, 9.14. Found: C, 75.63; H, 8.09; N, 9.12.

*6.8.2. 4-[(10-Allyl-9,10-diazatricyclo[4.2.1.1^{2,5}]dec-9-yl)-(3-hydroxyphenyl)methyl]-N,N-dimethylbenzamide (**1Bb**)*

General procedure VII was used to convert **1Ab** into the title product. Yield 90%; R_f 0.25 (petroleum ether/ethyl acetate 3:7); mp 99–101 °C; IR (nujol): 1650, 3300; ^{1}H NMR ($CDCl_3$) δ 1.50–2.10 (m, 8H), 2.50–3.10 (m, 12H), 4.30 (s, 1H), 5.30–5.55 (m, 2H), 6.40–6.60 (m, 1H), 6.65–6.80 (m, 1H), 7.00–7.80 (m, 7H), 8.70 (bs, 1H); ^{13}C NMR ($CDCl_3$) δ 24.6, 25.1, 29.6× 2, 38.6, 54.9, 55.2, 61.3, 67.3, 68.0, 68.3, 71.7, 112.4, 113.8, 119.8, 124.9, 127.2, 127.6, 127.7, 127.8, 128.7, 130.8, 135.6, 142.7, 143.1, 159.8, 171.0. Anal. calcd for $C_{27}H_{33}N_3O_2$: C, 75.14; H, 7.71; N, 9.74. Found: C, 75.07; H, 7.70; N, 9.71.

*6.8.3. {4-[(10-Allyl-9,10-diazatricyclo[4.2.1.1^{2,5}]dec-9-yl)-(3-hydroxyphenyl)methyl]phenyl}-pyrrolidin-1-yl-methanone (**1Bc**)*

General procedure VII was used to convert **1Ac** into the title product. Yield 93%; R_f 0.45 ($CHCl_3$/CH_3OH 9:1); mp 156–158 °C; IR (nujol): 1650, 3300; ^{1}H NMR ($CDCl_3$) δ 1.60–2.20 (m, 12H), 2.50–3.10 (m, 8H), 3.55–3.80 (m, 3H), 4.28 (s, 1H), 5.20–5.60 (m, 2H), 6.40–6.60 (m, 1H), 6.85–7.00 (m, 1H), 7.20–7.60 (m, 6H), 8.53 (bs, 1H); ^{13}C NMR ($CDCl_3$) δ 19.1, 24.4, 24.6, 25.2, 26.3, 29.7, 46.4, 49.9, 61.2, 61.3, 67.4, 67.5, 68.1, 68.3, 114.6, 115.2, 118.9, 125.1, 124.4, 127.6× 2, 128.7, 129.9, 130.8, 136.1, 144.0, 157.4, 169.4. Anal. calcd for $C_{29}H_{35}N_3O_2$: C, 76.12; H, 7.71; N, 9.18. Found: C, 75.88; H, 7.69; N, 9.17.

*6.8.4. {4-[(10-Allyl-9,10-diazatricyclo[4.2.1.1^{2,5}]dec-9-yl)-(3-hydroxyphenyl)methyl]phenyl}-piperidin-1-yl-methanone (**1Bd**)*

General procedure VII was used to convert **1Ad** into the title product. Yield 99%; R_f 0.20 (petroleum ether/ethyl acetate 7:3); mp 133–135 °C; IR (nujol): 1680, 3300; ^{1}H NMR ($CDCl_3$) δ 1.40–1.90 (m, 10H), 1.95–2.00 (m, 4H), 2.55–2.75 (m, 4H), 3.00–3.20 (m, 2H), 3.22–3.80 (m, 4H), 4.35 (s, 1H), 5.35–5.60 (m, 2H), 6.45–6.70 (m, 1H), 6.75–6.85 (m, 1H), 7.00–7.40 (m, 5H), 7.53 (d, 2H, J = 8.2 Hz), 8.95 (bs, 1H); ^{13}C NMR ($CDCl_3$) δ 19.1, 24.4× 2, 24.7× 2, 25.2× 2, 54.9, 55.3× 2, 61.4× 2, 67.2, 67.3, 68.4, 112.4, 113.9, 119.9, 124.8, 127.6, 127.7, 127.9, 128.8, 130.0, 130.9135.4, 142.8, 143.1, 159.9, 169.8. Anal. calcd for $C_{30}H_{37}N_3O_2$: C, 76.40; H, 7.91; N, 8.91. Found: C, 76.26; H, 7.89; N, 8.89.

*6.8.5. 4-[(10-Allyl-9,10-diazatricyclo[4.2.1.1^{2,5}]dec-9-yl)-(3-hydroxyphenyl)methyl]-N-cyclohexylbenzamide (**1Be**)*

General procedure VII was used to convert **1Ae** into the title product. Yield 80%; R_f 0.29 ($CHCl_3$/CH_3OH 95:5); mp 68–70 °C; IR (nujol): 1690, 3300; ^{1}H NMR ($CDCl_3$) δ 1.00–1.50 (m, 10H), 1.55–2.05 (m, 9H), 2.08–2.25 (m, 2H), 2.40–2.80 (m, 4H), 4.31 (s, 1H), 5.40–5.60 (m, 2H), 6.20–6.45 (m, 1H), 6.70 (d, 1H, J = 7.8 Hz), 6.90–7.25 (m, 4H), 7.56 (d, 2H, J = 8.0 Hz), 7.74 (d, 2H, J = 8.0 Hz), 8.40–8.50 (bs, 1H); ^{13}C NMR ($CDCl_3$) δ 23.7× 2, 24.3× 2, 24.4× 2, 24.8, 32.2× 2, 48.1× 2, 53.9, 60.5, 60.6, 66.7, 67.7, 113.8, 114.4, 117.7, 124.5, 126.8× 2, 126.9, 127.2× 2, 129.2, 134.2, 141.9, 144.2, 157.1, 165.8. Anal. calcd for $C_{31}H_{39}N_3O_2$: C, 76.67; H, 8.09; N, 8.65. Found: C, 76.61; H, 8.07; N, 8.64.

*6.8.6. 4-[(10-Allyl-9,10-diazatricyclo[4.2.1.1^{2,5}]dec-9-yl)-(3-hydroxyphenyl)methyl]-N-pyrrolidin-1-yl-benzamide (**1Bf**)*

General procedure VII was used to convert **1Af** into the title product. Yield 95%; R_f 0.40 ($CHCl_3$/CH_3OH 9:1); mp 76–78 °C; IR (nujol): 1680, 3200, 3400; ^{1}H NMR ($CDCl_3$) δ 1.20–2.05 (m, 10H), 2.10–2.40 (m, 6H), 3.80–4.10 (m, 2H), 4.81 (d, 2H, J = 7.0 Hz), 4.82–5.05 (m, 4H), 5.50–5.70 (m, 2H), 5.90–6.15 (m, 1H), 6.60–6.85 (m, 2H), 7.00–7.40 (m, 4H), 7.90–8.10 (m, 2H), 11.60 (bs, 1H); ^{13}C NMR ($CDCl_3$) δ 10.3, 13.5, 18.5, 20.7, 22.3, 23.1, 27.1, 29.0, 29.7, 41.2, 64.6, 65.4, 67.4, 71.1, 113.1, 115.4, 119.3, 124.8, 127.6, 127.7, 127.9, 128.2, 128.5, 128.9, 130.4, 140.7, 146.8, 156.9, 166.1. Anal. calcd for $C_{29}H_{36}N_4O_2$: C, 73.70; H, 7.68; N, 11.85. Found: C, 73.59; H, 7.66; N, 11.82.

*6.8.7. 4-[(7-Allyl-2,7-diazatricyclo[4.4.0.0^{3,8}]dec-2-yl)-(3-hydroxyphenyl)methyl]-N,N-diethylbenzamide (**2Ba**)*

General procedure VII was used to convert **2Aa** into the title product. Yield 75%; R_f 0.32 ($CHCl_3$/CH_3OH 9:1); mp 147–150 °C; IR (nujol): 1685, 3330; ^{1}H NMR ($CDCl_3$) δ 1.10–2.30 (m, 16H), 2.85–4.00 (m, 8H), 4.85 (s, 1H), 5.30–5.60 (m, 2H), 6.40–7.60 (m, 9H), 9.55 (bs, 1H); ^{13}C NMR ($CDCl_3$) δ 12.8, 14.2, 16.8, 22.6, 29.7× 2, 39.8, 43.8, 50.7, 51.9, 54.9, 58.6, 58.8, 69.4, 114.15, 114.4, 115.1, 115.4, 118.4, 118.9, 125.1, 126.8, 127.3, 127.9, 128.3, 129.8, 157.4, 157.5, 171.4. Anal. calcd for $C_{29}H_{37}N_3O_2$: C, 75.78; H, 8.11; N, 9.14. Found: C, 75.68; H, 8.08; N, 9.11.

*6.8.8. {4-[(7-Allyl-2,7-diazatricyclo[4.4.0.0^{3,8}]dec-2-yl)-(3-hydroxyphenyl)methyl]phenyl}pyrrolidin-1-yl-methanone (**2Bc**)*

General procedure VII was used to convert **2Ac** into the title product. Yield 99%; R_f 0.33 ($CHCl_3$/CH_3OH 9:1); mp 140–142 °C; IR (nujol): 1670, 3300; ^{1}H NMR ($CDCl_3$) δ 1.30–2.40 (m, 12H), 2.80–3.15 (m, 2H), 3.20–4.00 (m, 8H), 4.90 (s, 1H), 5.35–5.60 (m, 2H), 6.30–6.55 (m, 1H), 6.70–6.80 (m, 1H), 6.85–6.95 (m, 1H), 7.00–7.15 (m, 1H), 7.20–7.40 (m, 3H), 7.50–7.60 (m, 2H), 9.20 (bs, 1H); ^{13}C NMR ($CDCl_3$) δ 19.0× 2, 22.8, 23.6, 24.2, 27.6, 46.5, 49.8, 53.4, 54.8, 58.6, 59.9, 68.0, 71.7, 114.6, 115.3, 118.1, 118.8, 125.1, 127.5, 127.7, 128.7× 2, 129.7, 130.8× 2, 142.7, 157.6, 169.5. Anal. calcd for $C_{29}H_{35}N_3O_2$: C, 76.12; H, 7.71; N, 9.18. Found: C, 76.02; H, 7.70; N, 9.17.

*6.8.9. {4-[(7-Allyl-2,7-diazatricyclo[4.4.0.0^{3,8}]dec-2-yl)-(3-hydroxyphenyl)methyl]phenyl}piperidin-1-yl-methanone (**2Bd**)*

General procedure VII was used to convert **2Ad** into the title product. Yield 91%; R_f 0.38 ($CHCl_3$/CH_3OH 9:1); mp 70–73 °C; IR (nujol): 1680, 3400; ^{1}H NMR ($CDCl_3$) δ 1.20–1.90 (m, 20H), 3.15–3.40 (m, 2H), 3.55–3.80 (m, 2H), 5.20–5.45 (m, 3H), 6.10–6.20 (m, 1H), 6.60–7.30 (m, 6H), 7.80–8.00 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 10.9, 14.0, 19.1× 2, 22.9, 23.7, 24.3, 27.7, 28.9, 29.7, 30.3, 38.7, 50.2, 68.1, 71.8, 114.5, 115.5, 120.1, 120.7, 127.0, 128.6, 128.7, 128.8, 128.9, 130.9, 140.5, 141.0, 142.5, 156.8, 168.0. Anal. calcd for $C_{30}H_{37}N_3O_2$: C, 76.40; H, 7.91; N, 8.91. Found: C, 76.30; H, 7.89; N, 8.90.

6.9. Chemicals and drugs for in vitro and in vivo assays

[^{3}H]-DAMGO, [^{3}H]-DPDPE, and [^{3}H]-U 69,593 were purchased from Perkin Elmer Italia. Naltrindole, Naloxone, CTAP, and U 69,593 were obtained from Tocris Cookson Ltd (Bristol, UK). Where not differently specified, all the other chemicals were purchased from Sigma Aldrich (Milan, Italy).

In vivo assays were carried out by solubilizing compounds in saline solution containing Cremophor®EL (Basf GmbH) and Ethanol (both at 5 wt%). All animal experiments were performed according to the UE guidelines for the care and use of experimental animals (CEE N° 86/609). Male CD-1 mice (Charles River, Calco, LC, Italy), weighing 20–30 g, were housed in the animal care quarters; temperatures were maintained at 22 ± 2 °C (humidity 55 ± 5%) on a 12 h light/dark cycle. Food and water were available *ad libitum* before to start with the experimental procedures.

6.10. Radioligand binding methods

Ligand binding assays were carried out according to previously reported procedures [32]. Improvements were assured by slight modifications. Briefly, whole brain minus cerebellum was homogenized with Polytron in 50 volumes (w/v) of 50 mM Tris–HCl (pH 7.4), centrifuged at 48,000× *g* for 20 min at 4 °C, re-suspended in 50 volumes of the same buffer solution, and incubated at 37 °C for 45 min. After a further centrifugation step at 48,000× *g* for 20 min at 4 °C, the final pellet was re-suspended in the same buffer solution. Brain membranes were incubated with the appropriate concentration of [^{3}H]-DAMGO or [^{3}H]-DPDPE or [^{3}H]-U 69,593 in Tris–HCl buffer at 25 °C for 60 min in the absence or presence of naloxone (1 μM) (for mu and delta receptors) or U 69,593 (10 μM) (kappa receptors). The binding reaction was stopped by rapid filtration under vacuum through glass-fiber filters (Whatman GF/B) using a Brandell 36-sample harvester (Gaithesburg, MD, USA) and thereafter the filters were washed with 4 × 5 mL ice-cold 50 mM Tris–HCl buffer (pH 7.4). Filter-bound radioactivity was counted in a liquid scintillation counter (Tricarb 2900; PerkinElmer Life Sciences, Boston, MA, USA) using 4 mL of scintillation fluid (Packard Ultima Gold MV, Packard, USA). Displacement curves were carried out using serial dilutions ranging from 100 μM to 0.1 nM of the unlabeled compound. Drugs were dissolved in DMSO. To avoid possible undesired effects on radioligand binding, DMSO concentration in the different assays never exceeded 0.1% (v/v). Protein determination was performed by means of Bradford protein assay using bovine serum albumine (BSA, Sigma–Aldrich, Milan, Italy) as a standard, according to the protocol of the supplier (Bio-Rad, Milan, Italy) [35].

All receptor binding experiments were performed in triplicate and results were confirmed in at least four independent experiments. Data from radioligand inhibition experiments were analyzed by nonlinear regression analysis of a Sigmoid Curve using GraphPad Prism program (GraphPad Software, Inc., San Diego, CA, USA). Ki values were calculated from the obtained IC50 values by means of the equation of Cheng and Prusoff [36]. Values of 0.92 nM, 1.34 nM and 0.68 nM for the dissociation constants of [3H]-DAMGO, [^{3}H]-DPDPE and [^{3}H]-U 69,593 were used respectively.

6.11. Isolated organs

Assays were performed according to the method described by Bilsky et al. on vas deferent segments taken from mice immediately after sacrifice [21]. After the explant, the vas deferent was transferred in a Petri dish containing a Krebs oxygenated solution (NaCl 118.2 mM, KCl 4.75 mM, KH_2PO_4 1.19 mM, $NaHCO_3$ 25.0 mM, glucose 11.0 mM, and $CaCl_2$ 2.54 mM) in order to proceed to the cleaning of the tissue and its subsequent dissection in segments having 1.0–1.2 cm length. Vas deferent segments were placed in tubs and they were immersed in 10 mL of an oxygenated Krebs solution (95% O_2 and 5% CO_2) and kept at 37 °C. One end of the vas deferens segment was attached to a fixed support, at the tub bottom, while the other end was connected to an isometric force transducer (WPI Fort10, Biological Instruments, Besozzo, Italy) for the registration of the contractions induced by electric stimuli. The samples were then equilibrated for 60 min, changing the Krebs solution every 15 min. The vas deferens segments were then subjected to treatment cycles wherein the electrical stimulation lasted 3 min, with an interval of 15 min before the following stimulation. The isometric contractions were evoked with sequences of 3 pulses (sequence frequency 0.1 Hz; pulse duration 2 ms) by means of platinum electrodes placed at the sides of the samples. The electrical stimuli were generated by a Grass S88K stimulator and amplified (multiplexing pulse booster 316S; Ugo Basile, Comerio, Italy). The musculature contractions of the vas deferens were monitored by a computer, recorded, and analysed by analysis system (PowerLab 400). The compounds to be tested were added to the vas deferens in cumulative doses, in the absence or in the presence of Naltrindole or CTAP, delta and mu reference antagonists, respectively.

The effect of the tested compounds on the contractions of vas deferens musculature was expressed in percentage. Values were calculated by referring the amplitude of the contractions induced by the electrical stimulations after each addition of the compound to the amplitude of the contractions obtained in the absence of the same compound (100%). The reported results are an average of the data obtained in seven different experiments.

6.12. In vivo assays: antinociceptive activity

Tail-flick test was adopted to assess antinociception in mice. Compounds to be tested were administered by intraperitoneal (i.p.) injection.

A tail-flick meter (Ugo Basile) equipped with an irradiant heat source that focused 2.5 cm of the distal tip of the tail was used. A 15 s cut-off time for heat exposure was used to avoid cutaneous damage and the intensity of the thermal source was adjusted to produce a 3- to 5-sec latency in vehicle-treated mice.

Each animal was tested before drug administration to determine control latency and the animals were used only in the determination of one time point. Data were transformed to the %MPE by the following equation [37]:

$$\%\,\mathrm{MPE} = [(\mathrm{test\ latency} - \mathrm{control\ latency})/ \times (\mathrm{cut} - \mathrm{off} - \mathrm{basal\ latency})] \times 100$$

where the latencies were expressed in the seconds and the cut-off was of 15 s.

All the assays were carried out with groups of ten animals. Mice were tested after 0.5, 1, and 2 h from i.p. administration of opioids (5 mg/kg) or corresponding vehicles. Statistical analysis was carried out using two-way ANOVA followed by Newman–Keuls post hoc test.

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