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Deconstructing 14-phenylpropyloxymetopon: Minimal requirements for binding to mu opioid receptors

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ABSTRACT

A series of phenylpropyloxyethylamines and cinnamyloxyethylamines were synthesized as deconstructed analogs of 14-phenylpropyloxymetopon and analyzed for opioid receptor binding affinity. Using the Conformationally Sampled Pharmacophore modeling approach, we discovered a series of compounds lacking a tyrosine mimetic, historically considered essential for μ opioid binding. Based on the binding studies, we have identified the optimal analogs to be *N*-methyl-*N*-phenylpropyl-2-(3-phenylpropoxy)ethanamine, with 1520 nM, and 2-(cinnamyloxy)-*N*-methyl-*N*-phenethylethanamine with 1680 nM affinity for the μ opioid receptor. These partial opioid structure analogs will serve as the novel lead compounds for future optimization studies.

1. Introduction

The μ opioid agonist morphine (**I**) is the standard for severe pain management.[1,2] Despite the ability of **I** to treat severe pain, there are significant side effects which often cause undermedication in clinical settings. Such effects are tolerance, dependence,[3] constipation, nausea, and respiratory depression.[4,5]

Opioid therapy is often accompanied by additional medications to treat or prevent some of the undesirable side effects.[6] One of the most problematic side effects associated with the μ opioids is constipation,[7] which becomes more severe as the dosage increases due to analgesic tolerance.[3] Though, constipation can be managed using laxatives and stool softeners during the initial stages of therapy, they are less effective during chronic use of opioid therapy.[6] Recently, peripherally- restricted μ opioid receptor antagonists, alvimopan,[8] and methylnaltrexone bromide, [9] have been approved by the FDA for treatment of opioid induced constipation. These agents do not cross the blood brain barrier (BBB), thus avoiding the antagonist effect in the CNS while reversing the unwanted side effects in the gastrointestinal tract (GI).[8,9] A significant limitation to chronic use of alvimopan is the increased risk of a heart attack.[8,10] Moreover, methylnaltrexone must be administered subcutaneously as it exhibits poor oral bioavailability.[9] Another problem associated with co-administration of these drugs with opioid agonists is that it adds to the regimen of drugs already taken by the patients.

Tremendous effort has been put towards the development of novel opioids lacking side effects that are commonly seen in opioid treatment.[11] Lack of tolerance and physical dependence has been observed after repeated treatment with 14-methoxymetopon (**II**, Fig. 1), a member of the alkoxymorphinan opioid series.[12] Studies also showed that **II** has reduced constipation[13] as compared to **I** and respiratory depression as compared to sufentanil[14] and has been characterized as a μ selective opioid with 500-fold greater systemic antinociceptive potency than **I**.[13,12] Upon superaspinal administration, **II** can elicit potency of up to one million-fold greater than morphine.[13] Another derivative that belongs to the 14-alkoxymorpinan family is the 14-phenylpropyloxymetopon (**III**, Fig. 1), an agonist which is even more potent than **II** (24000-fold higher in the tail flick assay and 8500-fold higher in the hot plate assay as compared to **I**).[15] Although **III** is unsuitable for clinical use due to its extreme potency, it can serve as a lead compound for structural development of a novel opioid skeleton.

The structure of **III** is comprised of 6 rings: aromatic A, cyclohexyls B and C, piperidine D, epoxy E, and an aromatic ring coming off position 14 (Fig. 1).[15] Our current work aimed to deconstruct **III** in an effort to develop a novel opioid class that exhibits high affinity at the μ opioid receptor. Our hypothesis is that opioid activity can be achieved in the presence of a basic amine and a phenylpropyloxy group alone. By removing fundamental rings A–E, the skeleton will be able to adopt an alternate binding mode with the receptor, thereby potentially causing alternate receptor trafficking events[16] and post-receptor mechanisms, all of which are involved in the development of tolerance.[3] To test our hypothesis, phenylpropyloxyethylamine (**IV**, Fig. 1) and analogs with flexible and ring-constrained

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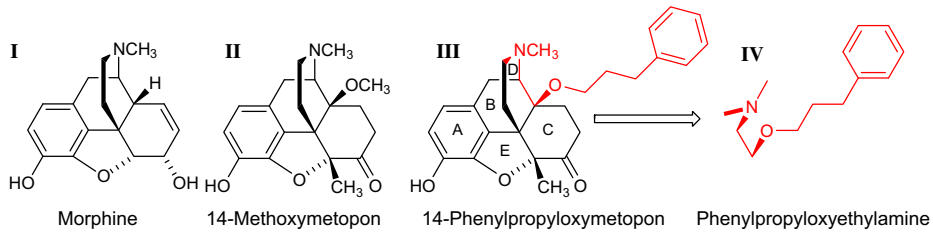


Figure 1. Opioids used for hypothesis and the proposed analog.

N-substituents were synthesized, characterized, and pharmacologically evaluated. Specifically, the synthesis of phenylpropyloxyethylamines containing *N*,*N*-dimethyl, diethyl, dipropyl, and dibutyl, as well as pyrrolidine, pyridine, and azepane substituents is described. In addition, a cinnamyloxyethylamine series containing identical *N*-substituents was generated in an effort to understand the effect of saturation in this group. In order to investigate differences and similarities in increasing affinities[11] between the morphinans and this series, *N*-benzyl, *N*-phenethyl and *N*-phenylpropyl analogs were synthesized. The results show that the novel series of compounds differ in their affinity for the μ opioid receptor. Additionally, we discovered a series of compounds lacking a tyrosine mimetic, historically considered essential for μ opioid binding.

2. Results and discussion

2.1. Chemistry

In our initial studies, *N*,*N*-dimethyl-2-(3-phenylpropoxy)ethanamine (**3**), 2-(cinnamyloxy)-*N*,*N*-dimethylethanamine (**5**), and 1-(2-(3-phenylpropoxy)ethyl)pyrrolidine (**7**) were synthesized and characterized following literature procedures[17] as shown in Scheme 1. The appropriate chloroethylamines **2**, **6** were treated with the alcohols **1**, **4** in the presence of NaH and heated at 50 °C for 3 h. Compounds **3, 5** and **7** were successfully synthesized in moderate yields (**3**, 40%; **5**, 17%; **7**, 22%). Due to the hygroscopic nature of the salts, the final products remained in oil form.

To improve the yield of amino ethers and use a less hazardous compound than NaH, an alternate approach was developed and utilized for subsequent reactions. Potassium hydroxide proved to be a good substitute for NaH, and reactions were found to proceed well, with less side-products, at room temperature. Targets **13–18**, **20**, and **21** (Scheme 2) were prepared following the new procedure. Compound **13** was attained from starting materials **8** and **10**; **14** from **9** and **10**; **15** from **8** and **11**; **16** from **9** and **11**; **17** from **8** and **12**; **18** from **9** and **12**; **20** from **8** and **19**; and **21** from **9** and **19**. The final products were converted into oxalic salts using diethyl ether and oxalic acid. All of the compounds were synthesized in moderate 22–37% yields.

To investigate the effect of constrained *N*-substituents, targets **24–28** were synthesized (Scheme 3) following the same procedure as developed for the alkyl analogs. Compound **24** was prepared from **4** and **6**; **25** from **1** and **22**; **26** from **4** and **22; 27** from **9** and **23**; and **28** from **8** and **23**.

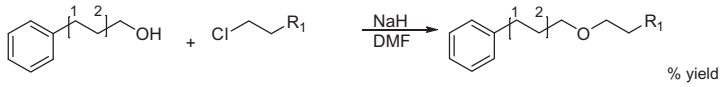
The *N*-arylalkyl and *N*-diallyl series (Scheme 4) was selected based on the established SAR of increasing affinity in opioids. Specifically, *N*-allyl, *N*-phenethyl, and *N*-phenylpropyl tended to yield high affinity while the *N*-benzyl groups tended to yield low affinity at the μ opioid receptor.[11] Compounds **33** (**8**, **29**), **34** (**9**, **29**), **35** (**8**, **30**), **36** (**9**, **30**), **37** (**8**, **31**), **38** (**9**, **31**), **39** (**8**, **32**), and **40** (**9**, **32**) were synthesized in order to investigate the differences and similarities that compounds without the traditional rings have within this series.

2.2. Molecular modeling studies

The novel series of compounds consist of an aromatic moiety, similar to that of morphine and its analogs. To investigate if the aromatic moiety on compounds **17** and **18** mimic the aromatic moiety coming off position 14 on 14-cinnamyloxymetopon, and not the A-ring on morphine, the conformationally sampled pharmacophore (CSP)[18–22] modeling approach was applied and pharmacophore models were designed. The CSP method, developed by MacKerell and coworkers, is a novel approach for ligand-based drug design.[19–22] This method maximizes the probability of inclusion of the bioactive conformation for model development by considering all the energetically accessible conformations of each ligand in the set rather than individual low energy conformers traditionally used. The CSP method has been previously used to predict the affinity and efficacy of the peptidic and nonpeptidic δ opioids[20–22] as well as to a number of conjugated bile acids,[18,19] with many of the compounds studied being highly flexible. Considering that the studied compounds also have a high degree of conformational freedom, the CSP method was performed in order to ensure that conformational flexibility of the ligands was properly taken into account during model development.

For the analysis, only the first replica corresponding to room temperature was used from which 2500 conformations were obtained. The 1D probability distribution of distances between the basic nitrogen (N) and the centroid of the aromatic moieties (*X* and *Y*) of compounds **17** and **18**, are displayed in Figure 2. As expected, there is a significant overlap for the YN distances (Table 1) of the molecules indicated in red (**14-COM**), blue (**17**), and magenta (**18**) and no evident overlap is observed with compound **17** and the A-ring (XN: indicated in green). However, when the OC values are analyzed for compound **18** (Table 1), a small amount of overlap occurs indicating that, although the aromatic moiety on phenylpropyloxyethylamines does not have large overlap with A-ring (OC = 0.0024), some overlap is possible.

Additionally, the similar approach was utilized to determine the 1D probability distribution of maximum distances between the aromatic moieties on the *N*-arylalkyl series (compounds **33**–**38**) and the

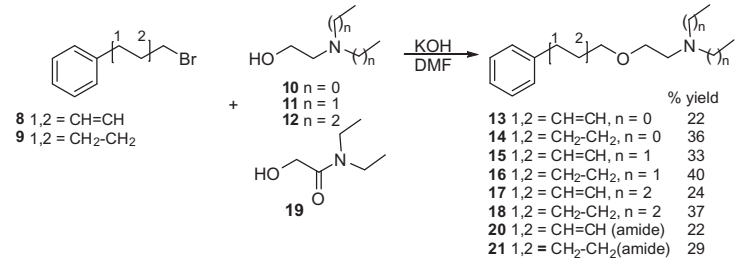


1 1,2 = CH_2-CH_2
4 1,2 = CH=CH

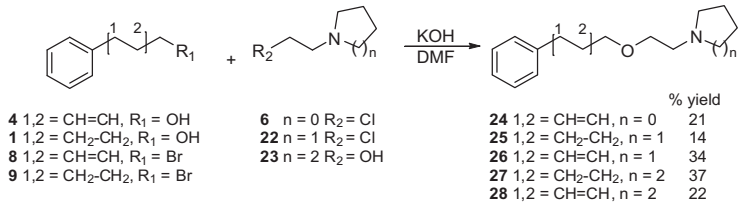
2 R_1 = dimethylamine
6 R_1 = pyrrolidine

	% yield
3 1,2 = CH_2-CH_2, R_1 = dimethylamine	40
5 1,2 = CH=CH, R_1= dimethylamine	17
7 1,2 = CH_2-CH_2, R_1 = pyrrolidine	22

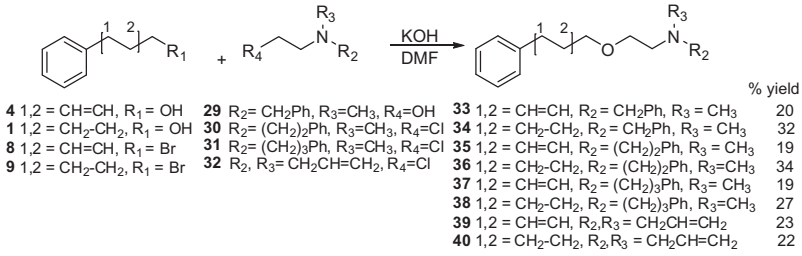
Scheme 1. Synthesis of analogs **3**, **5** and **7** and their yields.



Scheme 2. Synthesis of *N*,*N*-dialkyl analogs and their yields.



Scheme 3. Synthesis of pyrrolidine, piperdine and azepane containing analogs and their yields.



Scheme 4. Synthesis of *N*-arylalkyl and *N*-diallyl analogs and their yields.

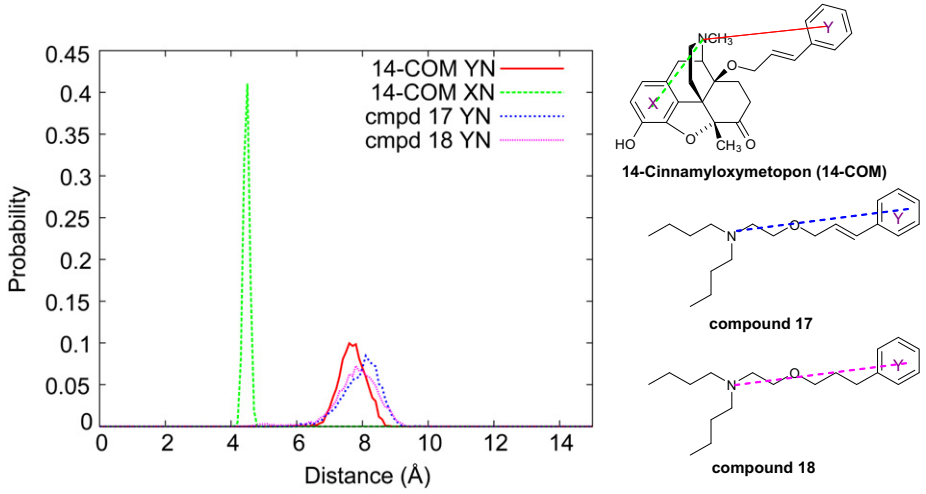


Figure 2. 1D probability distribution of distances between the basic nitrogen (N) and the aromatic moieties (*X*, *Y*) of compounds **17** and **18**. Green represents the probability distribution of the XN distance on the 14-cinnamyloxymetopon (14-COM); red the YN on the 14-cinnamyloxymetopon; blue the YN on **17** and magenta the YN on **18**.

basic nitrogen and compared to the distribution between the aromatic A-ring and the basic nitrogen on morphine. Results displayed in Figure 3 illustrate that the distance distribution between the aromatic ring coming off the oxygen position ('Left' phenyl) and the nitrogen on the phenylpropyloxyethylamines had some overlap with the conformations that are sampled by the aromatic A-ring and the basic nitrogen on morphine in the vicinity of 5–6 Å. The extent of overlap is quantified based on the OC values in Table 2. Thus, while the probability is low, it is possible for the aromatic rings in **33**–**38** to assume a conformation of the A-ring relative to the basic N similar to that in morphine. It is more likely when considering morphine analogues which possess more flexible distances between aromatic ring and basic nitrogen such as tramadol and tapentadol (Fig. S1, Supplementary data). However, the cinnamyl analogs are

Table 1
Overlap coefficients for compounds **17** and **18**

Compd	OC with respect to XN of 14-COM	OC with respect to YN of 14-COM
17	0	0.6838
18	0.0024	0.7648

Table 2
Overlap coefficients for compounds **33**–**38**

Compd	OC with respect to morphine A-ring	
	'Left' Phenyl[a]	'Right' phenyl[a]
33	0	0.0002
34	0.0204	0.0002
35	0	0.025
36	0.0172	0.0158
37	0	0.0344
38	0.0126	0.0426

[a] 'Left' and 'Right' refer to the rings relative to the basic N as shown in Figures 3 and 4.

less likely to mimic the A-ring as they are less flexible and therefore sample a narrower range of conformations.

Similar to the above results, the *N*-benzyl derivatives ('Right' phenyl) have only a very small amount of overlap with the morphine A-ring probability distribution (Fig. 4, Table 2). In contrast, more overlap in the conformational sampling between the basic nitrogen and the aromatic ring on the *N*-phenethyl and *N*-phenylpropyl is observed with that of the A-ring on morphine. These results indicate that the aromatic moiety on compounds **35**–**38** may be mimicking the A-ring.

2.3. Opioid receptor binding

Opioid binding studies for the compounds were performed at all three opioid receptors (μ, δ, κ) via a displacement assay, following standard procedures.[23] The phenylpropyloxyethylamine and cinnamyloxyethylamine analogs showed low to negligible (>10,000 nM) affinity at the μ opioid receptor. Table 3 contains data for compounds possessing <10,000 nM binding affinity. The *N*-dibutyl analogs (**17**, **18**) in the *N*-dialkyl series both displayed similar weak binding affinity (2490 nM) for the μ receptor and negligible (>10,000 nM) affinity for the δ receptor, independent of the level of the unsaturation.

N-heterocycles were examined to delineate the effect of conformational freedom of these substituents on opioid activity. From our results, it appears that constraining the flexible chains in the *N*-dialkyl analogs to give ring-constrained *N*-heterocyclic analogs (**7**, **24**–**27**) is not favorable for interaction with the opioid receptors and results in negligible binding affinity in the displacement assays (data not shown).

The *N*-arylalkyl and *N*-diallyl analogs were selectively synthesized motivated by established opioid SAR.[11] From the results in Table 3, it appears that the second aromatic ring is important for binding. Among the *N*-arylalkyl analogs, compounds **35** and **38** displayed the highest affinity for the μ opioid binding site (1680 and 1520 nM, respectively), weak affinity for δ (6850 and 6650 nM, respectively), and negligible (>10,000 nM) affinity for κ. The *N*-benzyl analogs (**33**, **34**), which tend to yield lower affinity as compared to *N*-phenethyl and *N*-phenylpropyl substituents (in the established opioid SAR)[11] displayed similar binding affinity for the μ opioid receptor (2760–3040 nM) as the *N*-phenethyl and *N*-phenylpropyl analogs (**35**–**38**, 1520–6450 nM), while the *N*-diallyl analogs showed no activity at either receptor type (data not shown). The present results on differing *N*-arylalkyl analogs provided evidence that the current series does not possess the typical opioid SAR profile for the *N*-aryl alkyl analogs.

3. Conclusion

A series of phenylpropyloxyethylamines with differing *N*-substituents were synthesized to test the hypothesis that opioid activity can be achieved in the presence of a basic amine and a phenylpropyloxy group alone. The phenylpropyloxyethylamines are capable of binding to the μ opioid receptor, possessing a fairly weak affinity while maintaining negligible affinity for κ and δ

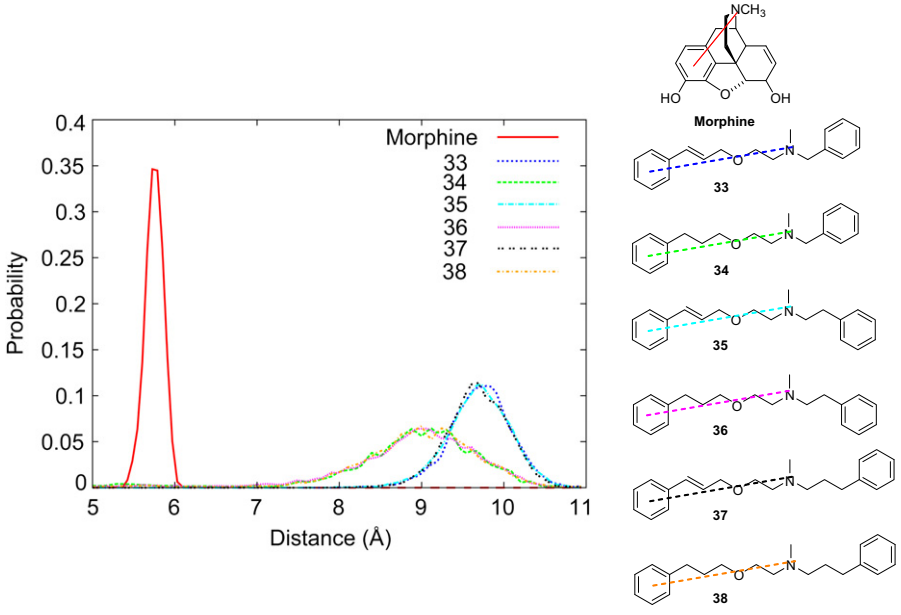


Figure 3. 1D probability distribution of distances between the basic nitrogen and the aromatic moiety coming off the oxygen on compounds **33**–**38** and the aromatic A-ring on morphine.

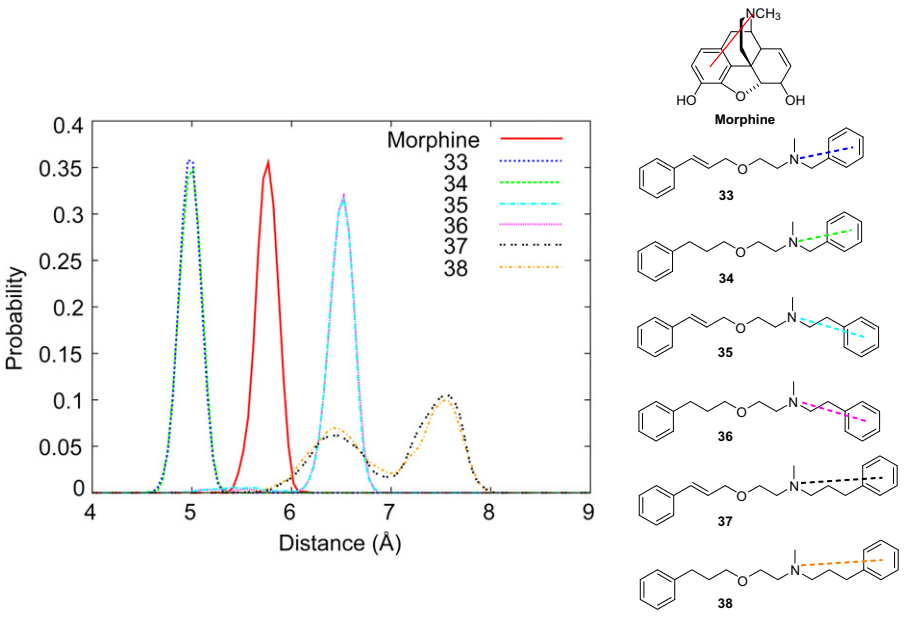


Figure 4. 1D probability distribution of distances between the basic nitrogen and the aromatic moiety coming off the nitrogen on compounds **33**–**38** and the aromatic A-ring on morphine.

Table 3
Opioid receptor binding affinities

Compd	K_i ± SEM (nM)		
	[^{3}H] DAMGO (μ)	[^{3}H] DPDPE (δ)	[^{3}H] U69,593 (κ)
17	2490 ± 206	>10,000	>10,000
18	2490 ± 165	>10,000	>10,000
33	3040 ± 250	>10,000	>10,000
34	2760 ± 146	>10,000	>10,000
35	1680 ± 155	6850 ± 453	>10,000
36	2310 ± 193	8530 ± 669	>10,000
37	6450 ± 315	>10,000	>10,000
38	1520 ± 175	6650 ± 405	>10,000
Naltrexone	0.46 ± 0.12	11 ± 1.1	1.07 ± 0.06

The affinity results showed that the optimal N-substituents include *N*-phenethyl and *N*-phenylpropyl. Overall, there was no noticeable trend between the saturated and unsaturated derivatives in the phenylpropyloxyethylamine series. None of the compounds exhibited sufficient affinity to enable the determination of their efficacy.

receptors. Based on the opioid binding studies, we have identified the optimal analogs in the current series to be **38**, with 1520 nM, and **35**, with 1680 nM affinity for the μ opioid receptor. Conformational analysis based on the CSP modeling approach showed that although the aromatic rings in the novel series have only minimal spatial overlap with the A-ring, their mimicking the A-ring cannot be totally excluded. Nonetheless, compounds **35** and **38** will serve as the novel lead compounds for further optimization studies that will focus on restricting the conformation via reintroduction of the opioid rings B, D and C.

4. Methods

4.1. Computational methods

Compounds were modeled using the program CHARMM[24] with the CHARMM General Force Field[25] (CGenFF) parameters. Energy minimizations were performed using the steepest descent and adopted basis Newton-Raphson (ABNR) to a RMS force of 10^{-6} kcal/mol Å in vacuum with infinite non-bond interaction lists. MD simulations were performed with a 2 fs integration time step using the Leap-Frog integrator[26] with covalent bonds involving hydrogen atoms constrained to their equilibrium bond length by the SHAKE algorithm.[27] Aqueous solvation was treated using the generalized born continuum solvent model,[28] with non-bond interactions truncated at 18 Å with smoothing over the region 16–18 Å using a switching function.[29] For conformational sampling, the molecules were subjected to Temperature Replica Exchange-Molecular Dynamic (TREX-MD) simulations.[30] TREX-MD is an efficient sampling method used to overcome local minima and to sample diverse conformational space.[30] TREX-MD performs a range of independent MD simulations (replicas) in which each replica is under different temperatures, representing system of different degrees of kinetic energy to overcome energy barriers.[30] Exchanges of conformations occuring between the adjacent simulations are selected according to the Metropolis criterion,[31], such that exchanges that lead to a lower energy are always accepted and the exchanges leading a higher energy are conditionally accepted. In this study, 8 replicas with exponential scaling of temperatures between 300–400 K (300, 313, 326, 339, 354, 368, 384, 400 K) were used. MD simulations on each replica were carried out for 5 ns using Langevin dynamics[32] in implicit solvent using the GBMV (generalized born using molecular volume) method.[33] Exchanges were attempted every 0.5 ps. To confirm that the simulation was sampling distinctive conformations, the probability of geometric distributions was compared with increasing simulation time. For example, the probability distribution of distances between basic nitrogen and aromatic ring of **5** was calculated over 0.5 ns intervals. Overlap between the probability distributions at 4.5 and 5 ns reached 99% and a significant shift in the population was not observed. Therefore 5 ns sampling was deemed converged enough to perform further model development. Distance probability distributions were calculated with a bin size of 0.1 Å. To measure the degree of overlap in the probability distributions between compounds the overlap coefficient (OC) was calculated. Given two probability distributions, the OC is obtained using equiv 1

$$\sum_i \min(P_i, Q_i) \quad (1)$$

where, *i* is any descriptors such as distance between two pharmacophoric points and P_i and Q_i are the normalized probabilities of compounds P and Q.

4.2. Opioid binding assay

Opioid binding studies for the compounds were performed at all three opioid receptors (μ, δ, κ) via a displacement assay, following standard procedures.[23] Briefly, μ opioid receptor membrane protein were labeled with 1.3 nM [^{3}H]DAMGO (53.4 Ci/mmol). δ Opioid receptor membrane protein were labeled with 1.2 nM [^{3}H]DPDPE (45 Ci/mmol). κ Opioid receptor membrane protein were labeled with 1.7 nM [^{3}H]U69,593 (42.7 Ci/mmol). Nonspecific binding was defined as the radioactivity bound in the presence of 1 μM unlabelled DAMGO, DPDPE and U69,593 for the respective subtypes. Competition binding studies were performed using 12 concentrations of each test compound and were incubated for 1 h at 25 °C. Reactions were terminated by rapid vacuum filtration through GF/B glass fiber filters previously soaked in 0.5% polyethyleneimine. Bound radioactivity was quantified by liquid scintillation counting. Affinities (K_i) were calculated using the Cheng-Prusoff equation.

4.3. Experimental methods

All reagents and solvents were purchased from Sigma–Aldrich unless stated otherwise and used without further purification. All reactions were carried out under an atmosphere of nitrogen. Thin layer chromatography was performed on silica 60 F_{254} plated (Analtech). All compounds were purified using standard techniques (crystallization, etc) and characterized using standard spectroscopic methods such as ^{1}H NMR (Varian Inova 500 MHz) and MS (ThermoFinnigan LCQ Classic). Elemental analysis was performed by atlantic microlabs.

4.3.1. Experimental procedures

*N,N-Dimethyl-2-(3-phenylpropyloxy)ethanamine (**3**).* *Method 1:* A solution of 3-phenyl1-propanol, **1** (5.99 mL, 44.6 mmol) in dry DMF was added to a stirring solution of 2.39 g (104 mmol) of NaH at room temperature. After 30 min, 1.60 g (14.9 mmol) of 2-(dimethylamino)ethylchloride hydrochloride, **2** was added in small portions over a 30 min period. The resulting mixture was allowed to stir for another 3 h at 50 °C and 30 min at room temperature. After completion, the reaction mixture was quenched with ethanol and the solvent was removed under reduced pressure. The crude product was dissolved in H_2O and extracted with Et_2O. The product was then extracted into 6 M HCl from Et_2O. The solution was basified to pH 12–13 with 5 M NaOH (aq) and extract with Et_2O. The combined organic layers were washed with brine solution and dried over Na_2SO_4. After removal of the solvent under reduced pressure, the crude product was purified by column chromatography (silica gel, 5% $CHCl_3$/MeOH/1% NH_4OH) followed by formation of oxalate salt from ether. Yield 40% (1.23 g); mp 120–121 °C

Method 2: To obtain target **3**, alcohol **1** (1.25 mL, 9.30 mmol) was reacted with **2** (1 g, 9.30 mmol) in the presence of KOH (2.5 equiv, 1.30 g) in DMF (20 mL/g). The reaction mixture was allowed to stir overnight at room temperature. After completion, the crude reaction mixture was dissolved in H_2O and extracted with Et_2O. The product was then extracted into 6 M HCl from Et_2O. The solution was basified to pH 12–13 with 5 M NaOH (aq) and extract with Et_2O. The combined organic layers were washed with brine solution and dried over Na_2SO_4. After removal of the solvent under reduced pressure, the crude product was purified by column chromatography (silica gel, 5% $CHCl_3$/MeOH/1% NH_4OH) followed by formation of oxalate salt from ether. Yield 57%, (1.10 g); mp 120–121 °C

^{1}H NMR (D_2O) δ 7.36–7.42 (m, 2H), δ 7.27–7.35 (m, 3H), δ 3.77–3.81 (m, 2H), δ 3.56–3.61 (m, 2H), δ 3.33–3.38 (m, 2H), δ 2.90–2.93 (m, 6H), δ 2.69–2.75 (m, 2H), δ 1.91–1.98 (m, 2H); MS ESI m/z = 208 ($M+H^+$); Anal. ($C_{13}H_{21}NO$ ($C_2H_2O_4$)$_1$) C, H, N.

*2-(Cinnamyloxy)-N,N-dimethylethanamine (**5**)* was prepared through alkylation of cinnamyl alcohol, **4** (3.74 g 27.9 mmol) with 2-(dimethylamino)ethylchloride hydrochloride, **2** (1 g, 9.30 mmol) following both method 1 and 2 described above. Yield 17% (0.32 g); ^{1}H NMR (D_2O) δ 7.54 (d, 3.50 Hz, 2H), δ 7.42–7.49 (m, 3H), δ 6.75–6.80 (m, 1H), δ 6.39–6.46 (m, 1H), δ 4.29 (d, 3.33 Hz, 2H), δ 3.88 (t, 5.25 Hz, 2H), δ 3.41 (t, 4.90 Hz, 2H), δ 2.91–2.96 (m, 6H); MS ESI m/z = 206 ($M+H^+$); Anal. ($C_{13}H_{19}NO$ ($C_2H_2O_4$)$_1$) C, H, N.

*1-(2-(3-Phenylpropoxy)ethyl)pyrrolidine (**7**)* was prepared through alkylation of 3-phenyl1-propanol, **1** (2.01 mL, 15.0 mmol) with 1-(2-Chloroethyl)pyrrolidine hydrochloride (1 g, 7.4 8 mmol) following both method 1 and 2 described above. Yield 22% (0.38 g);1H NMR (D_2O) δ 7.41 (t, 7.67 Hz, 2H), δ 7.27–7.35 (m, 3H), δ 3.76–3.80 (m, 2H), δ 3.64–3.70 (m, 2H), δ 3.58 (t, 6.61 Hz, 2H), δ 3.39 (t, 4.84 Hz, 2H), δ 3.09–3.18 (m, 2H), δ 2.71 (t, 7.44 Hz, 2H), δ 2.11–2.21 (m, 2H), δ 1.91–2.07 (m, 4H); MS ESI m/z = 234 ($M+H^+$); Anal. ($C_{15}H_{23}NO$ ($C_2H_2O_4$)$_1$) C, H, N.

*2-(Cinnamyloxy)-N,N-diethylethanamine (**13**)* was prepared through alkylation of 2-(diethylamino)ethanol, **10** (1.14 mL, 8.53 mmol) with cinnamyl bromide, **8** (1.85 g, 9.39 mmol) in presence of KOH (1.19 g, 21.3 mmol) following method 2 described previously. Yield 22% (0.44 g); ^{1}H NMR (D_2O) δ 7.54 (d, 3.94 Hz, 2H), δ 7.44 (t, 7.42 Hz, 2H), δ 7.35–7.41 (m, 1H), δ 6.74–6.80 (m, 1H), δ 6.38–6.46 (m, 1H), δ 4.27 (d, 3.48 Hz, 2H), δ 3.87 (t, 4.87 Hz, 2H), δ 3.40 (t, 4,87 Hz, 2H), δ 3.22–3.36 (m, 4H), δ 1.31 (t, 7.19 Hz, 6H); MS ESI m/z = 234 ($M+H^+$); Anal. ($C_{15}H_{23}NO$ ($C_2H_2O_4$)$_1$) C, H, N.

*N,N-Diethyl-2-(3-phenylpropoxy)ethanamine (**14**)* was prepared through alkylation of 2-(diethylamino)ethanol, **10** (1.14 mL, 8.53 mmol) with 1-bromo-3-phenylpropane, **9** (1.43 mL, 9.39 mmol) in presence of KOH (1.19 g, 21.3 mmol) following method 2 described previously. Yield 36% (0.72 g); ^{1}H NMR (D_2O) δ 7.39 (t, 7.37 Hz, 2H), δ 7.26–7.35 (m, 3H), δ 3.76–3.81 (m, 2H), δ 3.58 (t, 6.47 Hz, 2H), δ 3.19–3.37 (m, 6H), δ 2.71 (t, 7.37 Hz, 2H), δ 1.90–1.98 (m, 2H), δ 1.30 (t, 7.19 Hz, 6H); MS ESI m/z = 236 ($M+H^+$); Anal. ($C_{15}H_{25}NO$ ($C_2H_2O_4$)$_1$) C, H, N.

*2-(Dipropylamino)ethanol (**11**)* A mixture of dipropylamine (1.35 mL, 9.88 mmol), 2-chloroethanol (0.86 mL, 9.88 mmol) and K_2CO_3 (13.7 g, 99 mmol) in DMF (20 mL/g) was vigorously stirred at room temperature under N_2. After completion, H_2O was added and extracted with Et_2O. The combined organic layers were washed with brine solution and dried over Na_2SO_4. After removal of the solvent under reduced pressure, the crude product was purified by column chromatography (silica gel, 1–3% $CHCl_3$/MeOH/1% NH_4OH). Yield 78% (1.12 g); MS ESI m/z = 146 ($M+H^+$).

*2-(Cinnamyloxy)-N,N-diethylethanamine (**15**)* was prepared through alkylation of 2-(dipropylamino)ethanol, **11** (0.80 g, 5.51 mmol) with cinnamyl bromide, **8** (1.09 g, 5.51 mmol) in presence of KOH (0.46 g, 8.26 mmol) following method 2 described previously. Yield 33% (0.48 g); ^{1}H NMR (D_2O) δ 7.49–7.54 (m, 2H), δ 7.43 (t, 7.57 Hz, 2H), δ 7.31 (m, 1H), δ 6.71–6.77 (m, 1H), δ 6.35–6.44 (m, 1H), δ 4.25 (d, 3.53 Hz, 2H), δ 3.87 (t, 4.44 Hz, 2H), δ 3.41 (t, 4.70 Hz, 2H), δ 3.08–3.21 (m, 4H), δ 1.66–1.77 (m, 4H), δ 0.94 (t, 7.31 Hz, 6H); MS ESI m/z = 262 ($M+H^+$); Anal. ($C_{17}H_{27}NO$ ($C_2H_2O_4$)$_1$ (H_2O)$_{0.75}$) C, H, N.

*N,N-Diethyl-2-(3-phenylpropoxy)ethanamine (**16**)* was prepared through alkylation of 2-(dipropylamino)ethanol, **11** (0.8 g, 5.51 mmol) with 1-bromo-3-phenylpropane, **9** (0.84 mL, 5.51 mmol) in presence of KOH (0.46 g, 8.26 mmol) following method 2 described previously. Yield 40% (0.58 g); ^{1}H NMR (D_2O) δ 7.37 (t,

6.98 Hz, 2H), δ 7.25–7.33 (m, 3H), δ 3.75–3.81 (m, 2H), δ 3.53–3.59 (m, 2H), δ 3.33–3.38 (m, 2H), δ 3.07–3.20 (m, 4H), δ 2.70 (t, 7.46 Hz, 2H), δ 1.88–1.97 (m, 2H), δ 1.66–1.77 (m, 4H), δ 0.96 (t, 6.98 Hz, 6H); MS ESI *m*/*z* = 264 ($M+H^+$); Anal. ($C_{17}H_{29}NO$ ($C_2H_2O_4$)$_1$) C, H, N.

*2-(Cinnamyloxy)-N,N-dibutylethanamine (**17**)* was prepared through alkylation of 2-(dibutylamino)ethanol, **12** (1.16 g, 5.77 mmol) with cinnamyl bromide, **8** (1.25 g, 6.35 mmol) in presence of KOH (0.81 g, 14.43 mmol) following method 2 described previously. Yield 24% (0.40 g); ^1H NMR (D_2O) δ 7.53 (d, 3.65 Hz, 2H), δ 7.43 (t, 7.57 Hz, 2H), δ 7.33–7.38 (m, 1H), δ 6.72–6.78 (m, 1H), δ 6.37–6.44 (m, 1H), δ 4.24 (d, 3.13 Hz, 2H), δ 3.84–3.88 (m, 2H), δ 3.41 (t, 4.83 Hz, 2H), δ 3.12–3.25 (m, 4H), δ 1.64–1.73 (m, 4H), δ 0.92 (t, 7.31 Hz, 6H); MS ESI *m*/*z* = 290 ($M+H^+$); Anal. ($C_{19}H_{31}NO$ ($C_2H_2O_4$)$_1$ (H_2O)$_{0.25}$) C, H, N.

*N,N-Dibutyl-2-(3-phenylpropoxy)ethanamine (**18**)* was prepared through alkylation of 2-(dibutylamino)ethanol, **12** (1.16 mL, 5.77 mmol) with 1-bromo-3-phenylpropane, **9** (0.96 mL, 6.35 mmol) in presence of KOH (0.81 g, 14.43 mmol) following method 2 described previously Yield 37% (0.62 g); ^1H NMR (D_2O) δ7.39 (t, 7.50 Hz, 2H), δ 7.26–7.35 (m, 3H), δ 3.76–3.82 (m, 2H), δ 3.58 (t, 6.52 Hz, 2H), δ 3.34–3.40 (m, 2H), δ 3.12–3.26 (m, 4H), δ 2.72 (t, 7.50 Hz, 2H), δ 1.90–1.97 (m, 2H), δ 1.63–1.74 (m, 4H), δ 1.33–1.43 (m, 4H), δ 0.90–0.98 (m, 6H); MS ESI *m*/*z* = 292 ($M+H^+$); Anal. ($C_{19}H_{33}NO$ ($C_2H_2O_4$)$_1$) C, H, N.

*2-(Cinnamyloxy)-N,N-diethylacetamide (**20**)* was prepared through alkylation of *N,N*-diethyl-2-hydroxyacetamide, **19** (1.00 mL, 7.62 mmol) with cinnamyl bromide, **8** (1.65 g, 8.39 mmol) in presence of KOH (1.07 g, 19.06 mmol) following method 2 described previously. Yield 22% (0.42 g);; ^1H NMR (D_2O) δ 7.39 (d, 3.74 Hz, 2H), δ 7.32 (t, 7.65 Hz, 2H), δ 7.22–7.28, (m, 1H), δ 6.60–6.66 (m, 1H), δ 6.27–6.35 (m, 1H), δ 4.24–4.28 (m, 2H), δ 4.19 (s, 2H), δ 3.39 (q, 7.12 Hz, 2H), δ 3.31 (q, 7.12 Hz, 2H), δ 1.11–1.22 (m, 6H); MS ESI *m*/*z* = 248 ($M+H^+$); Anal. ($C_{15}H_{21}NO$) C, H, N.

*N,N-Diethyl-2-(3-phenylpropoxy)acetamide (**21**)* was prepared through alkylation of *N,N*-diethyl-2-hydroxyacetamide, **19** (1.00 mL, 7.62 mmol) with 1-bromo-3-phenylpropane, **9** (1.27 mL, 8.39 mmol) in presence of KOH (1.07 g, 19.1 mmol) following method 2 described previously. Yield 29% (0.55 g); ^1H NMR (D_2O) δ 7.91–7.98 (m, 2H), δ 7.81–7.89 (m, 3H), δ 4.20 (t, 6.49 Hz, 2H), δ 3.96–4.08 (m, 4H), δ 3.38 (t, 7.79 Hz, 2H), δ 2.52–2.66 (m, 2H), δ 2.29 (s, 2H), δ 1.76–1.89 (m, 6H); MS ESI *m*/*z* = 250 ($M+H^+$); Anal. ($C_{15}H_{23}NO$) C, H, N.

*1-(2-(Cinnamyloxy)ethyl)pyrrolidine (**24**)* was prepared through alkylation of cinnamyl alcohol, **4** (3.01 g, 22.5 mmol) with 1-(2-Chloroethyl)pyrrolidine hydrochloride, **6** (1.00 g, 7.48 mmol) in presence of KOH (1.05 g, 18.71 mmol) following method 2 described previously. Yield 21%; ^1H NMR (D_2O) δ 7.55 (d, 10.79 Hz, 2H), δ 7.46 (t, 7.73 Hz, 2H), δ 7.39 (t, 7.33 Hz, 1H), δ 6.76–6.82 (m, 1H), δ 6.40–6.48 (m, 1H), δ 4.29 (d, 3.05 Hz, 2H), δ 3.88 (t, 16.90 Hz, 2H), δ 3.67–3.76 (m, 2H), δ 3.44–3.49 (m, 2H), δ 3.11–3.21 (m, 2H), δ 2.11–2.23 (m, 2H), δ 1.98–2.09 (m, 2H); MS ESI *m*/*z* = 232 ($M+H^+$); Anal. ($C_{13}H_{21}NO$ ($C_2H_2O_4$)$_1$ (H_2O)$_{0.25}$) C, H, N.

*1-(2-(3-Phenylpropoxy)ethyl)piperidine (**25**)* was prepared through alkylation of 3-phenyl1-propanol, **1** (0.92 mL, 6.77 mmol) with 1-(2-chloroethyl)piperidine hydrochloride, **22** (1 g, 6.77 mmol) in presence of KOH (0.95 g, 17.0 mmol) following method 2 described previously. Yield 14% (0.24 g); ^1H NMR (D_2O) δ 7.41 (t, 7.43 Hz, 2H), δ 7.29–7.36 (m, 3H), δ 3.82 (t, 5.04 Hz, 2H), δ 3.59 (t, 6.44 Hz, 2H), δ 3.56 (d, 3.56 Hz, 2H), δ 3.32 (t, 5.04 Hz, 2H), δ 3.00 (t, 12.87 Hz, 2H), δ 2.76 (t, 7.57 Hz, 2H), δ 1.92–2.00 (m, 4H), δ 1.71–1.88 (m, 3H), δ 1.46–1.55 (m, 1H); MS ESI *m*/*z* = 248 ($M+H^+$); Anal. ($C_{16}H_{23}NO$ ($C_2H_2O_4$)$_1$) C, H, N.

*1-(2-(Cinnamyloxy)ethyl)piperidine (**26**)* was prepared through alkylation of cinnamyl alcohol, **4** (1.82 g, 13.55 mmol) with 1-(2-chloroethyl)piperidine hydrochloride, **22** (1.00 g, 6.77 mmol) in presence of KOH (0.95 g, 16.93 mmol) following method 2 described previously. Yield 34% (0.57 g); ^1H NMR (D_2O) δ 7.53 (d, 3.86 Hz, 1H), δ 7.43 (t, 7.61 Hz, 2H), δ 7.37 (t, 7.17 Hz, 1H), δ 6.73–6.79 (m, 1H), δ 6.38–6.45 (m, 1H), δ 4.26 (d, 3.20 Hz, 2H), δ 3.88 (t, 4.97 Hz, 2H), δ 3.57 (d, 6.40 Hz, 2H), δ 3.35 (t, 4.85 Hz, 2H), δ 2.99 (t, 12.35 Hz, 2H), δ 1.94 (d, 7.50 Hz, 2H), δ 1.69–1.85 (m, 3H), δ 1.43–1.54 (m, 1H); MS ESI *m*/*z* = 246 ($M+H^+$); Anal. ($C_{16}H_{25}NO$ ($C_2H_2O_4$)$_1$ (H_2O)$_{0.25}$) C, H, N.

*1-(2-(3-Phenylpropoxy)ethyl)azepane (**27**)*. was prepared through alkylation of 2-(1-azepanyl)ethanol, **23** (1 g, 6.98 mmol) with 1-bromo-3-phenylpropane, **9** (1.17 mL, 7.68 mmol)in presence of KOH (0.98 g, 17.5 mmol) following method 2 described previously. Yield 37% (0.68 g); ^1H NMR (D_2O) δ 7.36–7.43 (m, 2H), δ 7.26–7.36 (m, 3H), δ 3.77–3.83 (m, 2H), δ 3.58 (t, 6.10 Hz, 2H), δ 3.45–3.53 (m, 2H), δ 3.33–3.39 (m, 2H), δ 3.19–3.27 (m, 2H), δ 2.72 (t, 7.09 Hz, 2H), δ 1.64–2.00 (m, 10H); MS ESI *m*/*z* = 262 ($M+H^+$); Anal. ($C_{17}H_{27}NO$ ($C_2H_2O_4$)$_1$) C, H, N.

*1-(2-(Cinnamyloxy)ethyl)azepane (**28**)* was prepared through alkylation of 2-(1-azepanyl)ethanol, **23** (1.00 g, 6.98 mmol) with cinnamyl bromide, **8** (1.51 g, 7.68 mmol) in presence of KOH (0.98 g, 17.45 mmol) following method 2 described previously. Yield 22% (0.39 g); ^1H NMR (D_2O) δ 7.49–7.54 (m, 2H), δ 7.43 (t, 7.40 Hz, 2H), δ 7.37 (t, 7.40 Hz, 1H), δ 6.71–6.78 (m, 1H), δ 6.36–6.44 (m, 1H), δ 4.22–4.26 (m, 2H), δ 3.87 (t, 4.81 Hz, 2H), δ 3.46–3.53 (m, 2H), δ 3.39 (t, 4.81 Hz, 2H), δ 3.18–3.27 (m, 2H), δ 1.77–1.95 (m, 4H), δ 1.61–1.74 (m, 4H); MS ESI *m*/*z* = 260 ($M+H^+$); Anal. ($C_{17}H_{25}NO$ ($C_2H_2O_4$)$_1$) C, H, N.

*N-Benzyl-2-(cinnamyloxy)-N-methylethanamine (**33**)* was prepared through alkylation of *N*-benzyl-*N*-methylethanolamine, **29** (0.99 mL, 6.05 mmol) with cinnamyl bromide, **8** (1.31 g, 6.66 mmol) in presence of KOH (0.85 g, 15.1 mmol) following method 2 described previously. Yield 20% (0.34 g); ^1H NMR (D_2O) δ 7.47–7.55 (m, 7H), δ 7.43 (t, 7.48 Hz, 2H), δ 7.32–7.38 (m, 1H), δ 6.67–6.73 (m, 1H), δ 6.32–6.40 (m, 1H), δ 4.26–4.50 (m, 2H), δ 4.15–4.24 (m, 2H), δ 3.80–3.92 (m, 2H), δ 3.26–3.54 (m, 2H), δ 2.88 (s, 3H); MS ESI *m*/*z* = 282 ($M+H^+$); Anal. ($C_{19}H_{23}NO$ ($C_2H_2O_4$)$_1$) C, H, N

*N-Benzyl-N-methyl-2-(3-phenylpropoxy)ethanamine (**34**)* was prepared through alkylation of *N*-benzyl-*N*-methylethanolamine, **29** (0.99 mL, 6.05 mmol) with 1-bromo-3-phenylpropane, **9** (1.01 mL, 6.05 mmol) in presence of KOH (0.85 g, 15.13 mmol) following method 2 described previously. Yield 32% (0.55 g);^1H NMR (D_2O) δ 7.22–7.58 (m, 10H), δ 4.37–4.47 (m, 1H), δ 4.23–4.35 (m, 1H), δ 3.69–3.87 (m, 2H), δ 3.38–3.59 (m, 3H), δ 3.21–3.33 (m, 1H), δ 2.80–2.90 (m, 3H), δ 2.66 (t, 7.09 Hz, 2H), δ 1.84–1.93 (m, 2H)); MS ESI *m*/*z* = 284 ($M+H^+$); Anal. ($C_{19}H_{25}NO$ ($C_2H_2O_4$)$_1$) C, H, N.

*2-(Methyl(phenethyl)amino)ethanol (**30**)* A mixture of (2-bromoethyl)benzene (5.48 mL, 39.9 mmol), 2-chloroethanol (1.08 mL, 13.3 mmol), and K_2CO_3 (18.4 g, 133 mmol) in DMF (20 mL/g) was vigorously stirred at room temperature under N_2. After completion, H_2O was added and extracted with Et_2O. The combined organic layers were washed with brine solution and dried over Na_2SO_4. After removal of the solvent under reduced pressure, the crude product was purified by column chromatography (silica gel, 1–3% $CHCl_3$/MeOH/1% NH_4OH). Yield 64% (1.53 g); MS ESI *m*/*z* = 180 ($M+H^+$).

*2-(Cinnamyloxy)-N-methyl-N-phenethylethanamine (**35**)* was prepared through alkylation of 2-(methyl(phenethyl)amino)ethanol, **30** (0.75 g, 4.18 mmol) with cinnamyl bromide, **8** (2.47 g, 12.6 mmol) in presence of KOH (0.59 g, 10.5 mmol) following method 2 described above. Yield 19%; ^1H NMR (D_2O) δ 7.16–7.4o (m, 10H), δ 6.57–6.63 (m, 1H), δ 6.26–6.33 (m, 1H), δ 4.18 (d, 2.97 Hz, 2H), δ 3.62–3.69 (m, 2H), δ 2.82–2.88 (m, 2H), δ 2.73–2.80 (m, 4H), δ 2.44 (s, 3H); MS ESI *m*/*z* = 296 ($M+H^+$); Anal. ($C_{20}H_{25}NO$ ($C_2H_2O_4$)$_1$ (H_2O)$_{0.5}$) C, H, N.

*N-Methyl-N-phenethyl-2-(3-phenylpropoxy)ethanamine (**36**)* was prepared through alkylation of 2-(methyl(phenethyl)amino)ethanol, **30** (0.75 g, 4.18 mmol) with 1-bromo-3-phenylpropane, **9**

(1.91 mL, 12.6 mmol) in presence of KOH (0.59 g, 10.46 mmol) following method 2 described previously. Yield 34% (0.42 g); ^{1}H NMR (D_2O) δ 7.31–7.43 (m, 6H), δ 7.23–7.30 (m, 4H), δ 3.78 (t, 4.47 Hz, 2H), δ 3.44–3.60 (m, 4H), δ 3.28–3.43 (m, 2H), δ 3.02–3.16 (m, 2H), δ 2.94 (s, 3H), δ 2.66 (t, 7.45 Hz, 2H), δ 1.84–1.93 (m, 2H); MS ESI m/z = 298 ($M+H^+$); Anal. ($C_{20}H_{27}NO$ ($C_2H_2O_4$)$_1$) C, H, N.

*2-(Methyl(3-phenylpropyl)amino)ethanol (**31**)* A mixture of 1-bromo-3-phenylpropane, **9** (6.07 mL, 39.9 mmol), 2-chloroethanol (1.08 mL, 13.31 mmol), and K_2CO_3 (18.4 g, 133 mmol) in DMF (20 mL/g) was vigorously stirred at room temperature under N_2. After completion, H_2O was added and extracted with Et_2O. The combined organic layers were washed with brine solution and dried over Na_2SO_4. After removal of the solvent under reduced pressure, the crude product was purified by column chromatography (silica gel, 1–3% $CHCl_3$/MeOH/1% NH_4OH). Yield 71% (1.83 g); MS ESI m/z = 194 ($M+H^+$).

*2-(Cinnamyloxy)-N-methyl-N-phenylpropylethanamine (**37**)* was prepared through alkylation of 2-(methyl(3-phenylpropyl)amino) ethanol, **31** (1.0 g, 5.17 mmol) with cinnamyl bromide, **8** (3.06 g, 15.52 mmol) in presence of KOH (7.26 g, 12.93 mmol) following method 2 described previously. Yield 19% (0.30 g); ^{1}H NMR (D_2O) δ 7.15–7.40 (m, 10H), δ 6.57–6.63 (m, 1H), δ 6.25–6.34 (m, 1H), δ 4.14–4.18 (m, 2H), δ 3.57 (t, 6.23 Hz, 2H), δ 2.60–2.66 (m, 4H), δ 2.42–2.48 (m, 2H), δ 2.30 (s, 3H), δ 1.79–1.87 (m, 2H); MS ESI m/z = 310 ($M+H^+$); Anal. ($C_{21}H_{27}NO$ ($C_2H_2O_4$)$_1$) C, H, N.

*N-Methyl-N-phenylpropyl-2-(3-phenylpropoxy)ethanamine (**38**)* was prepared through alkylation of 2-(methyl(3-phenylpropyl)amino)ethanol, **31** (1.00 g, 5.17 mmol) with 1-bromo-3-phenylpropane, **9** (2.36 mL, 15.52 mmol) in presence of KOH (0.73 g, 12.9 mmol) following method 2 described previously. Yield 27% (0.44 g); ^{1}H NMR (D_2O) δ 7.26–7.32 (m, 4H), δ 7.15–7.25 (m, 6H), δ 3.66 (t, 4.88 Hz, 2H), δ 3.42 (t, 6.21, 2H), δ 3.28 (s, 2H), δ 3.09 (s, 2H), δ 2.79 (s, 3H), δ 2.59–2.65 (m, 4H), δ 1.96 (q, 7.84 Hz, 2H), δ 1.76–1.84 (m, 2H); MS ESI m/z = 312 ($M+H^+$); Anal. ($C_{21}H_{29}NO$ ($C_2H_2O_4$)$_1$ (H_2O)$_{0.25}$) C, H, N.

*2-(Diallylamino)ethanol (**32**)* A mixture of diallylamine (1.27 mL, 10.29 mmol), 2-chloroethanol (0.89 mL, 10.29 mmol), and K_2CO_3 (14.2 g, 103 mmol) in DMF (20 mL/g) was vigorously stirred at room temperature under N_2. After completion, H_2O was added and extracted with Et_2O. The combined organic layers were washed with brine solution and dried over Na_2SO_4. After removal of the solvent under reduced pressure, the crude product was purified by column chromatography (silica gel, 1–3% $CHCl_3$/MeOH/1% NH_4OH). Yield 49% (0.71 g); MS ESI m/z = 142 ($M+H^+$).

*2-(Cinnamyloxy)-N,N-diallylethanamine (**39**)* was prepared through alkylation of 2-(diallylamino)ethanol, **32** (2.00 g, 14.2 mmol) with cinnamyl bromide, **8** (2.79 g, 14.2 mmol) in presence of KOH (1.19 g, 21.2 mmol) following method 2 described above. Yield 22% (0.84 g); ^{1}H NMR (D_2O) δ 7.52 (d, 3.54 Hz, 2H), δ 7.42 (t, 7.58 Hz, 2H), δ 7.32–7.37 (m, 1H), δ 6.72–6.78 (m, 1H), δ 6.35–6.46 (m, 1H), δ 5.86–6.00 (m, 2H), δ 5.56–5.65 (m, 4H), δ 4.22–4.29 (m, 2H), δ 3.80–3.91 (m, 6H), δ 3.39–3.44 (m, 2H); MS ESI m/z = 258 ($M+H^+$); Anal. ($C_{17}H_{23}NO$ ($C_2H_2O_4$)$_1$) C, H, N.

*N,N-Diallyl-2-(3-phenylpropoxy)ethanamine (**40**)* was prepared through alkylation of 2-(diallylamino)ethanol, **32** (0.71 g, 5.03 mmol) with 1-bromo-3-phenylpropane, **9** (0.76 mL, 5.03 mmol) in presence of KOH (0.42 g, 7.54 mmol) following method 2 described previously. Yield 22% (0.29 g); ^{1}H NMR (D_2O) δ 7.38 (t, 7.36 Hz, 2H), δ 7.23–7.33 (m, 3H), δ 5.86–5.97 (m, 2H), δ 5.56–5.65 (m, 4H), δ 3.75–3.85 (m, 6H), δ 3.56 (t, 6.56 Hz, 2H), δ 3.32–3.37 (m, 2H), δ 2.70 (t, 7.52 Hz, 2H), δ 1.87–1.96 (m, 2H); MS ESI m/z = 260 ($M+H^+$); Anal. ($C_{17}H_{25}NO$ ($C_2H_2O_4$)$_1$) C, H, N.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bmc.2012.05.006.

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