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Synthesis of Some Nefopam Analogues as Potential Analgesics

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Some derivatives of the non-narcotic analgesic nefopam containing amidine and guanidine substituents have been prepared and their analgesic activity assessed by their ability to block the uptake of noradrenaline. The compounds have been shown to inhibit noradrenaline uptake but they also display possible α_1 antagonist activity at higher concentration. An ester derivative was also active and was more selective as it did not exhibit α_1 adrenoreceptor antagonism.

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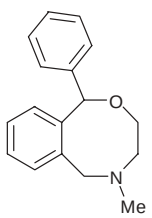
Introduction

Nefopam (1) (see Diagram 1)[1] is a non-narcotic analgesic which does not lead to the unacceptable neurophysiological and behavioural effects associated with the opioids.[2] Nefopam, however, has undesirable side-effects causing nausea, vomiting, nervousness, sweating and to a lesser extent dizziness, drowsiness and blurred vision.[2,3] These side-effects have been associated with interactions of nefopam within the central nervous system (CNS). Introduction of strongly basic groups such as amidines or guanidines, which are protonated at physiological pH precludes the compounds passing through the blood–brain barrier into the CNS. This strategy has been used previously to convert mianserin, a potent antihistamine but also a tranquiliser, into a useful, non-drowsiness inducing antihistamine.[4] Such a methodology, when applied to opiate analgesics, restricts the mode of action to the suppression of peripheral pain. This has been shown to be successful in preparing non-CNS acting derivatives of morphine and diprenorphine which are still effective analgesics.[5] Other workers have employed a similar methodology using zwitterionic groups such as amino acids to exclude morphine analogues from the CNS[6] as well as guanidine substituents.[7]



(1)

Diagram 1

Results and Discussion

Synthesis

The extension reported by Bremner[8] of Aeberli and Houlihan's work[9,10] gives facile access to *N*-cyanonor-nefopam (2a) and nor-nefopam (3a) (Scheme 1). The *N*-cyano compound (2a) was converted into the guanidine (4a) by reaction with Me_3Al/NH_4Cl.[11] The pure guanidine was isolated in low yield (38%) but an improved yield of the hydrochloride salt (50%) was obtained by reaction of nor-nefopam (3a) with the commercially available pyrazole carboxamidine reagent.[12] Similar reactions of the *p*-tolyl homologues (2b) and (3b) gave the guanidine (4b) as the free base (29%) or the hydrochloride salt (39%).

It is possible that introduction of the substituent directly onto the nefopam azepine ring can lead to adverse steric interactions which may disrupt analgesic action by restricting access to the receptor site. Accordingly the guanidine substituent was attached to the azepine by a three-carbon spacer (Scheme 1). Reaction of nor-nefopam (3a) with acrylonitrile[13] gave the cyano compound (5) which, after reduction to the amine (6) and reaction with the pyrazole carboxamidine reagent, gave the guanidine (7) in 47% yield as its hydrochloride salt. Reduction was most successfully carried out using catalytic hydrogenation over Adams' catalyst in acidic methanol[14] and gave the amine

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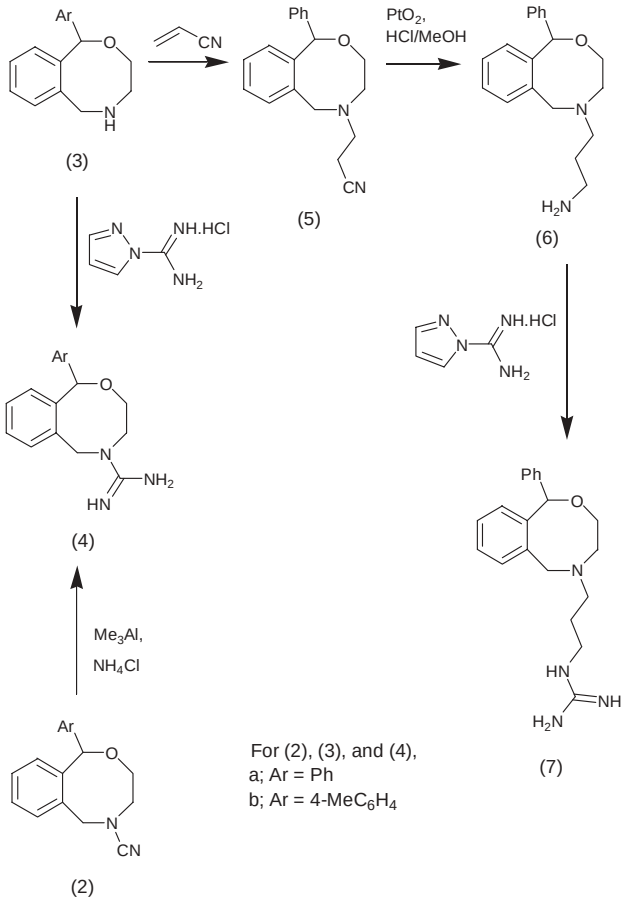
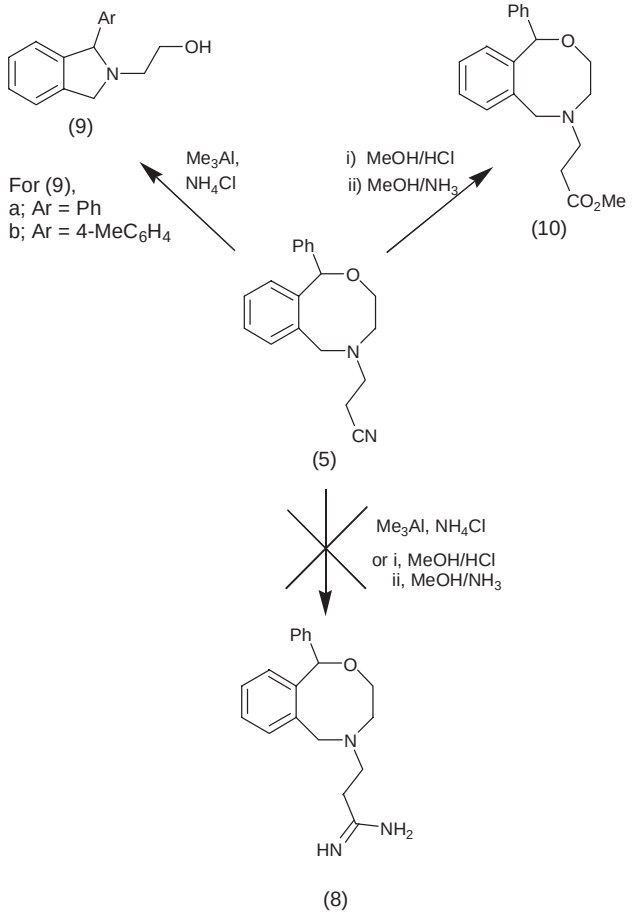


Scheme 1



Scheme 2

(6) in 79% yield. Attempted reduction using lithium aluminium hydride in refluxing tetrahydrofuran led to regeneration of nor-nefopam (3a).

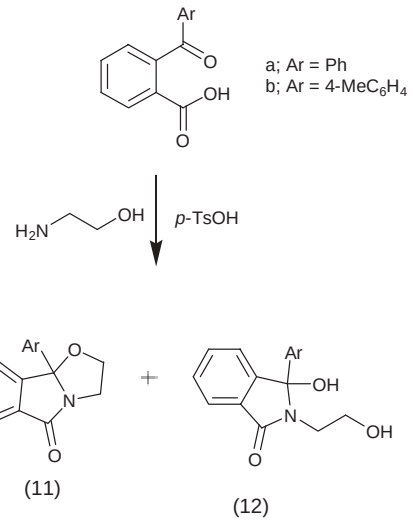
Preparation of the amidine (8) from the cyano compound (5) was attempted (Scheme 2). Reaction with Me_3Al/NH_4Cl surprisingly gave the ethanolamine derivative (9)[8] in 60% yield and an attempted Pinner reaction[15] of (5) with MeOH/HCl followed by $MeOH/NH_3$ gave the methyl ester (10) (67%).

It should be noted that the initial acid-catalysed condensation of the aroylbenzoic acids with ethanolamine gave the isoindolone (11) together with small amounts of the ring-opened compound (12) (Scheme 3). The phenyl compounds (11a) and (12a) were readily separated by chromatography and the structure of (12a) confirmed by a single crystal X-ray structure determination (Fig. 1). The compound (12a) has been prepared previously under neutral[9] or basic[16] conditions. Its presence does not affect the synthesis as lithium aluminium hydride reduction of both (11) and (12) gives the key intermediate (9).

Preparation of the *N*-cyano compound (2a) was attempted by von Braun reaction[17] of nefopam (1) with cyanogen bromide. Surprisingly, the product (13) (see Diagram 2) arising from cleavage of the C4–N bond in the azepine ring was obtained in high yield (79%). Ring cleavage of the 5-membered ring in (9a) occurs on reaction with CNBr but this involves formation of an intermediate diarylcarbenium ion.[8]

Pharmacology

Nefopam (1) is a weak inhibitor of [^{3}H] naloxone binding to brain homogenates[18] and its analgesic effects are not blocked by the opiate antagonist naloxone.[19] No respiratory



Scheme 3

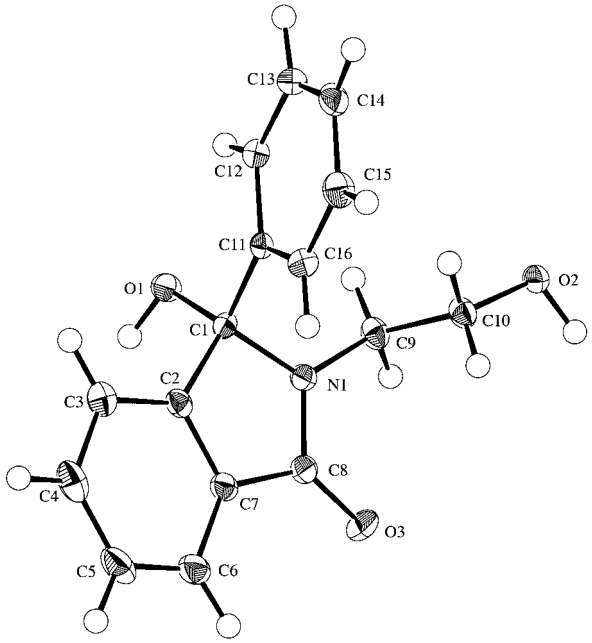


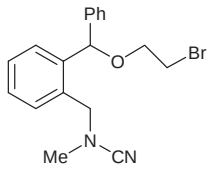
Fig. 1. ORTEP diagram of 3-hydroxy-2-(2-hydroxyethyl)-3-phenyl-2,3-dihydroisoindol-1-one (12a).

depression is observed[20,21] and there is no evidence of tolerance development.[1] Several reports have shown that nefopam is a potent inhibitor of synaptosomal uptake of the monoamines dopamine, serotonin and noradrenaline.[18,19] Fuller and Snoody showed that nefopam inhibits noradrenaline and serotonin uptake in vivo in mice (in the brain and in the heart) at doses which have been shown to be analgesic.[22] In rat and mouse tests, nefopam has an analgesic spectrum more similar to amphetamine than to the tricyclic anti-depressants or serotonin uptake blockers, and is not blocked by naloxone, atropine, yohimbine, propranolol or haloperidol.[19] The potency of nefopam's anti-nociceptive action[23] and effects on synaptosomal uptake of monoamines[24] is enantiomer dependant [(+) > (±) > (–)]. However, Rosland and Hole have suggested that this monoamine uptake inhibition may not be the sole mechanism of action for analgesia.[24] Fasmer[23] and Guirimand[20] have suggested a spinal and/or supraspinal site of action for nefopam, although complementary peripheral mechanisms cannot be excluded.[20]

In this investigation, a series of nefopam analogues have been synthesized, three of which (4a), (4b), and (7), contain guanidine groups. This substituent will be protonated at physiological pH and thus excluded from the CNS. In contrast, the ester (10) should be more lipophilic than nefopam itself and have more facile access to the CNS. Calculated partition coefficients (log P) and ionization constants (pK_a) for these compounds are shown in Table 1.[25] The values of log P at physiological pH (i.e. log D) show that the guanidines (4a), (4b), and (7) are significantly ionised and are more water soluble than nefopam (1) and the ester (10) (by a factor of 400–500). The relative activity of these five compounds could give valuable information as to the mechanism of action of nefopam derivatives. The inhibition of noradrenaline (NA) uptake in rat-isolated vas deferens was studied. Representative concentration–response curves to noradrenaline in the presence of nefopam (1) and the guanidine (4a) (Fig. 2) and nefopam (1) and the ester (10) (Fig. 3) are included. Table 2 summarizes the increased inhibition of binding of noradrenaline (leftward shift of the curves) with concentration for nefopam (1), the guanidines (4a), (4b), and (7) and the ester (10). The blank time-control data showing the changes observed in the absence of additives are also included.

The general trend for nefopam (1) (Fig. 2*a* and Table 2) was a leftward shift of the NA curve at lower concentrations (0.1 and 1 μM) while at higher concentrations the curves begin to shift rightwards, back towards the control (NA alone) curve. This suggests that at higher concentrations nefopam may have some α_1 adrenoceptor antagonist activity. Therefore, at lower concentrations the noradrenaline uptake inhibitor activity predominates, but as the concentrations increase the possible α_1 antagonist activity begins to counteract any effect of uptake inhibition, shifting the curves rightward. Similar trends were observed for the guanidines (4a) and (4b) (see Fig. 2*b* and Table 2) but the compounds were clearly not as potent, suggesting that the guanidine group confers a lower affinity for the uptake site. The guanidine (7) was even less potent and the shifts were not significant. The effects of the novel compounds on NA curves are in agreement with the classic uptake inhibitors desimipramine and cocaine.[26]

In contrast, the ester (10) showed increasing leftward shifts as the concentration increased, suggesting that this compound has the ability to inhibit the uptake of noradrenaline but lacks the possible α_1 adrenoreceptor antagonism displayed by nefopam.



(13)

Diagram 2

Table 1. Theoretical calculations of partition coefficients and ionisation constants

Compound	Log P	pK_a	Log D[A]
(1)	2.81	7.11	2.64
(3a)	2.52	8.42	1.47
(3b)	2.96	8.45	1.88
(4a)	1.61	11.49	−1.20
(4b)	2.04	11.53	−0.82
(7)	1.89	16.72	−1.08
(10)	2.77	6.45	2.72

[A] Log D = Log P at pH 7.4

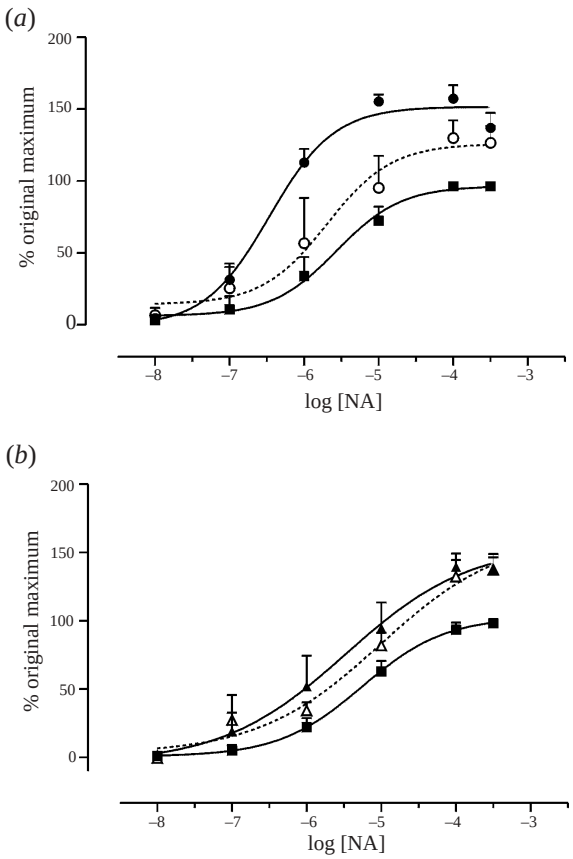


Fig. 2. (*a*) Cumulative concentration-response curves to noradrenaline (NA) alone (closed squares) and in the presence of nefopam (1), 1 μM (closed circles) and 100 μM (open circles) ($n = 4$). (*b*) Cumulative concentration–response curves to NA alone (closed squares) and in the presence of (4a), 1 μM (closed triangles) and 100 μM (open triangles) ($n = 4$).

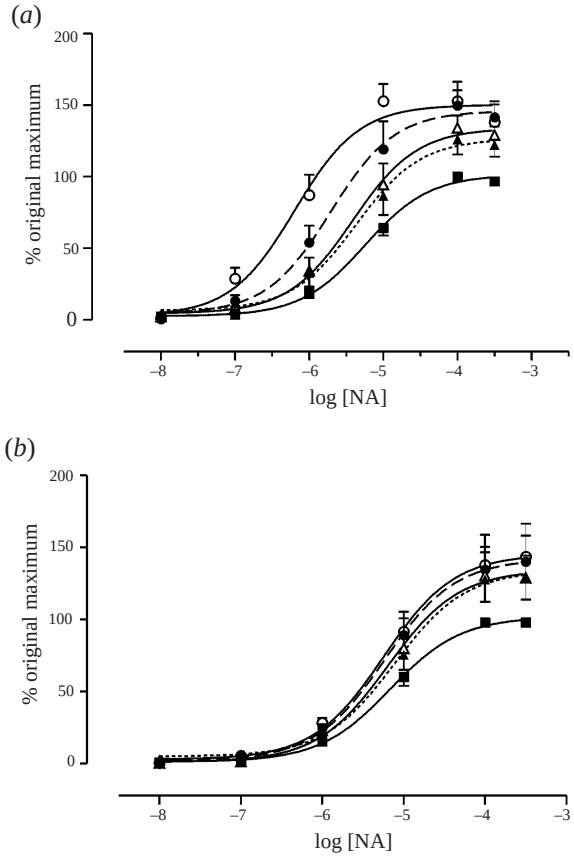


Fig. 3. (*a*) Cumulative concentration–response curves to NA alone (closed squares) and in the presence of increasing concentrations of (10), 0.1 μM (closed triangles), 1 μM (open triangles), 10 μM (closed circles) and 100 μM (open circles) ($n = 4$). (*b*) Cumulative concentration–response curves to NA alone at time zero (closed squares) and after 30 min (closed triangles), 60 min (open triangles), 90 min (closed circles) and 120 min (open circles) ($n = 4$–8).

The fact that the increase in maximum response to NA caused by all compounds was similar to a time-dependent increase observed in the time control experiments complicates the evaluation of the results (see Table 2 and Figs 1 and 2). This is a preliminary study on the pharmacology that has given some insight into the appropriate modifications which give the most promising activity. The active compounds need further study using binding assays and more specific uptake inhibition assays.

Conclusions

Nefopam (1) and the guanidines (4a) and (4b) all showed activity as noradrenaline uptake inhibitors but may also have α_1 adrenoceptor antagonist activity that may counteract their uptake inhibition. The guanidine (7) also appeared to show the same trend but the shift was not significant. The ester (10) appears to be the most promising candidate for in vivo testing as an analgesic as it was more selective, causing concentration-dependent inhibition of noradrenaline uptake without the apparent α_1 antagonist activity of the other compounds.

Experimental

Melting points (m.p.) are uncorrected. Infrared (IR) spectra were recorded on a Perkin–Elmer 1600 FT-IR spectrophotometer. ^{1}H (300 MHz) and ^{13}C (75 MHz) NMR spectra were recorded using a Bruker AM-300 spectrometer for solutions in $CDCl_3$ unless otherwise stated. Electron impact (EI) mass spectra were recorded on a VG TRIO-1 Quadrupole Mass Spectrometer at 70 eV with a source temperature of 200°C. Low resolution electrospray ionization (ESI^+) mass spectra were recorded on a Micromass Platform Electrospray mass spectrometer with a cone voltage of 25 V as solutions in methanol. High resolution mass spectra (HRMS, ESI^+) were measured on a Bruker BioApex 47 e^- FTMS (Fourier Transform Mass Spectrometer) with a 4.7 Tesla magnet and an Analytica electrospray source. Microanalyses were performed by Chemical and Microanalytical Services Pty Ltd, Melbourne. Merck Silica Gel 60 (230–400 mesh, no. 9385) was used for flash chromatography.

9b-Phenyl-2,3-dihydrooxazolo[2,3-a]isoindol-5-(9bH)-one (11a) and 3-hydroxy-2-(2-hydroxyethyl)-3-phenyl-2,3-dihydroisoindol-1-one (12a)

The isoindolone (11a) was prepared as described in the literature[8] from 2-benzoylbenzoic acid (6.00 g, 26.5 mmol), ethanolamine (3.34 g, 54.7 mmol) and 4-toluenesulfonic acid (0.45 g, 2.6 mmol) to give a crude product as yellow needles. ^{1}H NMR spectroscopy indicated a mixture of the isoindolone (11a) and the hydroxy compound (12a) in

Table 2. Table summarising leftward shifts and increases in maximum responses to NA in the presence of increasing concentrations of nefopam (1) and compounds (4a), (4b), (7) and (10) and time controls

Compound	Conc. μM	Leftward Shift[A]	Increase in max[A]
Nefopam (1)	0.1	20.1 ± 6.3	56.3 ± 12.3
	1	18.7 ± 6.8	60.5 ± 7.2*
	10	5.2 ± 2.4	80.9 ± 15.8*
	100	9.5 ± 8.1	33.7 ± 14
(4a)	0.1	2.1 ± 0.1	23.5 ± 3.2
	1	6.7 ± 4.4	43.8 ± 7.5
	10	4.0 ± 0.4*	34.5 ± 4.4
	100	5.1 ± 2.6	44.5 ± 10.4
(4b)	0.1	1.8 ± 0.1	24.9 ± 1.1
	1	3.7 ± 0.3*	37.4 ± 3.5
	10	8.8 ± 2.8	26.0 ± 5.1
	100	5.2 ± 2.0	15.9 ± 10.0
(7)	0.1	2.2 ± 0.5	33.0 ± 2.6
	1	2.5 ± 0.6	50.2 ± 12.9
	10	6.7 ± 2.8	39.8 ± 9.5
	100	6.0 ± 3.2	51.3 ± 11.8
(10)	0.1	2.4 ± 0.6	26.5 ± 10.4
	1	2.5 ± 0.5	34.8 ± 8.5
	10	4.9 ± 0.7*	49.9 ± 10.7
	100	16.7 ± 2.8*	54.2 ± 13.1
Time control	0.1	1.8 ± 0.2	26.7 ± 7.3
	1	1.9 ± 0.2	27.5 ± 7.8
	10	2.3 ± 0.5	40.6 ± 18.2
	100	2.5 ± 0.5	43.6 ± 23.1

[A]Entries marked with a '*' indicate those with a significant difference ($P < 0.05$) from the appropriate time control.

the ratio of 9 : 1. The mixture was used in the next step without purification (6.5 g, 100% combined), m.p. 141–145°C (for (11a) lit.[8] 147–149°C). Mass Spectrum (ESI): *m/z* 252.1 $[M(11a)+H]^+$, 270.1 $[M(12a)+H]^+$.

A portion was purified by flash chromatography (1 : 1 ethyl acetate/hexane with 10% dichloromethane) to give pure samples of (11a) followed by (12a). Slow evaporation of a solution of (12a) in ethyl acetate/hexane gave crystals suitable for X-ray crystal structure determination, m.p. 121–122°C (lit.[9] 124–126, lit.[16] 124–125°C).

^{1}H NMR for (11a) δ 3.23–3.32, m, 1H, H3; 4.08–4.17, m, 2H, H2,3; 4.32–4.40, m, 1H, H2; 7.27–7.30, m, 1H, ArH; 7.32–7.40, m, 3H, ArH; 7.41–7.51, m, 2H, ArH; 7.56–7.61, m, 2H, ArH; 7.77–7.81, m, 1H, ArH. ^{13}C NMR for (11a) δ 41.50, C3; 70.14, C2; 100.39, C9b; 123.53, 124.27, C6,7; 125.74, C2′,6′; 128.74, C3′,5′; 128.76, C4′; 130.06, C9; 131.17, C5a; 133.15, C8; 138.01, C9a; 146.80, C1′; 173.89, C5. ^{1}H NMR for (12a) δ 2.99, ddd, *J* 14.8, 8.1, 3.6 Hz, 1H, H1′; 3.55–3.78, m, 2H, H1′,2′; 3.83, ddd, *J* 14.8, 4.8, 2.9 Hz, 1H, H2′; 5.51, s, 1H, OH; 7.22–7.26, m, 1H, ArH; 7.30–7.36, m, 5H, ArH; 7.37–7.49, m, 2H, ArH; 7.70–7.73, m, 1H, ArH. ^{13}C NMR for (12a) δ 42.24, C1′; 61.55, C2′; 91.07, C3; 122.66, 123.34, C6,7; 126.15, C2′′,6′′; 128.53, C4′′; 128.72, C3′′,5′′; 129.36, C4; 129.74, C7a; 132.91, C5; 138.69, C3a; 149.13, C1′′; 168.97, C1.

9b-(4-Tolyl)-2,3-dihydrooxazolo[2,3-a]isoindol-5-(9bH)-one (11b) and 3-hydroxy-2-(2-hydroxyethyl)-3-(4-tolyl)-2,3-dihydroisoindol-1-one (12b)

The isoindolone (11b) was prepared as described above from 4-toluoylbenzoic acid (10 g, 41.7 mmol) and ethanolamine (5.08 g, 83.3 mmol) to give a crude product as a viscous orange oil. ^{1}H NMR spectroscopy indicated a mixture of the isoindolone (11b) and the hydroxy compound (12b) in the ratio of 98 : 2. The mixture was used in the next step without purification (12.14 g, 100% combined). ^{1}H NMR for (11b) δ 2.36, s, 3H, Me; 3.21–3.30, m, 1H, H3; 4.06–4.15, m, 2H, H2,3; 4.29–4.37, m, 1H, H2; 7.20, d, *J* 8.4 Hz, 2H, H2′,6′; 7.28–7.35, m, 1H, ArH; 7.49, d, *J* 8.4 Hz, 2H, H3′,5′; 7.59–7.41, m, 2H, ArH; 7.75–7.81, m, 1H, ArH. ^{13}C NMR for (11b) δ 21.23, Me; 41.58, C3; 70.20, C2; 100.53, C9b; 123.61, 124.31, C6,7; 125.80, C2′,6′; 129.57, C3′,5′; 130.09, C9; 131.27, C4′; 133.23, C8; 135.10, C5a; 138.72, C9a; 147.08, C1′; 173.97, C=O. Partial spectra for (12b): ^{1}H NMR δ 3.02–3.16, m, 1H, 3.70–3.84, m, 2H and 3.89–3.98, m, 1H, H1′, 2′. ^{13}C NMR δ 21.49, Me; 42.61, C1′; 61.67, C2′; 91.07, C1; 168.75, C=O. Mass Spectrum (ESI): *m/z* 266.1 $[M+H]^+$.

2-(1-Phenyl-2,3-dihydro-1H-isoindol-2-yl)ethanol (9a)

The isoindolylethanol (9a) was prepared following the literature method[8] by lithium aluminium hydride reduction of a 9 : 1 mixture of the isoindolones (11a) and (12a) (3.00 g, 11.9 mmol). The reaction was quenched with sodium sulfate decahydrate to give (9a) as a red oil (2.75 g, 96%). ^{1}H NMR δ 2.77, apparent dt, *J* 12.4, 3.8 Hz, 1H, H2; 3.00, ddd, *J* 12.4, 9.2, 4.7 Hz, 1H, H2; 3.50, apparent dt, *J* 11.0, 4.3 Hz, 1H, H1; 3.67, ddd, *J* 11.0, 9.3, 3.7 Hz, 1H, H1; 3.80, dd, *J* 12.6, 2.8 Hz, 1H, H3′; 4.50, dd, *J* 12.6, 1.5 Hz, 1H, H3′; 4.82, bs, 1H, H1′; 6.76, d, *J* 7.4 Hz, 1H, ArH; 7.12–7.43, m, 8H, ArH. ^{13}C NMR δ 55.24, C2; 58.04, C3′; 59.94, C1; 74.25, C1′; 122.10, 123.14, 127.09, 127.21, 127.88, ArCH; 128.60, 128.65, C2′′,3′′,5′′,6′′; 139.11, C3a′; 142.39, C7a′; 144.17, C1′′. Mass Spectrum (ESI): *m/z* 240.0 $[M+H]^+$.

2-[1-(4-Tolyl)-2,3-dihydro-1H-isoindol-2-yl]ethanol (9b)

Reduction of a 98 : 2 mixture of the isoindolones (11b) and (12b) (10 g, 37.7 mmol) as described above gave the isoindolylethanol (9b) as a highly viscous dark green oil (7.76 g, 81%) (Found: *m/z* 254.1459. $C_{17}H_{20}NO$ $[M+H]^+$ requires *m/z* 253.1467). ν_{max} (CH_2Cl_2) 3380(br)s, 3028m, 2941m, 2885m, 1675s, 1612m, 1512m, 1467s, 1409m, 1348s, 1178m, 1058s, 739s, 702m cm^{-1}. ^{1}H NMR δ 2.34, s, 3H, Me; 2.76, apparent dt, *J* 12.4, 3.8 Hz, 1H and 2.99, ddd, *J* 12.4, 9.3, 4.7 Hz, 1H, H2; 3.49, ddd, *J* 10.9, 4.7, 4.1 Hz, 1H and 3.66, ddd, *J* 10.9, 9.3, 3.7 Hz, 1H, H1; 3.79, dd, *J* 12.6, 3.0 Hz, 1H and 4.50, dd, *J* 12.6, 1.8 Hz, 1H, H3′; 4.79, br s, 1H, H1′; 6.76, d, *J* 7.4 Hz, 1H, ArH; 7.10–7.49, m, 7H, ArH. ^{13}C NMR δ 21.08, Me; 55.06, C2; 57.89, C3′; 59.89, C1; 73.85, C1′; 121.95, 122.99, 126.93, 127.00, ArCH; 128.42, C2′′,6′′; 129.23, C3′′,5′′; 137.23, 139.04, 139.07, 144.22, ArC. Mass Spectrum (ESI): *m/z* 254.2 $[M+H]^+$.

1-Phenyl-3,4,5,6-tetrahydro-1H-2,5-benzoxazocine-5-carbonitrile (2a)

The isoindolylethanol (9a) (7.00 g, 29.3 mol) was reacted with cyanogen bromide (6.25 g, 59.6 mmol) as described by Bremner.[8] The crude product was purified by flash chromatography using dichloromethane to afford the carbonitrile (2a) as a green solid (2.2 g, 30%). A portion was recrystallized using ethyl acetate/hexane (1 : 1) to yield (2a) as yellow crystals, m.p. 115–116°C (lit.[8] 120–121°C). ^{1}H NMR δ 3.29, ddd, *J* 14.4, 3.9, 2.0 Hz, 1H and 3.50, ddd, *J* 14.4, 9.4, 2.0 Hz, 1H, H4; 3.89, ddd, *J* 12.1, 9.4, 2.0 Hz, 1H and 4.15, ddd, *J* 12.1, 3.9, 2.5 Hz, 1H, H3; 4.18, d, *J* 13.8 Hz, 1H and 5.03, d, *J* 13.8 Hz, 1H, H6; 5.81, s, 1H, H1; 7.13–7.38, m, 9H, ArH. ^{13}C NMR δ 51.73, C4; 54.10, C6; 68.44, C3; 85.29, C1; 118.09, CN; 127.49, C2′,6′; 128.12, 128.69, ArCH; 128.77, C3′,5′; 129.33, 130.06, ArCH; 133.29, C5a; 133.37, ArCH; 139.37, 141.73 C9a,1′. Mass Spectrum (EI): *m/z* 264 (M^+, 4%), 263 (9), 233 (49), 221 (28), 195 (68), 179 (100), 178 (87), 165 (41), 89 (40), 76 (17).

1-(4-Tolyl)-3,4,5,6-tetrahydro-1H-2,5-benzoxazocine-5-carbonitrile (2b)

The isoindolylethanol (9b) (7.00 g, 27.7 mol) was reacted with a mixture of cyanogen bromide (5.61 g, 53.1 mmol) and anhydrous potassium carbonate (50 g) in dichloromethane under nitrogen. The mixture was refluxed for 19 h and workup gave a crude residue which was purified by flash chromatography using dichloromethane to afford the carbonitrile (2b) as a green solid (2.06 g, 26%). A portion was recrystallized using ethyl acetate/hexane (1 : 1) to yield (2b) as cream coloured *crystals*, m.p. 79.8–81.0°C (Found: C, 77.5; H, 6.7; N, 10.0%. $C_{18}H_{18}N_2O$ requires C, 77.7; H, 6.5; N, 10.1%). ν_{max} (CH_2Cl_2) 3053m,

3022m, 2928s, 2870s, 2207s, 1512m, 1067s cm^{-1}. ^1H NMR δ 2.30, s, 3H, Me; 3.28, ddd, *J* 14.4, 3.9, 2.0 Hz, 1H and 3.49, ddd, *J* 14.4, 9.4, 2.5 Hz, 1H, H4; 3.85, ddd, *J* 12.1, 9.4, 2.0 Hz, 1H and 4.15, ddd, *J* 12.1, 3.9, 2.5 Hz, 1H, H3; 4.17, d, *J* 13.8 Hz, 1H and 5.04, d, *J* 13.8 Hz, 1H, H6; 5.77, s, 1H, H1; 7.10–7.15, m, 5H, ArH; 7.29–7.35, m, 3H, ArH. ^{13}C NMR δ 21.26, Me; 51.73, C4; 54.14, C6; 68.43, C3; 85.28, C1; 118.14, CN; 127.49, C2′,6′; 128.67, 129.31, ArCH; 129.46, C3′,5′; 130.02, 133.36, ArCH; 133.25, C5a; 137.97, 138.87, 139.58, C9a,1′,4′. Mass Spectrum (EI): *m/z* 278 (M^+, 4%), 277 (10), 263 (6), 247 (63), 233 (35), 209 (75), 195 (26), 194 (26), 193 (36), 192 (41), 179 (100), 178 (88), 165 (26), 95 (26), 89 (37), 82 (19).

*1-Phenyl-3,4,5,6-tetrahydro-1*H*-2,5-benzoxazocine (Nor-nefopam) (3a)*

i) Preparation Using Lithium Aluminium Hydride

Nor-nefopam (3a) was prepared following a modification of a procedure used in the literature.[8] A solution of the carbonitrile (2a) (0.81 g, 3.1 mmol) in dry tetrahydrofuran (5 mL) was added dropwize over 10 min to a stirred suspension of lithium aluminium hydride (0.35 g, 9.2 mmol) in dry tetrahydrofuran (60 mL) in an ice bath. After the addition was complete, the mixture was refluxed for 2 h. The vessel was cooled in an ice bath and the reaction quenched by the addition of sodium sulfate decahydrate. The mixture was filtered and the solid washed with tetrahydrofuran. The filtrate was evaporated to yield nor-nefopam (3a) as a pure brown oil (0.72 g, 99%) (Found: *m/z* 240.1383. Calc. for $C_{16}H_{18}NO$ $[M+H]^+$: 240.1388). ^1H NMR δ 2.83, ddd, *J* 14.6, 5.3, 2.5 Hz, 1H and 2.91, ddd, *J* 14.6, 7.4, 2.7 Hz, 1H, H4; 3.68, ddd, *J* 12.0, 7.4, 2.5 Hz, 1H, H3; 3.81, d, *J* 13.2 Hz, 1H, H6; 3.89, ddd, *J* 12.0, 5.3, 2.7 Hz, 1H, H3; 4.57, d, *J* 13.3 Hz, 1H, H6; 5.82, s, 1H, H1; 6.92, d, *J* 7.3 Hz, 1H, ArH; 7.03–7.23, m, 8H, ArH. ^{13}C NMR δ 47.75, C4; 51.49, C6; 71.60, C3; 83.69, C1; 127.38, C2′,6′; 127.42, 127.43, 128.21, ArCH; 128.40, C3′,5′; 129.21, 131.74, ArCH; 139.32, 139.85, 142.73, ArC. The NMR data were consistent with literature data.[27]

ii) Preparation Using Sodium Hydroxide[28]

A solution of the carbonitrile (2a) (0.30 g, 1.1 mmol) and sodium hydroxide (0.09 g, 2.27 mmol) in ethylene glycol (10 mL) was stirred and heated at 130°C for 15 min. The mixture was cooled and the free base (3a) extracted using 40 mL of an ether/water mixture (1 : 1). Purification by acid/base extraction gave (3a) as an oil (0.11 g, 40%). The spectroscopic data was identical to that described above.

*1-(4-Tolyl)-3,4,5,6-tetrahydro-1*H*-2,5-benzoxazocine (4′-Methyl-nor-nefopam) (3b)*

The 4′-methyl nor-nefopam analogue (3b) was prepared using lithium aluminium hydride as described above. Reaction of the carbonitrile (20) (0.60 g, 2.16 mmol) with lithium aluminium hydride (0.25 g, 6.48 mmol) gave the title compound (3b) as a brown *oil* (0.54 g, 100%) (Found: *m/z* 254.1539. $C_{17}H_{20}NO$ $[M+H]^+$ requires *m/z* 254.1545). ν_{max} (neat) 2922s, 2863m, 1620m, 1512m, 1448m, 1378w, 1177m, 1108s, 1086s, 1019m, 909m, 781m, 740s, 732s, 634m cm^{-1}. ^1H NMR δ 2.29, s, 3H, Me; 2.93, ddd, *J* 14.5, 5.3, 2.5 Hz, 1H and 3.01, ddd, *J* 14.5, 7.4, 2.7 Hz, 1H, H4; 3.78, ddd, *J* 12.0, 7.4, 2.5 Hz, 1H, H3; 3.91, d, *J* 13.3 Hz, 1H, H6; 4.00, ddd, *J* 12.0, 5.3, 2.7 Hz, 1H, H3; 4.70, d, *J* 13.3 Hz, 1H, H6; 5.78, s, 1H, H1; 7.01, d, *J* 7.3 Hz, 1H, ArH; 7.09, d, *J* 8.2 Hz, 2H, H2′,6′; 7.13–7.25, m, 3H, ArH; 7.18, d, *J* 8.2 Hz, 2H, H3′,5′. ^{13}C NMR δ 21.18, Me; 47.81, C4; 51.62, C6; 71.70, C3; 83.87, C1; 127.42, C2′,6′; 127.48, 128.19, ArCH; 129.18, C3′,5′; 129.26, 131.84, ArCH; 137.19, 139.33, 139.92, 140.15, ArC. Mass Spectrum (ESI): *m/z* 254.1 $[M+H]^+$.

*1-Phenyl-3,4,5,6-tetrahydro-1*H*-2,5-benzoxazocine-5-carboxamidine (4a)*

i) From the Carbonitrile (2a) Using an Aluminium Reagent[11]

A solution of trimethylaluminium in toluene (2.0 M, 0.6 mL, 1.20 mmol) was added under nitrogen to a suspension of ammonium chloride (0.0655 g, 1.23 mmol) in dry benzene (5 mL) in an ice/salt bath. The mixture was stirred at ambient temperature for 1 h. A solution of the carbonitrile (2a) (0.20 g, 0.76 mmol) in dry benzene (5 mL) was added to the solution of the aluminium reagent and the mixture was heated under nitrogen at 80°C for 17 h. The mixture was cooled to ambient temperature and poured over a slurry of silica gel (3 g) in dichloromethane which was stirred (30 min) then filtered. The filtercake was washed with methanol (70 mL) and the filtrate concentrated to give a green solid (0.23 g), which was washed with chloroform to leave the insoluble carboxamidine (4a). The solid was collected by filtration and dried to give (4a) as a white *solid* (80 mg, 38%), m.p. 225–227°C (Found: *m/z* 282.1596. $C_{17}H_{20}N_3O$ $[M+H]^+$ requires *m/z* 282.1596). ^1H NMR (CD_3OD) δ 3.47–3.64, m, 2H, H4; 3.87, apparent dt, *J* 12.7, 4.2, Hz, 1H and 4.18, ddd, *J* 12.7, 8.7, 5.0 Hz, 1H, H3; 4.72, d, *J* 13.1 Hz, 1H and 5.11, d, *J* 13.1 Hz, 1H, H6; 5.84, s, 1H, H1; 7.13–7.16, m, 1H, ArH; 7.22–7.42, m, 8H, ArH. ^{13}C NMR (CD_3OD) δ 47.01, C4; 54.26, C6; 69.25, C3; 85.74, C1; 128.47, C2′,6′; 128.92, ArCH; 129.54, C3′,5′; 129.67, 130.38, 130.70, ArCH; 132.85, ArC; 134.00, ArCH; 143.02, 143.82 ArC; 158.24, C=NH. Mass Spectrum (ESI): *m/z* 282.3 $[M+H]^+$.

*ii) From Nor-nefopam (3a) Using Pyrazole-1*H*-carboxamidine hydrochloride*[12]

Nor-nefopam (3a) (0.23 g, 0.96 mmol), pyrazole-1*H*-carboxamidine hydrochloride (0.14 g, 0.96 mmol) and diisopropylethylamine (0.13 g, 1 mmol) were dissolved in acetonitrile (1 mL) and the mixture stirred for 16 h at ambient temperature. Addition of diethyl ether (5 mL) gave a precipitate, which was collected by filtration and washed with ether and dichloromethane. The crude product was purified by flash chromatography using a mixture of dichloromethane/methanol/ammonia (aq, 25%) (40 : 10 : 1 v/v). The appropriate fractions were collected and further purified by trituration with hexane and chloroform. The residual solid was collected by filtration to give the hydrochloride salt of the guanidine (4a) as a white *solid* (153 mg, 50%), m.p. 168–171°C (Found: C, 63.8; H, 6.6; N, 13.0%. $C_{17}H_{20}ClN_3O$ requires C, 64.3; H, 6.3; N, 13.2%). ^1H NMR (CD_3OD) δ 3.55–3.71, m, 2H, H4; 3.95, apparent dt, *J* 12.7, 4.2, Hz, 1H and 4.26, ddd, *J* 12.7, 8.7, 5.2 Hz, 1H, H3; 4.78, d, *J* 13.0 Hz, 1H and 5.19, d, *J* 13.0 Hz, 1H, H6; 5.91, s, 1H, H1; 7.21–7.25, m, 1H, ArH; 7.30–7.49, m, 8H, ArH. ^{13}C NMR (CD_3OD) δ 46.92, C4; 54.24, C6; 69.20, C3; 85.79, C1; 128.44, C2′,6′; 128.93, ArCH; 129.53, C3′,5′; 129.68, 130.40, 130.70, ArCH; 132.78, ArC; 133.98, ArCH; 142.96, 143.78, ArC; 158.21, C=NH.

A similar reaction in *N,N*-dimethylformamide gave the guanidine (4a) in 23% yield.

*1-(4-Tolyl)-3,4,5,6-tetrahydro-1*H*-2,5-benzoxazocine-5-carboxamidine (4b)*

The carboxamidine (4b) was prepared from the carbonitrile (2b) using the aluminium reagent described above. A solution of the carbonitrile (2b) (200 mg, 0.719 mmol) in dry benzene (5 mL) was added to a solution of the aluminium reagent [prepared from trimethylaluminium in toluene (2.0 M, 0.6 mL, 1.20 mmol) and ammonium chloride (0.061 g, 1.14 mmol) in dry benzene (5 mL)] and the mixture was heated under nitrogen at 80°C for 21 h. Workup as described above using a slurry of silica gel (3 g) in dichloromethane and washing of the filtercake with methanol (80 mL) gave a green solid (0.21 g). The solid was washed with dichloromethane to leave the insoluble carboxamidine, which was collected by filtration and dried to give (4b), as a white *solid* (60 mg, 29%), m.p. 248–257°C (Found: *m/z* 296.1756. $C_{18}H_{22}N_3O$ $[M+H]^+$ requires *m/z* 296.1763). ν_{max} (Nujol) 3305m, 3144m, 1648s, 1606m, 1461s, 1095m, 790m, 752s cm^{-1}. ^1H NMR (CD_3OD) δ 2.30, s, 3H, Me; 3.42–3.62, m, 2H, H4; 3.80, apparent dt, *J* 12.6, 4.2, Hz, 1H and 4.16, ddd, *J* 12.6, 8.8, 5.1 Hz, 1H, H3; 4.70, d, *J* 13.0 Hz, 1H and 5.11, d, *J* 13.0 Hz, 1H, H6; 5.79, s, 1H, H1; 7.1–7.2, m, 5H, ArH; 7.32–7.40, m, 3H, ArH. ^{13}C NMR (CD_3OD) δ 21.24, Me; 46.92, C4; 54.28, C6; 69.19, C3; 85.83, C1; 128.46, C2′,6′; 129.61, ArCH; 130.13, C3′,5′; 130.37, 130.69, ArCH; 132.76, ArC; 134.37, ArCH; 138.81, 140.09, 144.01, ArC; 158.25, C=NH. Mass Spectrum (ESI): *m/z* 296.2 $[M+H]^+$.

The hydrochloride salt of the guanidine (4b) was prepared from the nor-nefopam homologue (3b) (0.18 g, 0.71 mmol), pyrazole-1*H*-carboxamidine hydrochloride (0.10 g, 0.71 mmol) and diisopropylethylamine (0.09 g, 0.71 mmol) in acetonitrile (0.36 mL).

The mixture was stirred for 8 h at ambient temperature. Addition of diethyl ether (5 mL) gave a precipitate, which was collected by filtration and washed with ether and dichloromethane. The crude product was purified by flash chromatography using a mixture of dichloromethane/methanol/ammonia (aq, 25%) (40 : 10 : 1 v/v). The appropriate fractions were collected and further purified by trituration with dichloromethane. The residual solid was collected by filtration to give the hydrochloride salt of the guanidine (4b) as a white *solid* (92 mg, 39%) (Found: C, 64.9; H, 6.8; N, 12.6%. $C_{18}H_{22}N_3O$ requires C, 65.2; H, 6.7; N, 12.7%). ^{1}H NMR (CD_3OD) δ 2.36, s, 3H, Me; 3.52–3.66, m, 2H, H4; 3.91, apparent dt, *J* 12.7, 4.2 Hz, 1H and 4.22, ddd, *J* 12.7, 8.8, 5.1 Hz, 1H, H3; 4.76, d, *J* 13.0 Hz, 1H and 5.17, d, *J* 13.0 Hz, 1H, H6; 5.85, s, 1H, H1; 7.15–7.23, m, 5H, ArH; 7.36–7.47, m, 3H, ArH. ^{13}C NMR (CD_3OD) δ 21.25, Me; 46.91, C4; 54.27, C6; 69.18, C3; 85.82, C1; 128.46, C2′,6′; 129.61, ArCH; 130.13, C3′,5′; 130.37, 130.69, ArCH; 132.74, ArC; 133.98, ArCH; 138.81, 140.07, 144.00, ArC; 158.24, C=NH.

*1-Phenyl-1,3,4,6-tetrahydro-1*H*-2,5-benzoxazocine-5-propanenitrile (5)*

The cyanoethylated compound (5) was prepared following a modification of a procedure used in the literature.[13] A solution of nor-nefopam (3a) (0.41 g, 1.7 mmol) and acrylonitrile (0.25 mL, 3.8 mmol) in absolute ethanol (30 mL) was stirred at ambient temperature for 24 h. The solvent and excess acrylonitrile were removed under reduced pressure and the residue purified by flash chromatography using ethyl acetate/hexane (1 : 1 v/v). The appropriate fractions were evaporated to give a brown *oil* (12) (0.43 g, 84%). (Found: *m/z* 293.1653. $C_{19}H_{21}N_2O$ $[M+H]^+$ requires *m/z* 293.1654). ν_{max} (neat) 3061m, 3028m, 2942s, 2854s, 2247m, 1669m, 1600m, 1493s, 1452s, 1356m, 1180m, 1098s, 1074s, 1002, 752s, 700s cm^{-1}. ^{1}H NMR δ 2.51, t, *J* 6.9 Hz, 2H, C**H**$_2$CN; 2.72, ddd, *J* 14.2, 5.8, 2.9 Hz, 1H, H4; 2.77–2.87, m, 2H and 2.89–3.00, m, 1H, H4, C**H**$_2$N; 3.73, d, *J* 12.8 Hz, 1H, H6; 3.80, ddd, *J* 12.4, 5.8, 2.5 Hz 1H and 4.12, ddd, *J* 12.4, 7.9, 2.9 Hz, 1H, H3; 4.79, d, *J* 12.8 Hz, 1H, H6; 5.78, s, 1H, H1; 6.99, m, 1H, ArH; 7.11–7.33, m, 8H, ArH. ^{13}C NMR δ 16.99, **C**H$_2$CN; 51.60, 52.20, C4, **C**H$_2$N; 56.88, C6; 68.64, C3; 84.25, C1; 118.98, CN; 127.57, 128.67, 127.78, 128.52, 128.92, 132.71, ArCH; 134.77, 141.11, 142.69, ArC. Mass Spectrum (ESI): *m/z* 293.2 $[M+H]^+$.

*5-(3-Aminopropyl)-1-phenyl-1,3,4,6-tetrahydro-1*H*-2,5-benzoxazocine (6)*

i) Using Adams' Catalyst in Acidic Conditions

The synthesis of the propylamine (6) was achieved using conditions similar to that described in the literature.[14] The cyanoethylated compound (5) was dissolved in methanol (10 mL) acidified with hydrochloric acid (5 drops, 9 M). The solution was placed in a Fisher–Porter vessel with platinum oxide (0.08 g). The vessel was charged with hydrogen (60 p.s.i.) and heated to 50°C and stirred. The reaction was stopped after 4 h when the solution became colourless. The solution was filtered through Celite and the solvent evaporated to yield an orange semi-solid, which was washed with a mixture of ether/saturated aqueous sodium hydroxide (20 mL, 50% v/v). The ether layer was collected, dried with magnesium sulfate, filtered and the solvent was evaporated to yield the propylamine (6) as a yellow oil (0.15 g, 79%) (Found: *m/z* 297.1963. Calc. for $C_{19}H_{25}N_2O$ $[M+H]^+$: 297.1967). ν_{max} (neat) 3367w, 3298w, 3060w, 3021w, 2931s, 2854m, 1493m, 1452m, 1074m, 753s, 699s cm^{-1}. ^{1}H NMR δ 1.68–1.77, m, 2H, H2′′; 2.51–2.79, m, 5H, H4,1′′,3′′; 2.84, ddd, *J* 14.2, 8.2, 2.3 Hz, 1H, H4; 3.75, d, *J* 12.7 Hz, 1H, H6; 3.83, ddd, *J* 12.4, 5.8, 2.3 Hz, 1H and 4.15, ddd, *J* 12.4, 8.2, 2.7 Hz, 1H, H3; 4.71, d, *J* 12.7 Hz, 1H, H6; 5.80, s, 1H, H1; 6.97, d, *J* 7.3 Hz, 1H, ArH; 7.12–7.30, m, 8H, ArH. ^{13}C NMR δ 31.68, C2′′; 40.75, C3′′; 52.79, 54.22, C1′′,4; 56.67, C6; 68.74, C3; 84.06, C1; 127.42, 127.47, 127.52, 127.59, 128.47, 128.70, 132.77, ArCH; 135.41, C6a, 141.13, 142.95, ArC. Mass Spectrum (ESI): *m/z* 297.2 $[M+H]^+$.

ii) Attempted Synthesis Using a Lithium Aluminum Hydride Reduction

A solution of the cyanoethylated compound (5) (0.42 g, 1.4 mmol) in dry tetrahydrofuran (5 mL) was added dropwise over 10 min to a stirred suspension of lithium aluminium hydride (0.16 g, 4.3 mmol) in dry tetrahydrofuran (10 mL) in an ice bath. After the addition was completed, the mixture was refluxed for 24 h. The vessel was cooled in an ice bath and the reaction quenched by the addition of sodium sulfate decahydrate. The mixture was filtered and the solid washed with tetrahydrofuran. The filtrate was evaporated to yield nor-nefopam (3a) as a brownish-green oil (0.29 g, 88%). The spectroscopic data was consistent with that described previously.

A similar reaction for 4 h at ambient temperature also gave nor-nefopam (3a) as a brownish-green oil (0.21 g, 85%).

iii) Attempted Synthesis Using a Palladium on Charcoal Hydrogenation

The cyanoethylated compound (5) (0.29 g, 1 mmol) was dissolved in methanol (10 mL) in a Fisher–Porter vessel and reacted with palladium on charcoal (10%, 0.04 g) and hydrogen (60 p.s.i.) at ambient temperature for 24 h. The solution was filtered through Celite and the solvent removed under reduced pressure to give recovered starting material (0.28 g, 0.95 mmol).

A similar reaction for 72 h also gave starting material.

5-(3-Guanidinopropyl)-1-phenyl-1,3,4,6-tetrahydro-2,5-benzoxazocine (7)

The propylamine (6) (0.12 g, 0.41 mmol), pyrazole-1*H*-carboxamidine hydrochloride (0.063 g, 0.43 mmol) and diisopropylethylamine (0.052 g, 0.42 mmol) were dissolved in *N*,*N*-dimethylformamide (1 mL) and stirred for 24 h at ambient temperature as described previously. The solvent was removed under a high vacuum and the crude product was purified by flash chromatography using dichloromethane/methanol/ammonia (aq, 25%) (90 : 10 : 1 v/v). The appropriate fractions were collected and the solvent removed under reduced pressure to yield the hydrochloride salt of the guanidine (7) as a white *solid* (70 mg, 46%). m.p. 148–150°C (Found: *m/z* 339.2178. $C_{20}H_{27}N_4O$ $[M+H]^+$ requires *m/z* 339.2185). ν_{max} (CH_2Cl_2) 3317s, 3162s, 2931m, 2871m, 1650s, 1631s, 1611s, 1448m, 1095m, 758m, 732s, 699s cm^{-1}. ^{1}H NMR (CD_3OD) δ 1.79–1.88, m, 2H, H2′′; 2.53–2.69, m, 3H, H1′′,4; 2.77, ddd, *J* 14.3, 9.3, 2.7 Hz, 1H, H4; 3.23–3.28, m, 2H, H3′′; 3.73, d, *J* 12.6 Hz, 1H, H6; 3.83, ddd, *J* 12.7, 4.6, 2.7 Hz, 1H and 4.16, ddd, *J* 12.7, 9.3, 3.0 Hz, 1H, H3; 4.81, d, *J* 12.6 Hz, 1H, H6; 5.77, s, 1H, H1; 6.98, d, *J* 7.1 Hz, 1H, ArH; 7.08–7.38, m, 8H, ArH. ^{13}C NMR (CD_3OD) δ 27.81, C2′′; 40.62, C3′′; 52.05, C1′′; 53.14, C4; 57.32, C6; 69.62, C3; 85.90, C1; 128.59, 128.68, ArCH; 128.72, C2′,6′; 128.93, ArCH; 129.46, C3′,5′; 129.80, 134.17, ArCH; 134.73, C6a; 143.44, 144.42, ArC; 159.22, C=NH. Mass Spectrum (ESI): *m/z* 339.3 $[M+H]^+$.

*Attempted Synthesis of 1-Phenyl-1,3,4,6-tetrahydro-1*H*-2,5-benzoxazocine-5-propylamidine (8)*

i) Using the Aluminium Reagent

A solution of the carbonitrile (5) (0.18 g, 0.61 mmol) in dry benzene (5 mL) was added to a solution of the aluminium reagent [prepared from trimethylaluminium in toluene (2.0 M, 0.9 mL, 1.8 mmol) and a suspension of ammonium chloride (0.050 g, 0.95 mmol) in dry benzene (10 mL) as described above]. The mixture was heated under nitrogen at 80°C for 23 h, cooled to ambient temperature and poured over a slurry of silica gel (3 g) in dichloromethane which was stirred (30 min) then filtered. The filtercake was washed with methanol (50 mL) and the filtrate was concentrated to give a green semi-solid (0.14 g) which was triturated with dichloromethane. The suspension was filtered and the solvent removed under reduced pressure to yield the isoindolylethanol (9a) as a green oil (0.11 g). The ^{1}H and ^{13}C NMR data was consistent with data described above. Mass spectrum (EI): *m/z* 239 (M^+, 6%), 222 (3), 208 (100), 194 (5), 179 (21), 162 (12), 103 (9), 91 (20). The residual solid was insoluble in methanol.

ii) Using a Pinner Reaction

*Methyl 1-phenyl-1,3,4,6-tetrahydro-1*H*-2,5-benzoxazocine-5-propanoate* (*10*). The synthesis of the amidine (8) was attempted using a similar method to that described in the literature.[15] An ice-cold

solution of the carbonitrile (5) (50 mg, 0.17 mmol) in anhydrous methanol (1 mL) was saturated with anhydrous hydrogen chloride and the mixture was stirred for 1.5 h at ambient temperature. The solvent was removed under reduced pressure leaving a solid that was washed with dry ether (2 mL). A solution of saturated ammonia in methanol (2 mL) was added and the mixture was stirred for 1 h at ambient temperature. The solvent was removed under reduced pressure and the residual solid was triturated with dichloromethane. The suspension was filtered, giving a residual solid, which was inorganic material with no evidence of the amidine (8). The filtrate was evaporated to yield the methyl ester (10) as a green *oil* (37 mg, 70%) (Found: C, 73.8; H, 7.0; N, 4.3%; $[M+]^+$, 326.1752. $C_{20}H_{23}NO_3$ requires C, 73.8; H, 7.1; N, 4.3%; $[M+]^+$, 326.1756). ν_{max} (neat) 1736s, 1676m, 1494m, 1453s, 1266s, 1108m, 736s, 700s cm^{-1}. ^1H NMR δ 2.60, t, *J* 7.3 Hz, 2H, C**H**$_2$CO$_2$Me; 2.72, ddd, *J* 14.1, 6.1, 2.8 Hz, 1H, H4; 2.82–2.92, m, 2H, H4, C**H**$_2$N; 2.99, dt, *J* 12.8, 7.4 Hz, 1H, C**H**$_2$N; 3.69, s, 3H, OCH_3; 3.75, d, *J* 12.8 Hz, 1H, H6; 3.83, ddd, *J* 12.5, 6.1, 2.4 Hz, 1H, H3; 4.14, ddd, *J* 12.5, 7.8, 2.8 Hz, 1H, H3; 4.73, d, *J* 12.8 Hz, 1H, H6; 5.81, s, 1H, H1; 6.98, d, *J* 7.3 Hz, 1H, ArH; 7.14–7.33, m, 8H, ArH. ^{13}C NMR δ 33.45, **C**H$_2$CO$_2$Me; 51.83, OCH_3; 51.95, 52.82, C4, **C**H$_2$N; 56.95, C6; 68.79, C3; 84.20, C1; 127.69, 127.72, 128.63, 128.95, 132.92, ArCH; 135.55, 141.12, 142.98, ArC; 173.18, C=O. Mass Spectrum (ESI): m/z 326.3 $[M+H]^+$.

2-[(4-Bromo-2-oxo-1-phenyl)butyl]-N-*methylbenzenemethanamine*-N-*carbonitrile (13).* A solution of nefopam (1) (0.67 g, 2.65 mmol) in dry benzene (3 mL) was added slowly to a solution of cyanogen bromide (0.34 g, 3.18 mmol) in dry benzene over 5 min. The mixture was stirred for 18 h and diluted with ether (10 mL) and water (10 mL). The organic layer was separated and the aqueous layer was extracted with ether (3 × 10 mL). The combined organic fractions were dried and the solvent was removed under reduced pressure to give the carbonitrile (13) as a yellow *oil* (0.75 g, 79%). ν_{max} (KBr) 2908m, 2669m, 1453m, 1104m, 1067m, 762m, 700m, 607m cm^{-1}. ^1H NMR δ 2.9, s, 3H, CH_3; 3.24–3.29, m, 2H and 3.69–3.74, m, 2H, H3′,4′; 4.45, d, *J* 10.4 Hz, 1H and 4.52, d, *J* 10.4 Hz, 1H, CH_2N; 5.79, s, 1H, H1′; 7.26–7.56, m, 9H, ArH. ^{13}C NMR δ 31.1, C4′; 39.3, CH_3; 52.8, CH_2N; 66.1, C3′; 80.5, C1′; 118.4, CN; 127.2, 127.9, 128.0, 128.3, 128.5, 129.1, 131.1, ArCH; 135.3, 139.6, 140.3, ArC. Mass Spectrum (ESI): *m/z* 359.1 $[M(^{79}Br)+H]^+$, 361.1 $[M(^{81}Br)+H]^+$.

Pharmacology Methods

Rat-Isolated Vas Deferens

Male Spague–Dawley rats (300–400 g) were decapitated and the epididymal segment of the vas deferens removed. Tissues were mounted on wire tissue holders and placed in 5 mL organ baths containing Krebs solution (composition in mM: NaCl, 118.4; KCl, 4.7; $MgSO_4$, 1.2; KH_2PO_4, 1.2; $NaHCO_3$, 25.0; glucose, 11.1; $CaCl_2$, 2.5) maintained at 32°C and bubbled with 95% O_2, and 5% CO_2. Vas deferens were kept under 1 gram resting tension and allowed to equilibrate for at least 45 min before the addition of drugs.

Drugs

Noradrenaline (NA) and nefopam (1) were obtained from Sigma Chemical Co.

Protocol

To determine the ability nefopam and the test compounds to inhibit NA uptake, cumulative concentration–response (CR) curves were obtained for NA alone and in the presence of increasing concentrations (10^{-7} to 10^{-4} M) of nefopam or test compound and the leftward shift and increase in maximum response calculated. Each concentration of nefopam or test compound was allowed to equilibrate for 30 min before repeating the CR curve to NA. Using the same time course NA-CR curves were obtained in the absence of other drugs to act as time controls. The time control shifts were not subtracted but statistics were used to compare the shifts of the novel compounds to the shifts of the appropriate time controls. In this way, substantial time effects have been taken into account.

Statistics

Unpaired *t*-tests (assuming equal or unequal variances as tested using Graphpad Prism) were used to compare leftward shifts and increases in maximum response caused by nefopam or test compounds to the appropriate time control and the initial NA curve (i.e. shift of 1.0 and increase in maximum of 0.0) (Microsoft Excel97, data analysis function). Values of $P < 0.05$ were considered significant. Data are expressed as mean ± S.E.

Crystal Data

(12a). $C_{16}H_{15}NO_3$; *M* 269.30, monoclinic, space group $P2_1/n$ (No. 14), *a* 7.2037(2), *b* 12.6924(5), *c* 15.0534(5) Å, β 103.535(2)°, *V* 1338.14(7) Å^3, *Z* 4, D_c 1.337 g·cm^{-3}, *F*(000) 568.00, Mo Kα (λ 0.71073 Å), μ 0.93 cm^{-1}, transmission factors 0.9815–0.9902.

Intensity measurements: A colourless acicular crystal having approximate dimensions of 0.20 × 0.12 × 0.10 mm^3 was mounted on a glass fiber and measurements were made on a Nonius KappaCCD area detector with graphite monochromated Mo Kα radiation. Data were collected at a temperature of –150 ± 1°C using a 360° ϕ scan followed by a second ω scan, $2\theta_{max}$ 55.7°; unique data: 3320 (R_{int} 0.044). Data were processed using Nonius software[29] and corrections for Lorentz-polarization[30] and absorption[31] were applied. A correction for secondary extinction was applied (coefficient 2.09612e–06). The structure was solved by and expanded using Fourier techniques[32] and refined with full-matrix least-squares technique (least squares: function minimized: $\Sigma w(|F_o|-|F_c|)^2$) The non-hydrogen atoms were refined anisotropically. Hydrogen atoms were included but not refined. The final *R* ($\Sigma||F_o|-|F_c||\,\Sigma|F_o|$) value was 0.033 for 182 parameters and 1989 observed reflections [$I > 3.00\,\sigma(I)$]; the R_w ($[\Sigma w(|F_o|-|F_c|)^2 / \Sigma w(|F_o|^2]^{1/2}$) value for all 3320 reflections was 0.038.The standard deviation of an observation of unit weight* was 1.09. Neutral atom scattering factors were taken from reference 33. Anomalous dispersion effects were included in F_c;[34] the values for Δf′ and Δf′′ were taken from reference 35. The values for the mass attenuation coefficients were taken from reference 36 and all calculations were performed using the teXsan crystallographic software package.[37]

All the bond lengths and angles were in the expected range. Listings of bond lengths, bond angles, atomic coordinates and anisotropic thermal parameters have been deposited at the Cambridge Crystallographic Data Centre (file CCDC 184314).

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* Standard deviation of an observation of unit weight: $[\Sigma w(|F_o|-|F_c|)^2 / (N_o - N_v)]^{1/2}$ where N_o = number of observations and N_v = number of variables.

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