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Rapid access towards follow-up NOP receptor agonists using a knowledge based approach

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ABSTRACT

A knowledge based approach has been adopted to identify novel NOP receptor agonists with simplified hydrophobes. Substitution of the benzimidazol-2-one piperidine motif with a range of hydrophobic groups and pharmacophore guided bio-isosteric replacement of the benzimidazol-2-one moiety was explored. Compound **51** was found to be a high affinity, potent NOP receptor agonist with reduced affinity for the hERG channel.

The ORL1 receptor (opioid receptor like-1 receptor, known as NOP) and its endogenous ligand nociceptin (NC, also known as orphanin FQ), a 17-amino acid neuropeptide, was discovered in 1994.[1–4] Although its sequence is closely related to traditional opioid receptors, the NOP receptor shows low binding affinities for selective opioid agonists and antagonists (such as dynorphin A).[5,6] Furthermore, the NOP ligand NC does not bind to the three traditional opioid receptors (MOP, DOP, KOP). Activation of the G protein-coupled NOP receptor inhibits adenylate cyclase activity, reduces intracellular cAMP and regulates ion channels. The NOP receptor and NC have been implicated in several physiological pathways including cognition, pain, locomotion, anxiety, neuroendocrine control and modulation of cardiovascular and respiratory function.[7] Supraspinal administration of nociceptin in rodents produces hyperalgesia[8] whereas spinal intrathecal administration causes hyperalgesia in low doses and analgesia in high doses.[9] In addition to complex biological data there are limitations in using NC because of the inherent poor metabolic stability. Therefore, the development of highly selective and potent NOP ligands could help elucidate the role of the NOP receptor in pain. Several research groups have disclosed their efforts in the search for small molecule NOP agonists and antagonists.[10–13] Some of these ligands (**1**, **2** and **3**) have high selectivity and potency for the NOP receptor versus the other opioid receptors (Fig. 1). Many different classes of NOP ligands have been reported however only **3**, has progressed into clinical trials for multiple target indications using an experimental medicine approach.[14]

In earlier work we had identified a series of 3-phenoxypropyl piperidine benzimidazol-2-ones that led to the optimised compounds **4** and **5**.[15–17] These agonists have high affinity for NOP (K_i = 0.5 nM and 2 nM, respectively) with excellent selectivity over the other opioid receptors, in particular MOP (K_i = 54 nM, NOP/MOP = 108 for **4**). We attributed the higher affinity and selectivity of **4** to both the H-bond donating and accepting capacity of the terminal amide appended from the N-3 position of the benzimidazol-2-one and have since capitalised on these properties with a host of bio-isosteric replacements.[18] The synthetic feasibility of these compounds is a key issue. The route is a four step process involving an asymmetric hydrogenation and a moderate yielding Mitsunobu coupling even after extensive optimisation.[16] In this Letter we report a knowledge based strategy to rapidly access a back-up series focussing on simplified hydrophobes and pharmacophoric replacements of the benzimidazol-2-one to simplify the synthetic route, maintain NOP affinity and selectivity.

Simplified hydrophobes were selected for synthesis on the basis of literature precedent for NOP ligands and appropriate physicochemical properties for known CNS active drugs. A 3D

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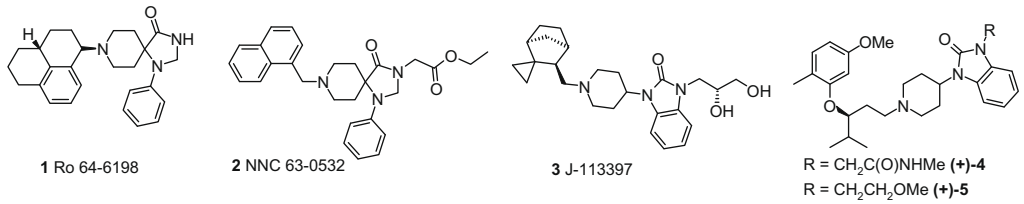


Figure 1. Structure of NOP lead compounds.

pharmacophore approach was adopted to aid the prioritisation of potential bio-isosteric replacements for the benzimidazol-2-one piperidine of **4**. Previous superposition analysis between the benzimidazol-2-one piperidine moiety of **4** and the 1-phenyl-1,3,8-triaza-spiro[4.5]decan-4-one moiety characteristic of a number of known NOP receptor ligands such as **1** highlighted the aromatic hydrophobe, basic amine and associated acceptor site as the key common pharmacophoric features.[17] Two 3-D pharmacophore queries were generated based on the superposition model. Both queries contained the common aromatic hydrophobe, basic amine and associated acceptor site. One query had an additional acceptor atom functionality derived from the carbonyl of the benzimidazol-2-one piperidine, the other query had an additional acceptor atom functionality derived from the carbonyl of the 1-phenyl-1,3,8-triaza-spiro[4.5]decan-4-one moiety. The two queries were used to search a database of approximately 60 potential benzimidazol-2-one piperidine bio-isosteres using Unity flexible 3D searching.[19] Pharmacophore model hits were prioritised on the basis of fit to the query, conformational penalties and the ability to bear a potential potency and selectivity enhancing amide substituent in a similar direction to that of the benzimidazol-2-one piperidine. Several of which have been synthesised. The fit of the 1,3-dihydro-2,1,3-benzothiadiazol-2,2-dione piperidine moiety (core **E**) with the benzimidazol-2-one piperidine and its derived 3D query is shown in Figure 2.

The previously disclosed benzimidazol-2-one piperidine **52**[17] was treated with sodium triacetoxy borohydride in the presence of titanium isopropoxide in ethanol with the appropriate ketone or aldehyde at high temperature in a microwave reactor to give compounds **6–31** (Scheme 1, Table 1). The cores **A**–**E** highlighted from the pharmacophore analysis were constructed and the *N*-methyl amide proven to give an enhancement in potency and selectivity in the initial series was included before the attachment of a selection of hydrophobes. Synthesis of core **A** was carried out according to the protocol of Clark et al. (Scheme 2).[20] Dilithiation of (*tert*-butoxycarbonyl)aniline **53** and condensation with (*tert*-butoxycarbonyl)piperidinone results in the protected spiro[4*H*-3,1-benzoxazine-4,4′-piperidin]-2-(1*H*)-one **54**. Compound **54** could be treated with ethyl chloroacetate followed by methylamine in aqueous ethanol to install the *N*-methyl amide from N-1 to give **55**. The hydrophobe could then be appended after deprotection of **55** to afford **32**, **37**, **41** and **44** using the previously mentioned reductive amination conditions. Core **B** was constructed following the protocols of Takai et al.[21] 2-Aminobenzamide **57** was treated with 1-benzyl-4-piperidinone under reductive amination conditions followed by reductive cleavage of the intermediate dihydro-4-quinazoline to give the diamine **58** (Scheme 3). Cyclisation of **58** with *N*,*N*′-carbonyldiimidazole gave the protected quinazoline **59**. In a similar manner to core **A**, the N-methyl amide can be installed onto **59** before attachment of the hydrophobe to give **33** and **46**. Core **C** is described in the patent literature by Eurocelitique and is prepared starting from ethyl 1-benzyl piperidine-4-carboxylate **62** (Scheme 4).[22] Deprotonation adjacent to the ester and quenching with benzoyl chloride gave the keto ester **63**. Compound **63** was then cyclised to the spiropyrazole **64** with a large excess of hydrazine under microwave conditions. Previous attempts using conventional heating in ethylene glycol gave disappointing yields (~20%). Treatment of **64** with ethyl chloroacetate followed by methylamine appended the *N*-methyl amide to afford **66**. Subsequent deprotection and reductive amination to introduce the hydrophobes gave **34**, **38**, **42**, **45** and **47**. With diamine **58** in hand we were able to access 3,4-dihydro-1*H*-2,1,3-benzothiadiazin-2,2-diones (core **D**). In a method described by Goehring et al.[23] towards similar NOP ligands, diamine **58** was treated with sulfamide in diglyme at 170 °C to affect the cyclisation and afford **68** (Scheme 3). Again the *N*-methyl amide can be installed in a similar manner to previously described and a host of hydrophobes attached using the reductive amination conditions to afford **35**, **39** and **48**. Synthesis of 1,3-dihydro-2,1,3-benzothiadiazol-2,2-diones (core **E**) is also described by Goehring et al.[23] Firstly the diamine **73** is constructed via a reductive amination between 1,2-phenylene diamine **72** and (*tert*-butoxycarbonyl)piperidinone (Scheme 5). Refluxing **73** with sulfamide in diglyme gave the desired cyclic material **74**. Furthermore **74** could be transformed to the *N*-methyl amide **76** and the hydrophobes added after deprotection to give **36**, **40**, **43** and **49**.

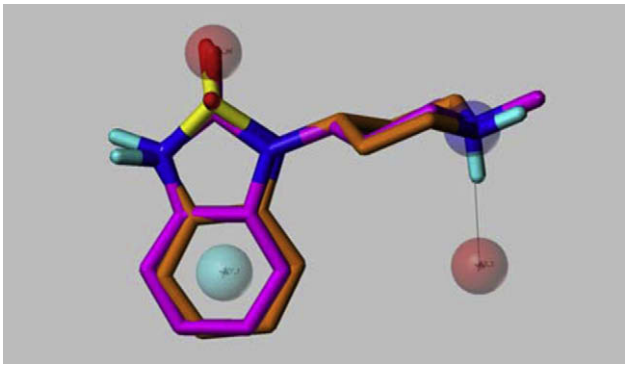
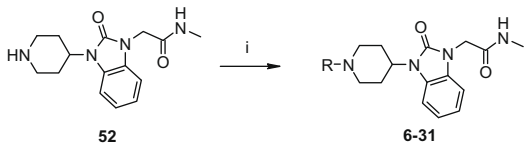


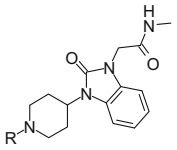
Figure 2. Unity fit of the 1,3-dihydro-2,1,3-benzothiadiazol-2,2-dione piperidine moiety (core **E**, orange) to the benzimidazol-2-one piperidine moiety of **4** (magenta) and its derived 3D pharmacophore query.

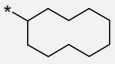
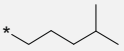
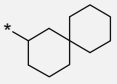
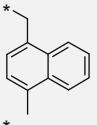
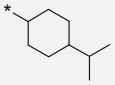
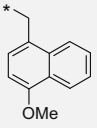
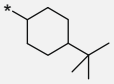
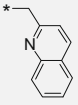
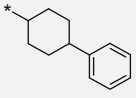
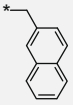
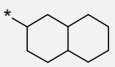
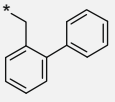


Scheme 1. Reagents and conditions: (i) $NaBH(OAc)_3$, $Ti(O^iPr)_4$, EtOH, ketone/aldehyde, microwave 180 °C, 300 s.

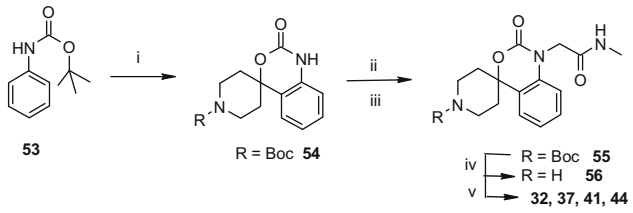
The affinities (K_i values) of compounds at the opioid receptors were determined by radioligand binding experiments performed in triplicate. Compounds showing high NOP affinity were profiled for selectivity over MOP, selected compounds were further evaluated for NOP agonism in a cAMP functional assay and compared to the reference NOP agonist nociceptin (NC). All assays were carried out as described previously.[17]

Table 1



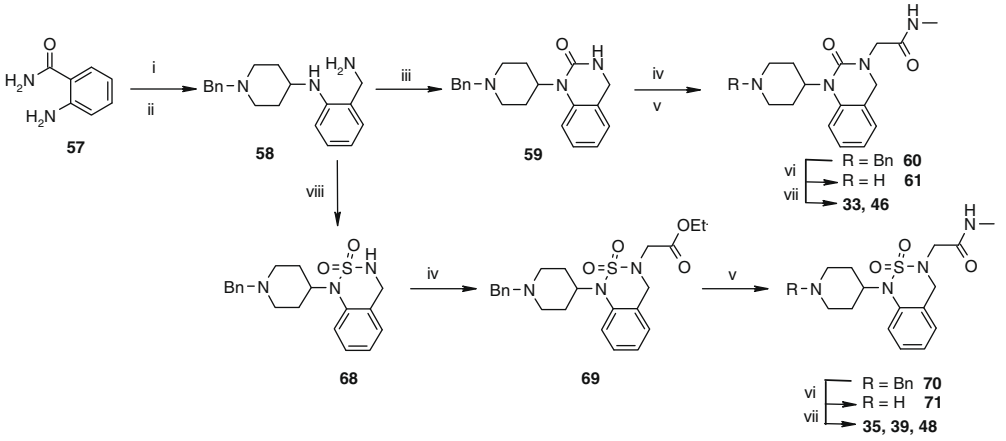
No.	R	NOP K_i (nM)	MOP K_i (nM)	NOP/MOP	No.	R	NOP K_i (nM)	MOP K_i (nM)	NOP/MOP
6		470	NT		**19**		487	NT	
7		227	NT		**20**		2560	NT	
8		35	1794	51	**21**		259	1883	7.3
9		15	608	41	**22**		1118	NT	
10		0.2	11	55	**23**		471	NT	
11		1.3	34	26	**24**		186	2707	15
12		62	350	5.6	**25**		29	67	2.3
13		5.2	282	54	**26**		2.7	138	51
14		1.7	201	118	**27**		18	120	6.7
15		5.5	77	14	**28**		1050	NT	
16		4.7	47	10	**29**		4082	NT	
17		253	NT		**30**		454	NT	
18		3.5	127	36	**31**		16	3.7	0.2

NT = not tested.

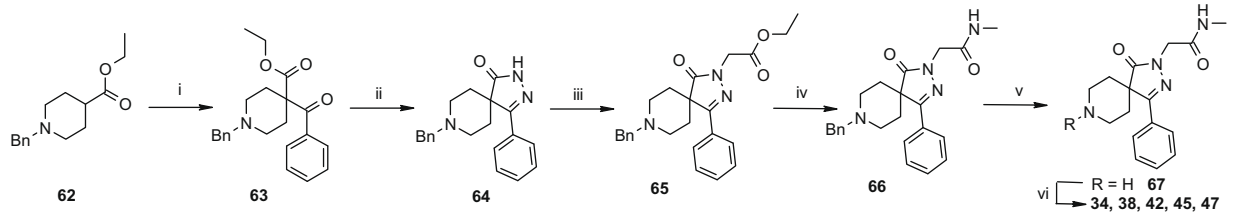


Scheme 2. Reagents and conditions: (i) (*tert*-butoxycarbonyl)piperidinone, ^{t}BuLi, THF, −78 °C; (ii) ethyl chloroacetate, NaH, DMF, NaI; (iii) 2 M methylamine in methanol, ethanol, rt; (iv) 20% TFA, dichloromethane, rt; (v) $NaBH(OAc)_3$, $Ti(O^iPr)_4$, EtOH, ketone, microwave 180 °C, 300 s.

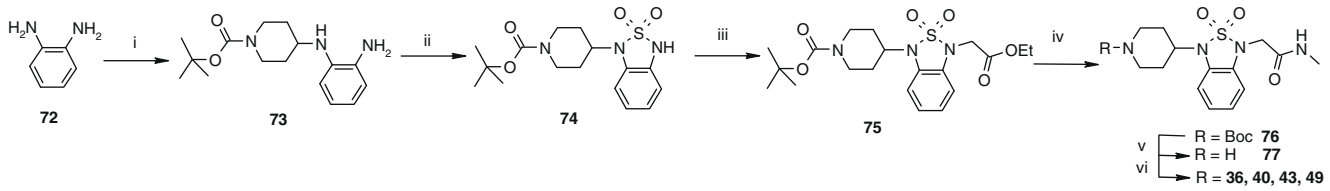
Table 1 shows the NOP and MOP binding affinities for the simplified hydrophobes. Cycloalkyl systems **6**–**10** increase in affinity with increasing ring size. The cyclodecyl derivative **10** exhibits high NOP affinity (K_i = 0.2 nM) and 55-fold selectivity over MOP. Spiro compound **11** maintains high NOP affinity however selectivity over MOP is decreased to 26-fold. 2,2-Dimethyl substituted cyclopentyl **12** showed a modest 7.6-fold increase in NOP affinity upon comparison to the unsubstituted cyclopentyl **6**. However the 4,4-dimethyl substituted cyclohexyl **13** yielded a 44-fold increase in NOP affinity compared to the parent cyclohexyl **7** resulting in a promising 54-fold selectivity over MOP for **13**. This suggested that additional steric bulk at the cyclohexyl 4 position may be beneficial for NOP affinity. 4-Isopropyl cyclohexyl analogue **14** afforded a high affinity NOP ligand (K_i = 1.7 nM) with good selectivity over MOP. However *tert*-butyl analogue **15** showed a 3.2-fold decrease in NOP affinity compared to **14** which coupled with an increase in MOP affinity resulted in a significant decrease in selectivity. Derivatives **16** and **18** also showed decreased NOP affinity compared to **14** although **18** maintained a reasonable 36-fold selectivity over NOP. Phenyl substituted cyclohexyl **17** exhibited a profound decrease in NOP affinity as did norbornane analogue **19**. Methylene insertion between the piperidine nitrogen and cycloalkyl resulted in poor NOP affinity for cyclobutyl **20** while cyclohexyl **21** showed no improvement over the direct linked analogue **7**. Branched alkyl derivatives **22**–**24** all showed relatively poor NOP affinities. Naphthyl analogue **25** exhibited reasonable NOP affinity (K_i = 29 nM) indicating that both aliphatic and



Scheme 3. Reagents and conditions: (i) 1-benzyl-4-piperidinone, $NaBH(OAc)_3$, AcOH, DCE, rt; (ii) $LiAlH_4$, 1,4-dioxane, 0–100 °C; (iii) *N,N′*-carbonyldiimidazole, dichloromethane, rt; (iv) ethyl chloroacetate, NaH, DMF, NaI; (v) 2 M methylamine in methanol, ethanol, rt; (vi) 10 wt % palladium on carbon, hydrogen, methanol, 2 M HCl, 5 bar; (vii) $NaBH(OAc)_3$, $Ti(O^iPr)_4$, EtOH, ketone/aldehyde, microwave 180 °C, 300 s; (viii) sulfamide, diglyme, 170 °C.



Scheme 4. Reagents and conditions: (i) benzoyl chloride, LDA, THF, −78 °C to rt; (ii) hydrazine hydrate, ethanol, microwave, 160 °C; (iii) ethyl chloroacetate, NaH, DMF, NaI; (iv) 2 M methylamine in methanol, ethanol, rt; (v) 30 wt % palladium hydroxide, hydrogen, methanol, 5 bar; (vi) $NaBH(OAc)_3$, $Ti(O^iPr)_4$, EtOH, ketone, microwave 180 °C, 300 s.



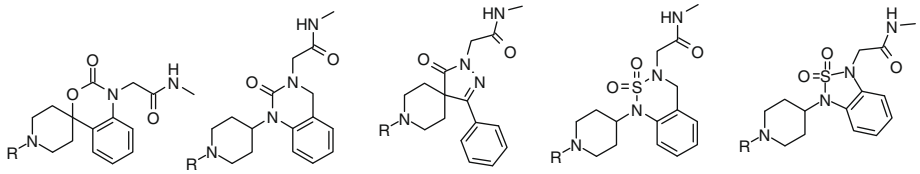
Scheme 5. Reagents and conditions: (i) (*tert*-butoxycarbonyl)piperidinone, $NaBH(OAc)_3$, AcOH, DCE, rt; (ii) sulfamide, diglyme, 170 °C; (iii) ethyl chloroacetate, NaH, DMF, NaI; (iv) 2 M methylamine in methanol, ethanol, rt; (v) 20% TFA, dichloromethane, rt; (vi) $NaBH(OAc)_3$, $Ti(O^iPr)_4$, EtOH, ketone, microwave 180 °C, 300 s.

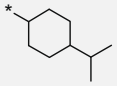
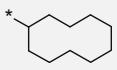
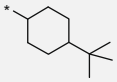
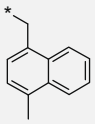
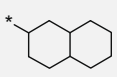
aromatic ring systems are tolerated for NOP. 4-Methyl substitution of the naphthyl ring gave an 11-fold increase in NOP affinity and a 2-fold decrease in MOP affinity resulting in 51-fold selectivity for compound **26** but 4-methoxy naphthyl substitution to give **27** was less successful. Insertion of a nitrogen atom into the naphthyl moiety to yield isoquinoline **28** gave a 36-fold decrease in NOP affinity compared to naphthyl **25**. Low NOP affinity was also observed for the 2-naphthyl compound **30** and its quinoline analogue **29** however biphenyl **31** showed good NOP affinity (K_i = 16 nM) but no selectivity over MOP.

The hydrophobes with the most promising selectivity over MOP were selected for combination with the prioritised benzimidazol-2-one bio-isosteres. *tert*-Butyl cyclohexyl was preferred over 4,4-dimethyl cyclohexyl based upon reagent availability and cost. Results are detailed in Table 2 although not all combinations were synthesised. Initially core **C** was evaluated with all hydrophobes except the 4-methyl naphthyl. SAR for core **C** typically mirrored that of the benzimidazol-2-one series where cycloheptyl and 4-*tert*-butyl cyclohexyl show lower NOP affinities. SAR was expanded around the 4-isopropyl cyclohexyl hydrophobe with all 5 cores then followed up with selected analogues around the remaining hydrophobes within the series. 4-Methyl naphthyl was only synthesised with core **B** and failed to show any preliminary advantage over 4-isopropyl cyclohexyl and was therefore not pursued further. Core **A** showed a significant reduction in NOP affinity compared to the equivalent benzimidazol-2-one analogues, ranging from 54-fold for **44** to 140-fold for **37**. High NOP affinity was achieved for cores **B**, **C** and **D** with 3,4-dihydro-1*H*-2,1,3-benzothiadiazin-2,2-dione core **D** showing affinity similar to that of the benzimidazol-2-one derivatives. However, surprisingly high MOP affinities for compounds containing cores **B**, **C** and **D** resulted in loss of selectivity. 1,3-Dihydro-2,1,3-benzothiadiazol-2,2-dione core **E** showed lower NOP affinity than equivalent core **D** containing compounds but afforded appreciable selectivity over MOP perhaps suggesting that core **E** maintained the *N*-methyl acetamide substituent in an optimal location. Compounds **36**, **40** and **49** all showed high NOP affinity, greater than 35-fold selectivity over MOP and good functional potency as NOP receptor agonists. It is noteworthy that analogues of **35**, **36**, **48** and **49** without the *N*-methyl acetamide substituent have been reported in the literature with differing SAR.[23] Unsubstituted analogues of core **E** generally showed lower NOP affinity and limited selectivity over MOP whereas the unsubstituted analogue of **35** (core **D**) exhibited high NOP affinity and good selectivity over MOP. This suggests that N-3 substitution of 1,3-dihydro-2,1,3-benzothiadiazol-2,2-dione (core **E**) is preferred for high NOP affinity and selectivity but N-3 unsubstituted analogues are more favourable for 3,4-dihydro-1*H*-2,1,3-benzothiadiazin-2,2-dione (core **D**).

The high affinity and highly selective benzimidazol-2-one **14** was selected for further profiling. Separation of the cis and trans stereoisomers was achieved by preparative HPLC using a Chiralpak AD column and 80:20 isohexane/propanol as eluant. Stereochemistry was assigned from spin–spin coupling constants and subsequent evaluation indicated that cis stereochemistry across the

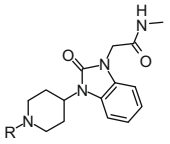
Table 2

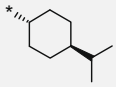
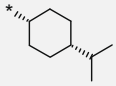


No.	R	Core	NOP K_i (nM)	MOP K_i (nM)	NOP/MOP	cAMP IC_{50} (nM) (%NC resp.)
32		**A**	106	108	1.0	448 (78)
33		**B**	21	21	1.0	NT
34		**C**	11	5.2	0.5	53 (75)
35		**D**	2.9	12	4.1	16 (95)
36		**E**	6.4	346	54	21 (110)
37		**A**	28	27	1.0	103 (82)
38		**C**	2.3	1.1	0.5	9.6 (81)
39		**D**	0.6	2.2	3.7	5.2 (93)
40		**E**	2.5	107	43	7.5 (104)
41		**A**	2152	527	0.2	NT
42		**C**	227	NT		NT
43		**E**	111	3177	29	339 (81)
44		**A**	295	113	0.4	NT
45		**C**	44	7.3	0.2	685 (109)
46		**B**	22	19	0.9	NT
47		**C**	7.7	5.8	0.8	18 (74)
48		**D**	5.0	14	2.8	28 (84)
49		**E**	7.1	268	38	12 (104)

NT = not tested.

Table 3



No.	R	NOP K_i (nM)	MOP K_i (nM)	NOP/MOP	cAMP IC_{50} (nM) (%NC resp.)
50		31	30	1.0	59 (92)
51		0.7	69	99	2.6 (101)

cyclohexyl ring was preferable (Table 3). Compound **51**[24] shows high NOP affinity (K_i = 0.7 nM), almost 100-fold selectivity over MOP and acts as a high potency NOP agonist in the cAMP functional assay (IC_{50} = 2.6 nM). Furthermore **51** exhibited low affinity for KOP (K_i = 2.7 μM) and DOP (K_i = 7.0 μM) receptors. During the course of this work it was discovered that **4** prolonged (approx. 10%) the QTc interval in conscious dogs at therapeutic doses. hERG channel inhibition is considered an indicator of the potential for a compound to prolong the QT interval[25] therefore **4** was subsequently evaluated for hERG channel affinity using a dofetilide binding assay and found to exhibit high affinity (K_i = 56 nM).[26] However **51** showed 75-fold decreased affinity for hERG (K_i = 4.2 μM) compared to **4**. Compound **51** was taken further for in vivo evaluation. The compound demonstrated an ED_{50} = 0.23 μmol/kg (in comparison to 1.03 μmol/kg for compound **4**, iv administration) in the second phase of the mouse formalin paw test thus illustrating this compound has antinociceptive properties. Furthermore evaluation of the sedative/anaesthetic effect following iv administration in the loss of righting reflex (LRR) assay in mice showed the compound to have a calculated HD_{50} value of 0.08 μmol/kg (compared to a HD_{50} = 4.7 μmol/kg for compound **4**).

In summary we have developed a knowledge based strategy to rapidly access simplified hydrophobes to replace the more complex 3-phenoxypropyl piperidine found in **4**. Replacement of the benzimidazol-2-one core resulted in ligands that demonstrated a lower level of selectivity for NOP over MOP. Only core **E** afforded appreciable selectivity over MOP thus highlighting once again the importance of the orientation of the *N*-methyl acetamide for selectivity. Compound **51** given iv produced antinociceptive effects comparable to morphine in the formalin paw test and showed potent anaesthetic activity in a loss of righting reflex assay. Furthermore **51** had a lower propensity to bind the hERG channel. Compound **51** had the ideal attributes as a follow-up compound to **4**.

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References and notes

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