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4-Substituted anilides as selective melatonin MT_2 receptor agonists

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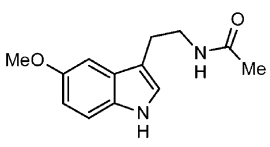
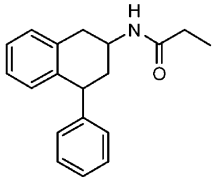
Abstract—A series of 4-substituted anilides with human melatonergic affinity is reported. Butyramides **26**, **39**, **42**, **52**, **57**, and **58** all demonstrated subnanomolar MT_2 binding affinity and MT_2 selectivity of at least 70-fold over the MT_1 receptor. Compound **26** demonstrated full agonism at the MT_2 receptor.

Melatonin (**1**) is a pineal hormone involved in circadian and photoperiodic behavior and helps regulate the sleep/wake cycle.[1] Melatonin transmits its effects, in part, through G-protein coupled receptors.[2] In humans, the MT_1 and MT_2 melatonin receptors have been identified in the brain.[3,4] The MT_2 receptor now appears to play a major role in mammalian circadian entrainment.[5] In mice lacking the MT_1 receptor,[6] melatonin produced phase shifts, and the MT_2 selective antagonist 4-P-PDOT (**2**) blocked this effect.[7]

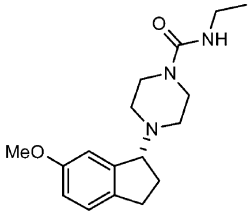


1
Melatonin



2

Recently, structurally rigid *N*-acyl-4-indanylpiperazines **3** were reported to be MT_2 selective agonists.[8] In contrast to these indanylpiperazines, conformationally flexible *N*-acyl benzylpiperazines **4** possessed only modest melatonergic affinity. We now report a series of 4-substituted anilides which are potent and selective agonists at the human melatonin MT_2 receptor. These anilides have similar conformational flexibility to benzylpiperidines **4** and demonstrate that structural rigidity is not an absolute requirement for either potency or selectivity.



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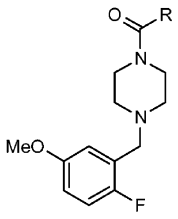

4

The synthesis of the anilides consisted of two parts: (1) assembly of a substituted nitrobenzene intermediate by one of five methods (Scheme 1) and (2) reduction and acylation of that intermediate to form the anilide (Scheme 2). 4-Aryloxy- and 4-arylthio- intermediates **7** were prepared by nucleophilic displacement of 4-fluoronitrobenzene (**6**) with a phenol or thiophenol **5** under basic conditions (method a). 3-Aryloxy intermediate **10** was prepared in modest yield by a modified Ullmann procedure[9] employing PhCCCu to couple 3-nitrophenol (**9**) with 3-methoxybromobenzene (**8**) (method b). 4-Ketoaryl intermediate **13** was prepared under Stille conditions[10] to couple 4-nitrobenzoyl chloride (**12**) with 3-methoxyphenyltributyl stannane (**11**) (method c). 4-Benzyl intermediate **16** was prepared under Suzuki

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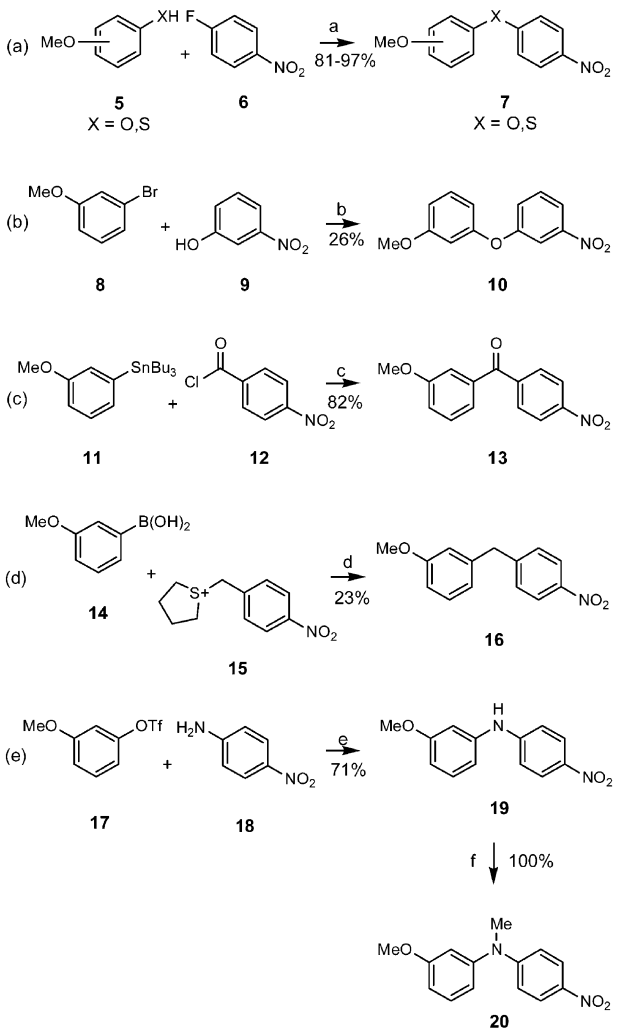
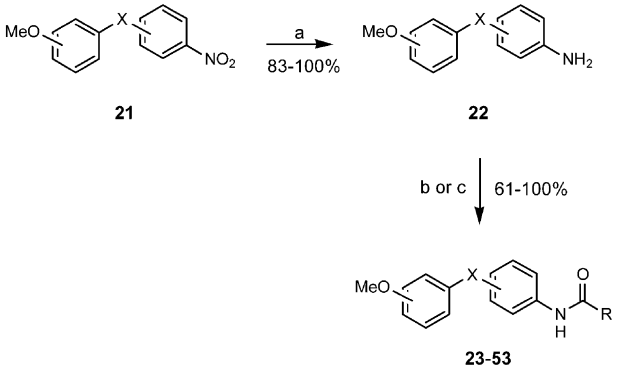


Scheme 1. Synthesis of nitrobenzene intermediates. Reagents and conditions: (a) K_2CO_3, CH_3CN, reflux; (b) PhCCCu, pyridine, reflux; (c) $Bn(Cl)(Ph_3P)_2Pd$, CH_2Cl_2, 25 °C; (d) $PdCl_2$, dppf, K_2CO_3, THF, reflux; (e) $Pd(OAc)_2$, BINAP, Cs_2CO_3, toluene, 80 °C; (f) MeI, solid KOH, THF, reflux.



Scheme 2. Synthesis of anilides. Reagents and conditions: (a) H_2, Pd/C, EtOAc or EtOH; (b) RCOCl, TEA, cat. DMAP, CH_2Cl_2; (c) RNCO, CH_2Cl_2.

conditions reported by Liebeskind[11] (method d). In this method, 4-nitrobenzyl chloride was reacted with tetrahydrothiophene to form the stable sulfonium salt **15**.[12] This salt then underwent Suzuki coupling with 3-methoxyphenylboronic acid (**14**) employing a Pd/dppf catalyst system. Finally, 4-anilinyl intermediate **19** was prepared under improved Buchwald conditions for coupling aryl triflate **17** with aniline **18** under mild basic conditions (method e).[13] Intermediate **19** was also methylated to afford methylamino intermediate **20**.

The intermediate nitrophenyl compounds **21** were then hydrogenated to afford penultimate anilines **22** and subsequently acylated with acid chlorides or isocyanates to afford anilides **23–53** (Scheme 2).[14]

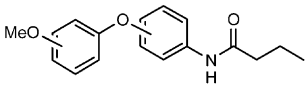
Additionally, thioether **38** was cleanly oxidized to provide sulfone **39**. Keto compounds **13** and **53**, however, could not be reduced to methylene compound **52** under a variety of conditions (acidic, basic, and neutral pH) either directly or through the reduced hydroxy compounds. This led to the Liebeskind modified Suzuki coupling to obtain methylene bridged analogues.

Cyclic isosteres of the 3-methoxy moiety were also prepared (compounds **54–59**). Thus, 2,3-dihydro-4-hydroxybenzofuran[15] and 5-hydroxybenzodioxane[16] were coupled with 4-fluoronitrobenzene to form intermediates analogous to **7**. 2,3-Dihydro-4-hydroxybenzofuran was also coupled to 4-nitroaniline by Buchwald coupling via the triflate to form intermediates analogous to **19** and **20**. These intermediates were then converted to *N*-acylanilides **54–57** by the methods of Scheme 2. The syntheses of compounds **58** and **59** were prepared from (benzofuran-4-yl)methanol and (2,3-dihydrobenzofuran-4-yl)methanol[17] by conversion to the benzyl sulfonium salt (allyl bromide, CDI, followed by THT, $NaClO_4$, 30% for two steps) and coupling with 4-formylphenylboronic acid.[18] The resulting aldehyde was oxidized to the acid (Ag_2O, 87%) and converted to the aniline by Curtius rearrangement (DPPA, TEA, *t*BuOH followed by HCl, EtOH, 25% for two steps) before acylation as in Scheme 2.

Compounds **23–59** were evaluated for human melatonin MT_1 and MT_2 receptor binding using published methods.[3,19,20] The regiochemical optimization of (methoxy)phenoxybutyranilides is summarized in Table 1. Compound **26** had the optimum placement of substituents for this pharamacophore.[21] Compounds **23**, **24**, and **26** show the preferred phenoxy group orientation is para to the anilide moiety for MT_2 binding and selectivity. Compounds **25–27** demonstrate the preferred location for the methoxy substituent on the phenoxy group is the 3-position. In these regioisomers, compound **26** was clearly unique and possessed excellent MT_2 binding affinity of 0.75 nM and 84-fold selectivity for the MT_2 receptor.

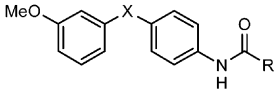
Using compound **26** as a lead pharmacophore, a variety of related amides were evaluated and are summarized in Table 2 (compounds **28–37**). Although butyramide **26** had the most potent MT_2 binding and highest MT_2 selectivity, acetamide **28**, propionamide **29**, crotonamide **34**, and methoxyacetamide **35** were also potent MT_2 ligands, albeit with less MT_2 selectivity. Valeramide **30** did not possess melatonergic affinity and demonstrated the limits for binding activity in linear alkanamides.

Table 1. Melatonin receptor binding of regioisomers **23–27**



Compd	Methoxy substitution	Aryloxy substitution	MT_1	MT_2	MT_1/MT_2
			K_i (nM)	K_i (nM)	
1			0.53	0.32	1.6
23	3-MeO	2-	> 500	130	3.9
24	3-MeO	3-	> 500	26.8	19
25	2-MeO	4-	> 500	108	4.6
26	3-MeO	4-	63	0.75	84
27	4-MeO	4-	> 500	> 400	na

Table 2. Melatonin receptor binding of compounds **28–53**



Compd	X	R	MT_1	MT_2	MT_1/MT_2
			K_i (nM)	K_i (nM)	
1			0.53	0.32	1.6
28	O	Me	84	4.1	20
29	O	Et	300	6.8	44
26	O	nPr	63	0.75	84
30	O	nBu	> 500	> 400	na
31	O	iPr	> 500	122	4
32	O	iBu	> 500	15	30
33	O	cPr	99	13	13
34	O	1-propenyl	98	2.1	47
35	O	CH_2OMe	180	5.9	31
36	O	propargyl	> 500	110	5
37	O	NHEt	> 500	250	2
38	S	nPr	29	0.19	150
39	SO_2	nPr	> 500	10	50
40	NH	Me	84	4.2	20
41	NH	Et	61	1.8	34
42	NH	nPr	31	0.39	81
43	NH	iPr	> 500	84	6
44	NH	cPr	61	64	1
45	NH	OEt	> 500	150	3
46	NMe	Me	0.05	0.23	0.22
47	NMe	Et	1	0.17	6.1
48	NMe	nPr	1.1	0.1	11
49	NMe	iPr	106	5.5	19
50	NMe	cPr	12	4.8	3
51	NMe	OEt	34	7.2	5
52	CH_2	nPr	10.9	0.12	91
53	CO	nPr	> 500	33	15

Isovalerylamide **32** and cyclopropylcarboxamide **33** had some MT_2 binding with little MT_1 binding, while isobutyramide **31** had poor binding at both receptors. 2-Butynamide **36** and ethyl urea **37** were also poor ligands at both receptors.

In addition to ether compounds **23–37**, a number of analogues replacing the diaryl ether oxygen were also evaluated (Table 2, compounds **38–53**). Compounds replacing the ether oxygen with electron-donating groups (S, NH, and NMe) or electron-neutral groups (CH_2) were potent and selective MT_2 ligands, whereas compounds with electron-withdrawing groups (SO_2, CO) had attenuated melatonergic activity.

Thus, thioether **38**,[22] the compound which proved to be the most selective of this study, had MT_2 binding of 0.19 nM and MT_2 selectivity of 150. Sulfone **39**, on the other hand, was 50-fold less active at the MT_2 receptor, but still had MT_2 selectivity of 50.

Diarylamines **40–51** were also evaluated. In this class, butyramides were again the most potent MT_2 ligands (**42** and **48**). Compound **42**, with a bridging NH group, had MT_2 affinity of 0.39 nM and MT_2 selectivity of 81. Conversely, compound **48**, with an NMe bridge, had good binding at both MT_1 and MT_2 receptors (1.1 and 0.10 nM, respectively). Consequently, the MT_2 selectivity of **48** was only 11. As a result, isobutyramide **49** had the best selectivity (19-fold) among the NMe compounds.

Finally, carbon-bridged compounds were evaluated. Methylene bridged butyramide **52**[23] demonstrated excellent MT_2 affinity and selectivity of 91. Keto bridged compound **53** had attenuated MT_2 affinity and selectivity relative to **52** (MT_2 $K_i = 33$, $MT_1/MT_2 = 15$).

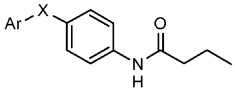
In all of these cases, the most potent MT_2 binding resided with butyramides. When optimally bridged, these compounds had subnanomolar affinity, and except for one compound (**48**), the highest MT_2 selectivity also resided with butyramides, with a selectivity range of 81- to 150-fold over the MT_1 receptor.

Compounds in which the 3-methoxy moiety was replaced with a variety of cyclic ethers were evaluated in four differently bridged series: O, NH, NMe, and CH_2 (Table 3). Except for NH-bridged compound **56**, all compounds in this series had potent MT_2 affinity (all but **55** had subnanomolar affinity), and all possessed some MT_2 selectivity. Ether compounds **54** and **55** had selectivity of 27 and 19. NH Compound **56** had selectivity of 12 while NMe compound **57** had selectivity of 73. This situation is the reverse of the NH- and NMe-bridged methoxy analogues, **42** and **48**, where the NH compound had selectivity of 81 and the NMe compound had selectivity of 11. Methylene bridged compounds **58** and **59**[24] also had good selectivity, 118 and 57 respectively, with **58** having the highest selectivity of the cyclic ether series.

Compound **26** was selected for functional evaluation at the MT_2 receptor and demonstrated full agonism in an assay measuring the inhibition of forskolin-stimulated cAMP accumulation in NIH-3T3 cells stably expressing the MT_2 receptor ($EC_{50} = 1.07$ nM; intrinisic activity $= 1.09$).[8]

In summary, we have discovered a series of anilides, the butyramides of which are often potent and selective human MT_2 ligands. In particular, butyramides **26**, **39**, **42**, **52**, **57**, and **58** all demonstrated subnanomolar MT_2 binding affinity and MT_2 selectivity of at least 70-fold over the MT_1 receptor. Compound **26** of this series demonstrated full agonism at the MT_2 receptor.

Table 3. Melatonin receptor binding of cyclic compounds **54**–**59**



Compd	Ar	X	MT_1	MT_2	MT_1/MT_2
			K_i (nM)	K_i (nM)	
1			0.53	0.32	1.6
54		O	18	0.68	27
55		O	92	4.7	19
56		NH	> 500	39	12
57		NMe	36	0.49	73
58		CH_2	92	0.78	118
59		CH_2	41	0.71	57

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20. K_i values were the mean of at least three determinations run at five concentrations with the radioligand at the K_d concentration. Standard errors were typically ±20% of the mean value.
21. ***N*-[4-(3-Methoxyphenoxy)phenyl] butanamide** (**26**). Mp 45–47 °C; ^1H NMR ($CDCl_3$) δ 7.76 (bs, 1H), 7.46 (d, J = 8.9 Hz, 2H), 7.15 (t, J = 7.6 Hz, 1H), 6.94 (d, J = 8.9 Hz, 2H), 6.60 (d, J = 7.6 Hz, 1H), 6.51 (m, 2H), 3.73 (s, 3H), 2.30 (t, J = 7.3 Hz, 2H), 1.72 (sex, J = 7.3 Hz, 2H), 0.96 (t, J = 7.3 Hz, 3H). Anal. calcd for $C_{17}H_{19}NO_3$: C, 71.56; H, 6.71; N, 4.91. Found: 71.39; H, 6.62; N, 4.80.
22. ***N*-[4-(3-Methoxyphenyl)thiophenyl] butanamide** (**38**). Mp 48–49 °C; ^1H NMR ($CDCl_3$) δ 7.80 (bs, 1H), 7.50 (d, J = 8.6 Hz, 2H), 7.33 (d, J = 8.6 Hz, 2H), 7.15 (t, J = 7.9 Hz, 1H), 6.73 (m, 3H), 3.72 (s, 3H), 2.32 (t, J = 7.3 Hz, 2H), 1.73 (sex, J = 7.3 Hz, 2H), 0.96 (t, J = 7.3 Hz, 3H). Anal. calcd for $C_{17}H_{19}SNO_2$: C, 67.75; H, 6.35; N, 4.65. Found: 67.69; H, 6.30; N, 4.89.
23. ***N*-[4-(3-Methoxybenzyl)phenyl] butanamide** (**52**). Mp 73–75 °C; ^1H NMR ($CDCl_3$) δ 7.40 (d, J = 8.4 Hz, 2H), 7.18 (t, J = 7.7 Hz, 1H), 7.12 (d, J = 8.4 Hz, 3H), 6.73 (m, 3H), 3.90 (s, 2H), 3.75 (s, 3H), 2.31 (t, J = 7.3 Hz, 2H), 1.74 (sex, J = 7.3 Hz, 2H), 0.99 (t, J = 7.3 Hz, 3H). Anal. calcd for $C_{18}H_{21}NO_2 \cdot 0.425H_2O$: C, 71.56; H, 6.71; N, 4.91. Found: 74.30; H, 7.99; N, 4.21.
24. ***N*-[4-(4-Benzofuranyloxy)phenyl] butanamide**. (**58**). Mp 110–113 °C; ^1H NMR ($CDCl_3$) δ 7.56 (d, J = 2.2 Hz, 1H), 7.45 (m, 3H), 7.29 (m, 2H), 7.18 (d, J = 11 Hz, 1H), 7.06 (d, J = 7.3 Hz, 1H), 6.68 (d, J = 2.2 Hz, 1H), 4.18 (s, 2H), 2.31 (t, J = 7.3 Hz, 2H), 1.75 (q, J = 14.9, 7.4 Hz, 2H), and 0.99 (t, J = 7.4 Hz, 3H); MS: 292.3 $(M-H)^-$. Anal. calcd for $C_{19}H_{19}NO_2 \cdot 0.20H_2O$: C, 76.84; H, 6.59; N, 4.72. Found: 76.90; H, 6.64; N, 4.70.