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ROYAL SOCIETY OF CHEMISTRY View Article Online
DOI: 10.1039/C8MD00604K

Journal Name

COMMUNICATION

Fluorine substituted methoxyphenylalkyl amides as potent melatonin receptor agonists

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Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

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A series of fluorine substituted methoxyphenylalkyl amides was prepared with different orientation of the fluorine and methoxy groups with respect to the alkylamide side chain and with alkyl side of differing lengths (n = 1-3). β-Dimethyl and α-methyl derivatives were also synthesised. The compounds were tested as melatonin agonists and antagonists using the pigment aggregation of *Xenopus* melanophores as the biological assay. A number of the compounds were potent melatonin agonists, the potency depending on the length of the alkyl chain, the orientation of the methoxy and fluorine substituents, the amide chain length and, for the ethyl side-chain analogues, the presence of β-substituents.

Introduction

Melatonin (**1**, Figure 1) is the hormone secreted by the human pineal gland and appears to be involved in sleep onset[1] and other functions associated with the bodies clock, the suprachiasmic nucleus (SCN).[2] It is ubiquitous throughout both the animal and plant kingdoms and must have a long evolutionary history as a hormone. Melatonin has a major role in the regulation of circadian rhythms in non-mammalian vertebrates and forms part of their control in mammals.[3-5] Administration of melatonin to humans and other mammals has a sleep-promoting action.[6] Sleep problems become more common in the elderly[7,8] in whom there is also a loss in the production of melatonin. A prolonged-release melatonin formulation has been approved for short-term treatment of primary insomnia in elderly patients,[9] and an analogue, ramelteon, has recently been approved as a treatment for insomnia characterised by difficulty with sleep onset.[10] Ramelteon is the first prescription medication for insomnia with a novel therapeutic mechanism of action to be licensed for 35 years, and the only hypnotic indicated for long-term treatment of insomnia as it does not have hangover, addiction or withdrawal effects.[11] Tasimelteon has been recently licensed for the treatment of non-24-hour sleep–wake disorder.[12] Another melatonin analogue, agomelatine, was earlier introduced as an antidepressant and also appears to have few side effects.[13] Melatonin treatment has therapeutic value in some blind subjects, restoring their disturbed circadian rhythm.[14] It also has potential in the treatment of seasonal affective disorder (SAD) which afflicts some people during the short winter days, [15] and it has been used to reset the clock in sufferers from jet lag.[16,17] Melatonin has been implicated in a range of other conditions, including Parkinson's disease,[18] Alzheimer's and other neurological conditions,[19-21] and in certain cancers.[22,23] There is an ongoing controversy with regard to the action of melatonin as an antioxidant and, if it is, how it functions.[24-26]

The melatonin receptor belongs to the family of G protein-coupled receptors (GPCR). MT_1 and MT_2 receptors share high sequence homology, while GPR50 is an orphan receptor and is considered the mammalian ortholog of Mel1c, a melatonin receptor found exclusively in fish, *Xenopus* species, and chickens.[27] An atypical melatonin-binding site has been discovered to be the enzyme quinine reductase 2 (QR2) and it has been proposed that inhibition of this enzyme may be responsible for the anti-oxidant actions of the hormone.[28] A nuclear melatonin receptor, member of the RZR/ROR receptor superfamily,[29] has also been reported. Moreover, it has recently been shown that melatonin can be synthesised by mammalian skin, where it may be important in regulating hair growth and pigmentation physiology.[30]

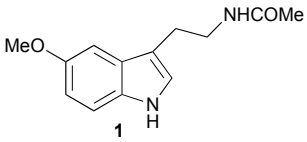

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Figure 1. Melatonin (**1**).

We have been interested in the interaction of melatonin with its receptors and have prepared a large number of analogues in an attempt to map the receptors requirements.[31] We prepared a series of substituted phenylalkylamides and showed that these simple derivatives could have high binding affinities at the melatonin receptor.[32] Following this work, other groups have recently reported similar compounds with high affinities for the melatonin receptor,[33-36] and have shown that enantiomers have different affinities.[33,37] We

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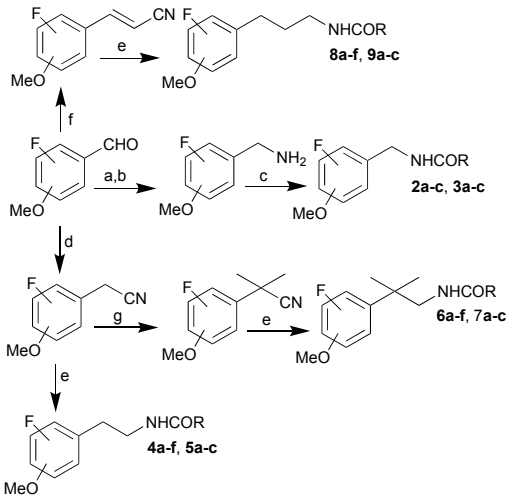
Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x

now describe the preparation of a series of fluorine containing phenylalkylamides, which show high agonist activity in the *Xenopus* assay and further define the steric requirements of the melatonin receptor, as shown in Figure 1. It has been reported that fluorinated tryptamine has increased selectivity and functional activity.[38] Fluorine substitution modifies the biophysical and chemical features such as lipophilicity, acidity, as well as the reactivity and conformation of the resulted derivatives.[39]

Results and Discussion

A number of fluorine substituted phenylalkylamides were prepared using the appropriately substituted benzaldehyde, as shown in the Scheme. Treatment of the aldehyde with hydroxylamine followed by reduction of the oxime gave the amine, which was acylated with the appropriate anhydride to give compounds **2a-c**, **3a-c**. Reaction of the aldehyde with *p*-toluenesulphonylmethyl isocyanide (TosMIC) gave the phenyl methyl cyanide which on treatment with the appropriate anhydride together with Raney nickel and hydrogen gave compounds **4a-f** and **5a-c**. A Wittig reaction of the aldehyde with (cyanomethyl)triphenylphosphonium chloride followed by treatment with the appropriate anhydride with Raney nickel and hydrogen gave compounds **8a-f**, **9a-c**. The β,β-substituted derivatives **6a-f** and **7a-c** were prepared by the previously described method,[31] as shown in the Scheme. The appropriately substituted phenylacetonitrile was treated with NaH followed by methyl iodide and the resulting dimethylcyanide on reaction with the appropriate anhydride with Raney nickel and hydrogen gave the desired dimethyl derivatives. The α-methyl derivative **10** was synthesised from 4-fluoro-3-methoxybenzaldehyde by treatment with nitroethane followed by reduction of the nitro group with LAH and treatment of the resulting amine with butyric anhydride. The compounds are shown in **Figure 2**.



Scheme. *Reagents and conditions:* (a) $H_2NOH.HCl$, CH_3CO_2Na / EtOH-H_2O, 70 °C, 1.5 h; (b) H_2 / 10% Pd-C /EtOH-EtOAc, 4 atm, 6 h; (c) appropriate anhydride, Et_3N, DCM, 0 °C, after addition rt, 1.5 h; (d) TosMIC / DME, *tert*-ButOK, -30 °C, after addition of appropriate aldehyde, -60 °C, 1.5 h; (e) appropriate acid anhydride / dry THF, H_2 / Raney-Ni ,4 atm, 50 °C, 9-14 h; (f) $Ph_3P^+CH_2CN,Cl^-$, DBU, toluene, reflux, 1 h; (g) MeI, NaH, DMF.

The biological activity of the analogues was assessed in a well-established model of melatonin action, the pigment aggregation response of *Xenopus laevis* melanophores.[40] In these cells many thousands of black pigment granules are normally distributed throughout the cell and the addition of melatonin induces their rapid movement to the center of the cell. This response is termed pigment aggregation and can be quantified by measuring the change in light absorbance of the cells as the pigment concentrates near the cell centre. In the present study, a clonal melanophore cell line, generously provided by Dr. Michael Lerner (Department of Dermatology, University of Texas), was used.

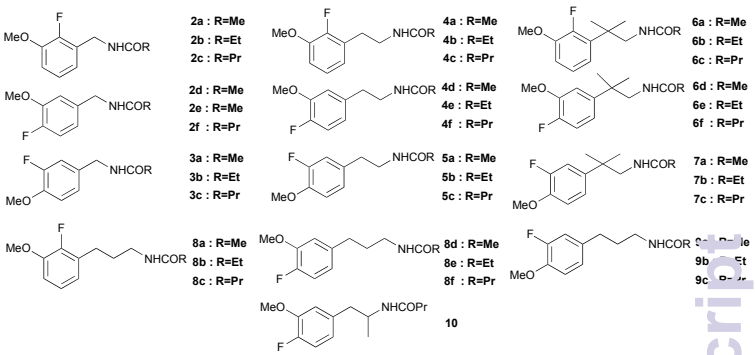


Figure 2. Fluorine substituted methoxyphenylalkyl amides.

Table 1. Agonist and Antagonist activity in the *Xenopus* melanophore assay of the Fluorine Substituted Phenylalkyl Amides

Compound	Agonist Potency pEC_{50} ± SEM[a]	Agonist Efficacy IA± SEM[a]	Antagonist Activity (% inhibition)
Melatonin	9.91 ± 0.03	100	
Luzindole[41]	-	-	100%
2a	5.71 ± 0.02	100 ± 1	NA [b]
2b	5.62 ± 0.15	69 ± 1	23%
2c	5.87 ± 0.04	43 ± 1	44%
2d	5.82 ± 0.05	77 ± 1	NA
2e	5.98 ± 0.01	51 ± 1	24%
2f	6.18 ± 0.06	57 ± 1	37%
3a	5.68 ± 0.02	83 ± 1	NA
3b	5.54 ± 0.01	86 ± 1	NA
3c	5.60 ± 0.08	75 ± 1	NA
4a	5.61 ± 0.24	100 ± 1	NA
4b	6.10 ± 0.28	100 ± 1	NA
4c	6.60 ± 0.15	100 ± 1	NA
4d	6.56 ± 0.16	100 ± 1	NA
4e	7.07 ± 0.12	100 ± 1	NA
4f	7.18 ± 0.03	100 ± 1	NA
5a	5.62 ± 0.14	80 ± 1	NA
5b	5.87 ± 0.08	80 ± 1	NA
5c	5.92 ± 0.11	52 ± 1	48%
6a	6.74 ± 0.12	100 ± 1	NA
6b	6.57 ± 0.10	100 ± 1	NA
6c	7.01 ± 0.20	100 ± 1	NA
6d	8.74 ± 0.01	100 ± 1	NA
6e	9.27 ± 0.02	100 ± 1	NA
6f	10.64 ± 0.02	100 ± 1	NA
7a	7.09 ± 0.04	100 ± 1	NA
7b	7.03 ± 0.01	100 ± 1	NA
7c	7.10 ± 0.01	100 ± 1	NA
8a	7.69 ± 0.07	100 ± 1	NA
8b	8.43 ± 0.02	100 ± 1	NA
8c	8.02 ± 0.04	100 ± 1	NA
8d	8.41 ± 0.01	92 ± 1	NA
8e	8.96 ± 0.02	89 ± 1	NA
8f	9.05 ± 0.02	89 ± 1	NA
9a	5.74 ± 0.02	79 ± 1	NA
9b	6.06 ± 0.01	78 ± 1	8%
9c	6.38 ± 0.03	73 ± 1	19%
10	6.98 ± 0.04	89 ± 1	NA

[a] Concentration–response curves were analyzed by non-linear regression. Agonist potency (pEC_{50}) is the mean ± SEM of triplicate determinations of log EC_{50}, while the agonist efficacy (IA ± SEM) was expressed as a percentage of the maximal pigment aggregation response observed with melatonin (=100%). Data are mean

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DOI: 10.1039/C8MD00604K

of at least 3 independent experiments. [b] NA indicates no antagonist activity up to 10^{-4} M, or the percentage inhibition of aggregation induced by melatonin (10^{-9} M). Data from triplicate assays.

The results are shown in the **Table 1**. The majority of the compounds examined were full agonists in the melanophore model, with a few showing considerable partial agonist activity with some antagonism at the highest concentration tested (10^{-4} M). As expected from our previous observations,[32] the benzyl derivatives **2a-c** and **3a-c** are poor agonists, the side chain being too short to adequately bind into the receptor pocket. Increasing the side chain length increases the agonist effect, the ethylamine derivatives being better agonists and now the relative position of the methoxy and fluorine substituents has an effect. The introduction of methyl groups at the beta position of the ethylacetamide side chain to give the methylpropylacetamide derivatives **6** and **7** provides a surprising increase in melatonin activity since the side chain length is not optimal. This substantial increase in agonist activity appears to arise from a number of factors. Thus the 2-fluoro-5-methoxy derivatives **6a-c** have very similar agonist activities to the analogues **4a-c** with no methyl substituents whereas the 4-fluoro-3-methoxy compounds **6d-f** show a substantial increase in agonist activity compared to the non-methylated derivatives **4d-f**, with the *N*-propanoyl analogue **6f** having an agonist activity greater than melatonin. This increase appears to result from a combination of increasing the population of the optimal binding conformation with an increase in the length of *N*-acyl group. Thus, **6d** (R =Me) and **6e** (R = Me) are both *ca.* 150fold more active than the non-methylated analogues **4d** and **4e**, while **6f** (R = Pr) is *ca*. 2900 fold more active than **4f**. The *beta*-dimethyl-3-fluoro-4-methoxy derivatives **7a** – **c** are *ca.* 30 times more active than the non-methylated compounds **5a-c**, but there is no increase in activity with increasing length of the *N*-acyl group, suggesting that this group is not accommodated in its normal binding site. The 3-methoxy-4-fluoro derivatives (**4d-e**) are better agonists than the corresponding 5-methoxy-2-fluoro derivatives (**4a-c**), while the 3-fluoro-4-methoxy derivatives (**5a-c**), in which the methoxy group is *para* to the side chain are poorer still, though these latter compounds are still agonists. Increasing the side chain to three carbon atoms leads to a further improvement as a melatonin agonist, as expected from previous studies. Again, the 4-fluoro-5-methoxy compounds (**8d-f**) are better agonists than the 2-fluoro-5-methoxy analogues (**8a-c**), with the 3-fluoro-4-methoxy compounds (**9a-c**) considerably poorer agonists. It is also notable that the position of the fluorine atom at 2 has little or no effect on the agonist activity of the non-methyl substituted analogues **4a-f** and **8a-f**, whereas it has a major effect on the methyl substituted analogues **6a-f**. Compound **10**, with an alpha methyl group, has a similar agonist activity to the corresponding non-methylated derivative **4f**.

Conclusions

The most potent sets of compounds are **6d-f** and **8d-f** with the fluorine atom in position 4. The compounds **6d-f**, with the dimethyl group on the side chain, presumably have a higher probability to fit into the melatonin receptor than compounds **8d-f** with a linear side chain, although the length of the side chain in the latter compounds is probably more optimal. It will be of interest to examine the lifetime affinity of **6d-f** compared to melatonin to determine whether the fluorine atom slows the metabolism of the compounds.

Conflicts of interest

There are no conflicts to declare.

Experimental Section

General Procedure for the Preparation of Arylacetonitriles from Aldehydes

A solution of *p*-tolouenesulfonylmethyl isocyanide (TosMIC) (2.04 g, 10.4 mmol) in dimethoxyethane (DME) (11 mL) was added dropwise to a suspension of potassium *tert*-butoxide (2.35 g, 21.2 mmol) in DME (11 mL) at -30 ^{o}C. After the addition, the mixture was cooled to -60 ^{o}C and a solution the appropriate aldehyde (9.74 mmol) in DME (22 mL) was cautiously added. The reaction was stirred at this temperature for 1.5 h and methanol (33 mL) added. The mixture was allowed to thaw and then refluxed for 0.5 h. The solvent was removed *in vacuo* and H_2O (33 mL) and then acetic acid (2 mL) was added. The resulting suspension was extracted with dichloromethane (3 x 50 mL), the combined organic extracts washed with saturated aqueous $NaHCO_3$, brine and then dried (Na_2SO_4). The solvent was evaporated under reduced pressure and the residue was purified by column chromatography (cyclohexane/ethyl acetate) to give the desired compound as an off-yellow solid.

General Procedure for the Preparation of Arylacrylonitriles from Aldehydes

1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU) (746 mg, 4.91 mmol) and cyanomethyltriphenylphosphine chloride (1.54 mg, 4.55 mmol) were added to a stirred solution of the appropriate aldehyde (3.25 mmol) in toluene (6.5 mL) under argon. The resulting suspension was stirred under reflux for 1 h, cooled to room temperature and the solvent removed *in vacuo*. The residue was dissolved in CH_2Cl_2 (30 mL) washed with saturated aqueous NH_4Cl, dried (Na_2SO_4) and concentrated under reduced pressure to give a brownish oil, which was purified by flash column chromatography (cyclohexane/AcOEt). The desired arylacrylonitrile (yellowish light oil) was obtained as a 1:1 *cis*/*trans* mixture.

General Procedure for Reductive Acylation

A solution of phenylacetonitrile or phenylacrylonitrile (1.03 mmol) and the appropriate acid anhydride (10.3 mmol in the case of phenylacetonitriles or 16.9 mmol in the case of phenylacrylonitrines) in anhydrous THF (20 mL) was stirred under hydrogen (4 atm) at 50 ^{o}C in the presence of Raney-Ni for 9-14 h. The reaction mixture was then diluted with AcOEt (15 mL), filtered through Celite and the filtrate concentrated *in vacuo* to give the crude product, which was purified by flash column chromatography (cyclohexane/AcOEt) followed by trituration with AcOEt.

General Procedure for the Preparation of 1^{o} Amines from Aldehydes

Sodium acetate (23.3 mmol) was added to a mixture of the appropriate aldehyde (7.73 mmol) and hydroxylamine hydrochloride (15.5 mmol) in ethanol (15 mL) and water (15 mL). The resulting suspension was heated at 70 ^{o}C for 1.5 h and the solvents were then removed under vacuum. The residue was treated with a small quantity of water and extracted with ether (3 x 25 mL). The organic layers were dried (Na_2SO_4) and the solvent removed *in vacuo* to give the desired oxime in crystalline form as a 9:1 *anti*/*syn*-mixture. A solution of the appropriate oxime (6.98 mmol) in anhydrous methanol (20 mL) and AcOEt (20 mL) was hydrogenated in the

presence of 10% Pd/C (728 mg) at ambient temperature for 6 h under a pressure of 4 atm. The reaction mixture was then diluted with AcOEt (15 mL), filtered through Celite and the filtrate concentrated *in vacuo* to give the desired primary amine, which was then used without further purification.

General Procedure for the Preparation of Amides

Solution of corresponding amine (2.32 mmol) in dry dichloromethane (10 mL) was treated with triethylamine (0.5 mL) at 0 °C. The appropriate anhydride (3.48 mmol) was then added dropwise at the same temperature, and the resulting reaction mixture was left stirring at room temperature for 1.5 h. The solution was then poured into a separatory funnel, CH_2Cl_2 was added, and the yellow organic layer was washed with H_2O (20 mL). After drying over Na_2SO_4, the solvent was evaporated under reduced pressure to give the crude product, which was chromatographed (flash column) to give the desired amide.

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View Article Online DOI: 10.1039/C8MD00604K