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Mild and regioselective straightforward synthesis of isomelatonin analogues

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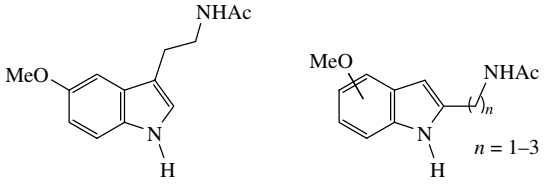
A mild and regioselective strategy for 3-arylisomelatonins, compounds with prominent potential use as ligands for melatonin receptors, is developed.

Melatonin **I** (*N*-acetyl-5-methoxytryptamine, Scheme 1) is secreted by the pineal gland in brain and is important in the regulation of many hormonal processes in the body. In addition to its hormone actions, melatonin also possesses strong antioxidant properties; preliminary evidence that it may strengthen the immune system is obtained.[1] The pharmacological effects of melatonin in humans have also been investigated in psychiatric disorders and in the cardiovascular system.[2] The molecular mechanisms underlying the reported antioxidant,[3] neuroprotective,[4] anticarcinogenic[5] and immunostimulatory[6] properties of melatonin are under thorough investigation.

Melatonin is a derivative of indolylalkylamines (tryptamines), which have importance as the main structural unit of indole alkaloids, many biologically active substances and remedies.[7] Recently, derivatives of tryptamines have attracted a lot of attention because of their high selectivity for serotonin,[8] melatonin[9] and gonadotropin releasing hormone[10] receptors.

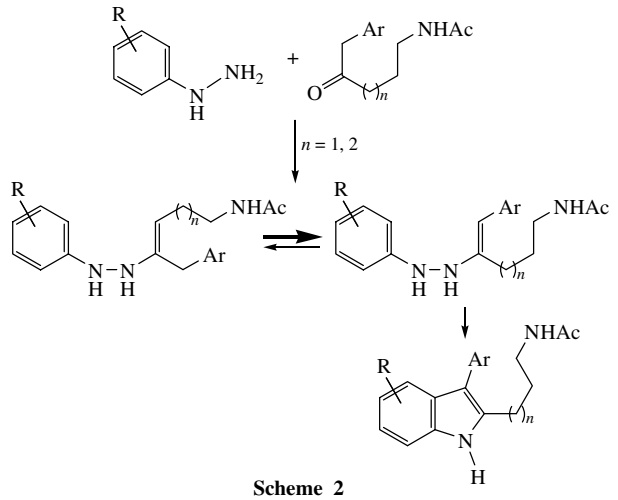


Scheme 1

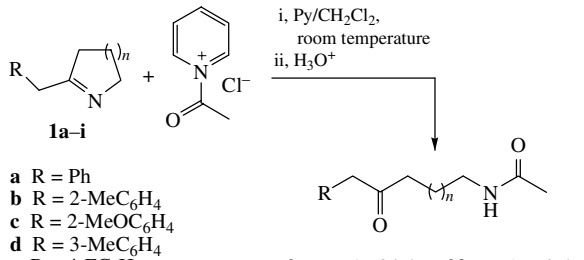
Derivatives of relative 2-indolylalkylamides **II** are investigated more feebly, mainly due to the absence of facile methods for their preparation.

A new series of partial agonists and antagonists of melatonin **I** were discovered by transposing the amidoalkyl side chain from C_3 to C_2 of the indole nucleus (Scheme 1, structures **II**, derivatives of isomelatonin).[11] Only two approaches to *N*-acyl-2-indolylalkylamines are described, *i.e.*, the acylation of preliminary prepared isotryptamines[11] and the decarboxylation of α-acetylaminoindol-2-yl acetic acid.[12] Both methods are lacking of structural diversity of the target molecules.

The two-component Fischer reaction seems to be satisfactory of diversity requirements. Note that acylamino groups remain intact during this reaction.



Scheme 2



a R = Ph
b R = 2-MeC_6H_4
c R = 2-$MeOC_6H_4$
d R = 3-MeC_6H_4
e R = 4-FC_6H_4
f R = 4-ClC_6H_4
g R = 4-MeC_6H_4
h R = 4-$MeOC_6H_4$
i R = cyclohexyl

2a *n* = 1, 84% **2f** n = 1, 79%
2b *n* = 1, 89% **2g** n = 2, 78%
2c *n* = 2, 75% **2h** n = 2, 86%
2d *n* = 2, 91% **2i** n = 2, 75%
2e *n* = 2, 81%

Scheme 3

Here, we describe an effective and facile straightforward route to isomelatonin derivatives. We proposed that benzyl (ω-amidoalkyl) ketones should give rise regioselectively to 3-aryl-2-(ω-amidoalkyl)indoles during the Fischer reaction with arylhydrazines, due to the more favourable conjugation of the ene bond of an intermediate enehydrazine with the aromatic core (Scheme 2).

Recently, we developed a new general method[13] for the synthesis of amidoketones from cyclic imines such as **1a–i** using *N*-acetylpyridinium chloride. Amidoketones **2a–i** were obtained in high yields (Scheme 3).†

The known procedures for the preparation of 3-arylindoles from benzylketones involve various catalysts such as AcOH,[14] HCl in H_2O[15] or EtOH,[16] H_2SO_4,[17] $ZnCl_2$,[18] TsOH in AcOH,[19] montmorillonite clay,[20] PCl_3/benzene,[21] mordenite or zeolite Y in xylene,[22] CCl_3COOH,[23] polyphosphoric acid[24] and $BF_3{\cdot}Et_2O$ in AcOH.[25] However, to the best of our knowledge, examples of

† ^1H and ^{13}C NMR spectra were recorded at 400 and 100 MHz, respectively; TMS was used as an internal standard. IR spectra were recorded in Nujol. TLC was performed with Silufol UV-254 plates, and flash chromatography was carried out with silica gel (63–200 mesh) using EtOAc as an eluent.

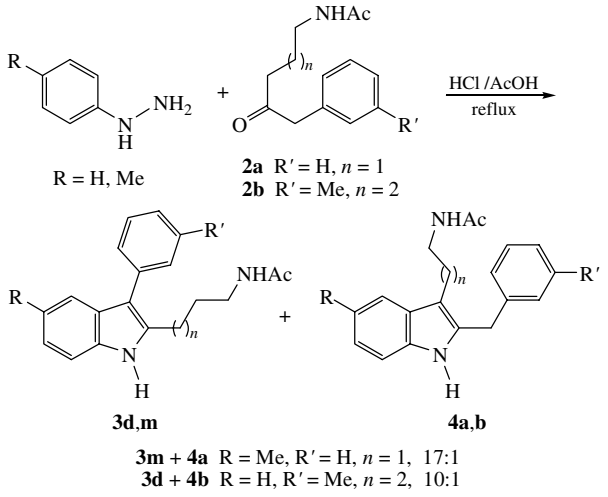
General procedure for the synthesis of amidoketones **2a–i**. To a well stirred solution of 1.6 ml (20 mmol) of pyridine in 20 ml of abs. CH_2Cl_2 a solution of 0.71 ml (0.8 g, 10 mmol) of AcCl in 10 ml of abs. CH_2Cl_2 was added for 30 min, and the mixture was stirred for additional 15 min.

To a suspension of *N*-acetylpyridinium chloride an obtained solution of 10 mmol of cyclic imine **1a–i** in 25 ml of abs. CH_2Cl_2 was added dropwise with stirring. After addition, the reaction mixture was stirred until *N*-acetylpyridinium salt was dissolved totally and then for 3 h.

To a clear solution obtained 20 ml of 5% HCl was added and stirred overnight; then, the organic layer was separated, washed with water (2×10 ml), dried with Na_2SO_4 and evaporated. Amidoketone **2a** was subjected to flash chromatography (hexane–EtOAc, 1:1), and amidoketones **2b–i** were used in the next step without isolation.

All compounds obtained were reliably characterised by their ^1H, ^{13}C NMR and IR spectra and satisfactory elemental analyses.

N-*(4-Oxo-5-phenylpentyl)acetamide* **2a**: yellowish crystal solid, yield 86%, mp 43–44 °C. IR (ν/cm^{-1}): 1640 (O=CNH), 1700 ($PhCH_2C$=O). ^1H NMR ($CDCl_3$) δ: 1.72 (q, 2H, $CH_2CH_2CH_2NHCOMe$, *J* 6.7 Hz), 1.87 (s, 3H, COMe), 2.50 (t, 2H, $CH_2CH_2CH_2NHCOMe$, *J* 6.7 Hz), 3.14 (q, 2H, $CH_2CH_2CH_2NHCOMe$, *J* 6.7 Hz), 3.67 (s, 2H, $PhCH_2$), 5.80 (br. s, 1H, NHCOMe), 7.18 (d, 2H, *J* 7.0 Hz), 7.25 (tt, 1H, *J* 7.3 and 7.0 Hz), 7.31 (t, 2H, *J* 7.3 Hz). ^{13}C NMR ($CDCl_3$) δ: 23.1, 23.2, 38.9, 39.2, 50.1, 127.0, 128.7 (2C), 129.3 (2C), 134.0, 170.2, 208.2. Found (%): C, 71.29; H, 7.81. Calc. for $C_{13}H_{17}NO_2$ (%): C, 71.21; H, 7.81.



3m + **4a** R = Me, R′ = H, *n* = 1, 17:1
3d + **4b** R = H, R′ = Me, *n* = 2, 10:1

Scheme 4

regioselective synthesis of 3-arylindoles from $ArCH_2COCH_2R$ ketones are missing.

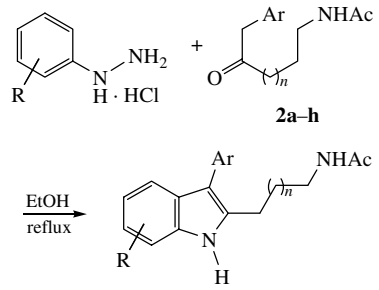
In our experiments, we tested a solution of dry HCl in AcOH[13] as the catalyst of the Fischer reaction; however, a mixture of regioisomers **3** (3-arylisomelatonins, ~50–70%) and **4** (2-benzylmelatonins, ~5%) was obtained especially in the case of amidoketones with donor substituents (Scheme 4).‡

We found that the yields of 2-arylmethylmelatonins increased with the acidity of catalysts used. Therefore, we reasoned that milder conditions of the reaction may improve its regioselectivity. In fact, target isomelatonin analogues **3a**–**q** were prepared regioselectively in high yields (Scheme 5).§

Thus, conjugation of the ene bond of enehydrazine with the aromatic core is an effective decisive factor for regioselective indolization.

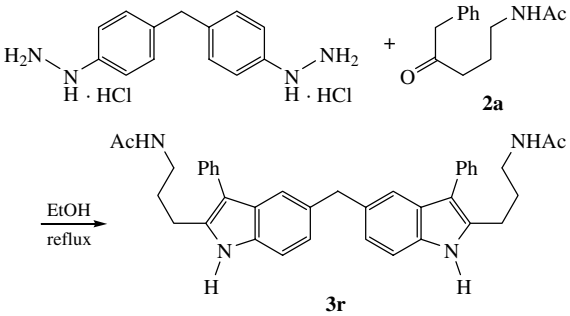
To investigate the scope of the method and the effect of substituents on the yield of the Fischer reaction, various arylhydrazines with electron donor and acceptor groups were synthesised.[26] In all cases, *N*-acetylindolylalkylamines were isolated in good to high yields, only arylhydrazines with strong electron-withdrawing substituents (4-CN and 2-CF_3) furnish indoles in moderate yields. Generally, no serious restriction in the structures of hydrazine or ketone components was found. Bis(4,4′-arylhydrazine) gave a 5,5′-methylene-linked derivative of isomelatonin **3r** in 73% yield (Scheme 6).

To compare the influence of steric and electronic factors on the regioselectivity of this method, we tested amidoketone **2i**,



3a Ar = Ph, R = H, *n* = 1, 77%
3b Ar = 2-MeC_6H_4, R = H, *n* = 1, 78%
3c Ar = 2-MeOC_6H_4, R = H, *n* = 2, 68%
3d Ar = 3-MeC_6H_4, R = H, *n* = 2, 49% (in HCl/AcOH)
3e Ar = 4-FC_6H_4, R = H, *n* = 2, 66%
3f Ar = 4-ClC_6H_4, R = H, *n* = 1, 77%
3g Ar = 4-MeC_6H_4, R = H, *n* = 2, 81%
3h Ar = 4-MeOC_6H_4, R = H, *n* = 2, 71%
3i Ar = Ph, R = 5-F, *n* = 1, 87%
3j Ar = Ph, R = 5-Cl, *n* = 1, 83%
3k Ar = Ph, R = 5-Br, *n* = 1, 90%
3l Ar = Ph, R = 5-I, *n* = 1, 87%
3m Ar = Ph, R = 5-Me, *n* = 1, 84% (68% in HCl/AcOH)
3n Ar = Ph, R = 5-MeO, *n* = 1, 93% (in arylhydrazine oxalate)
3o Ar = Ph, R = 5-CN, *n* = 1, 32%
3p Ar = Ph, R = 4-Br and 6-Br (1:1), *n* = 1, 72%
3q Ar = Ph, R = 7-CF_3, *n* = 1, 55%

Scheme 5



Scheme 6

which mimics the structure of **2a** except aromaticity. This experiment gave 3-(ω-amidoalkyl)substituted melatonin derivative **4c**, that is replacement of the phenyl ring by cyclohexyl

‡ *General procedure for the synthesis of* N-*acetylindolylalkylamines* **4a**,**b** *and* **3m**,**d**. A mixture of 1.1 mmol of arylhydrazine hydrochloride, 1.0 mmol of corresponding amidoketones in 15 ml of acetic acid, saturated preliminarily with gaseous HCl at 20 °C, was quickly warmed to boiling. When all solids were dissolved refluxing was continued for 15 min. Then, the reaction mixture was evaporated and distributed between water and CH_2Cl_2. The organic phase was washed with water (2×10 ml) and evaporated. The flash chromatography of the residue afforded the products.

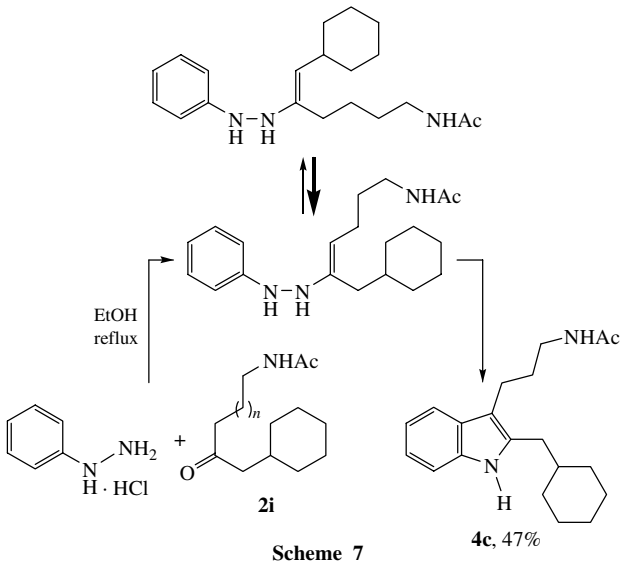
N-*[3-(2-Benzyl-5-methyl-1*H*-indol-3-yl)ethyl]acetamide* **4a**: reddish amorphous solid, 13 mg, yield 4%. R_f (EtOAc) 0.58. IR (ν/cm^{-1}): 1660 (O=C), 3400 (NHAc). ^{1}H NMR ($CDCl_3$) δ: 1.76 (s, 3H, COMe), 2.44 (s, 3H, 5-Me), 2.95 (t, 2H, CH_2CH$_2$NHCOMe, *J* 6.6 Hz), 3.50 (dt, 2H, CH$_2$CH_2NHCOMe, *J* 6.6 and 6.2 Hz), 4.08 (s, 2H, PhCH_2), 5.48 (br. s, 1H, N*H*COMe), 6.96 (d, 1H, *J* 7.6 Hz), 7.12–7.45 (m, 7H), 7.84 (br. s, 1H). ^{13}C NMR ($CDCl_3$) δ: 21.45, 23.1, 24.1, 32.1, 40.0, 108.8, 110.3, 117.9, 123.0, 126.7, 128.4 (2C), 128.5, 128.7, 128.8 (2C), 133.9, 134.3, 138.8, 170.1. Found (%): C, 78.57; H, 7.40. Calc. for $C_{20}H_{22}N_2O$ (%): C, 78.40; H, 7.24.

N-*[3-(5-Methyl-3-phenyl-1*H*-indol-2-yl)propyl]acetamide* **3m**: brownish crystals, 257 mg, yield 84%, mp 136–137 °C. R_f (EtOAc) 0.20. IR (ν/cm^{-1}): 1660 (O=C), 3405 (NHAc). ^{1}H NMR ($CDCl_3$) δ: 1.76–1.82 (m, 2H, CH$_2$CH_2CH$_2$NHCOMe), 1.92 (s, 3H, NHCO*Me*), 2.47 (s, 3H, 5-Me), 2.84 (t, 2H, CH_2CH$_2$CH$_2$NHCOMe, *J* 6.5 Hz), 3.24–3.29 (m, 2H, CH$_2$CH$_2$CH_2NHCOMe), 5.62 (br. s, 1H, N*H*COMe), 7.04 (d, 1H, *J* 8.2 Hz), 7.28–7.54 (m, 7H), 9.70 (br. s, 1H). ^{13}C NMR ($CDCl_3$) δ: 21.6, 22.4, 23.2, 30.1, 38.3, 110.7, 113.9, 118.4, 123.1, 125.9, 128.0, 128.7 (2C), 128.9, 129.7 (2C), 133.8, 135.3, 135.9, 171.3. Found (%): C, 78.31; H, 7.13. Calc. for $C_{20}H_{22}N_2O$ (%): C, 78.40; H, 7.24.

§ *General procedure for the synthesis of* N-*acetylindolylalkylamines* **3a**–**c**,**e**–**r** and **4c**. A mixture of 1.2 mmol of arylhydrazine hydrochloride and 1 mmol of amidoketones **2a**–**h** [2 mmol of amidoketone **2a** in the case of bis(4,4′-arylhydrazine)] in 15 ml of EtOH were refluxed until the end of the reaction (10–24 h; TLC control; eluent, EtOAc). Then, the reaction mixture was evaporated and distributed between water (10 ml) and EtOAc (20 ml). The organic phase was washed with water (2×5 ml) and evaporated. The flash chromatography of the residue afforded the products.

N-*[3-(5-Methoxy-3-phenyl-1*H*-indol-2-yl)propyl]acetamide* **3n**: cream crystals, 299 mg, yield 93%, mp 144–145 °C. R_f (EtOAc) 0.22. IR (ν/cm^{-1}): 1100–1150 (C–O–C), 1655 (O=C), 3405 (NHAc). ^{1}H NMR ($CDCl_3$) δ: 1.76–1.82 (m, 2H, CH$_2$CH_2CH$_2$NHCOMe), 1.93 (s, 3H, NHCO*Me*), 2.83 (t, 2H, CH_2CH$_2$CH$_2$NHCOMe, *J* 6.5 Hz), 3.26–3.30 (m, 2H, CH$_2$CH$_2$CH_2NHCOMe), 3.84 (s, 3H, 5-MeO), 5.68 (br. s, 1H, N*H*COMe), 6.87 (dd, 1H, *J* 8.8 and 2.4 Hz), 7.14 (d, 1H, *J* 2.4 Hz), 7.28–7.52 (m, 6H), 9.75 (br. s, 1H). ^{13}C NMR ($CDCl_3$) δ: 21.2, 23.1, 30.0, 38.4, 56.1, 101.4, 111.4, 111.8, 114.1, 126.0, 128.2, 128.8 (2C), 129.5 (2C), 130.8, 135.8, 136.4, 154.3, 171.4. Found (%): C, 74.41; H, 6.93. Calc. for $C_{20}H_{22}N_2O_2$ (%): C, 74.51; H, 6.88.

N-*{4-[2-(Cyclohexylmethyl)-1*H*-indol-3-yl]propyl}acetamide* **4c**: brownish yellow amorphous solid, 147 mg, yield 47%. R_f (EtOAc) 0.49. IR (ν/cm^{-1}): 1660 (O=C), 3400 (NHAc). ^{1}H NMR ($CDCl_3$) δ: 0.96–1.93 (m, 16H, cyclohexyl, NHCO*Me*, CH$_2$CH_2CH$_2$NHCOMe), 2.59 (d, 2H, cyclohexyl-CH_2, *J* 7.2 Hz), 2.75 (t, 2H, CH_2CH$_2$CH$_2$NHCOMe, *J* 7.4 Hz), 3.29 (m, 2H, CH$_2$CH$_2$CH_2NHCOMe), 5.62 (br. s, 1H, N*H*COMe), 7.07–7.14 (m, 2H), 7.29 (d, 1H, *J* 7.6 Hz), 7.51 (d, 1H, *J* 7.4 Hz), 8.04 (br. s, 1H). ^{13}C NMR ($CDCl_3$) δ: 21.8, 23.2, 26.2 (2C), 26.3, 30.4, 33.4 (2C), 34.0, 38.8, 39.8, 110.4, 111.3, 118.0, 119.0, 120.9, 128.3, 134.6, 135.4, 170.2. Found (%): C, 76.75; H, 9.09. Calc. for $C_{20}H_{28}N_2O$ (%): C, 76.88; H, 9.03.



Scheme 7

proved that the above mentioned conjugation is crucial for the direction of reaction (Scheme 7).

Due to mild reaction conditions, only the enehydrazine with less steric hindrance around the ene bond undergoes heterocyclisation. The formation of alternative regioisomer was not detected.

In summary, we have developed a new general strategy for the synthesis of 3-arylisomelatonins, compounds with prominent potential use as ligands for melatonin receptors. The method developed is a mild and regioselective and allows us to easily vary both ketone and arylhydrazine components.

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