Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron
ELSEVIER
Tetrahedron 60 (2004) 11719–11724

Convenient synthesis of melatonin analogues: 2- and 3-substituted -*N*-acetylindolylalkylamines

Valentine G. Nenajdenko,* Eugene P. Zakurdaev, Eugene V. Prusov and Elizabeth S. Balenkova

Department of Chemistry, Moscow State University, Leninskie Gory, 119992 Moscow, Russian Federation

Received 1 July 2004; revised 9 September 2004; accepted 1 October 2004

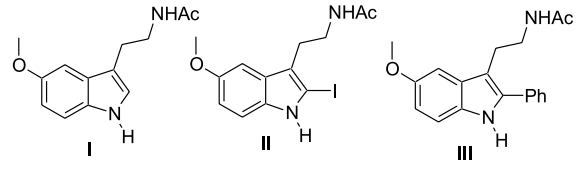
Available online 18 October 2004

Abstract—A new method for the synthesis of 2- and 3-substituted indolylalkylamides, derivatives of melatonin, from arylhydrazines and amidoketones by the Fischer reaction was elaborated. The amidoketones can be easily prepared from cyclic imines by reaction with acylpyridinium chloride. This method is a one-step synchronous creation of the selected alkylamide fragment and the indole core. Variation of the arylhydrazines create the desired substituents in the carbocycle of indolylalkylamides and suitable choice of amidoketone can direct the amidoalkyl chain to the 2- or 3-position of the indole.

1. Introduction

Melatonin **I** (5-methoxy-*N*-acetyltryptamine) is a hormone which regulates a number of neuroendocrine and physiological processes. Seasonal changes in various aspects of physiology in photoperiodic species, such as sheep and hamsters, are controlled by actions of melatonin. Melatonin administration can also entrain the circadian clock by a direct action on the CNS. Many studies have also indicated an influence on immune function and antioxidant actions.

Melatonin is a derivative of indolylalkylamines, which have importance as a main structural unit of indole alkaloids which contain many biologically active substances and remedies.[1] Recently, derivatives of 2-substituted tryptamines have attracted a lot of attention because of their high selectivity for serotonin,[2] melatonin[3] and gonadotropin releasing hormone[4] receptors. Substitution at the 2-position of the indole ring of melatonin also increases affinity and potency; in part because steric effects restrict the flexible C-3 side-chain allowing easier docking at the active site of the receptor. For example, 2-position substitution improves affinity at both melatonin receptor subtypes ML1 and ML2; 2-iodomelatonin **II** and 2-phenylmelatonin **III** show a ~10-fold improvement in affinity ($K_i \sim 60$ pM) over melatonin itself. Other analogues which have been used to characterise melatonin binding sites are 6-chloromelatonin, an agonist and *N*-acetyltryptamine, a partial agonist (Scheme 1).[5]



Scheme 1.

Four general approaches exist to *N*-acylindolylalkylamines. The first is an acylation of a previously synthesized indolylalkylamines.[6] The second consists in attaching the acylamine fragment to the indole core.[7] The third involves multi-step modification of the 3-indole substituent into the acylamine chain.[8] The forth lies in the synchronous creation of the selected acylamine fragment and the indole core and is the method of choice because it should provide a shortened and simplified procedure.

To fulfil such an approach there is the Fischer reaction. It has been applied to the synthesis of 2-unsubstituted indolylalkylamides from amidoaldehydes (with the aminogroup protected by Phth-,[9] Boc-[10] or Cbz[11]-group). Reaction of cyclic amidoketones (with Phth-,[12] carbamoyl-,[13] benzoyl-[14] or acetyl-[15] protective group) with arylhydrazines leads to indoles condensed with saturated cycle (with nitrogen atom in cycle or attached to it). It should be noted that in most cases protective groups remained intact during the Fischer reaction so it is the main way for the direct synthesis of melatonin derivatives.

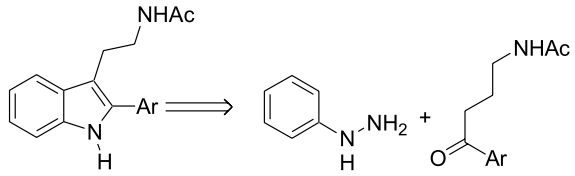
Keywords: Melatonin; Cyclic imines; Amidoketones; Arylhydrazines; Fischer reaction; Indoles.
* Corresponding author. Tel.: +70959392276; fax: +70959328846; e-mail: nen@acylium.chem.msu.ru

0040–4020/$ - see front matter © 2004 Published by Elsevier Ltd.
doi:10.1016/j.tet.2004.10.006

Recently,[16] we elaborated an easy and scaleable procedure for the synthesis of previously unknown 2-arylindolylalkylamines from arylhydrazones of 6-aminohexanones, which readily undergo Fischer rearrangement in glacial acetic acid. On the basis of this work we developed a new and effective synthesis of melatonin analogues from derivatives of aminoketones.

2. Results and discussion

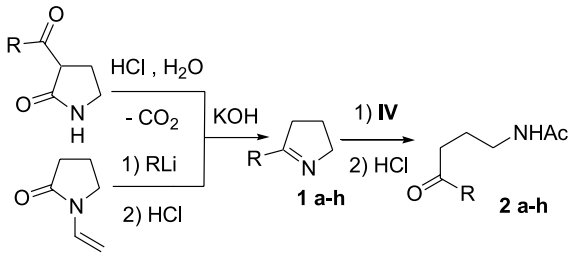
We proposed that arylketones with a *N*-acyl group should give rise to 2-aryl substituted indolylalkylamides in the Fischer reaction (Scheme 2).



Scheme 2.

At the first step we aimed at developing a convenient synthesis of arylketones with a *N*-acyl group from aminoketones. We chose α-acyllactams as the starting materials for synthesis of the aminocarbonyl compounds on the basis of literature analysis: they can be obtained by Claisen condensation of an *N*-protected lactam and ester. Recently we thoroughly investigated this condensation of the 5-, 6- and 7-membered lactams with various esters.[17] On the basis of NMR spectra we have found out that in the case of 5-membered 3-acyllactams, acidic hydrolysis and decarboxylation[18] leads to mixture of cyclic imines and aminoketones. Thus, the reaction mixture was basified by 50% KOH and pure cyclic imines were obtained. In the case of readily available organolithium derivatives or acidic-sensitive substituents reaction of organolithium reagents with *N*-vinylpyrrolidone was used,[19–24] and it was also basified to give the cyclic imines.

There are rare examples of acylation of cyclic imines to amidoketones,[20,25,26] but none lead to satisfactory results. So we developed a new method of acylation using *N*-acetylpyridinium chloride **IV**. The results are shown in Scheme 3 and Table 1.

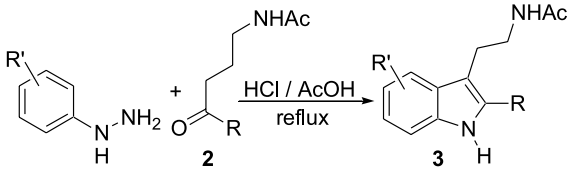


Scheme 3.

Table 1. Synthesis of 2-substituted cyclic imines **1a–c** (from 3-acyllactams), imines **1d–h** (by reaction of *N*-vinyllpirrolidone with RLi) and synthesis of amidoketones **2a–h**

R	Imine, yield, %	Amidoketone, yield, %
C_6H_5	**1a**, 89	**2a**, 91
$C_6H_5CH_2$	**1b**, 85	**2b**, 86
Me	**1c**, 70	**2c**, 75
4-Me–C_6H_4	**1d**, 65	**2d**, 95
2,4-MeO–C_6H_3	**1e**, 60	**2e**, 70
2-Thienyl	**1f**, 65	**2f**, 87
2-Furyl	**1g**, 65	**2g**, 80
n-Bu	**1h**, 50	**2h**, 85

We introduced amidoketones **2** in the Fischer reaction and the corresponding indolylalkylamides **3** and **4** were obtained in good to near quantitative yields using acetic acid saturated with gaseous HCl as catalyst (Scheme 4 and Table 2).



Scheme 4.

Table 2. Synthesis of 2-substituted *N*-acetyltryptamines **3a**, **d–g**, **i–m**

N-Acetyl-tryptamine	R	R′	Yield, %
3a	C_6H_5	H	93
3d	4-Me–C_6H_4	H	95
3e	2,4-MeO–C_6H_3	H	65
3f	2-Thienyl	H	66
3g	2-Furyl	H	43[a]
3i	C_6H_5	5-F	64
3j	C_6H_5	5-Cl	87
3k	C_6H_5	5-Br	80
3l	C_6H_5	5-MeO	85[b]
3m	C_6H_5	7-Et	84

[a] Ethyl ester of polyphosphoric acid (PPE, 3 equiv), 1 h, 85 °C.
[b] Glacial AcOH, reflux, 10 min.

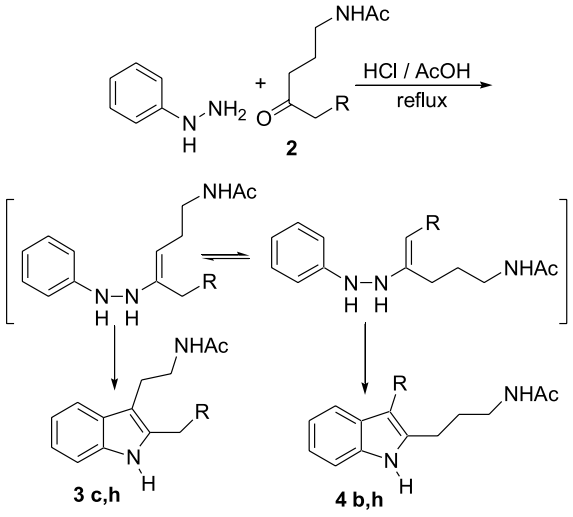
To investigate the scope of the method and the effect of substituents on the yield of the Fischer reaction, various arylhydrazines with donor and acceptor groups were synthesized.[27] It was found that in all cases *N*-acetyltryptamines were isolated in good to high yields. Generally no restriction of hydrazine or ketone structure for this approach was found. Yields are quite good except in the case of amidoketone **2g** with a furyl substituent, when this conditions of Fischer rearragement lead to tar formation. Thus, we selected a more soft catalyst, namely ethyl ester of polyphosphoric acid[28] (PPE, 3 equiv), to give 2-furyl-*N*-acetyltryptamine **3g**. 2-Phenylmelatonin was obtained in high yield from 4-methoxyphenylhydrazone of amidoketone **2a** by refluxing it for 10 min in pure acetic acid.

Amidoketones with two CH_2 units at carbonyl group has two ways for Fischer indolyzation. Thus, it opens possibilities to synthesize two different classes of

indolylalkylamides, containing an amidoalkyl chain in the 2- or 3-position of the indole core. To investigate the effect of substituents on the regioselectivity of the Fischer rearrangement, we synthesized compounds **2b**, **2c** and **2h**.

Reaction of **2b** with phenylhydrazine gives rises only to *N*-acetylizohomotryptamine **4b** with a Ph group in the 3-position of the indole core. We explain that regioselectivity due to stabilization of enehydrazine by mesomeric conjugation of ene-bond with the aromatic core. In the case of amidoketone **2c** also only **3c** was obtained, because one enehydrazine is more stable thermodynamically in comparison with the other terminal enhydrazine, so this factor is decisive for direction of the reaction to proceed.

4-Oxooctyl-*N*-acetamide **2h** reacted with phenylhydrazine giving a mixture of **3h** (2-butyl-*N*-acetyltryptamine) and **4h** (3-propyl-*N*-acetylizohomotryptamine) in 1:2 ratio, both of which can be easily separated by flash chromatography (Scheme 5 and Table 3).



Scheme 5.

Table 3. Direction of indolyzation of amidoketones **2b**, **2c** and **2h**

N-Acetylindolylalkylamine	R	Yield, %
4b	Ph	93
3c	H	77
3h/4h	Pr	90 (1/2)

The reaction of amidoketones with two alkyl substituents at the carbonyl group allows preparation of previously unknown 3-subsituted *N*-acetylizohomotryptamines and shows that preferable direction of indolyzation depends on the stability of the intermediate enehydrazines.

3. Conclusion

We have described a new method for the synthesis of 2- and 3-substituted indolylalkylamides, derivatives of melatonin, from arylhydrazines and amidoketones by the Fischer reaction. The amidoketones can be easily prepared from cyclic imines by reaction with acylpyridinium chloride. It should be noted especially, that our method is a one-step synchronous creation of the selected acylamine fragment and the indole core. Variation of the arylhydrazines creates the desired substituents in the carbocycle of indolylalkylamides and suitable choice of amidoketone directs the amidoalkyl chain to the 2- or 3-position of the indole.

4. Experimental

4.1. General

TLC was performed with 'Silufol UV-254' plates, and flash chromatography was carried out with silica gel (63–200 mesh), using EtOAc/CH_2Cl_2 in 1:2 proportions. ^1H and ^{13}C NMR spectra of $CDCl_3$ solutions (if not mentioned otherwise) were respectively recorded at 400 and 100 MHz, TMS was used as internal standard. IR spectra were recorded in thin layer for liquid and in nujol for solid substances.

4.2. General procedure for the synthesis of *N*-(4-oxo-4-substituted butyl)-acetamides

To a well stirred solution of 1.6 mL (20 mmol) pyridine in 20 mL abs. CH_2Cl_2 solution of 0.71 mL (0.8 g, 10 mol) AcCl in 10 mL abs. CH_2Cl_2 was slowly added and mixture was stirred an additional 15 min.

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

To a clear solution obtained 20 mL 5% HCl was added with intensive stirring and after 15 min of it organic layer was separated, washed with water (2×20 mL), dried with Na_2SO_4 and evaporated. The residue was triturated with hexanes giving amidoketones **2a–h**.

4.2.1. *N*-(4-Oxo-4-phenylbutyl)acetamide (2a). White crystal solid, 1.87 g, yield 91%, mp 95 °C. IR, (ν, cm^{-1}): 1640 (O=CNH), 1680 (PhC=O). ^1H NMR δ 1.93 (s, 3H), 1.96 (tt, J=6.7, 5.9 Hz, 2H), 3.03 (t, J=6.7 Hz, 2H), 3.32 (dt, J=6.7, 5.9 Hz, 2H), 5.93 (bs, 1H), 7.44 (t, J=7.6 Hz, 2H), 7.55 (t, J=7.6 Hz, 1H), 7.93 (d, J=7.6 Hz, 2H). ^{13}C NMR δ 23.3, 23.7, 36.0, 39.3, 128.0 (2C), 128.6 (2C), 133.2, 136.6, 169.0, 200.0. Calcd for $C_{12}H_{15}NO_2$, C 70.40, H 7.28; found C 70.22, H 7.37.

4.2.2. *N*-(4-Oxo-5-phenylpentyl)acetamide (2b). Brown crystal solid, 1.89 g, yield 86%, mp 43–44 °C. IR, (ν, cm^{-1}): 1640 (O=CNH), 1700 ($PhCH_2C$=O). ^1H NMR δ 1.72 (tt, J=6.7 Hz, 2H), 1.87 (s, 3H), 2.5 (t, J=6.7 Hz, 2H), 3.14 (dt, J=6.7 Hz, 2H), 3.67 (s, 2H), 5.8 (bs, 1H), 7.18 (d, J=7.0 Hz, 2H), 7.25 (tt, J=7.3, 7.0 Hz, 1H), 7.31 (t, J=7.3 Hz, 2H). ^{13}C NMR 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. Calcd for $C_{13}H_{17}NO_2$ C 72.21, H 7.81; found C 72.29, H 7.81.

4.2.3. *N*-(4-Oxopentyl)acetamide (2c). Red crystal solid, 1.07 g, yield 75%, mp 48–50 °C. IR, (ν, cm^{-1}): 1630 (O═CN), 1700 (CH_3C═O). ^1H NMR δ 1.71 (tt, J=7.0, 6.7 Hz, 2H), 1.9 (s, 3H), 2.1 (s, 3H), 2.45 (t, J=7.0 Hz, 2H), 3.16 (dt, J=6.7, 5.9 Hz, 2H), 6.2 (bs, 1H). ^{13}C NMR δ 23.0, 23.3, 30.0, 39.9, 40.9, 170.4, 208.7. Calcd for $C_7H_{13}NO_2$, C 58.72, H 9.15; found C 58.31, H 8.91.

4.2.4. *N*-(4-Oxo-4-(4-methylphenyl)-butyl)acetamide (2d). Yellowish crystal solid, 2.08 g, yield 95%, mp 118–120 °C. IR, (ν, cm^{-1}): 1630 (O═CNH), 1665 (ArC═O). ^1H NMR δ 1.92 (s, 3H), 1.93 (tt, J=7.0, 6.7 Hz, 2H), 2.38 (s, 3H), 3.0 (t, J=7.0 Hz, 2H), 3.35 (dt, J=6.7, 5.9 Hz, 2H), 6.00 (bs, 1H), 7.23 (d, J=8.1 Hz, 2H), 7.82 (d, J=8.1 Hz, 2H). ^{13}C δ NMR 21.5, 23.3, 23.7, 36.0, 39.3, 128.0 (2C), 129.3 (2C), 134.2, 144.0, 170.0, 200.0. Calcd for $C_{13}H_{17}NO_2$, C 72.21, H 7.81; found C 72.41, H 7.95.

4.2.5. *N*-(4-Oxo-4-(2,4-dimethoxyphenyl)butyl)acetamide (2e). Brown crystal solid, 1.86 g, yield 70%, mp 78–80 °C. IR, (ν, cm^{-1}): 1640 (O═CNH), 1680 (ArC═O). ^1H NMR δ 1.87 (tt, J=7.0, 6.7 Hz, 2H), 1.92 (s, 3H), 2.98 (t, J=7.0 Hz, 2H), 3.26 (dt, J=6.7, 5.6 Hz, 2H), 3.82 (s, 3H), 3.86 (s, 3H), 6.07 (bs, 1H), 6.42 (d, J=2.3 Hz, 1H), 6.49 (dd, J=8.8, 2.3 Hz, 1H), 7.76 (d, J=8.8 Hz, 1H). ^{13}C NMR δ 23.3, 23.7, 39.7, 41.3, 55.4, 55.5, 98.3, 105.2, 120.7, 132.5, 160.7, 164.5, 170.3, 200.0. Calcd for $C_{14}H_{19}NO_4$ C 63.38, H 7.22; found C 62.84, H 7.25.

4.2.6. *N*-(4-Oxo-4-thien-2-ylbutyl)acetamide (2f). White crystal solid, 1.84 g, yield 87%, mp 72 °C. IR, (ν, cm^{-1}): 1640 (O═CNH), 1660 (thienyl-CO). ^1H NMR δ 1.67 (tt, J=7.0, 6.7 Hz, 2H), 1.82 (s, 3H), 2.45 (t, J=6.7 Hz, 2H), 3.09 (dt, J=6.7, 5.9 Hz, 2H), 5.75 (bs, 1H), 7.08–7.27 (m, 3H). ^{13}C NMR δ 23.3, 23.7, 36.0, 39.3, 128.0, 131.8, 133.5, 143.8, 170.0, 192.0. Calcd for $C_{10}H_{13}NO_2S$, C 56.85, H 6.20; found C 56.65, H 6.07.

4.2.7. *N*-[4-(2-Furyl)-4-oxobutyl]acetamide (2g). Grey crystal solid, 1.56 g, yield 80%, mp 66–68 °C. IR, (ν, cm^{-1}): 1640 (O═CNH), 1655 (furyl-C═O). ^1H NMR δ 1.91 (tt, J=7.0, 6.7 Hz, 2H), 1.92 (s, 3H), 2.87 (t, J=7.0 Hz, 2H), 3.29 (dt, J=6.7, 5.9 Hz, 2H), 6.07 (bs, 1H), 6.50 (dd, J=3.5, 1.8 Hz, 1H), 7.17 (dd, J=3.5, 0.6 Hz, 1H), 7.55 (dd, J=1.8, 0.6 Hz, 1H). ^{13}C NMR δ 23.3, 23.7, 36.0, 39.3, 112.0, 146.5, 117.3, 152.5, 170.0, 189.0. Calcd for $C_{10}H_{13}NO_3$, C 61.53, H 6.71; found C 61.36, H 6.62.

4.2.8. *N*-(4-Oxooctyl)acetamide (2h). Brownish crystal solid, 1.57 g, yield 85%, mp 65–67 °C. IR, (ν, cm^{-1}): 1640 (O═CN), 1695 (CH_2C═O). ^1H NMR δ 0.84 (t, J=7.3 Hz, 3H), 1.24 (dt, J=7.6, 7.3 Hz, 2H), 1.48 (tt, J=7.6, 7.3 Hz, 2H), 1.72 (tt, J=7.0, 6.7 Hz, 2H), 1.91 (s, 3H), 2.35 (t, J=7.3 Hz, 2H), 2.42 (t, J=7.0 Hz, 2H), 3.17 (dt, J=6.7, 5.9 Hz, 2H), 6.16 (bs, 1H). ^{13}C NMR δ 13.7, 22.2, 23.1, 23.2, 25.8, 39.2, 40.0, 42.5, 170.3, 211.2. Calcd for $C_{10}H_{19}NO_2$, C 64.83, H 10.34; found C 64.56, H 10.20.

4.3. General procedure for the synthesis of *N*-acetylindolylalkylamines

Mixture of 11 mmol arylhydrazine (salt or free base), 10 mmol *N*-(4-oxo-4-substituted butyl)acetamide in 20 mL acetic acid, saturated with gaseous HCl at 20 °C, was quickly warmed to boiling. When all solids were dissolved refluxing was continued for 5 min. Then reaction mixture was evaporated and distributed between water and CH_2Cl_2. Organic phase was washed with water (2×20 mL) and evaporated. The flash chromatography of the residue afforded the products.

4.3.1. *N*-[2-(2-Phenyl-1*H*-indol-3-yl)ethyl]acetamide (3a). Cream crystal solid, 2.59 g, yield 93%, mp 114–116 °C. R_f (EtOAc)=0.45. IR, (ν, cm^{-1}): 1620 (O═CNH). ^1H NMR δ 1.73 (s, 3H), 3.11 (t, J=6.7 Hz, 2H), 3.52 (dt, J=6.7, 6.2 Hz, 2H), 5.53 (bs, 1H), 7.14 (t, J=7.0 Hz, 1H), 7.21 (t, J=7.0 Hz, 1H), 7.35 (t, J=7.3 Hz, 1H), 7.38 (d, J=8.1 Hz, 1H), 7.45 (t, J=7.3 Hz, 2H), 7.56 (d, J=7.3 Hz, 2H), 7.62 (d, J=8.1 Hz, 1H), 8.48 (bs, 1H). ^{13}C NMR δ 23.1, 24.4, 40.1, 109.6, 111.0, 118.8, 119.8, 122.3, 127.7, 127.9 (2C), 128.9 (2C), 132.9, 133.2, 135.3, 135.9, 170.1. Calcd for $C_{18}H_{18}N_2O$, C 77.67, H 6.52; found C 77.67, H 6.50.

4.3.2. *N*-[3-(3-Phenyl-1*H*-indol-2-yl)propyl]acetamide (4b). Grey crystal solid, 2.75 g, yield 93%, mp 123 °C. R_f (EtOAc)=0.6. IR, (ν, cm^{-1}): 1620 (O═CNH). ^1H NMR δ 1.72 (tt, J=6.5, 6.2 Hz, 2H), 1.84 (s, 3H), 2.76 (t, J=6.5 Hz, 2H), 3.19 (dt, J=6.5, 6.2 Hz, 2H), 5.63 (bs, 1H), 7.01 (t, J=7.0 Hz, 1H), 7.09 (t, J=7.0 Hz, 1H), 7.23 (t, J=7.0 Hz, 1H), 7.37 (m, 5H), 7.55 (d, J=7.9 Hz, 1H), 9.70 (bs, 1H). ^{13}C NMR δ 22.3, 23.0, 30.2, 38.3, 111.0, 114.0, 118.6, 116.6, 121.4, 125.8, 127.6, 128.6 (2C), 129.6 (2C), 135.1, 135.4, 135.6, 171.5. Calcd for $C_{19}H_{20}N_2O$, C 78.05, H 6.89; found C 77.93, H 6.86.

4.3.3. *N*-[2-(2-Methyl-1*H*-indol-3-yl)ethyl]acetamide (3c). Yellowish solid, 1.67 g, yield 77%, mp 83–85 °C. R_f (EtOAc)=0.4. IR, (ν, cm^{-1}): 1620 (O═CNH). ^1H NMR δ 1.88 (s, 3H), 2.36 (s, 3H), 2.90 (t, J=6.7 Hz, 2H), 3.48 (dt, J=6.7, 6.2 Hz, 2H), 5.57 (bs, 1H), 7.06 (t, J=7.3 Hz, 1H), 7.11 (t, J=7.3 Hz, 1H), 7.26 (d, J=7.3 Hz, 1H), 7.47 (d, J=7.3 Hz, 1H), 8.14 (bs, 1H). ^{13}C NMR δ 11.5, 23.3, 24.1, 40.0, 108.4, 110.3, 117.7, 119.3, 121.1, 128.6, 131.9, 135.3, 170.0. Calcd for $C_{13}H_{16}N_2O$, C 72.19, H 7.46; found C 72.09, 7.13 H.

4.3.4. *N*-{2-[2-(4-Methylphenyl)-1*H*-indol-3-yl]ethyl} acetamide (3d). White crystal solid, 2.78 g, yield 95%, mp 165–166 °C. R_f (EtOAc)=0.5. IR, (ν, cm^{-1}): 1620 (O═CNH). IR, (ν, cm^{-1}): 1620 (O═CNH). ^1H NMR δ 1.76 (s, 3H), 2.4 (s, 3H), 3.11 (t, J=6.7 Hz, 2H), 3.54 (dt, J=6.7, 6.2 Hz, 2H), 5.44 (bs, 1H), 7.14 (t, J=7.0 Hz, 1H), 7.21 (t, J=7.0 Hz, 1H), 7.28 (d, J=8.1 Hz, 2H), 7.38 (d, J=8.1 Hz, 1H), 7.44 (d, J=8.1 Hz, 2H), 7.62 (d, J=8.1 Hz, 1H), 8.16 (bs, 1H). ^{13}C NMR δ 21.2, 23.2, 24.4, 40.2, 109.5, 110.9, 118.8, 119.8, 122.3, 127.8 (2C), 129.1, 129.7 (2C), 130.0, 135.4, 135.8, 137.9, 170.0. Calcd for $C_{19}H_{20}N_2O$, C 78.05, H 6.89; found C 78.01, H 6.89.

4.3.5. *N*-{2-[2-(2,4-Dimethoxyphenyl)-1*H*-indol-3-yl]ethyl}acetamide (3e). Yellowish crystal solid, 2.2 g, yield 65%, mp 161–163 °C. R_f (EtOAc)=0.5. IR, (ν, cm^{-1}): 1620 (O═CNH). ^1H NMR δ 1.76 (s, 3H), 3.0 (t, J=6.4 Hz, 2H), 3.50 (dt, J=6.4, 6.2 Hz, 2H), 3.82 (s, 3H), 3.85 (s, 3H), 5.52 (bs, 1H), 6.58–6.61 (m, 2H), 7.11 (t, J=7.5 Hz, 1H),

7.18 (t, J=7.5 Hz, 1H), 7.37 (dd, J=8.0, 5.0 Hz, 2H) 7.61 (d, J=7.5 Hz, 1H), 8.47 (bs, 1H). ^{13}C NMR δ 23.1, 24.5, 39.7, 55.5, 55.6, 99.2, 104.9, 109.9, 110.7, 113.9, 118.5, 119.3, 121.9, 128.2, 132.0, 132.5, 135.6, 158.1, 161.0, 169.9. Calcd for $C_{20}H_{22}N_2O_3$, C 70.99, H 6.55; found C 70.81, H 6.57.

4.3.6. *N*-{2-[2-(2-Thienyl)-1*H*-indol-3-yl]ethyl}acetamide (3f). Cream crystal solid, 1.88 g, yield 66%, mp 113–116 °C. R_f (EtOAc)=0.55. IR, (ν, cm^{-1}): 1620 (O=CNH). ^{1}H NMR δ 1.81 (s, 3H), 3.17 (t, J=6.5 Hz, 2H), 3.51 (q, J=6.5 Hz, 2H), 5.57 (bs, 1H), 7.12 (m, 2H), 7.21 (t, J=7.0 Hz, 1H), 7.29 (d, J=4.3 Hz, 1H), 7.33 (d, J=4.3 Hz, 1H), 7.36 (d, J=8.1 Hz, 1H), 7.58 (d, J=8.1 Hz, 1H), 8.45 (bs, 1H). ^{13}C NMR δ 23.2, 24.7, 39.9, 110.5, 110.9, 118.8, 120.0, 122.9, 124.9, 125.3, 127.8, 129.1, 129.2, 134.4, 135.9 170.3. Calcd for $C_{16}H_{16}N_2OS$, C 67.58, H 5.67; found C 67.71, H 5.71.

4.3.7. *N*-[2-(2-Butyl-1*H*-indol-3-yl)ethyl]acetamide (3h). Yellowish oil, 0.78 g, yield 30%. R_f (EtOAc)=0.7. IR, (ν, cm^{-1}): 1620 (O=CNH). ^{1}H NMR δ 0.94 (t, J=7.3 Hz, 3H), 1.39 (m, 2H), 1.64 (m, 2H), 1.89 (s, 3H), 2.72 (t, J=7.6 Hz, 2H), 2.91 (t, J=6.7 Hz, 2H), 3.51 (dt, J=6.7, 6.2 Hz, 2H), 5.54 (bs, 1H), 7.07 (td, J=7.0, 1.2 Hz, 1H), 7.13 (td, J=7.0, 1.2 Hz, 1H), 7.28 (dd, J=7.0, 1.2 Hz, 1H), 7.5 (dd, J=7.0, 1.2 Hz, 1H), 8.02 (bs, 1H). ^{13}C NMR δ 14.3, 22.3, 23.2, 24.2, 26.3, 30.4, 38.6, 110.6, 111.5, 118.2, 118.5, 120.6, 128.5, 134.5, 135.3, 171.2. Calcd for $C_{16}H_{22}N_2O$, C 74.38, H 8.58; found C 74.28, H 8.47.

4.3.8. *N*-[3-(3-Propyl-1*H*-indol-2-yl)propyl]acetamide (4h). White solid, 1.55 g, yield 60%, mp 120 °C. R_f (EtOAc)=0.4. IR, (ν, cm^{-1}): 1620 (O=CNH). ^{1}H NMR δ 0.96 (t, J=7 Hz, 3H), 1.64 (m, 2H), 1.78 (m, 2H), 1.98 (s, 3H), 2.66 (t, J=6.5 Hz, 2H), 2.72 (m, 2H), 3.32 (dt, J=6.5, 6.2 Hz, 2H), 5.95 (bs, 1H), 7.02–7.15 (m, 2H), 7.32 (d, J=7.9 Hz, 1H), 7.51 (d, J=7.9 Hz, 1H), 9.35 (bs, 1H). ^{13}C NMR δ 14.2, 19.5, 23.0, 23.5, 27.6.2, 30.3, 41.2, 111.5, 114.4, 118.7, 119.2, 120.6, 130.8, 132.6, 135.2, 171.5. Calcd for $C_{16}H_{22}N_2O$, C 74.38, H 8.58; found C 74.33, H 8.45.

4.3.9. *N*-[2-(5-Fluoro-2-phenyl-1*H*-indol-3-yl)ethyl]acetamide (3i). Yellow crystals, 1.90 g, yield 64%, mp 147–149 °C. R_f (EtOAc)=0.62. IR, (ν, cm^{-1}): 1620 (O=CNH). ^{1}H NMR δ 1.71 (s, 3H), 3.06 (t, J=6.7 Hz, 2H), 3.49 (dt, J=6.7 Hz, 2H), 5.48 (bs, 1H), 6.94 (td, J=8.7, 2.5 Hz, 1H), 7.24–7.30 (m, 2H), 7.37 (t, J=7.3 Hz, 1H), 7.46 (t, J=7.3 Hz, 2H), 7.55 (d, J=7.3 Hz, 2H), 8.22 (bs, 1H). ^{13}C NMR (DMSO-d^6) δ 22.6, 25.0, 40.1, 103.2 (d, J=23.4 Hz), 109.3 (d, J=4.4 Hz), 109.6 (d, J=26.4 Hz), 112.12 (d, J=10.2 Hz), 127.6, 127.8 (2C), 128.7 (2C), 129.1 (d, J=10.3 Hz), 132.5, 132.6, 136.6, 156.9 (d, J=231.3 Hz), 169.2. Calcd for $C_{18}H_{17}N_2OF$, C 72.95, H 5.78; found C 72.79, H 5.73.

4.3.10. *N*-[2-(5-Chloro-2-phenyl-1*H*-indol-3-yl)ethyl]acetamide (3j). Brownish cubic crystals, 2.72 g, yield 87%, mp 147–149 °C. R_f (EtOAc)=0.4. IR, (ν, cm^{-1}): 1620 (O=CNH). ^{1}H NMR δ 1.76 (s, 3H), 3.05 (t, J=6.7 Hz, 2H), 3.48 (dt, J=6.7, 6.2 Hz, 2H), 5.50 (bs, 1H), 7.14 (dd, J=8.5, 1.5 Hz, 1H), 7.28 (d, J=8.5 Hz, 1H), 7.36 (t, J=7.5 Hz, 1H), 7.44 (t, J=7.5 Hz, 2H), 7.35 (t, J=7.5 Hz, 2H), 7.52 (m, 1H), 7.57 (dd, J=7.5, 1.5 Hz, 1H), 8.48 (bs, 1H). ^{13}C NMR δ 23.1, 24.4, 40.2, 109.6, 112.0, 118.3, 122.6, 125.5, 128.0 (2C), 128.2, 129.1 (2C), 130.2, 132.4, 134.2, 136.7, 170.1. Calcd for $C_{18}H_{17}N_2OCl$, C 69.12, H 5.48; found C 68.82, H 5.35.

4.3.11. *N*-[2-(5-Bromo-2-phenyl-1*H*-indol-3-yl)ethyl]acetamide (3k). Reddish crystal solid, 2.86 g, yield 80%, mp 113–115 °C. R_f (EtOAc)=0.4. IR, (ν, cm^{-1}): 1620 (O=CNH). ^{1}H NMR δ 1.76 (s, 3H), 3.03 (t, J=6.7 Hz, 2H), 3.47 (dt, J=6.7, 6.2 Hz, 2H), 5.55 (bs, 1H), 7.25 (m, 2H), 7.35 (d, J=7.3 Hz, 1H), 7.43 (t, J=7.3 Hz, 2H), 7.53 (d, J=7.3 Hz, 2H), 7.71 (s, 1H), 8.66 (bs, 1H). ^{13}C NMR δ 23.1, 24.4, 40.2, 109.4, 112.5, 112.9, 121.4, 125.1, 128.0 (2CH), 128.15, 129.0 (2CH), 130.8, 132.4, 135.4, 136.6, 170.3. Calcd for $C_{18}H_{17}BrN_2O$, C 60.52, H 4.80; found C 61.07, H 4.76.

4.3.12. *N*-[2-(7-Ethyl-2-phenyl-1*H*-indol-3-yl)ethyl]acetamide (3m). Brown crystal solid, 2.57 g, yield 84%, mp 147–149 °C. R_f (EtOAc)=0.5. IR, (ν, cm^{-1}): 1620 (O=CNH). ^{1}H NMR δ 1.39 (t, J=7.6 Hz, 3H), 1.74 (s, 3H), 2.91 (q, J=7.6 Hz, 2H), 3.10 (t, J=6.7 Hz, 2H), 3.53 (dt, J=6.7, 6.2 Hz, 2H), 5.52 (bs, 1H), 7.08–7.14 (m, 2H), 7.37 (m, 1H), 7.44–4.51 (m, 3H), 7.58 (m, 2H), 8.27 (bs, 1H). ^{13}C NMR δ 13.8, 23.1, 24.0, 24.5, 40.1, 110.3, 116.6, 120.2, 121.0, 126.5, 127.8, 128.1 (2C), 128.7, 129.0 (2C), 133.1, 134.7, 135.1, 170.0. Calcd for $C_{20}H_{22}N_2O$, C 78.40, H 7.24; found C 78.23, H 7.12.

4.4. Synthesis of *N*-[2-(5-methoxy-2-phenyl-1*H*-indol-3-yl)ethyl]acetamide (3l)

Mixture of 502 mg of 4-methoxyphenylhydrazine oxalate (2.2 mmol) and 411 mg of *N*-(4-oxo-4-phenylbutyl)acetamide (**2a**) (2 mmol) was refluxed in 20 mL of EtOH for 20 min. After evaporation the residue was refluxed in 15 mL of glacial AcOH for 10 min. Then reaction mixture was evaporated and distributed between water and CH_2Cl_2. Organic phase was washed with water (2×20 mL) and evaporated. The flash chromatography of the residue afforded the product as amorphous solid, 0.52 g, yield 85%. R_f (EtOAc)=0.4. All spectral data of the compound is identical to the literature.[29]

4.5. Synthesis of *N*-{2-[2-(2-furyl)-1*H*-indol-3-yl]ethyl}acetamide (3g)

Mixture of 380 mg 4-oxo-4-furylbutyl-*N*-acetamide (**2g**) (2 mmol), 216 mg (2 mmol) phenylhydrazine and 2.4 g (6 mmol) ethyl ester of polyphosphoric acid was warmed on the water bath at 85 °C for 1 h. Then reaction mixture was evaporated and distributed between water and CH_2Cl_2. Organic phase was washed with water (2×20 mL) and evaporated. The flash chromatography of the residue afforded the product as yellowish oil, 0.23 g, yield 43%. R_f (EtOAc)=0.55. IR, (ν, cm^{-1}): 1620 (O=CNH). ^{1}H NMR δ 1.82 (s, 3H), 3.17 (t, J=6.7 Hz, 2H), 3.55 (dt, J=6.7, 6.5 Hz, 2H), 5.80 (bs, 1H), 6.48 (dd, J=3.2, 1.8 Hz, 1H), 6.75 (d, J=3.2 Hz 1H), 7.09 (t, J=7.0 Hz, 1H), 7.18 (t, J=7.0 Hz, 1H), 7.35 (d, J=8.1 Hz, 1H), 7.44 (d, J=1.8 Hz, 1H), 7.55 (d, J=8.1 Hz, 1H), 9.0 (bs, 1H). ^{13}C NMR δ 23.2, 24.5, 39.7, 106.5, 109.4, 110.9, 111.9, 118.5, 119.7,

122.6, 126.2, 128.8, 137.8, 141.5, 147.4, 170.4. Calcd for $C_{16}H_{16}N_2O_2$, C 71.62, H 6.01; found C 71.35, H 6.07.

References and notes

1. (a) Glennon, R. A.; Jacyno, J. M.; Young, R.; McKenney, J. D.; Nelson, D. *J. Med. Chem.* **1984**, *27*, 41. (b) Person, H.; Pardo, M. D. A.; Founcaud, A. *Tetrahedron Lett.* **1979**, *21*, 281.
2. (a) Stevenson, G. I.; Smith, A. L.; Lewis, S.; Michie, S. G.; Neduvelil, J. G.; Patel, S.; Marwood, R.; Patel, S.; Castro, J. L. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 2697. (b) Glennon, R. A.; Lee, M.; Rangisetty, J. B.; Dukat, M.; Roth, B. L.; Savage, J. E.; McBride, A.; Rausen, L.; Hufeisen, S.; Lee, D. K. H. *J. Med. Chem.* **2000**, *43*, 1011.
3. Mor, M.; Spadoni, G.; Giacomo, B. D.; Diamantini, G.; Bedini, A.; Tarzia, G.; Plazzi, P. V.; Rivara, S.; Nonno, R.; Lucini, V.; Pannacci, M.; Fraschini, F.; Stankov, B. M. *Bioorg. Med. Chem.* **2001**, *9*, 1045.
4. Walsh, T. F.; Toupence, R. B.; Ujjainwalla, F.; Young, J. R.; Goulet, M. T. *Tetrahedron* **2001**, *57*, 5233.
5. Molinari, R. *Eur. J. Pharmacol.* **1996**, *301*, 159.
6. (a) Thomson, D. W.; Commeureuc, A. G. J.; Berlin, S.; Murphy, J. A. *Synth. Commun.* **2003**, *33*(20), 3631. (b) Revial, G.; Jabin, I.; Lim, S.; Pfau, M. *J. Org. Chem.* **2002**, *67*(7), 2252. (c) Chung, I. H.; Cha, K. S.; Seo, J. H.; Kim, J. H.; Chung, B. Y.; Kim, C. S. *Heterocycles* **2000**, *53*(3), 529.
7. (a) Snyder, M. *J. Am. Chem. Soc.* **1955**, *77*, 1257. (b) Legters, J.; Willems, G. H.; Thijs, L.; Zwanenburg, B. *Recl. Trav. Chim. Pays-Bas.* **1992**, *111*(2), 59. (c) Konda-Yamada, Y.; Okada, C.; Yoshida, K.; Umeda, Y.; Arima, S.; Sato, N.; Kai, T.; Takayanagi, H.; Harigaya, Y. *Tetrahedron* **2002**, *58*(39), 7851.
8. (a) Kirkup, M. P.; Moore, R. E. *Tetrahedron Lett.* **1983**, *24*(20), 2087. (b) Huebner, A. *J. Am. Chem. Soc.* **1953**, *75*, 5887. (c) Repke, D. B.; Ferguson, W. J.; Bates, D. K. *J. Heterocycl. Chem.* **1981**, *18*, 175. (d) Gatta, F.; Misiti, D. *J. Heterocycl. Chem.* **1987**, *24*, 1183.
9. Vinogradov, H. L.; Suvorov, N. N. *Chim. Heterocycl. Soed.* **1984**, *9*, 1206.
10. Gorohovsky, S.; Meir, S.; Shkoulev, V.; Byk, G.; Gellerman, G. *Synlett* **2003**, *10*, 1411.
11. Jandu, K. S.; Barret, V.; Brockwell, M.; Cambridge, D.; Farrant, D. R.; Foster, C.; Giles, H.; Glen, R.; Hill, A. P.; Hobbs, H.; Honey, A.; Martin, G. R.; Salmon, J.; Smith, D.; Woolard, P.; Sekwood, D. L. *J. Med. Chem.* **2001**, *44*, 681.
12. (a) Brennan, J. P.; Saxton, J. E. *Tetrahedron* **1987**, *43*(1), 191. (b) Glennon, R. A.; Hong, S. S.; Bondarev, M.; Law, H.; Dukat, M.; Rakhit, S.; Power, P.; Fan, E.; Kinneau, D.; Kamboj, R.; Teiler, M.; Herrick-Davis, K.; Smith, C. *J. Med. Chem.* **1996**, *39*, 314. (c) Barf, T.; Wikstrom, H.; Pauwels, P. J.; Palmier, C.; Tardif, S.; Lundmark, M.; Sundell, S. *Bioorg. Med. Chem.* **1998**, *6*, 1469.
13. Cloudsdale, I. S.; Kluge, A. F.; McClure, N. L. *J. Org. Chem.* **1982**, *47*(6), 919.
14. Gennet, D.; Michel, P.; Rassat, A. *Synthesis* **2000**, 3, 447.
15. Bird, C. W.; Wee, G. H. *Tetrahedron* **1985**, *41*(10), 2019.
16. Nenajdenko, V. G.; Zakurdaev, E. P.; Balenkova, E. S. *Tetrahedron Lett.* **2002**, *43*(47), 8449.
17. Nenajdenko, V. G.; Gololobov, A. M.; Zakurdaev, E. P.; Balenkova, E. S. *Russ. Chem. Bull.* **2003**, *252*(11), 2473.
18. Sorgi, K. L.; Maryanoff, A. C.; McComsey, D. F.; Maryanoff, B. E. *Org. Synth.* **1998**, *75*, 215.
19. Seeman, J. I. *Synthesis* **1977**, 498.
20. Bielawski, J.; Brandage, S.; Lindblom, L. *J. Heterocycl. Chem.* **1978**, *15*(1), 97.
21. Feringa, B.; Jansen, J. *Tetrahedron Lett.* **1986**, *27*(4), 507.
22. Hua, D.; Shon, W. M.; Narashima, S. *J. Org. Chem.* **1990**, *55*, 3682.
23. Koldobsky, A. B.; Vakhmistrov, V. E.; Solodova, E. V.; Shilova, O. S.; Kalinin, V. N. *Izv. Acad. Nauk.* **2002**, *387*(1), 61.
24. Giovanni, A.; Savoia, D.; Umani-Ronchi, A. *J. Org. Chem.* **1989**, *54*, 228.
25. Belleau, B. *Can. J. Chem.* **1957**, *35*, 651.
26. Poisel, H.; Schmidt, U. *Chem. Ber.* **1975**, *108*, 2917.
27. Barclay, B. M.; Campbell, N. *J. Chem. Soc.* **1945**, *8*, 530.
28. Fieser, L. F.; Fieser, M. In *Reagents for Organic Synthesis*, Wiley: New York, 1967; Vol. 1, p 892.
29. Garratt, P. J.; Jones, R.; Tocher, D. A. *J. Med. Chem.* **1995**, *38*, 1132.