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## Synthesis and study of pigment aggregation response of some melatonin derivatives

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This study was performed to investigate the reactivity of melatonin towards various chemical reagents to produce new derivatives of melatonin containing extra- or fused heterocyclic systems such as the imidazoindole derivatives **3**, **5**, **6**, the triazinoindole derivatives **8a**, **b**, the thiadiazoloindole derivative **12**, the pyridinoindole derivative **16** and the aminopyrazolomelatonin derivatives **21a**, **b** and **22a**, **b**. The structures of the compounds were established based on the analytical and spectral data. Agonist and antagonist potency of some melatonin derivatives in clonal *Xenopus laevis* melanophore cells was studied in comparison with melatonin.

### 1. Introduction

Melatonin (*N*-acetyl-5-methoxytryptamine, **1**) is the principle neuro-hormone secreted from the pineal gland [1]. A number of reports have been published on the medicinal importance of melatonin [2, 3]. Its role as a mediator of photoperiod in the regulation of seasonal physiological processes is well known [4]. Recent work has suggested its potential usefulness in a number of therapeutic areas related to the desynchronisation of biological rhythms, such as jet lag, disturbed sleep-wake cycles [5], seasonal disorders [6] and depression [7]. Melatonin may also play a role in the cardiovascular system [8] and in stimulating the immune system [9]. Furthermore, anticancer [10, 11], antioxidant [12] and ovulation inhibition properties of melatonin have been proposed [13]. The diverse biological activities of melatonin may be attributed to the presence of C–NH–C fragment, characteristics of the indole ring, one of the main targets of the metabolic degradation of melatonin. Thus, this nitrogen containing heterocyclic systems are potentially useful antiviral, antimetastatic or immune-stimulating agents [14, 15]. In this study, we designed new compounds, which provide basic pharmacological tools, using melatonin as the key starting material for the synthesis of extra- or fused heterocyclic systems like imidazole, pyrazole, pyridine, thiadiazole, thiophenes. The importance of such derivatives is due to their diverse biological and physiological potentialities [16–18]. The pharmacological activity of the new derivatives was examined in a specific *in vitro* model of melatonin action, the pigment aggregation response in *Xenopus laevis* melanophores [19, 20]. The agonist and antagonist potency of these derivatives was studied in comparison with melatonin.

### 2. Investigations, results and discussion

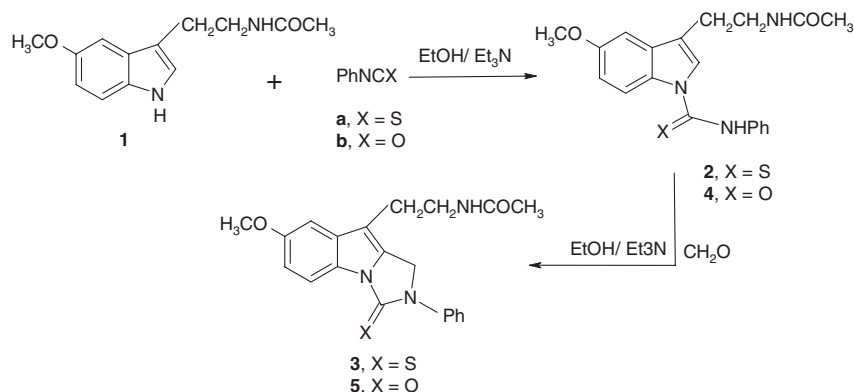
#### 2.1. Chemistry

The reaction of melatonin (**1**) with phenylisothiocyanate in refluxing ethanolic triethylamine solution gave the corresponding *N*-phenylaminothiocarbonylmelatonin derivative **2** (Scheme 1). The IR spectrum of compound **2** revealed the presence of C=O group stretching at 1695 cm<sup>-1</sup> and C=S stretching at 1190 cm<sup>-1</sup>. The <sup>1</sup>H NMR spectrum of compound **2** showed, in addition to the expected signals of melatonin moiety, two multiplet signals at  $\delta$  7.07–7.32 (3 H) and  $\delta$  7.42–7.65 (6 H) for aromatic protons and the indole 2-H proton and two D<sub>2</sub>O-exchangeable singlets at  $\delta$  8.75, 8.80 for the two NH protons. The structure of compound **2** was further confirmed by the reaction with formaldehyde in refluxing ethanolic triethylamine solution to give the imidazoindole derivative **3**. The IR spectrum of compound **3** revealed the presence of C=O group stretching at 1690 cm<sup>-1</sup> and C=S stretching at 1195 cm<sup>-1</sup>. Also, <sup>1</sup>H NMR spectrum of compound **3** revealed in addition to the expected signals, a singlet at  $\delta$  6.52 (2 H) corresponding to the CH<sub>2</sub>-imidazole protons.

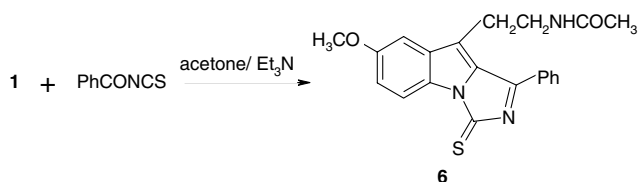
Similarly, the reaction of melatonin with phenylisocyanate in refluxing ethanolic triethylamine solution gave the *N*-phenylaminocarbonylmelatonin derivative **4** (Scheme 1). The latter product reacted with equimolar amount of formaldehyde in refluxing ethanolic triethylamine solution to give the imidazoindole derivative **5**.

In a similar manner, melatonin reacted with benzoyl-isothiocyanate in refluxing acetone solution containing a catalytic amount of triethylamine to give the imidazoindole derivative **6** in one step (Scheme 2). The IR spectrum of **6** showed the presence of C=S group stretching at 1195 cm<sup>-1</sup> and the <sup>1</sup>H NMR spectrum showed, in addition

Scheme 1



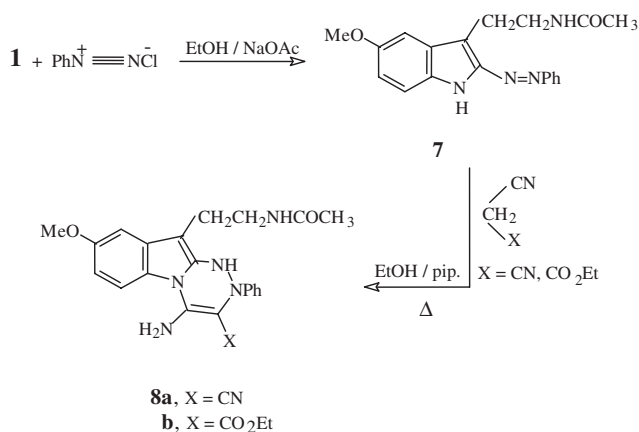
Scheme 2



to the expected signals, a multiplet signal at  $\delta$  7.35–7.95 corresponding to the  $\text{C}_6\text{H}_5$  protons.

Melatonin coupled with benzenediazonium chloride in ethanolic sodium acetate solution ( $0^\circ\text{C}$ ) to afford the phenylazo derivative 7. Further confirmation of the structure 7 was obtained by studying its reactivity towards some chemical reagents to give fused heterocyclic derivatives with potential biological activities. Thus, the reaction of compound 7 with either malononitrile or ethyl cyanoacetate in refluxing ethanolic piperidine solution afforded the corresponding triazinoindole derivatives 8a, b respectively (Scheme 3). The IR spectrum of compound 8a revealed the presence of one  $\text{NH}_2$  and two NH groups stretching at  $3360\text{--}3240\text{ cm}^{-1}$  and the presence of CN group stretching at  $2220\text{ cm}^{-1}$  and the  $^1\text{H}$  NMR spectrum showed, in addition to the expected signals of melatonin moiety,  $\text{D}_2\text{O}$ -exchangeable singlet at  $\delta$  6.65 for the  $\text{NH}_2$  protons and two  $\text{D}_2\text{O}$ -exchangeable singlet signals at  $\delta$  8.49, 9.25 (2 H) for the two NH groups. Also, the IR spectrum of 8b showed the presence of ester  $\text{C}=\text{O}$  group

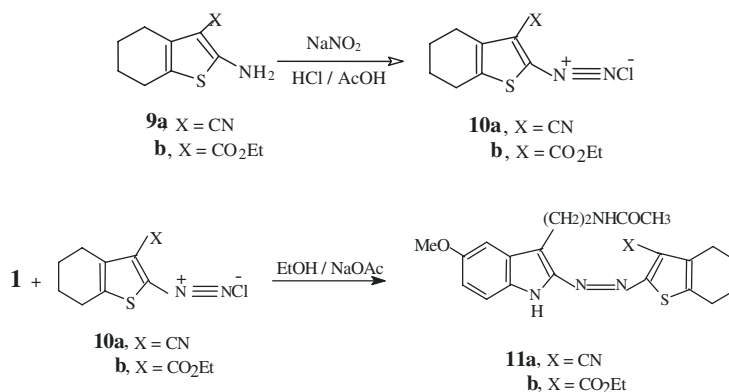
Scheme 3



stretching at  $1728\text{ cm}^{-1}$  and the  $^1\text{H}$  NMR spectrum of 8b showed, beside the expected signals, a triplet at  $\delta$  1.17 due to the ester  $\text{CH}_3$  group and a quartet at  $\delta$  4.28 ppm for the ester  $\text{CH}_2$  group.

In a similar manner, the reaction of melatonin (1) with either 2-diazo-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carbonitrile 10a or ethyl 2-diazo-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate 10b in ethanolic sodium acetate solution at  $0^\circ\text{C}$  gave the corresponding azo-derivatives 11a, b respectively (Scheme 4). The diazonium salts 10a, b can easily be obtained via simple addition of sodium nitrite solution

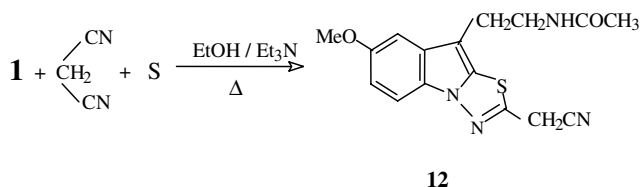
Scheme 4



to a solution of the parent amino derivatives **9a, b** in hydrochloric acid-acetic acid mixture at 0–5 °C with continuous stirring [21, 22].

The reaction of melatonin (**1**) with equimolar amounts of each of malononitrile and elemental sulphur in ethanolic triethylamine solution gave the thiadiazolindole derivative **12** (Scheme 5). The <sup>1</sup>H NMR spectrum of the product showed, in addition to the expected signals of melatonin moiety, a singlet at δ 6.52 corresponding to the CH<sub>2</sub>CN protons.

Scheme 5



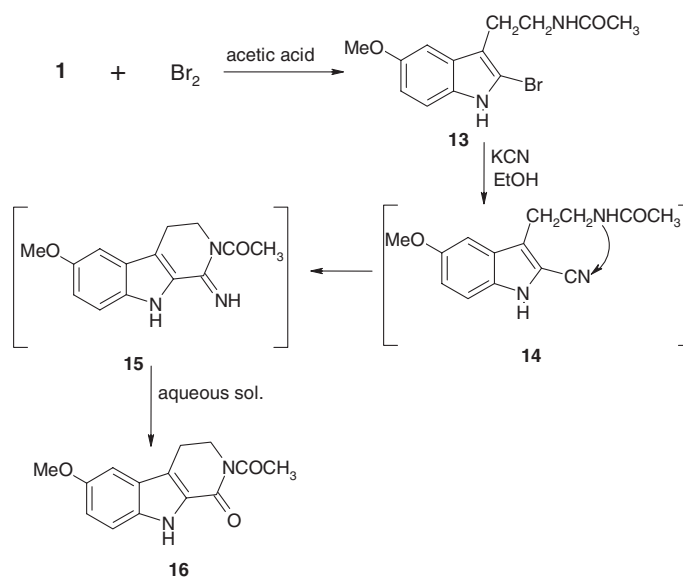
The reaction of melatonin (**1**) with bromine in acetic acid solution gave the 2-bromomelatonin **13**. Compound **13** reacted with potassium cyanide in warming ethanol to give pyridoindole derivative **16** (Scheme 6), formation of com-

pound **16** was assumed to proceed via the intermediacy of 2-cyanomelatonin **14** followed by intramolecular cyclization to give the intermediate **15** which hydrolyzed in the aqueous solution of the reaction to yield the isolatable product **16**.

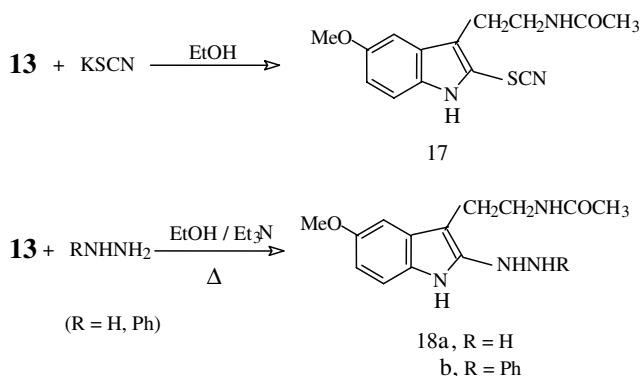
In a similar manner, the 2-bromomelatonin derivative **13** reacted with potassium thiocyanide in warming ethanol to give the 2-thiocyanomelatonin derivative **17**. On the other hand the reaction of compound **13** with either hydrazine hydrate or phenylhydrazine in refluxing ethanolic triethylamine solution gave the corresponding 2-hydrazinomelatonin derivatives **18a, b** respectively (Scheme 7).

The reaction of 2-bromomelatonin derivative **13** with either malononitrile **19a** or ethyl cyanoacetate **19b** in refluxing ethanolic triethylamine solution afforded the corresponding 2-alkyl melatonin derivatives **20a, b** respectively (Scheme 8). The reactivity of compounds **20a, b** towards nucleophilic reagents was studied, thus the reaction of **20a** with either hydrazine hydrate or phenylhydrazine in refluxing dimethylformamide/piperidine solution afforded the corresponding pyrazol-4-yl-melatonin derivatives **21a, b**. Similarly, compound **20b** reacted with either hydrazine hydrate or phenylhydrazine in dimethylformamide/piperidine solution to give the corresponding pyrazolo-4-yl-melatonin derivative **22a, b** (Scheme 9).

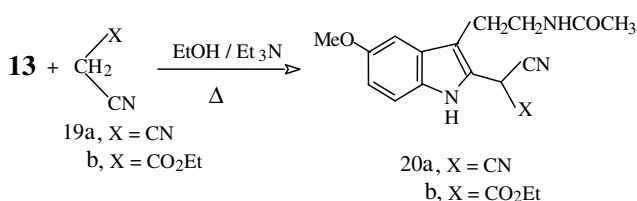
Scheme 6



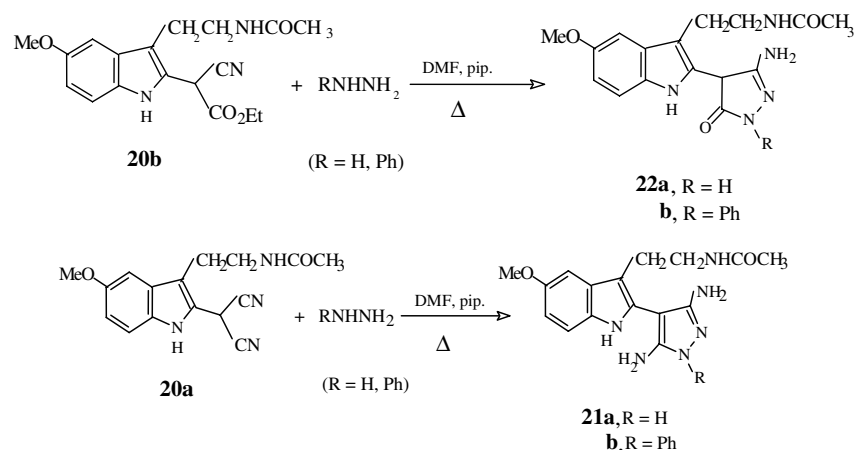
Scheme 7



Scheme 8



Scheme 9



## 2.2. Pharmacology

The biological activity of the new derivatives was examined in a specific *in vitro* model of melatonin action, the pigment aggregation response in *Xenopus laevis* melanophores [19, 20]. Addition of melatonin to these cells triggers a rapid redistribution (aggregation) of pigment granules toward the center of the cell. This change in pigment granule distribution in primary cultures of melanophores has been used previously to construct concentration-response curve to define agonist and antagonist potency of melatonin analogues [19, 20, 23].

In the present study, a clonal *Xenopus laevis* dermal a melanophore cell line was used [24]. Melanophores were grown as described previously in 96-well tissue culture plates [25] and changes in pigment granule distribution were quantitated by measuring absorbance (630 nm) before and after addition of the new compounds. Concentration-response curves were determined using a range of concentrations of the tested compounds in 2–4 wells of melanophores.  $\text{EC}_{50}$  values (concentration of the tested compound needed to produce 50% of maximal pigment aggregation) were determined. Antagonist potency was measured by adding test compounds to melanophores 1 h before challenging with melatonin ( $10^{-9}$  M), a concentration which consistently produces a maximal aggregation of pigment. Each concentration of antagonist was tested on 2–4 wells of melanophores.  $\text{IC}_{50}$  values (concentration of the tested compound, which blocked melatonin-induced pigment aggregation by 50%) were calculated. All tested compounds were dissolved in dimethylsulfoxide. The maximum concentration of dimethylsulfoxide (1%) did not alter specific binding or pigment granule distribution in melanophores.

Some of the synthesized derivatives, compounds **4**, **7**, **8a**, **11a**, **12**, **17** and **20b** were tested on the melanophore cell

line obtained from *Xenopus laevis*. The data measured for each concentration in the mean of two separate tests, using in each time 5–8000 melanophores. The effective concentration  $\text{EC}_{50}$  is the concentration of analog, which produces 50% of the maximal aggregation.

Compounds **4**, **7**, **8a**, **11a**, **12**, **17** and **20b** as shown in Table 1, and Fig. 1 showed an increase in the melatonin receptor binding affinity and potency as agonist, especially **8a** and **11a**. It is clear that the substitution in 2-position reveals more activity specially if the molecular weight of the substituent increase, e.g. compound **11a** or if the substitution gives macrocyclic (bulky) product, e.g. compound **8a**. This is clear if we compare compounds **8a** and **11a** with compounds **7** and **4**. As a rule, the substitution at

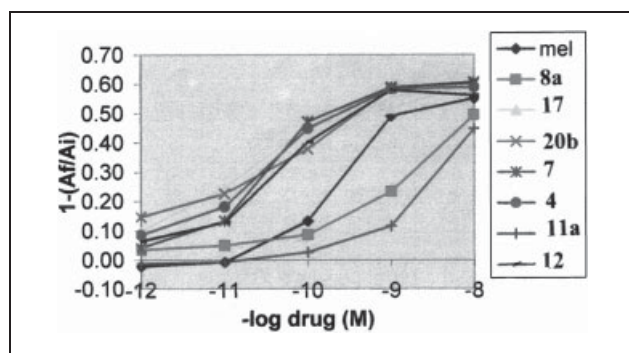


Fig. 1: Concentration-response curves for pigment aggregation by melatonin derivatives as agonists in melanophores. Initial absorbance ( $A_i$ , 630 nm) of the cells was measured in each well, and cells then treated with the concentration of the derivative indicated. The final absorbance ( $A_f$ ) was measured after 60 min. and the fractional change  $[1 - (A_f/A_i)]$  calculated. Each point represents the mean response of duplicate wells of melanophores at each concentration in signal experiment

Table 1: Drugs as agonists on melanophore assay

| (M)                     | Mel    | 8a    | 17    | 20b   | 7     | 4     | 11a    |
|-------------------------|--------|-------|-------|-------|-------|-------|--------|
| -12                     | -0.022 | 0.034 | 0.095 | 0.147 | 0.042 | 0.085 | -0.014 |
| -11                     | -0.008 | 0.049 | 0.243 | 0.227 | 0.133 | 0.181 | -0.008 |
| -10                     | 0.132  | 0.085 | 0.453 | 0.378 | 0.472 | 0.448 | 0.025  |
| -9                      | 0.490  | 0.233 | 0.515 | 0.585 | 0.590 | 0.584 | 0.115  |
| -8                      | 0.551  | 0.494 | 0.602 | 0.608 | 0.602 | 0.589 | 0.447  |
| $\text{EC}_{50}^*$ (nM) | 282    | 1.31  | 16.6  | 18.2  | 28.2  | 22.4  | 3.4    |

\* Concentration of the melatonin derivative needed to produce 50% of maximal pigment aggregation (nM)

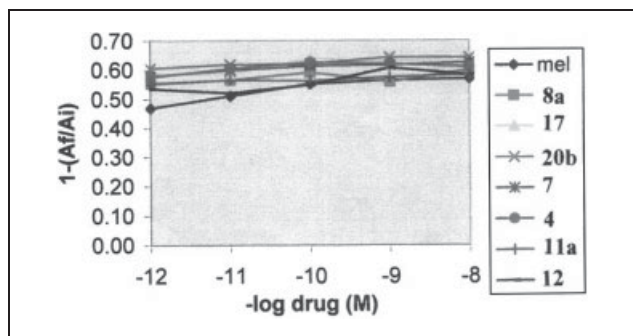


Fig. 2: Concentration-response curves for pigment aggregation by melatonin derivatives as antagonists in melanophores. Initial absorbance ( $A_i$ , 630 nm) of the cells was measured in each well, and cells then treated with the concentration of the derivative indicated. The final absorbance ( $A_f$ ) was measured after 60 min. and the fractional change  $[1 - (A_f/A_i)]$  calculated. Each point represents the mean response of duplicate wells of melanophores at each concentration in signal experiment

position 2 increases melatonin receptor binding affinity than any other substitution on the melatonin molecule.

Additionally, the new derivatives were tested for their ability to block melatonin responses as melatonin receptor antagonists. The results showed that the melatonin derivatives **4**, **7**, **8a**, **11a**, **12**, **17** and **20b** revealed no melatonin blocking activity as shown from Fig. 2. The effect and activity of these new derivatives in combination with the hydroquinone will be studied.

### 3. Experimental

All melting points are uncorrected. The IR spectra are expressed in  $\text{cm}^{-1}$  and were recorded in KBr pellets on a Pye Unicam SP-1000 spectrometer.  $^1\text{H}$  NMR spectra were obtained on a Varian EM-390 90 MHz spectrometer in  $\text{DMSO}-d_6$  as solvent and TMS as internal reference. Chemical shifts are expressed as  $\delta$  ppm. MS were recorded on a Finnigan SSQ 7000 instrument. Elemental analyses were carried out by Microanalytical Data Unit at National Research Centre, Giza, Egypt. All the elemental analyses results were in an acceptable range. The pharmacological study of the new synthesized compounds carried out at the laboratory of Prof. Dr. David Sugden, King's College London, England.

#### 3.1. *N*-[2-(5-Methoxy-1-phenylaminothiocarbonylindol-3-yl)ethyl]acetamide (**2**)

To a solution of melatonin (**1**) (1.16 g, 0.005 mol) and phenylisothiocyanate (0.67 g, 0.005 mol) in ethanol (20 ml), a catalytic amount of triethylamine (0.5 ml) was added. The reaction mixture was heated under reflux for 5 h, and then filtered off on hot then cooled at room temperature and poured over cold water/ice mixture. The solid product formed upon neutralizing the reaction mixture with few drops of hydrochloric acid, was filtered off, dried and crystallized.

White crystals, from EtOH, yield 79% (1.45 g), m.p. 144–146 °C.  $\text{C}_{20}\text{H}_{21}\text{N}_3\text{O}_2\text{S}$  (367.478). IR ( $\text{v}/\text{cm}^{-1}$ ): 3320–3250 (2 NH), 3035 (CH aromatic), 2970, 2865 ( $\text{CH}_3$ ,  $\text{CH}_2$ ), 1695 (C=O), 1190 (C=S);  $^1\text{H}$  NMR ( $\delta$  ppm): 1.78 (s, 3 H,  $\text{COCH}_3$ ), 2.87 (t, 2 H,  $\text{CH}_2$ ), 3.45 (s, 2 H,  $\text{CH}_2$ ), 3.82 (s, 3 H,  $\text{OCH}_3$ ), 7.07–7.32 (m, 3 H,  $\text{C}_6\text{H}_5$ ), 7.42–7.65 (m, 6 H,  $\text{C}_6\text{H}_5$ , indole 2-H), 8.75, 8.80 (2s, 2 H, 2 NH,  $\text{D}_2\text{O}$ -exchangeable). MS ( $m/z$ , %): 367 ( $\text{M}^+$ , 45), 335 (60), 307 (25), 290 (18), 154 (100), 136 (75), 107 (22), 93 (16), 77 (20).

#### 3.2. *N*-[2-(2,3-Dihydro-6-methoxy-2-phenyl-1-thioxo-1H-imidazo[1,5-a]indol-4-yl)ethyl]acetamide (**3**)

A mixture of compound **2** (1.83 g, 0.005 mol) and formaldehyde (0.15 g, 0.005 mol) in ethanol (20 ml) containing a catalytic amount of triethylamine (0.5 ml), was heated under reflux for 4 h, then cooled at room temperature and poured over ice/water mixture containing few drops of dilute hydrochloric acid. The solid product formed was filtered off, dried and crystallized.

White crystals, from EtOH, yield 75% (1.42 g), m.p. 239–241 °C.  $\text{C}_{21}\text{H}_{21}\text{N}_3\text{O}_2\text{S}$  (379.489); IR ( $\text{v}/\text{cm}^{-1}$ ): 3327 (NH), 3055 (CH aromatic), 2965, 2870 ( $\text{CH}_3$ ,  $\text{CH}_2$ ), 1690 (C=O), 1195 (C=S);  $^1\text{H}$  NMR ( $\delta$  ppm): 1.67 (s, 3 H,  $\text{COCH}_3$ ), 2.73 (t, 2 H,  $\text{CH}_2$ ), 3.35 (t, 2 H,  $\text{CH}_2$ ), 3.87 (s, 3 H,  $\text{OCH}_3$ ), 6.52 (s, 2 H, imidazole- $\text{CH}_2$ ), 7.35–7.62 (m, 8 H, aromatic-H),

8.82 (s, 1 H, NH,  $\text{D}_2\text{O}$ -exchangeable); MS ( $m/z$ , %): 379 ( $\text{M}^+$ , 35), 348 (28), 307 (20), 213 (25), 154 (100), 107 (17), 77 (15).

#### 3.3. *N*-[2-(5-Methoxy-1-phenylaminocarbonylindol-3-yl)ethyl]acetamide (**4**)

To a solution of melatonin **1** (1.16 g, 0.005 mol) in ethanol (30 ml) containing a catalytic amount of triethylamine, phenylisocyanate (0.59 g, 0.005 mol) was added. The reaction mixture was heated under reflux for 5 h, then poured into ice and neutralized with dilute hydrochloric acid. The formed solid product was filtered off, dried and crystallized.

White crystals, from dioxane, yield 71% (1.24 g), m.p. 199–201 °C.  $\text{C}_{20}\text{H}_{21}\text{N}_3\text{O}_3$  (351.412); IR ( $\text{v}/\text{cm}^{-1}$ ): 3325–3230 (2 NH), 3060 (CH aromatic), 2980, 2865 ( $\text{CH}_3$ ,  $\text{CH}_2$ ), 1705, 1698 (2 C=O, CONH,  $\text{COCH}_3$ );  $^1\text{H}$  NMR ( $\delta$  ppm): 1.72 (s, 3 H,  $\text{COCH}_3$ ), 2.72 (t, 2 H,  $\text{CH}_2$ ), 3.47 (t, 2 H,  $\text{CH}_2$ ), 3.87 (s, 3 H,  $\text{OCH}_3$ ), 6.92–7.45 (m, 9 H, aromatic-H, indole-2-H), 8.53, 9.07 (2s, 2 H, 2 NH,  $\text{D}_2\text{O}$ -exchangeable).

#### 3.4. *N*-[2-(2,3-Dihydro-6-methoxy-2-phenyl-1-oxo-1H-imidazo[1,5-a]indol-4-yl)ethyl]acetamide (**5**)

A mixture of equivalent amounts of compound **4** (1.75 g, 0.005 mol) and formaldehyde (0.15 g, 0.005 mol) in ethanol (20 ml) containing a catalytic amount of triethylamine (0.5 ml) was heated under reflux for 4 h, then poured over ice/water mixture and neutralized with few drops of hydrochloric acid. The formed solid product collected by filtration, dried and crystallized.

Pale yellow crystals, from EtOH, yield 69% (1.25 g), m.p. 125–126 °C;  $\text{C}_{21}\text{H}_{21}\text{N}_3\text{O}_3$  (363.423); IR ( $\text{v}/\text{cm}^{-1}$ ): 3420–3380 (NH), 3075 (CH aromatic), 2989, 2871 ( $\text{CH}_3$ ,  $\text{CH}_2$ ), 1715, 1695 (2 C=O, CONH,  $\text{COCH}_3$ );  $^1\text{H}$  NMR ( $\delta$  ppm): 1.65 (s, 3 H,  $\text{COCH}_3$ ), 2.67 (t, 2 H,  $\text{CH}_2$ ), 3.35 (t, 2 H,  $\text{CH}_2$ ), 3.78 (s, 3 H,  $\text{OCH}_3$ ), 6.43 (s, 2 H, imidazole- $\text{CH}_2$ ), 6.97–7.85 (m, 8 H, aromatic-H), 9.12 (s, 1 H, 1 NH,  $\text{D}_2\text{O}$ -exchangeable); MS ( $m/z$ , %): 363 ( $\text{M}^+$ , 55).

#### 3.5. *N*-[2-(6-Methoxy-3-phenyl-1-thioxo-1H-imidazo[1,5-a]indol-4-yl)ethyl]acetamide (**6**)

To freshly prepared benzoylisothiocyanate [prepared by the addition of benzoyl chloride (1.40 g, 0.01 mol) to a solution of potassium thiocyanate (0.97 g, 0.01 mol) in acetone (20 ml) and heating the reaction mixture under reflux for 20 min] a solution of melatonin (2.32 g, 0.01 mol) in acetone (20 ml) was added. The reaction mixture was heated under reflux for 4 h. The solid product formed upon dilution with water was collected by filtration, dried and crystallized.

Yellow crystals, from EtOH, yield 72% (2.72 g), m.p. 217–218 °C.  $\text{C}_{21}\text{H}_{19}\text{N}_3\text{O}_2\text{S}$  (377.473); IR ( $\text{v}/\text{cm}^{-1}$ ): 3309 (NH), 3050 (CH aromatic), 2970, 2860 ( $\text{CH}_3$ ,  $\text{CH}_2$ ), 1690 (C=O), 1195 (C=S);  $^1\text{H}$  NMR ( $\delta$  ppm): 1.76 (s, 3 H,  $\text{COCH}_3$ ), 2.75 (t, 2 H,  $\text{CH}_2$ ), 3.38 (t, 2 H,  $\text{CH}_2$ ), 3.79 (s, 3 H,  $\text{OCH}_3$ ), 6.78–7.20 (m, 3 H,  $\text{C}_6\text{H}_5$ ), 7.35–7.95 (m, 5 H,  $\text{C}_6\text{H}_5$ ), 9.25 (s, 1 H, 1 NH,  $\text{D}_2\text{O}$ -exchangeable).

#### 3.6. *N*-[2-(5-Methoxy-2-phenylazindol-3-yl)ethyl]acetamide (**7**)

A solution of melatonin (1.16 g, 0.005 mol) in ethanol (30 ml) containing sodium acetate (1.0 g) was cooled to 0–5 °C, then treated gradually with a cold solution of benzenediazonium chloride salt [prepared from aniline, the appropriate quantity of hydrochloric acid and sodium nitrite]. After the addition of the diazonium salt was completed, the reaction mixture was stirred at room temperature for 30 min. The precipitated product, separated upon dilution with cold water, was filtered off, washed several times, dried and crystallized.

Brown crystals, from EtOH– $\text{H}_2\text{O}$ , yield 79% (1.32 g), m.p. 88–90 °C.  $\text{C}_{19}\text{H}_{20}\text{N}_4\text{O}_2$  (336.401); IR ( $\text{v}/\text{cm}^{-1}$ ): 3455–3389 (NH), 3055 (CH aromatic), 2970, 2865 ( $\text{CH}_3$ ,  $\text{CH}_2$ ), 1698 (C=O);  $^1\text{H}$  NMR ( $\delta$  ppm): 1.75 (s, 3 H,  $\text{COCH}_3$ ), 2.82 (t, 2 H,  $\text{CH}_2$ ), 3.47 (t, 2 H,  $\text{CH}_2$ ), 3.82 (s, 3 H,  $\text{OCH}_3$ ), 7.32–7.93 (m, 8 H, aromatic-H), 10.62 (s, 1 H, 1 NH,  $\text{D}_2\text{O}$ -exchangeable).

#### 3.7. *N*-[2-(1-Amino-2-cyano-7-methoxy-3-phenyl-1,2,4-triazino[4,3-a]indol-5-yl)ethyl]acetamide (**8a**)

#### *N*-[2-(1-amino-2-ethoxycarbonyl-7-methoxy-3-phenyl-1,2,4-triazino[4,3-a]indol-5-yl)ethyl]acetamide (**8b**)

To a solution of compound **7** (0.67 g, 0.002 mol) in ethanol (30 ml) containing a catalytic amount of piperidine, either malononitrile (0.13 g, 0.002 mol) or ethyl cyanoacetate (0.23 g, 0.002 mol) was added. The reaction mixture, in each case, was heated under reflux for 5 h, then poured over ice/water mixture and neutralized with dilute hydrochloric acid. The formed solid product, in each case, was filtered off, dried and crystallized from the appropriate solvent.

Compound **8a**: Brown crystals, from EtOH, yield 78% (0.63 g), m.p. 105–107 °C.  $\text{C}_{22}\text{H}_{22}\text{N}_6\text{O}_2$  (402.466); IR ( $\text{v}/\text{cm}^{-1}$ ): 3360–3240 (NH<sub>2</sub>, 2 NH), 3035 (CH aromatic), 2975, 2863 ( $\text{CH}_3$ ,  $\text{CH}_2$ ), 2220 (CN), 1695 (C=O);  $^1\text{H}$  NMR ( $\delta$  ppm): 1.73 (s, 3 H,  $\text{COCH}_3$ ), 2.70 (t, 2 H,  $\text{CH}_2$ ), 3.45 (t, 2 H,  $\text{CH}_2$ ), 3.79 (s, 3 H,  $\text{OCH}_3$ ), 6.65 (s, 2 H,  $\text{NH}_2$ ,  $\text{D}_2\text{O}$ -exchangeable), 7.15–8.05 (m, 8 H, aromatic-H), 8.94, 9.25 (2s, 2 H, 2 NH,  $\text{D}_2\text{O}$ -exchangeable); MS ( $m/z$ , %): 402 ( $\text{M}^+$ , 25).

Compound **8b**: Reddish brown crystals, from DMF, yield 72% (0.64 g), mp 151–152 °C.  $C_{24}H_{27}N_5O_4$  (449.52); IR ( $\nu/cm^{-1}$ ): 3420–3290 (NH<sub>2</sub>, 2 NH), 3045 (CH aromatic), 2975, 2869 (CH<sub>3</sub>, CH<sub>2</sub>), 1728, 1698 (2 C=O, ester C=O, COCH<sub>3</sub>); <sup>1</sup>H NMR ( $\delta$  ppm): 1.17 (t, 3 H, ester CH<sub>3</sub>), 1.75 (s, 3 H, COCH<sub>3</sub>), 2.74 (t, 2 H, CH<sub>2</sub>), 3.43 (t, 2 H, CH<sub>2</sub>), 4.28 (q, 2 H, ester CH<sub>2</sub>), 6.52 (s, 2 H, NH<sub>2</sub>, D<sub>2</sub>O-exchangeable), 7.15–8.10 (m, 8 H, aromatic-H), 8.71, 9.12 (2s, 2 H, 2 NH, D<sub>2</sub>O-exchangeable).

### 3.8. *N*-[2-(2-azo(3-cyano-4,5,6,7-tetrahydrobenzo[*b*]thieno-2-yl)indol-3-yl)-ethyl]acetamide (**11a**);

*N*-[2-(2-azo(ethyl 4,5,6,7-tetrahydrobenzo[*b*]thieno-2-yl)indol-3-yl)ethyl]-acetamide (**11b**)

A solution of melatonin (1.16 g, 0.005 mol) in ethanol (20 ml) containing sodium acetate (0.5 g) was cooled to 0–5 °C, then treated gradually with a cold, clear solution of either 2-diazo-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carbonitrile (**10a**) or ethyl 2-diazo-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxylate (**10b**) [**10a**, **b** were prepared by adding sodium nitrite solution (0.34 g, 0.005 mol) in water to a cold solution of either 2-amino-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carbonitrile (**9a**, 0.89 g, 0.005 mol) or ethyl 2-amino-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxylate (**9b**, 1.12 g, 0.005 mol) in acetic-hydrochloric acids mixture (30 ml, 5:1) with continuous stirring]. After the addition of the diazonium salt, in each case, was completed, the reaction mixture stirred at room temperature for 1 h. The precipitated product separated upon dilution with cold water, in each case, filtered off, washed with water, dried and crystallized from the proper solvent.

Compound **11a**: Buff crystals, from EtOH, yield 81% (1.70 g), m.p. 139–141 °C.  $C_{22}H_{23}N_5O_2S$  (421.532); IR ( $\nu/cm^{-1}$ ): 3445–3255 (2 NH), 3050 (CH aromatic), 2989, 2865 (CH<sub>3</sub>, CH<sub>2</sub>), 2215 (CN), 1690 (C=O); <sup>1</sup>H NMR ( $\delta$  ppm): 1.69 (s, 3 H, COCH<sub>3</sub>), 1.78–1.92 (m, 4 H, 2 H-6, 2 H-7, cyclohexane), 2.35–2.53 (m, 4 H, 2 H-5, 2 H-8, cyclohexane), 2.82 (t, 2 H, CH<sub>2</sub>), 3.47 (t, 2 H, CH<sub>2</sub>), 3.89 (s, 3 H, OCH<sub>3</sub>), 7.12–7.52 (m, 3 H, C<sub>6</sub>H<sub>3</sub>), 8.95, 9.20 (2s, 2 H, 2 NH, D<sub>2</sub>O-exchangeable).

Compound **11b**: Red crystals, from EtOH, yield 75% (1.75 g), m.p. 92–93 °C.  $C_{24}H_{28}N_4O_4S$  (468.586); IR ( $\nu/cm^{-1}$ ): 3430–3290 (2 NH), 3045 (CH aromatic), 2965, 2856 (CH<sub>3</sub>, CH<sub>2</sub>), 1735, 1695 (2 C=O; ester C=O, COCH<sub>3</sub>); <sup>1</sup>H NMR ( $\delta$  ppm): 1.15 (t, 3 H, ester-CH<sub>3</sub>), 1.65 (s, 3 H, COCH<sub>3</sub>), 1.77–1.95 (m, 4 H, 2 H-6, 2 H-7, cyclohexane), 2.32–2.55 (m, 4 H, 2 H-5, 2 H-8, cyclohexane), 2.73 (t, 2 H, CH<sub>2</sub>), 3.67 (t, 2 H, CH<sub>2</sub>), 3.85 (s, 3 H, OCH<sub>3</sub>), 4.27 (q, 2 H, ester CH<sub>2</sub>), 7.20–7.72 (m, 3 H, C<sub>6</sub>H<sub>3</sub>), 8.75, 9.04 (2s, 2 H, 2 NH, D<sub>2</sub>O-exchangeable).

### 3.9. *N*-[2-(2-Cyanomethyl-6-methoxy-1,3,4-thiadiazolo[3,2-*a*]indol-4-yl)-ethyl]acetamide (**12**)

To a mixture of melatonin (1.16 g, 0.005 mol) and malononitrile (0.33 g, 0.005 mol) in ethanol (30 ml) containing a catalytic amount of triethylamine (0.5 ml), sulfur (0.16 g, 0.005 mol) was added. The reaction mixture was heated under reflux for 4 h, then poured into ice and neutralized with dilute hydrochloric acid, whereby the resulting solid product collected by filtration and crystallized.

Brown crystals, from EtOH, yield 69% (1.13 g), m.p. 107–108 °C.  $C_{16}H_{16}N_4O_2S$  (328.402); IR ( $\nu/cm^{-1}$ ): 3328 (NH), 3035 (CH aromatic), 2985, 2870 (CH<sub>3</sub>, CH<sub>2</sub>), 2225 (CN), 1695 (C=O), 1640 (C=C). <sup>1</sup>H NMR ( $\delta$  ppm): 1.76 (s, 3 H, COCH<sub>3</sub>), 2.75 (t, 2 H, CH<sub>2</sub>), 3.49 (t, 2 H, CH<sub>2</sub>), 3.78 (s, 3 H, OCH<sub>3</sub>), 6.52 (s, 2 H, CH<sub>2</sub>CN), 7.05–7.45 (m, 3 H, C<sub>6</sub>H<sub>3</sub>), 8.92 (s, 1 H, NH, D<sub>2</sub>O-exchangeable).

### 3.10. *N*-[2-(2-Bromo-5-methoxyindol-3-yl)ethyl]acetamide (**13**)

To a solution of melatonin (1.16 g, 0.005 mol) in acetic acid (20 ml), bromine (0.8 g, 0.005 mol) in acetic acid (5 ml), was added. The reaction mixture was kept at 50 °C for 30 min with stirring and the solid product formed upon pouring into ice/water was collected by filtration, dried and crystallized.

Yellow crystals, from EtOH, yield 79% (1.23 g), m.p. 184–185 °C.  $C_{13}H_{15}N_2O_2Br$  (311.195); IR ( $\nu/cm^{-1}$ ): 3325–3280 (2 NH), 3025 (CH aromatic), 2989, 2875 (CH<sub>3</sub>, CH<sub>2</sub>), 1690 (C=O), 1637 (C=C); <sup>1</sup>H NMR ( $\delta$  ppm): 1.82 (s, 3 H, COCH<sub>3</sub>), 2.95 (t, 2 H, CH<sub>2</sub>), 3.45 (t, 2 H, CH<sub>2</sub>), 3.83 (s, 3 H, OCH<sub>3</sub>), 7.20–7.75 (m, 3 H, C<sub>6</sub>H<sub>3</sub>), 8.73, 9.03 (2s, 2 H, 2 NH, D<sub>2</sub>O-exchangeable). MS ( $m/z$ , %): 311 ( $M^+$ , 59), 321 (30), 208 (25), 114 (30), 57 (45).

### 3.11. *N*-Acetyl-6-methoxy-1-oxo-1,2,3,4-tetrahydro-9H-pyrido[3,4-*b*]indole (**16**)

To a solution of compound **13** (1.55 g, 0.005 mol) in ethanol (30 ml), potassium cyanide (0.32 g, 0.005 mol) in water (5 ml) was added with stirring and warming at 70 °C for 1 h. The reaction mixture was poured over ice/water mixture and neutralized with dilute hydrochloric acid. The solid product, so formed, collected by filtration, dried and crystallized.

Grey crystals, from dioxane, yield 72% (0.93 g), m.p. 197–199 °C.  $C_{14}H_{14}N_2O_3$  (258.282); IR ( $\nu/cm^{-1}$ ): 3370–3625 (NH), 3070 (CH-a-

romatic), 2935, 2864 (CH<sub>3</sub>, CH<sub>2</sub>), 1705 (C=O), 1693 (C=O, COCH<sub>3</sub>), 1635 (C=C); <sup>1</sup>H NMR ( $\delta$  ppm): 1.76 (s, 3 H, COCH<sub>3</sub>), 2.83 (t, 2 H, CH<sub>2</sub>), 3.48 (t, 2 H, CH<sub>2</sub>), 3.82 (s, 3 H, OCH<sub>3</sub>), 7.75–7.96 (m, 3 H, C<sub>6</sub>H<sub>3</sub>), 9.12 (s, 1 H, NH, D<sub>2</sub>O-exchangeable).

### 3.12. *N*-[2-(5-methoxy-2-thiocyanoindol-3-yl)ethyl]acetamide (**17**)

To a solution of compound **13** (1.55 g, 0.005 mol) in ethanol (30 ml), a solution of potassium thiocyanate (0.48 g, 0.005 mol) in water (10 ml) was added with stirring and warming at 70 °C for 1 h. The reaction mixture was poured over ice/water mixture and neutralized with dilute hydrochloric acid. The solid product so formed collected by filtration, dried and crystallized.

Green crystals, from EtOH, yield 78% (1.12 g), m.p. 170–171 °C.  $C_{14}H_{15}N_3O_2S$  (289.364); IR ( $\nu/cm^{-1}$ ): 3374–3332 (2 NH), 3052 (CH-aromatic), 2972, 2833 (CH<sub>3</sub>, CH<sub>2</sub>), 2225 (CN), 1697 (C=O), 1642 (C=C); <sup>1</sup>H NMR ( $\delta$  ppm): 1.82 (s, 3 H, COCH<sub>3</sub>), 2.81 (t, 2 H, CH<sub>2</sub>), 3.47 (t, 2 H, CH<sub>2</sub>), 3.89 (s, 3 H, OCH<sub>3</sub>), 7.17–7.37 (m, 3 H, C<sub>6</sub>H<sub>3</sub>), 8.78, 9.22 (2s, 2 H, 2 NH, D<sub>2</sub>O-exchangeable); MS ( $m/z$ , %): 289 ( $M^+$ , 35), 262 (25), 232 (100), 173 (80), 144 (10), 72 (5).

### 3.13. *N*-[2-(2-Hydrazino-5-methoxyindol-3-yl)ethyl]acetamide (**18a**)

*N*-[2-(2-phenylhydrazino-5-methoxyindol-3-yl)ethyl]acetamide (**18b**)

A mixture of 2-bromomelatonin derivative **13** (1.55 g, 0.005 mol) and either hydrazine hydrate (0.25 g, 0.005 mol) or phenyl hydrazine (0.54 g, 0.005 mol) in ethanol (20 ml) containing a catalytic amount of triethylamine was heated under reflux for 4 h. The reaction mixture, in each case, was left to cool at room temperature, poured into ice and neutralized with dilute hydrochloric acid. The resulting solid product, in each case, was collected by filtration, dried and crystallized from the appropriate solvent.

Compound **18a**: Pale brown crystals, from EtOH/H<sub>2</sub>O, yield 70% (0.92 g), m.p. 234–235 °C.  $C_{13}H_{18}N_4O_2$  (262.319); IR ( $\nu/cm^{-1}$ ): 3390–3256 (NH<sub>2</sub>, 3 NH), 3070 (CH-aromatic), 2973, 2865 (CH<sub>3</sub>, CH<sub>2</sub>), 1696 (C=O), 1642 (C=C); <sup>1</sup>H NMR ( $\delta$  ppm): 1.77 (s, 3 H, COCH<sub>3</sub>), 2.87 (t, 2 H, CH<sub>2</sub>), 3.48 (t, 2 H, CH<sub>2</sub>), 3.87 (s, 3 H, OCH<sub>3</sub>), 7.55 (s, 2 H, NH<sub>2</sub>, D<sub>2</sub>O-exchangeable), 7.85–8.05 (m, 3 H, C<sub>6</sub>H<sub>3</sub>), 9.53–9.85 (m, 3 H, 3 NH, D<sub>2</sub>O-exchangeable).

Compound **18b**: Yellow crystals, from EtOH, yield 79% (1.33 g), m.p. 149 °C.  $C_{19}H_{22}N_4O_2$  (338.417); IR ( $\nu/cm^{-1}$ ): 3387–3255 (4 NH), 3065 (CH-aromatic), 2975, 2863 (CH<sub>3</sub>, CH<sub>2</sub>), 1702 (C=O), 1640 (C=C); <sup>1</sup>H NMR ( $\delta$  ppm): 1.72 (s, 3 H, COCH<sub>3</sub>), 2.85 (t, 2 H, CH<sub>2</sub>), 3.48 (t, 2 H, CH<sub>2</sub>), 3.82 (s, 3 H, OCH<sub>3</sub>), 7.05–7.52 (m, 5 H, C<sub>6</sub>H<sub>5</sub>), 7.80–8.03 (m, 3 H, C<sub>6</sub>H<sub>3</sub>), 9.50–9.87 (m, 4 H, 4 NH, D<sub>2</sub>O-exchangeable).

### 3.14. *N*-[2-(2-Dicyanomethino-5-methoxyindol-3-yl)ethyl]acetamide (**20a**)

*N*-[2-(2-ethyl cyanoacetato-5-methoxyindol-3-yl)ethyl]acetamide (**20b**)

To a solution of compound **13** (1.55 g, 0.005 mol) in ethanol (30 ml) containing a catalytic amount of triethylamine (0.5 ml), either malononitrile (0.33 g, 0.005 mol) or ethyl cyanoacetate (0.56 g, 0.005 mol) was added. The reaction mixture, in each case, was heated under reflux for 3 h, then left to cool, and poured into ice/water mixture containing few drops of dilute hydrochloric acid. The resulting solid product, in each case, was collected by filtration, dried and crystallized from the appropriate solvent.

Compound **20a**: Pale brown crystals, from dioxane, yield 73% (1.1 g), m.p. 154–155 °C.  $C_{16}H_{16}N_4O_2$  (296.336); IR ( $\nu/cm^{-1}$ ): 3342–3223 (2 NH), 3052 (CH-aromatic), 2979, 2870 (CH<sub>3</sub>, CH<sub>2</sub>), 2215, 2225 (2 CN), 1697 (C=O); <sup>1</sup>H NMR ( $\delta$  ppm): 1.79 (s, 3 H, COCH<sub>3</sub>), 2.87 (t, 2 H, CH<sub>2</sub>), 3.49 (t, 2 H, CH<sub>2</sub>), 3.87 (s, 3 H, OCH<sub>3</sub>), 4.05 (s, 1 H, CH), 7.37–7.85 (m, 3 H, C<sub>6</sub>H<sub>3</sub>), 8.87, 9.20 (2s, 2 H, 2 NH, D<sub>2</sub>O-exchangeable).

Compound **20b**: Pale brown crystals, from dioxane, yield 70% (1.2 g), m.p. 199–200 °C.  $C_{18}H_{21}N_3O_4$  (343.39); IR ( $\nu/cm^{-1}$ ): 3345–3230 (2 NH), 3035 (CH-aromatic), 2975, 2860 (CH<sub>3</sub>, CH<sub>2</sub>), 2220 (CN), 1735, 1692 (2 C=O, ester C=O, COCH<sub>3</sub>); <sup>1</sup>H NMR ( $\delta$  ppm): 1.18 (t, 3 H, ester-CH<sub>3</sub>), 1.75 (s, 3 H, COCH<sub>3</sub>), 2.83 (t, 2 H, CH<sub>2</sub>), 3.39 (t, 2 H, CH<sub>2</sub>), 3.82 (s, 3 H, OCH<sub>3</sub>), 4.07 (s, 1 H, CH), 4.25 (q, 2 H, ester-CH<sub>2</sub>), 7.41–7.90 (m, 3 H, C<sub>6</sub>H<sub>3</sub>), 8.95, 9.15 (2s, 2 H, 2 NH, D<sub>2</sub>O-exchangeable); MS ( $m/z$ , %): 343 ( $M^+$ , 19), 317 (10), 265 (100), 231 (35), 181 (50), 76 (25).

### 3.15. *N*-[2-(2-(3,5-Diaminopyrazolo-4-yl)-5-methoxyindol-3-yl)ethyl]-acetamide (**21a**)

*N*-[2-(2-(3,5-diamino-1-phenylpyrazolo-4-yl)-5-methoxyindol-3-yl)ethyl]-acetamide (**21b**)

To a solution of compound **20a** (1.48 g, 0.005 mol) in dimethylformamide (20 ml) containing a catalytic amount of piperidine, either hydrazine hydrate (0.25 g, 0.005 mol) or phenylhydrazine (0.54 g, 0.005 mol) was added. The reaction mixture, in each case, was heated under reflux for 5 h, then poured over ice/water mixture and neutralized with dilute hydrochloric acid. The solid that formed, in each case, was filtered off, dried and crystallized from the appropriate solvent.

Compound **21a**: Pale brown crystals, from EtOH, yield 69% (1.32 g), m.p. 176–177 °C.  $C_{16}H_{20}N_6O_2$  (328.384); IR ( $\nu/cm^{-1}$ ): 3367–3205 (2 NH<sub>2</sub>, 3 NH), 3060 (CH-aromatic), 2973, 2861 (CH<sub>3</sub>, CH<sub>2</sub>), 1702 (C=O), 1642 (C=C); <sup>1</sup>H NMR ( $\delta$  ppm): 1.75 (s, 3 H, COCH<sub>3</sub>), 2.97 (t, 2 H, CH<sub>2</sub>), 3.45 (t, 2 H, CH<sub>2</sub>), 3.84 (s, 3 H, OCH<sub>3</sub>), 7.20, 7.42 (2s, 4 H, 2 NH<sub>2</sub>, D<sub>2</sub>O-exchangeable), 7.67–7.95 (m, 3 H, C<sub>6</sub>H<sub>3</sub>), 8.87–9.12 (m, 3 H, 3 NH, D<sub>2</sub>O-exchangeable); MS ( $m/z$  %): 328 (M<sup>+</sup>, 45).

Compound **21b**: Orange crystals, from EtOH, yield 72% (1.46 g), m.p. 197–198 °C.  $C_{22}H_{24}N_6O_2$  (404.482); IR ( $\nu/cm^{-1}$ ): 3385–3220 (2 NH<sub>2</sub>, 2 NH), 3070 (CH-aromatic), 2963, 2856 (CH<sub>3</sub>, CH<sub>2</sub>), 1705 (C=O), 1638 (C=C); <sup>1</sup>H NMR ( $\delta$  ppm): 1.80 (s, 3 H, COCH<sub>3</sub>), 2.83 (t, 2 H, CH<sub>2</sub>), 3.47 (t, 2 H, CH<sub>2</sub>), 3.79 (s, 3 H, OCH<sub>3</sub>), 7.23–7.48 (m, 5 H, C<sub>6</sub>H<sub>5</sub>), 7.32, 7.55 (2s, 4 H, 2 NH<sub>2</sub>, D<sub>2</sub>O-exchangeable), 7.78–8.02 (m, 3 H, C<sub>6</sub>H<sub>3</sub>), 8.85, 9.05 (2s, 2 H, 2 NH, D<sub>2</sub>O-exchangeable).

**3.16. *N*-[2-(2-(3-Amino-5-oxopyrazolo-4-yl)-5-methoxyindol-3-yl)ethyl]-acetamide (22a)**

***N*-[2-(2-(3-amino-5-oxo-1-phenylpyrazolo-4-yl)-5-methoxyindol-3-yl)ethyl]-acetamide (22b)**

To a solution of compound **20b** (1.71 g, 0.005 mol) in dimethylformamide (25 ml) containing a catalytic amount of piperidine (0.5 ml), either hydrazine hydrate (0.25 g, 0.005 mol) or phenyl hydrazine (0.54 g, 0.005 mol) was added. The reaction mixture, in each case, was heated under reflux for 6 h, then poured into ice and neutralized with dilute hydrochloric acid. The solid formed, in each case, was filtered off, dried and crystallized from the appropriate solvent.

Compound **22a**: Pale brown crystals, from dioxane, yield 71% (1.17 g), m.p. 210–212 °C.  $C_{16}H_{19}N_5O_3$  (329.368); IR ( $\nu/cm^{-1}$ ): 3385–3220 (NH<sub>2</sub>, 3 NH), 3035 (CH-aromatic), 2975, 2850 (CH<sub>3</sub>, CH<sub>2</sub>), 1710 (C=O, 5-oxo-pyrazole), 1698 (C=O, COCH<sub>3</sub>), 1643 (C=C); <sup>1</sup>H NMR ( $\delta$  ppm): 1.82 (s, 3 H, COCH<sub>3</sub>), 2.78 (t, 2 H, CH<sub>2</sub>), 3.50 (t, 2 H, CH<sub>2</sub>), 3.82 (s, 3 H, OCH<sub>3</sub>), 5.03 (s, 2 H, NH<sub>2</sub>, D<sub>2</sub>O-exchangeable), 7.62–7.89 (m, 3 H, C<sub>6</sub>H<sub>5</sub>), 8.97–9.58 (m, 3 H, 3 NH, D<sub>2</sub>O-exchangeable).

Compound **22b**: Brown crystals, from DMF, yield 72% (1.45 g), m.p. 223–225 °C.  $C_{22}H_{23}N_5O_3$  (405.466); IR ( $\nu/cm^{-1}$ ): 3415–3270 (NH<sub>2</sub>, 2 NH), 3053 (CH-aromatic), 2965, 2870 (CH<sub>3</sub>, CH<sub>2</sub>), 1705 (C=O, 5-oxo-pyrazole), 1695 (C=O, COCH<sub>3</sub>), 1640 (C=C); <sup>1</sup>H NMR ( $\delta$  ppm): 1.73 (s, 3 H, COCH<sub>3</sub>), 2.85 (t, 2 H, CH<sub>2</sub>), 3.42 (t, 2 H, CH<sub>2</sub>), 3.87 (s, 3 H, OCH<sub>3</sub>), 5.25 (s, 2 H, NH<sub>2</sub>, D<sub>2</sub>O-exchangeable), 7.27–7.65 (m, 5 H, C<sub>6</sub>H<sub>5</sub>), 7.89–8.25 (m, 3 H, C<sub>6</sub>H<sub>3</sub>), 8.72, 9.05 (2s, 2 H, 2 NH, D<sub>2</sub>O-exchangeable).

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