# Novel Selective 5-HT<sub>3</sub> Receptor Ligands: Facile Generation Methods for 2-Amino- and 4-Aminopyrido[4',3':4,5]thieno[2,3-*d*]pyrimidines

Mohamed A. Ameen

Chemistry Department, Faculty of Science, El Minia University, El Minia 61519, Egypt

Reprint requests to Dr. M. A. Ameen. E-mail: m\_ameen10@yahoo.com

Z. Naturforsch. 61b, 1234-1238 (2006); received September 16, 2005

This work reports on the synthesis of new 2-amino- and 4-aminopyridothienopyrimidines, with a view to identify potent and selective ligands for the 5-HT<sub>3</sub> receptor, starting from derivatives of 2-aminothiophene-3-carboxylic ester, -3-carboxamide, or 2-amino-3-cyanothiophene.

Key words: 5-HT<sub>3</sub> Receptor, Aminopyridothienopyrimidines, Cyclodesulfurization, Diazotization

## Introduction

Derivatives of 2-aminothiophene-3-carboxylic ester, -3-carboxamide, or 2-amino-3-cyanothiophene have been found to be important intermediates in the preparation of thienopyrimidines. Therefore they attracted much attention during recent years [1-9]. The obtained thienopyrimidine derivatives have found wide application in a variety of synthetic transformations as well as biological activities. The serotonin neurotransmitter is involved in a number of different physiological functions through its interaction with 14 types of receptors [10]. These are G-protein-coupled receptors, with the exception of the 5-HT<sub>3</sub>, which is a ligand gated-ion channel receptor. 5-HT<sub>3</sub> receptor antagonists, such as ondansetron, granisetron, or tropisetron [11] are used as anti-emetic drugs to prevent vomiting associated with chemotherapy or radiation-induced emesis, but literature studies [12] indicated that they could possess numerous other potential therapeutic applications in the control of pain or in the treatment of psychosis, memory impairment, depression, anxiety, schizophrenia, and drugs abuse.

On the other hand, little is known about the therapeutic potential of  $5\text{-HT}_3$  receptor agonists although some potent and selective ligands with full agonistic properties [13] were recently reported. It has been suggested that stimulation of the  $5\text{-HT}_3$  receptor modulates in the central nervous system the release of dopamine, cholecystokinin, and acetylcholine [14]. Moreover,  $5\text{-HT}_3$  receptors are involved in the peripheral control of acetylcholine release of the distal colon [15]. These interesting results make it desirable to our work during the last few years in which we have been interested in the synthesis of thienopyrimidines [16-21]. They also prompted us to continue our longterm research aiming to obtain more potent and selective ligands for the 5-HT<sub>3</sub> receptor. The present work reports on the synthesis of 2-amino- and 4-aminothieno[2,3-*d*]pyrimidine derivatives which can be regarded or might behave prospectively as analogues to 5-HT<sub>3</sub> receptor ligands [22]. These compounds possess the three key pharmacophoric elements (an aromatic moiety, a hydrogen-bond acceptor and a basic amino group) required for interaction with the 5-HT<sub>3</sub> receptor [23] and are structurally related to quipazine, a potent ligand for the 5-HT<sub>3</sub> receptor [24].

## **Results and Discussion**

The reaction of 2-aminothiophene-3-carboxamide 1 with benzoyl isothiocyanate in acetone afforded the corresponding [*N*-benzoyl(thiocarbamoyl)]-aminothiophene derivative 2 in 67% yield (Scheme 1). The isolated compound 2 was hydrolyzed to yield the corresponding thiourea 3 (Scheme 1).

In the accomplishment of the cyclodesulfurization (Scheme 1) by use of a heavy metal salt, compound **3** was added to a suspension of a slight excess of the metal salt in aqueous sodium hydroxide. The reaction was completed after heating at 100 °C. Thereafter, the temperature of the reaction mixture was kept at 50 °C for 15 min and the formed copper sulfide was then filtered off. Compound **4** was obtained after purification and recrystallization processes (see Experimental Section). The best yields of **4** were obtained with copper

0932-0776 / 06 / 1000-1234 \$ 06.00 © 2006 Verlag der Zeitschrift für Naturforschung, Tübingen · http://znaturforsch.com

Table 1. Effect of the metal  $ion^a$ , the amount and concentration of base, and the temp. on conversion of **3** to **4**.

Metal salts <sup>b</sup>	Conc. of NaOH, <i>M</i>	Temp. [°C]	Time [h]	Yield [%]
Cu <sup>2+</sup>	0.1	100	1	74
Cu <sup>2+</sup>	1	25	45	90
Cu <sup>2+</sup>	1	100	1	97
Cu <sup>2+</sup>	3	100	1	97
Cu <sup>2+</sup>	3	100	0.5	89
$Ag^+$	3	100	2	98
Hg <sup>2+</sup>	3	100	2	87

<sup>a</sup> Metal salts used:  $Cu_2(OAc)_4$ , AgCl and HgCl<sub>2</sub>; <sup>b</sup> poor yields for 4 were obtained when the chloride salts of Pb<sup>+2</sup>, Zn<sup>+2</sup>, Bi<sup>+3</sup> and Fe<sup>+2</sup> were used; <sup>c</sup> at room temp. a 82% yield of 4 was obtained after 1 h.



Scheme 1. Cyclodesulfurization of **3** into **4** catalyzed by copper acetate in aqueous NaOH.

and silver salts, while mercury salts afforded a somewhat lower yield. Bismuth, lead and zinc gave only poor yields, and ferrous salts failed (Table 1). The molar ratio of hydroxyl ions to compound 3 turned out to be essential for the yield of the ring closure reaction, the preferable ratio being 6 equiv. of hydroxyl ions to 1 equiv. of compound 3 (Table 1). The molar concentration of hydroxyl ions had, on the other hand, only a small effect on the yield. It is worthy to mention that the utility of  $Cu^{2+}$  in the conversion of **3** into **4** can be enhanced using a moderately concentrated solution of NaOH (1 M) at 100 °C. With higher concentrations of NaOH, for example 3 M, the interconversion of 3 proceeds to give 4 with the same yield as for 1 M of NaOH (see Table 1). In the case of salts of  $Ag^+$  and  $Hg^{2+}$ , higher concentrations of NaOH were used. The advantage of this methodology is related to the lower cost of the available salts used, in addition to the productive yields of aminopyrimidines from the corresponding 1,2-imidothiourea derivatives (Scheme 3).

Under strongly acidic conditions, the 1,3-thiazine ring closure can be attained. On treatment of 2-thioureido-3-thiophenecarboxylate **5** with conc. sulfuric acid at r. t. for 5 d, 2-aminothieno[2,3-d][1,3]thiaz-



Scheme 2. Alternative method used to synthesize compound **4**.

in-4-one derivative **6** was obtained [18]. This method has been successfully improved herein by heating compound **5** at a temperature between 40 and 50  $^{\circ}$ C, so that the reaction was finished in about 10 h.

When compound **6** had reacted with hydrazine hydrate in the presence of pyridine, 2,3-diaminothieno [2,3-d]pyrimidin-4-one derivative **7** was formed in 87% yield. The NMR spectra of **7** were in a good agreement with the assigned structure. Further diazotization of **7**, with sodium nitrite in acetic acid [20], gave successfully our target compound **4** (Scheme 2), which was identical in all aspects with that obtained in Scheme 1.

The elemental analysis of **4** is in accordance with its molecular formula as  $C_{12}H_{14}N_4O_3S$ . The IR spectroscopy of **4** showed the absorption of the NH<sub>2</sub>, NH and the carbonyl group at  $\tilde{v} = 3380-3285$  and 1705 cm<sup>-1</sup>, respectively. The <sup>1</sup>H NMR spectrum of **4** revealed a triplet and a quartet corresponding to ester protons. Furthermore, two singlets appeared at  $\delta = 4.79$  and 8.35 ppm corresponding to the NH<sub>2</sub> and NH protons. Three distinctive carbon signals were detected in the <sup>13</sup>C NMR spectrum of **4** at  $\delta = 152.62$ , 156.16 and 158.24 ppm related to the C-NH<sub>2</sub> and two carbonyl groups (see Experimental Section).

We synthesized the novel tricyclic 4-aminothienopyrimidine derivative **12** starting from the aminothiophene derivative **8**, according to known examples of cyclizations with an *ortho*-aminonitrile. For the preparation of the 4-aminopyridothienopyrimidine derivative **12**, we used a method reported by Taylor and Berger [25] and Gewald and Martin [26]. Reaction of ammonia with the iminoester group in compound **9** [21] occurred to afford the thienopyridine-2-iminoformamide derivative **10**. Compound **10** on treatment with sodium ethoxide solution underwent ensuing cyclization and gave rise to **11**, which underwent tautomerization to form **12**. The constitution of



Scheme 3. Synthesis of aminopyridothienopyrimidine 12.

12 is supported by independent synthesis from the *o*-aminonitrile 8 with formamide under reflux and on the basis of IR and <sup>1</sup>H NMR spectra. Compound 12 showed no IR absorption bands for NH or CN groups and its <sup>1</sup>H NMR spectrum exhibited a broad singlet for the NH<sub>2</sub> group.

In conclusion, a new, simple and efficient synthesis of aminopyridothienopyrimidines has been developed. It has several merits over hitherto known methods, *i. e.* fewer reaction steps, mild reaction conditions, higher yields, and easy workup procedures.

## **Experimental Section**

Melting points were determined on a Boetius melting point apparatus and are uncorrected. Elemental analyses were performed on a Carlo Erba CHN-S Elemental Analyzer 1108. The <sup>13</sup>C and <sup>1</sup>H NMR spectra were obtained using a Bruker AC 300 instrument (<sup>1</sup>H: 300.13 MHz; <sup>13</sup>C: 75.5 MHz). The  $\delta$  values are given in ppm, and the internal standard was tetramethylsilane. Mass spectra were obtained on a spectrometer Perkin-Elmer SCIEX API-300 (by ion spray using a heated nebulizer). The IR spectra were recorded on a Nicolet 250 FT-IR spectrophotometer using potassium bromide pellets.

# *Ethyl* 2-[*N*-benzoyl(thiocarbamoyl)]amino-3-aminocarbonyl-4,5,6,7-tetrahydrothieno-[2,3-c]pyridine-6-carboxylate (2)

A mixture of **1** (2.7 g, 10 mmol) and benzoyl isothiocyanate (1.8 g, 11 mmol) was refluxed in acetone (30 ml) under N<sub>2</sub> for 4 h. The reaction mixture was then cooled and the precipitate formed was filtered off and washed with dry acetone (20 ml). Yellow needles of **2**, yield 2.9 g (67%); m. p. 235–237 °C – IR (KBr):  $\tilde{v} = 3360-3280$  (NH<sub>2</sub>, 2 NH), 3040 (arom. CH), 1708 (ester C=O), 1665 (C=O) cm<sup>-1</sup>. – <sup>1</sup>H NMR (300 MHz, [D<sub>6</sub>]-DMSO):  $\delta$  = 1.22 (t, 3 H, OCH<sub>2</sub>CH<sub>3</sub>), 2.79 (t, 2 H, 4-H), 3.65 (t, 2 H, 5-H), 4.08 (q, 2 H, OCH<sub>2</sub>CH<sub>3</sub>), 4.54 (s, 2 H, 7-H), 7.21 (b, 2 H, NH<sub>2</sub>), 7.46–7.97 (m, 5 H, Ar-H), 11.68 (br, s, 1 H, NH), 14.52 (br, s, 1 H, NH). – <sup>13</sup>C{H} NMR (75.5 MHz, [D<sub>6</sub>]-DMSO):  $\delta$  = 14.46 (CH<sub>3</sub>), 24.62 (C-4), 40.21 (C-5), 42.20 (C-7), 60.94 (CH<sub>2</sub>), 121.37 (C-3), 124.32 (C-7a), 126.11, 127.16, 131.17, 132.98 (Ar-C), 140.94 (C-3a), 154.69 (C=O), 165.58 (C-2), 166.69 (C=O), 172.83 (C=O), 174.10 (C=S). – C<sub>19</sub>H<sub>20</sub>N<sub>4</sub>O<sub>4</sub>S<sub>2</sub> (432.52): calcd. C 52.76, H 4.66, N 12.95; found C 52.55, H 4.39, N 12.73.

## *Ethyl 2-(thiocarbamoyl)amino-3-aminocarbonyl-4,5,6,7tetra-hydrothieno[2,3-c]pyridine-6-carboxylate (3)*

To compound 2 (4.32 g, 10 mmol) in acetone-methanol (1:1, 40 ml) was added potassium carbonate (5 mmol) in water (5 ml). The mixture was heated to reflux for 5 h, whereupon acetic acid (12 mmol) was added. After cooling in an ice bath the solid product was filtered off, washed with cold water and dried to give 3. Buff crystals (methanol); yield: 2.4 g (73%); m.p. 205–207 °C. – IR (KBr):  $\tilde{v} =$ 3385-3275 (2NH<sub>2</sub>, NH), 1711 (ester C=O), 1675 (C=O) cm<sup>-1</sup>. – <sup>1</sup>H NMR (300 MHz, [D<sub>6</sub>]-DMSO):  $\delta$  = 1.19 (t, 3 H, OCH<sub>2</sub>CH<sub>3</sub>), 2.79 (t, 2 H, 4-H), 3.59 (t, 2 H, 5-H), 4.09 (q, 2 H, OCH<sub>2</sub>CH<sub>3</sub>), 4.47 (s, 2 H, 7-H), 4.81 (br, s, 2 H, 2 NH<sub>2</sub>), 8.32 (br, s, 1 H, NH). –  $^{13}C$  {H} NMR (75.5 MHz, [D\_6]-DMSO):  $\delta = 14.44$  (CH<sub>3</sub>), 25.80 (C-4), 40.21 (C-5), 42.25 (C-7), 60.95 (CH<sub>2</sub>), 112.51 (C-3), 121.12 (C-7a), 129.42 (C-3a), 154.64 (C=O), 163.05 (C-2), 170.17 (C=O), 174.94 (C=S). - C<sub>12</sub>H<sub>16</sub>N<sub>4</sub>O<sub>3</sub>S<sub>2</sub> (328.41): calcd. C 43.89, H 4.91, N 17.06; found C 43.72, H 4.72, N 16.88.

*Ethyl 2-amino-4-oxo-1,2,3,4,5,6,7,8-octahydropyrido[4',3', 4,5]thieno[2,3-d]pyrimidine-7-carboxylate (4)* 

#### Method A

Compound **3** (3.28 g, 10 mmol) was dissolved in 1M aqueous sodium hydroxide (50 ml). Copper(II) acetate-H<sub>2</sub>O (2.2 g, 11 mmol) dissolved in water (10 ml) was added, and the mixture was heated to 100 °C for 1 h. Thereafter, the temperature of the reaction mixture was kept at 50 °C for 15 min, the formed copper(II) sulfide was then filtered off (Whatman GF/F). The resulting filter cake which was washed with 1M sodium hydroxide was acidified with acetic acid to pH 5.0. The obtained product was filtered off, washed with water and dried to give compound **4** in 97% yield.

#### Method B

To a suspension of 7 (0.31 g, 1 mmol) in acetic acid (2 ml) and water (10 ml), a solution of sodium nitrite (0.28 g, 4 mmol) in water (1 ml) was added. After stirring for 15 min at r. t, 40% sodium hydroxide solution was added (3 ml).

The reaction mixture was warmed to form a clear solution. After cooling, 50% sulfuric acid was added dropwise until pH 2. The precipitated product was filtered off, washed with water, dried, and crystallized from ethanol as pale yellow crystals. Yield 82%, m.p. > 300 °C – IR (KBr):  $\tilde{v} = 3380-3285$  (NH<sub>2</sub>, NH), 1705 (ester C=O), 1665 (C=O) cm<sup>-1</sup>. – <sup>1</sup>H NMR (300 MHz, [D<sub>6</sub>]-DMSO):  $\delta = 1.20$  (t, 3 H, OCH<sub>2</sub>CH<sub>3</sub>), 2.73 (t, 2 H, 5-H), 3.64 (t, 2 H, 6-H), 4.12 (q, 2 H, OCH<sub>2</sub>CH<sub>3</sub>), 4.52 (s, 2 H, 8-H), 4.79 (br, s, 2 H, NH<sub>2</sub>), 8.35 (br, s, 1 H, NH). – <sup>13</sup>C{H} NMR (75.5 MHz, [D<sub>6</sub>]-DMSO):  $\delta = 14.45$  (CH<sub>3</sub>), 26.08 (C-5), 40.89 (C-6), 42.69 (C-8), 60.90 (CH<sub>2</sub>), 119.77 (C-4a), 127.95 (C-4b), 129.74 (C-8a), 151.13 (C-9a), 152.62 (C-NH<sub>2</sub>), 156.16 (C=O), 158.24 (C=O). – C<sub>12</sub>H<sub>14</sub>N<sub>4</sub>O<sub>3</sub>S (294.33): calcd. C 48.97, H 4.79, N 19.04; found C 48.72, H 4.54, N 18.86.

## *Ethyl 2-amino-4-oxo-5,6,7,8-tetrahydropyrido*[4',3':4,5]thieno[2,3-d][1,3]thiazine-7-carboxylate (**6**)

A suspension of compound **5** (6.0 g, 13 mmol) in 98% sulfuric acid (60 ml) and few drops of water was stirred at 40-50 °C for 10 h. The resultant clear solution was slowly poured on ice-water and sodium bicarbonate (300 ml). The precipitate was collected, washed with ethanol and dried to give compound **6**. M. p. 254-256 °C [18].

## *Ethyl* 2,3-diamino-4-oxo-1,2,3,4,5,6,7,8-octahydropyrido-[4',3':4,5]thieno[2,3-d]pyrimidine-7-carboxylate (7)

To a stirred suspension of 6 (0.62 g, 2 mmol) in pyridine (10 ml), hydrazine hydrate (2.5 mmol) was added. The reaction mixture was refluxed for 4 h. The precipitate was filtered off, washed with ethanol and recrystallized from ethyl acetate. Pale yellow needles; yield 0.54 g (87%); m. p. 297-299 °C – IR (KBr):  $\tilde{v} = 3350 - 3390$  (2 NH<sub>2</sub>), 1710 (ester C=O), 1685 (C=O) cm<sup>-1</sup>. - <sup>1</sup>H NMR (300 MHz, [D<sub>6</sub>]-DMSO):  $\delta = 1.18$  (t, 3 H, OCH<sub>2</sub>CH<sub>3</sub>), 2.86 (t, 2 H, 5-H), 3.74 (t, 2 H, 6-H), 4.11 (q, 2 H, OCH<sub>2</sub>CH<sub>3</sub>), 4.61 (s, 2 H, 8-H), 4.85 (br, s, 2 H, NH2), 7.31 (br, s, 2 H, N-NH2). -<sup>13</sup>C {H} NMR (75.5 MHz, [D<sub>6</sub>]-DMSO):  $\delta = 14.48$  (CH<sub>3</sub>), 26.18 (C-5), 40.78 (C-6), 42.71 (C-8), 60.86 (CH<sub>2</sub>), 118.98 (C-4a), 126.95 (C-4b), 129.15 (C-8a), 151.09 (C-9a), 152.52 (C-NH<sub>2</sub>), 156.07 (C=O), 158.18 (C=O). - C<sub>12</sub>H<sub>15</sub>N<sub>5</sub>O<sub>3</sub>S (309.35): calcd. C 46.59, H 4.89, N 22.64; found C 46.42, H 4.71, N 22.43.

## *Ethyl 2-amidino-3-cyano-4,5,6,7-tetrahydrothieno[2,3-c]pyridine-6-carboxylate* (**10**)

A suspension of 8 (0.61 g, 2 mmol) and ammonium hydroxide solution (30%) (10 ml) was stirred at r.t. for 2 h. The product was filtered off, washed with water and recrystallized from ethyl acetate/acetonitrile. Compound 10 was obtained as white needles; yield 0.51 g (91%); m.p. 161-162 °C – IR (KBr):  $\tilde{v} = 3360$  (NH<sub>2</sub>), 1712 (ester C=O), 1615 (C=N) cm<sup>-1</sup>. - <sup>1</sup>H NMR (300 MHz, [D<sub>6</sub>]-DMSO):  $\delta = 1.21$  (t, 3 H, OCH<sub>2</sub>CH<sub>3</sub>), 2.85 (t, 2 H, 4-H), 3.65 (t, 2 H, 5-H), 4.12 (q, 2 H, OCH2CH3), 4.55 (s, 2 H, 7-H), 6.45 (br, s, 2 H, NH<sub>2</sub>), 8.35 (s, 1 H, CH). – <sup>13</sup>C{H} NMR (75.5 MHz, [D<sub>6</sub>]-DMSO):  $\delta = 14.38$  (CH<sub>3</sub>), 23.39 (C-4), 40.93 (C-5), 42.02 (C-7), 60.86 (CH<sub>2</sub>), 113.38 (CN), 123.99 (C-3), 129.60 (C-7a), 146.09 (C-3a), 154.55 (C=O), 159.07 (CH=N), 163.58 (C-2). - C<sub>12</sub>H<sub>14</sub>N<sub>4</sub>O<sub>2</sub>S (278.33): calcd. C 51.78, H 5.07, N 20.13; found C 51.62, H 4.91, N 19.98.

## *Ethyl 4-amino-3,4,5,6,7,8-hexahydropyrido[4',3':4,5]thieno[2,3-d]pyrimidine-7-carboxylate (12)*

### Method A

A mixture of **10** (1.0 g) and a solution of 1M alcoholic potassium hydroxide (10 ml) was refluxed for 1 h. The reaction mixture was acidified with 1M hydrochloric acid. The product was collected by filtration, washed with water, dried and recrystallized from DMF/*n*-hexane as colorless crystals in 91% yield.

## Method B

Compound **8** (1.2 g, 4 mmol) in formamide (10 ml) was refluxed for 5 h. The product that formed after cooling was filtered off and washed with ethanol. Yield 0.69 g (62%); m. p. 272–274 °C. – IR (KBr):  $\tilde{\nu} = 3375$  (NH<sub>2</sub>), 1707 (ester C=O), 1618 (C=N) cm<sup>-1</sup>. – <sup>1</sup>H NMR (300 MHz, [D<sub>6</sub>]-DMSO):  $\delta = 1.19$  (t, 3 H, OCH<sub>2</sub>*CH*<sub>3</sub>), 2.81 (t, 2 H, 5-H), 3.68 (t, 2 H, 6-H), 4.10 (q, 2 H, O*C*H<sub>2</sub>CH<sub>3</sub>), 4.57 (s, 2 H, 8-H), 7.55 (br, s, 2 H, NH<sub>2</sub>), 9.12 (s, 1 H, CH). – <sup>13</sup>C{H} NMR (75.5 MHz, [D<sub>6</sub>]-DMSO):  $\delta = 14.42$  (CH<sub>3</sub>), 26.18 (C-5), 40.76 (C-6), 42.68 (C-8), 60.95 (CH<sub>2</sub>), 119.71 (C-4a), 127.93 (C-4b), 129.76 (C-8a), 151.14 (C-9a), 155.75 (C-2), 157.14 (C-NH<sub>2</sub>), 158.27 (C=O). – C<sub>12</sub>H<sub>14</sub>N<sub>4</sub>O<sub>2</sub>S (278.30): calcd. C 51.78, H 5.07, N 20.13; found C 51.62, H 4.91, N 19.98.

- M. Modica, M. Santagati, A. Santagati, V. Cutuli, N. Mangno, A. Caruso, Pharmazie 55, 500 (2000).
- [2] Ho Yuh-Wen, J. Chin. Chem. Soc. 48, 1163 (2001).
  [3] C.G. Dave, A.B. Shah, H.C. Shah, J. Heterocycl.
  - Chem. 34, 937 (1997).

- [4] H. Vicueg, S. Leistner, N. Böhmen, J. Prantz, G. Wagner, Pharmazie 48, 26 (1993).
- [5] A.O. Abd-allah, Phosphorus, Sulfur and Silicon 178, 1115 (2003).
- [6] N. Böhmen, R. Pech, Pharmazie **39**, 19 (1984).

- [7] S. Leistner, U. Krasselt, S. Dumke, G. Wagner, Pharmazie 47, 682 (1992).
- [8] H.S. El-Kadhef, A.A. Geies, A.M. Kamal, A.A. Abdel-Hafez, J. Chem. Technol Biotechnol. 57, 15 (1993).
- [9] H. Marouko, K. Yamagata, M. Yamazaki, J. Heterocycl. Chem. 38, 269 (2001).
- [10] S. P. H. Alexander, A. Mathie, J. A. Peters, Trends Pharmacol. Sci. 2001, Nomenclature Supplement.
- [11] I. M. Gaster, F. D. King, Med. Res. Rev. 17, 163 (1997).
- [12] A.J. Greenshaw, P.H. Silverstone, Drugs **53**, 20 (1997).
- [13] C. Campiani, E. Morelli, S. Gemma, V. Nacci, S. Butini, M. Hamon, E. Novellino, G. Greco, A. Cagnotto, M. Goegan, I. Cervo, F. Dalla Valle, C. Fracasso, S. Caccia, T. Mennini, J. Med. Chem. 42, 4362 (1999).
- [14] H. Gozlan, in B. Olivier, I. van Wijngaarden, W. Soudijn (eds): Serotonin Receptors and their Ligands, pp. 221–308, Elsevier Science B.V., Amsterdam (1997).
- [15] J.G. Jin, A.E. Foxx-Orenstein, J.R. Grider, J. Pharm. Exp. Ther. 288, 93 (1999).

- [16] E. Kh. Ahmed, Heteroatom Chem. 13, 280 (2002).
- [17] E. Kh. Ahmed, A. M. N. Gohar, M. A. Ameen, Pharmazie 55, 31 (2000).
- [18] E. Kh. Ahmed, Phosphorus, Sulfur and Silicon 178, 1 (2003).
- [19] E. Kh. Ahmed, Heteroatom Chem. 14, 201 (2003).
- [20] E. Kh. Ahmed, F.F. Abdel-Latif, M. A. Ameen, Phosphorus, Sulfur and Silicon 180, 989 (2005).
- [21] E. Kh. Ahmed, M. A. Ameen, F. F. Abdel-Latif, Z. Naturforsch. 60b, 504 (2005).
- [22] M. Modica, G. Romeo, L. Materia, F. Russo, A. Cagnotto, T. Mennini, R. Gaspar, G. Falkay, F. Fulop, Biorg. Med. Chem. **12**, 3891 (2004).
- [23] M. Modica, M. Santagati, S. Guccione, F. Russo, A. Cagnotto, M. Goegan, T. Mennini, Eur. J. Med. Chem. 36, 287 (2001).
- [24] S. Rault, J. Lancelot, H. Prunier, M. Robba, P. Renard, P. Delagrange, B. Pfeier, D. Caignard, B. Guardiola Lemaitre, M. Hamon, J. Med. Chem. **39**, 2068 (1996).
- [25] E. C. Taylor, J. G. Berger, J. Org. Chem. 32, 2376 (1967).
- [26] K. Gewald, E. Martin, J. Prakt. Chem. 323, 843 (1981).