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Short communication

Synthesis and antidepressant evaluation of new 3-phenyl-5-sulfonamidoindole derivatives

Nedime Ergenç[a]*, Nur Sibel Günay[a], Rümeysa Demirdamar[b]

[a]*Department of Pharmaceutical Chemistry, Faculty of Pharmacy, University of Istanbul, 34452 Beyazıt, Istanbul, Turkey*
[b]*Department of Pharmacology, Faculty of Pharmacy, University of Hacettepe, Ankara, Turkey*

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Abstract – Ten new arylidenehydrazides were synthesized by reacting 3-phenyl-5-sulfonamidoindol-2-carboxylic acid hydrazide with various aldehydes and a new N_2-substituted hydrazide was prepared by reduction of 3-phenyl-5-sulfonamidoindole-2-carboxylic acid benzylidene-hydrazide **2** with sodium borohydride. The chemical structures of the compounds were verified by means of their IR, ^{1}H-NMR, El mass spectroscopic data and elemental analyses. The antidepressant activity of these compounds were evaluated by the Porsolt forced swimming (behavioral despair) test using tranylcypromine as the standard. 3-Phenyl-5-sulfonamidoindole-2-carboxylic acid 3,4-methylenedioxybenzylidenehydrazide, 3-phenyl-5-sulfonamidoindole-2-carboxylic acid 4-methylbenzylidenehydrazide, 3-phenyl-5-sulfonamidoindole-2-carboxylic acid 4-nitrobenzylidenehydrazide and 3-phenyl-5-sulfonamidoindole-2-carboxylic acid benzylidenehydrazide showed antidepressant activity at 100 mg/kg. © Elsevier, Paris

indole / arylidenehydrazides / N_2-substituted hydrazide / antidepressant activity

1. Introduction

After the discovery of the antidepressant activity of iproniazid, hydrazine derivatives have been extensively studied for their potential as therapeutic agents for the treatment of CNS depression. Iproniazid as well as the other antidepressants isocarboxazid and nialamid which are hydrazide derivatives exert their action by inhibiting the enzyme monoamine oxydase (MAO). Inhibition results in increased levels of norepinephrine, dopamine, normetanephrine, tyramine and seretonin in brain neurons and various other tissues. It is hypothesized that increased intracellular levels of the biogenic amines as a result of MAO inhibitors (MAOI) produce an overflow of these potential transmitters from the neuron and subsequent CNS stimulation [1].

There have been many reports on the antidepressant/MAO inhibiting activity of hydrazones derived from indole-2-carboxylic acid hydrazides and their reduction products. Alemany et al. [2] investigated the in vitro MAO inhibiting activity of N_2-substituted indole-2-carboxylic acid hydrazides synthesized by the reduction of hydrazones with sodium borohydride. Monge Vega and Fernandez Alvarez [3] indicated that hydrazones of 5-substituted indole-2-carboxylic acid hydrazides and N_2-substituted hydrazides gained from the reduction of these compounds with sodium borohydride possessed MAO inhibiting activity. Monge Vega et al. [4] evaluated the MAO inhibiting activity of N_2-substituted hydrazides prepared by the reduction of hydrazones of 3,5-disubstituted indole-2-carboxylic acid hydrazides with sodium borohydride and reported that the compounds showed significant activity. Prompted by these findings, we synthesized 3-phenyl-5-sulfonamido-indole-2-carboxylic acid arylidenehydrazides **2–11** to evaluate them for antidepressant activity. In addition we selected compound **2** as a prototype and reduced this compound with sodium borohydride and obtained **12** to investigate the antidepressant activity of the N_2-substituted hydrazide structure.

2. Chemistry

Ethyl 3-phenyl-5-sulfonamidoindole-2-carboxylate was obtained via cyclization of the coupling product of the diazonium salt of sulfanilamide with ethyl

*Correspondence and reprints

α-benzylacetoacetate using the Fischer indole procedure. Subsequent reaction with hydrazine hydrate furnished the key intermediate 3-phenyl-5-sulfonamidoindole-2-carboxylic acid hydrazide **1** [5]. Condensation of **1** with various aldehydes employing literature methods [6, 7] with some modification of the media to facilitate solubility afforded **2–11** in yields ranging from 43 to 89% (*figure 1*). Further reduction of compound **2** with sodium borohydride furnished **12** in 53% yield [2] (*figure 2*).

The synthesized compounds were characterized by their combustion analyses, m.p.'s and TLC analyses on silicagel (*table I*). The IR spectra of compounds **2–11** showed NH stretching bands of the indole ring, hydrazide–hydrazone and sulfonamide groups at 3482–3177 cm^{-1}. The presence of the carbonyl functionality was confirmed by the bands observed in the

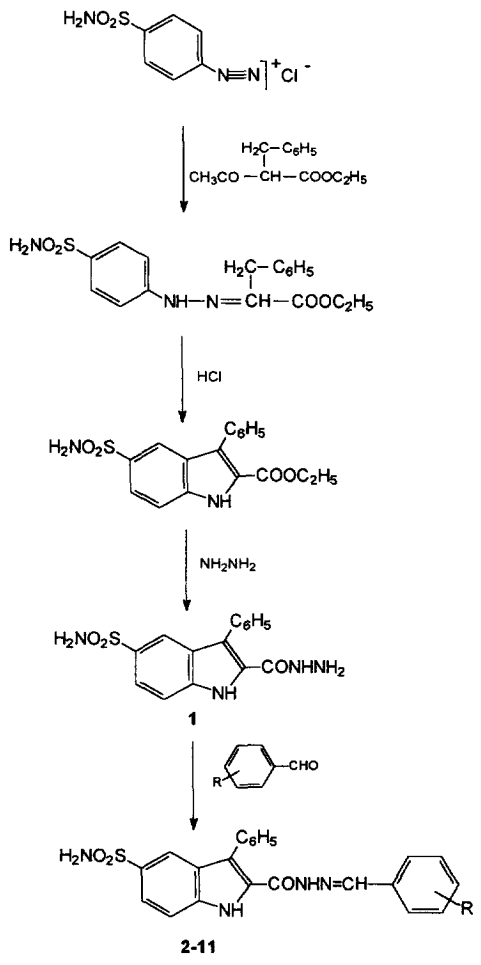

Figure 1.

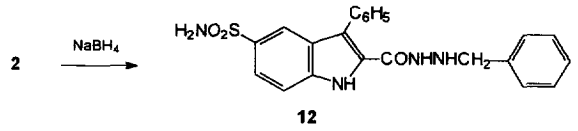

Figure 2.

1672–1620 cm^{-1} region. The C=N stretching band of compounds **2–11** occurred at 1643–1598 cm^{-1}, whereas this band was not observed in compound **12** because of the conversion of the azomethine group into the NH–CH group. Strong absorption bands observed in the 1350–1304 cm^{-1} and 1159–1142 cm^{-1} regions were attributed to the asymmetric and symmetric SO_2 stretching vibrations of the sulfonamide group.

The ^{1}H-NMR spectra of compounds **2–11** displayed the N–H, C_4–H, C_6–H and C_7–H protons of the indole ring at 12.32–12.19, 8.41–7.79, 7.76–7.74 and 7.76–7.32 ppm, respectively [7, 8]. The NH proton and the azomethine proton (N=CH) of the hydrazide hydrazone structure exhibited the expected singlets at 11.73–11.01 and 8.16–8.12 ppm, respectively [7–9]. The SO_2NH_2 protons resonated at 7.18–7.05 ppm [5]. All the other protons were observed at the expected regions (*table II*).

The structure of compound **12** was confirmed by the ^{1}H-NMR spectrum which displayed the CONH signal at 9.14, a new D_2O exchangeable doublet assigned to the NH proton adjacent to the benzyl group at 5.57 ppm and a two-proton doublet arising from the benzylic methylene group at 3.93 ppm.

Molecular ions confirmed the molecular weights of compounds **2–11** (*table II*). The major fragmentation pattern observed in the EI mass spectra of compounds **2–11** was in accordance with the fragmentation modes proposed for hydrazide–hydrazones [10]. Thus the cleavage of the exocyclic C–N bond or the N–N bond with consecutive losses of NH_2 and H from the molecule furnished the base peaks at *m/z* 299 (**2–10**) or at *m/z* 298 (**11**) (*figure 3*).

3. Results and discussion

The antidepressant activity of compounds **2–12** was evaluated via the Porsolt forced swimming (behavioral despair) test [11] with some modification [12] using the well-known MAO inhibiting agent tranylcypromine as standard. Although there are a number of tests currently used to evaluate the antidepressant activity of drugs, the Porsolt forced swimming test is the widely accepted screening method for new mole-

Table I. Physicochemical data of compounds **2–12**.

Compound[a]	R	Formula (M.W.)	M.p. (°C)	Yield (%)
2	H	$C_{22}H_{18}N_4O_3S$ (418.45)	277 (dec.)	72
3	4-Cl	$C_{22}H_{17}ClN_4O_3S$ (452.90)	262–263	77
4	4-NO_2	$C_{22}H_{17}N_5O_5S$ (463.46)	> 300	89
5	2-OCH_3	$C_{23}H_{20}N_4O_4S$ (448.48)	266 (dec.)	46
6	4-OCH_3	$C_{23}H_{20}N_4O_4S$ (448.48)	272–275	74
7	4-$N(CH_3)_2$	$C_{24}H_{23}N_5O_3S$ (461.52)	264 (dec.)	43
8	4-CH_3	$C_{23}H_{20}N_4O_3S{\cdot}H_2O$ (450.50)	279–281	43
9	2-OH	$C_{22}H_{18}N_4O_4S{\cdot}C_2H_5OH$ (480.52)	296 (dec.)	87
10	4-F	$C_{22}H_{17}FN_4O_3S{\cdot}H_2O$ (454.47)	268	49
11	3,4-OCH_2O	$C_{23}H_{18}N_4O_5S{\cdot}C_2H_5OH$ (508.53)	240–243	89
12	–	$C_{22}H_{20}N_4O_3S$ (420.47)	241–244	53

[a]Compounds **8** and **10** retain 1 mol of H_2O and compounds **9** and **11** retain 1 mol of C_2H_5OH (see *table II*).

cules due to its effectiveness in predicting the activity of a wide variety of antidepressants, including tricyclics, MAO inhibitors, atypical antidepressants and electroconvulsive shock. As can be seen in *table III*, although none of the compounds were found to be as active as the standard, the 3,4-methylenedioxy-substituted, the 4-methyl-substituted, the 4-nitrosubstituted and the unsubstituted entries (**11**, **8**, **4** and **2**) showed significant antidepressant activity at 100 mg/kg. In this series there was no preference for the electronic nature of the substituent or the substitution pattern of the aromatic ring. The most active compound was **11**, the 3,4-methylenedioxy-substituted derivative, which supported an earlier report stressing the significance of the 3,4-methylenedioxyphenyl radical in structures with MAO inhibiting activity [13]. **12** was synthesized in an attempt to enhance the antidepressant activity of **2**. Although the precursor **2** had significant antidepressant activity, reduction of the C=N linkage led to an inactive compound presumably due to the alteration of the optimal stuctural features in the whole of the molecule (*table III*).

4. Experimental protocols

4.1. Chemistry

Melting points were determined with a Buchi (Tottoli) melting point apparatus in open capilleries and are uncorrected. IR (KBr) and ^{1}H-NMR (DMSO-d_6) spectra were recorded on Perkin-Elmer 1600 FTIR and Bruker AC 200 instruments, respectively. El mass spectra were taken at Pennsylvania State University, USA. TLC was carried on precoated plates (Silica gel 60 Merck Art. 5735) employing the solvent system $CHCl_3/CH_3OH$ (90:10).

Table II. Spectral data of compounds **2–11**.

Compound	IR (KBr, cm^{-1})	^{1}H-NMR (DMSO-d_6, ppm)	EIMS *m/z* (rel. abs.)
2	3376, 3261, 3190 (NH); 1666 (C=O); 1643 (C=N); 1350, 1150 (SO_2).	12.19 (s, 1H, indole NH); 11.32 (s, 1H, CONH); 8.15 (s, 1H, N=CH); 8.04 (s, 1H, C_4-H); 7.76 (d, *J*: 9.06 Hz, 1H, C_6-H); 7.65 (d, *J*: 8.74 Hz, 1H, C_7-H); 7.57–7.47 (m, 5H, ar); 7.39 (s, 5H, ar); 7.08 (s, 2H, SO_2NH_2)	418 (M^+, 44)
3[a]	3310, 3270, 3177 (NH); 1672 (C=O); 1610 (C=N); 1333, 1142 (SO_2)	12.32 (s, 1H, indole NH); 11.51 (s, 1H, CONH); 8.15 (s, 1H, N=CH); 8.07 (s, 1H, C_4-H); 7.76 (d, *J*: 7.97 Hz, 2H, C_6-H, C_7-H); 7.65 (d, *J*: 8.69 Hz, 2H, ar); 7.52 (s, 7H, ar); 7 18 (s, 2H, SO_2NH_2)	452 (M^+, 17)
4	3347, 3268 (NH); 1645 (C=O); 1611 (C=N); 1513, 1302 (NO_2); 1329, 1148 (SO_2)	12.27 (s, 1H, indole NH); 11.73 (s, 1H, CONH); 8.23 (d, *J*: 8.39 Hz, 2H, ar); 8.16 (s, 1H, N=CH) 7.79 (d, *J*: 1.29 Hz, 1H, C_4-H); 7.74 (s, 1H, C_6-H); 7.65 (d, *J*: 8.68 Hz, 2H, ar); 7.55–7.32 (m, 6H, C_7-H and ar); 7.12 (s, 2H, SO_2NH_2)	463 (M^+, 22)
5	3373, 3247 (NH); 1656 (C=O); 1629 (C=N); 1328, 1159 (SO_2); 1257, 1069 (C-O)	12.24 (s, 1H, indole, NH); 11.39 (s, 1H, CONH); 8.41 (s, 1H, C_4-H); 8.15 (s, 1H, N=CH); 7.76 (dd, $J_{6,7}$: 8.79 Hz, $J_{4,6}$: 1.19 Hz, 1H, C_6-H); 7.64 (d, *J*: 8.70 Hz, 1H, C_7-H); 7.52–7.40 (m, 7H, ar); 7.14–7.05 (m, 4H, SO_2NH_2 and ar); 3.82 (s, 3H, OCH_3)	448 (M^+, 27)
6	3369, 3268 (NH); 1653 (C=O); 1598 (C=N); 1328, 1153 (SO_2); 1250, 1066 (C-O)	12.25 (s, 1H, indole NH); 11.22 (s, 1H, CONH); 8.14 (s, 1H, N=CH); 8.00 (s, 1H, C_4-H); 7.76 (dd, $J_{6,7}$: 8.51 Hz, $J_{4,6}$: 1.50 Hz, 1H, C_6-H); 7.64 (d, *J*: 8.70 Hz, 1H, C_7-H); 7.53 (s, 7H, ar); 7.14 (s, 2H, SO_2NH_2); 7.00 (s, 2H, ar); 3.80 (s, 3H, OCH_3) (D_2O exchange)	448 (M^+, 27)
7	3409, 3197 (NH); 1637 (C=O); 1612 (C=N); 1370 (C-N); 1304, 1149 (SO_2)	12.24 (s, 1H, indole NH); 11.01 (s, 1H, CONH); 8.12 (s, 1H, N=CH); 7.91 (s, 1H, C_4-H); 7.74 (dd, $J_{6,7}$: 8.70 Hz, $J_{4,6}$: 1.58 Hz, 1H, C_6-H); 7.63 (d, *J*: 8.66 Hz, 1H, C_7-H); 7.52–7.37 (m, 7H, ar); 7.11 (s, 2H, SO_2NH_2); 6.72 (d, *J*: 7.89 Hz, 2H, ar); 2.95 (s, 6H, $N(CH_3)_2$)	461 (M^+, 14)
8	3307, 3280 (NH, OH); 1659 (C=O); 1602 (C=N); 1329, 1154 (SO_2)	12.22 (s, 1H, indole NH); 11.29 (s, 1H, CONH), 8.14 (s, 1H, N=CH); 8.00 (s, 1H, C_4-H); 7.75 (d, *J*: 8.76 Hz, 1H,C_6-H); 7.64 (d, *J*: 8.65 Hz, 1H, C_7-H); 7.52–7.39 (m, 7H, ar); 7.22 (d, *J*: 6.46 Hz, 2H, ar); 7.11 (s, 2H, SO_2NH_2); 2.32 (s, 3H, CH_3)	432 (M^+, 20)
9	3461, 3301 (NH, OH); 1620 (C=O); 1609 (C=N); 1314, 1151 (SO_2)	12.26 (s, 1H, indole NH); 11.59 (s, 1H, CONH); 10.93 (s, 1H, phenol O-H); 8.30 (s, 1H, C_4-H); 8.14 (s, 1H, N=CH); 7.76 (dd, $J_{6,7}$: 8.56 Hz, $J_{4,6}$: 1.57 Hz, 1H, C_6-H); 7.65 (d, *J*: 8.68 Hz, 1H, C_7-H); 7.56–7.38 (m, 7H, ar); 7.27 (t, *J*: 7.83 Hz, 1H, ar); 7.12 (s, 2H, SO_2NH_2); 6.89 (d, *J*: 7.79 Hz, 1H, ar); 4.23 (s, 1H, OHEtOH); 3.45 (q, 2H, CH_2EtOH); 1.06 (t, 3H, CH_3EtOH)	434 (M^+, 34)
10	3350, 3322, 3300 (NH, OH); 1667 (C=O); 1601 (C=N); 1331, 1148 (SO_2)	12.22 (s, 1H, indole NH); 11.39 (s, 1H, CONH); 8.14 (s, 1H, N=CH); 8.03 (s, 1H, C_4-H); 7.75 (dd, $J_{6,7}$: 8.42 Hz, $J_{4,6}$: 1.31 Hz, 1H, C_6-H); 7.64 (d, *J*: 8.67 Hz, 1H, C_7-H); 7.55–7.37 (m, 7H, ar); 7.23 (t, *J*: 8.22 Hz, 2H, ar); 7.11 (s, 2H, SO_2NH_2)	436 (M^+, 25)
11	3482, 3303 (NH, OH); 1658 (C=O); 1623 (C=N); 1320, 1154 (SO_2)	12.20 (s, 1H, indole NH); 11.24 (s, 1H, CONH); 8.14 (s, 1H, N=CH); 7.95 (s, 1H, C_4-H); 7.75 (dd, $J_{6,7}$: 8.56 Hz, $J_{4,6}$: 1.69 Hz, 1H, C_6-H); 7.64 (d, *J*: 8.68 Hz, 1H, C_7-H); 7.55–7.21 (m, 8H, ar); 7.11 (s, 2H, SO_2NH_2); 6.06 (s, 2H, OCH_2O); 4.23 (s, 1H, OHEtOH); 3.45 (q, 2H, CH_2EtOH); 1.06 (t, 3H, CH_3EtOH)	462 (M^+, 7)

[a]454 ($[M + 2]^+$, 13).

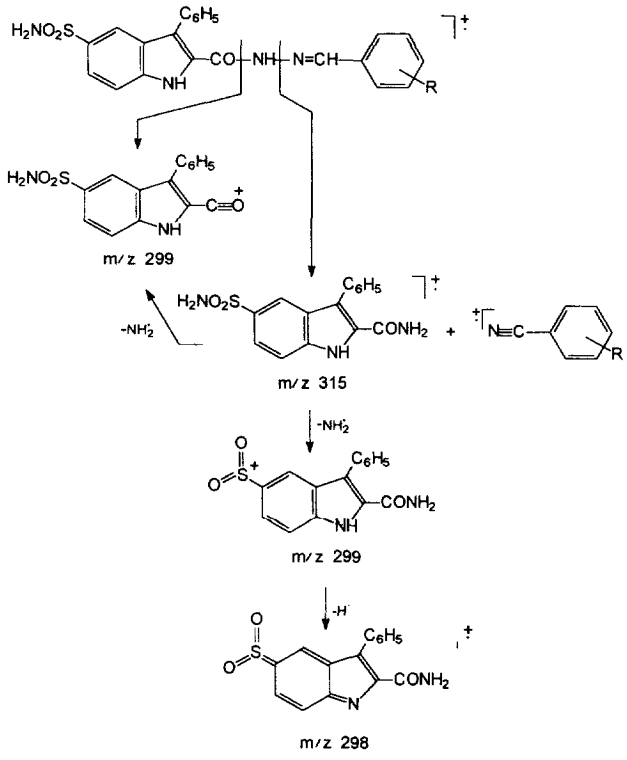

Figure 3.

4.1.1. 3-Phenyl-5-sulfonamidoindole-2-carboxylic acid arylidenehydrazides

4.1.1.1. Compounds 2–6: To a suspension of 3-phenyl-5-sulfonamidoindole-2-carboxylic acid hydrazide **1** (0.005 mol) in 35–45 mL absolute ethanol, an appropriate aldehyde (0.006 mol) was added. The reaction mixture was refluxed for 3.5–8 h. The crude product was filtered and purified by washing with hot ethanol several times.

4.1.1.2. Compounds 7–11: To a suspension of 3-phenyl-5-sulfonamidoindole-2-carboxylic acid hydrazide **1** (0.005 mol) in 35 mL absolute ethanol, 5 mL dimethylformamide and an appropriate aldehyde (0.006 mol) were added. The reaction mixture was refluxed for 3–8 h and allowed to stand overnight. The crude product that separated out was filtered and purified by washing with hot ethanol several times.

4.1.2. 3-Phenyl-5-sulfonamidoindole-2-carboxylic acid benzylhydrazide 12

To a suspension of compound **2** (0.005 mol) in 30 mL absolute ethanol, 3 mL water was added. Sodium borohydride (0.015 mol) was added portionwise to the reaction mixture at 60–70 °C. The solution was stirred for a further 3 h. The excess of sodium borohydride was removed with 1.5 mL glacial acetic acid, and water [1]. The crude product formed on cooling was filtered and purified by washing with hot ethanol several times. IR (KBr, cm^{-1}): 3374, 3255 (N–H); 1642 (C=O); 1313, 1155 (SO_2). ^{1}H-NMR (DMSO-d_6/TMS) (ppm): 12.18 (s, 1H, indole NH); 9.14 (d, 1H, CONH); 8.00 (s, 1H, C_4–H); 7.75 (d, J = 9.72 Hz, 1H, C_6–H); 7.68 (s, 1H, C_7–H); 7.61–7.30 (m, 10H, ar); 7.17 (s, 2H, SO_2NH_2); 5.57 (d, 1H, CONH*NH*CH_2); 3.93 (d, 2H, CH_2) (D_2O exchange).

4.2. Pharmacology

The Porsolt forced swimming (behavioral despair) test was employed. Local-breed, female (20 ± 2 g) mice were used with

Table III. Antidepressant activity of compounds **2–12**.

Compound[a]	Duration of immobility (sec)	Change from control (%)[b]
2	23.45 ± 2.53	–41.81[x]
3	36.60 ± 3.73	–9.18
4	23.01 ± 2.47	–42.90[x]
5	36.77 ± 3.75	–8.75
6	38.45 ± 1.23	–4.59
7	36.99 ± 6.16	–8.21
8	22.05 ± 2.63	–45.28[x]
9	33.65 ± 4.53	–16.50
10	37.47 ± 2.00	–7.02
11	19.59 ± 1.59	–51.38[x]
12	34.95 ± 4.53	–13.27
Tranylcypromine (10 mg/kg)	21.76 ± 2.90	–46.00[x]
Tranylcypromine (20 mg/kg)	8.27 ± 2.35	–79.50
Control	40.30 ± 3.26	–

[a]Compounds were tested at 100 mg/kg dose level, i.p.; [b]$p < 0.01$.

free access to food and water. They were housed in groups of six. The synthesized compounds (100 mg/kg) and tranylcypromine (10 mg/kg) dissolved in dimethylsulphoxide were injected i.p. to mice (n = 6). 0.1 mL dimethylsulphoxide was also injected i.p. to the control group at a constant volume of 5 mL/kg 1 h before testing. The mice were dropped one at a time into a plexiglass cylinder (25 cm height, 30 cm diameter) containing 20 cm height of water at 22 °C and left there for 6 min. At the end of the first 2 min, the animals showing initial vigorous struggling were immobile. The immobility time of each mouse was measured over a period of 4 min. Dunnet's test was used to evaluate the results, employing the Pharmacological Calculation System, Version 4.1.

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