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Original article

# Synthesis and studies on antidepressant and anticonvulsant activities of some 3-(2-furyl)-pyrazoline derivatives

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**Abstract**

Twelve 1-phenyl-, 1-thiocarbamoyl- and 1-*N*-substituted thiocarbamoyl-3-(2-furyl)-5-phenyl/(2-furyl)-2-pyrazoline derivatives were synthesized. The chemical structures of the compounds were proved by IR, $^1$H NMR, Mass spectrometric data and microanalyses. The antidepressant activities of the compounds were investigated by Porsolt's behavioural despair (forced swimming) test on albino mice. 1-*N*-Ethylthiocarbamoyl-3-(2-furyl)-5-phenyl-2-pyrazoline (**6**) and 1-*N*-allylthiocarbamoyl-3,5-di(2-furyl)-2-pyrazoline (**11**) reduced 33.80–31.42% duration of immobility times at 10 mg kg$^{-1}$ dose level. Anticonvulsant activities of the compounds were determined by maximal electroshock seizure (MES) and subcutaneous pentylenetetrazole (metrazol) (*sc*Met.) tests, neurotoxicities were determined by rotarod toxicity test on albino mice. 1,5-Diphenyl-3-(2-furyl)-2-pyrazoline (**2**), 1-*N*-allylthiocarbamoyl-3-(2-furyl)-5-phenyl-2-pyrazoline (**7**), 1-*N*-allylthiocarbamoyl-3,5-di(2-furyl)-2-pyrazoline (**11**) and 1-*N*-phenylthiocarbamoyl-3,5-di(2-furyl)-2-pyrazoline (**12**) were active at 100–300 mg kg$^{-1}$ dose levels. 1-Thiocarbamoyl-3,5-di(2-furyl)-2-pyrazoline (**4**), 1-*N*-methylthiocarbamoyl-3,5-di(2-furyl)-2-pyrazoline (**9**) and 1-*N*-ethylthiocarbamoyl-3,5-di(2-furyl)-2-pyrazoline (**10**) were found protective against MES and *sc*Met. at 30–300 mg kg$^{-1}$ dose levels.


*Keywords:* Pyrazolines; Thiocarbamoyl compounds; Antidepressant activity; Anticonvulsant activity

## 1. Introduction

Increasing evidence suggests that pyrazoline derivatives possess a broad spectrum of biological activities such as tranquillizing, muscle relaxant, antidepressant, anticonvulsant, psychoanaleptic, and antihypotensive activities. Earlier studies by Parmar et al. [1] and Soni et al. [2] demonstrated that 1,3,5-triphenyl-2-pyrazolines have monoamine oxidase (MAO) inhibitory activities. In a recent paper Chimenti et al. [3] reported enantioselective MAO-A and MAO-B inhibiting properties of 1-thiocarbamoyl-2-pyrazolines.

In our previous studies, we synthesized several pyrazoline derivatives and tested them for their antidepressant and anticonvulsant activities [4–9]. We reported that 1,3,5-triphenyl- [4], 1-thiocarbamoyl-3,5-diphenyl-2-pyrazolines [5] and their condensed analogs 8-thiocarbamoyl-7,8-diazabicyclo[4.3.0]non-6-enes [6] and 1-*N*-substituted thiocarba moyl-3-phenyl-5-thienyl-2-pyrazolines [7] have significant antidepressant activities. In our recent studies, some 1-thiocarbamoyl-3-phenyl-5-heteroaryl-2-pyrazolines [8] and their 3-(2-napthyl) analogs [9] were also found to have significantly high antidepressant or anticonvulsant activity against the MES-induced seizures.

As part of our continuous efforts in this area, a series of some new 1-phenyl-, 1-thiocarbamoyl- and 1-*N*-substituted thiocarbamoyl-3-(2-furyl)-5-phenyl/(2-furyl)-2-pyrazoline derivatives have been synthesized according to Scheme 1 and evaluated for their antidepressant activities by using Porsolt's behavioural despair (forced swimming) test [10]. Anticonvulsant activities of the synthesized compounds were also determined by maximal electroshock (MES) and subcutaneous pentylenetetrazole (metrazol) (*sc*Met.) tests. Seizure assays

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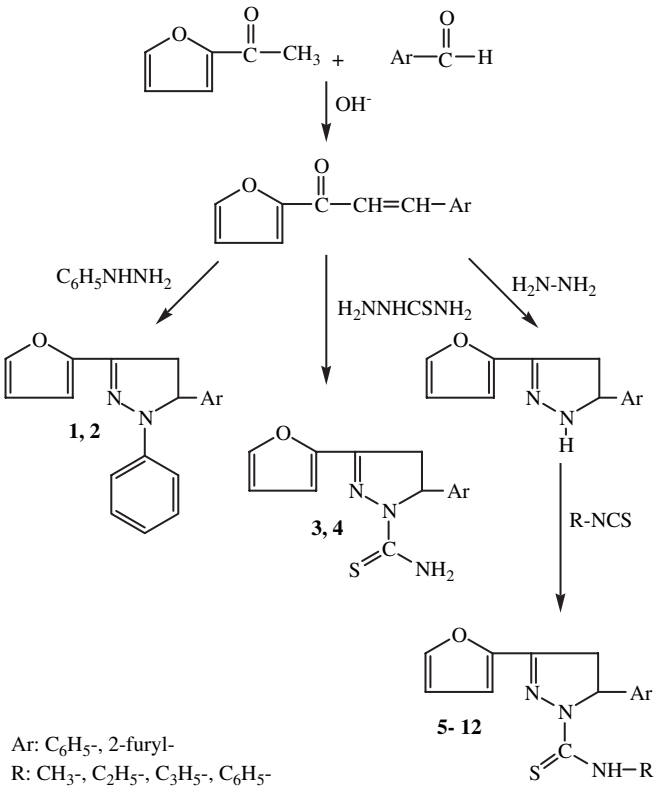



Scheme 1. Synthetic route.

and neurotoxicity were determined by rotarod toxicity test according to the phase I tests of antiepileptic drug development (ADD) programme which were developed by the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) [11,12].

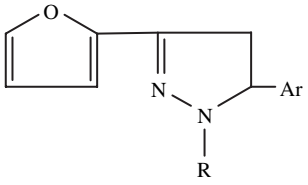
Three of the reported compounds have been previously synthesized – [1,5-diphenyl-3-(2-furyl)-2-pyrazoline (**1**) and 1-phenyl-3,5-di(2-furyl)-2-pyrazoline (**2**)] by Ried and Dankert [13] and [1-*N*-phenylthiocarbamoyl-3,5-di(2-furyl)-2-pyrazoline (**12**)] by Angeloni et al. [14] but have not been tested for their pharmacological activities.

## 2. Chemistry

The synthetic work was carried out beginning from 2-acetylfuran according to Scheme 1. 2-Acetylfuran in a Claisen–Schmidt condensation with benzaldehyde and 2-furylaldehyde afforded 1-(2-furyl)-3-phenyl/(2-furyl)-2-propen-1-ons which gave with phenylhydrazine (sodium hydroxide, ethanol) 1-phenyl- (**1** and **2**), with thiosemicarbazide (sodium hydroxide, ethanol) 1-thiocarbamoyl- (**3** and **4**), with hydrazine hydrate (ethanol) followed by thiocyanates (triethylamine, ether) 1-*N*-substituted thiocarbamoyl-3-(2-furyl)-5-phenyl/(2-furyl)-2-pyrazolines (**5**–**12**), respectively.

The structures, yields and melting points of the synthesized compounds are given in Table 1.

Table 1
Structures, yields and melting points of the synthesized compounds



| Compounds | Ar | R | Yield (%) | m.p. (°C) | Crystallization solvents |
|---|---|---|---|---|---|
| **1** | Phenyl | Phenyl | 64 | 125–126 | Ethanol |
| **2** | 2-Furyl | Phenyl | 78 | 92–93 | Ethanol–water |
| **3** | Phenyl | $CSNH_2$ | 63 | 176–177 | Ethanol |
| **4** | 2-Furyl | $CSNH_2$ | 57 | 162–163 | Ethanol |
| **5** | Phenyl | $CSNHCH_3$ | 58 | 133–134 | Ethanol–water |
| **6** | Phenyl | $CSNHC_2H_5$ | 61 | 99–100 | Ethanol–water |
| **7** | Phenyl | $CSNHC_3H_5$ | 47 | 116–117 | Ethanol–water |
| **8** | Phenyl | $CSNHC_6H_5$ | 77 | 126–127 | Ethanol |
| **9** | 2-Furyl | $CSNHCH_3$ | 36 | 164–165 | Ethanol–water |
| **10** | 2-Furyl | $CSNHC_2H_5$ | 47 | 135–136 | Methanol |
| **11** | 2-Furyl | $CSNHC_3H_5$ | 49 | 113 | Methanol |
| **12** | 2-Furyl | $CSNHC_6H_5$ | 68 | 149–150 | Ethanol |

## 3. Pharmacology

### 3.1. Antidepressant activity

The synthesized compounds were screened for their antidepressant activity using Porsolt's behavioural despair (forced swimming) test [10]. The synthesized compounds (10 mg $kg^{-1}$), and tranylcypromine sulfate, as a reference antidepressant drug (10 mg $kg^{-1}$) were suspended in a 1% aqueous solution of Tween 80. The drugs were injected intraperitoneally (*ip*) in a standard volume of 0.5 ml/20 g body weight, 1 h prior to the test. Control animals received 1% aqueous solution of Tween 80. Then, the mice were dropped individually into the Plexiglass cylinder and left in the water for 6 min. After the first 2 min of the initial vigorous struggling the animals were immobile. A mouse was judged immobile if it floated in the water in an upright position and made only slight movements in order to prevent sinking. The duration of immobility was recorded during the last 4 min of the 6 min test.

### 3.2. Anticonvulsant activity

The compounds were tested for their anticonvulsant activity against MES and *sc*Met.-induced seizures and rotarod toxicity test was performed for neurological toxicity according to the phase I tests of ADD (Antiepileptic Drug Development) programme [11,12]. The synthesized compounds were suspended in 30% aqueous solution of PEG 400 and administered *ip* in a standard volume of 0.5 ml/20 g body weight at 30, 100, 300 mg $kg^{-1}$ doses. Control animals received 30% aqueous PEG 400. Pentylenetetrazole (metrazol) was administered subcutaneously (*sc*) from the back of the neck. Rotarod

toxicity test was performed on a 1 inch diameter knurled wooden rod, rotating at 6 rpm.

## 4. Results and discussion

The structures, yields and melting points of the compounds are listed in Table 1. All spectral data are in accordance with assumed structures. In the UV spectra of the compounds two absorption maxima were observed at 206–244 and 327–353 nm due to C=N and Ar–N–N=C–Ar groups, respectively. The IR spectra of the compounds afforded pyrazoline C=N stretching (1501–1576 $cm^{-1}$), $C^4$–H deformation (1362–1464), $C^5$–$N^1$ stretching (1069–1189), furan C–O–C stretching (1048–1075) and except Compounds **1** and **2**, thiocarbamoyl group N–H stretching (3112–3481 $cm^{-1}$) and C=S stretching (1315–1357 $cm^{-1}$) bands.

In the $^1H$ NMR spectra of the compounds $H_A$, $H_B$ and $H_X$ protons of pyrazoline ring were observed as doublet of doublet at $\delta$ 2.98–3.30 ($J_{AB}$: 17.44–17.69 Hz), 3.43–3.71 ($J_{AX}$: 4–10 Hz) and 5.98–6.97 ppm ($J_{BX}$: 11.34–11.66 Hz), respectively. N–H protons of the thiocarbamoyl group were seen at 7.23–9.10 ppm generally as broad bands. The protons of methyl, ethyl, allyl, phenyl groups and benzene and furan rings were observed at expected ppms.

In the Mass spectra of the compounds molecular ion ($M^+$) and $M^{+2}$ (5.5% M) pics were observed. Microanalysis results were also in accordance with the theoretical amounts (performed only for the new compounds).

The forced swimming test is a behavioural test used to predict the efficacy of antidepressant treatments [10]. It is used effectively in predicting the activity of a wide variety of antidepressants such as MAO inhibitors and atypical antidepressants [15]. It has good predictive value for antidepressant potency in humans [16]. The obtained data on the antidepressant activity of the compounds and reference drug are given in Table 2. In our study, 1-*N*-ethylthiocarbamoyl-3-(2-furyl)-5-phenyl-2-pyrazoline (**6**) and 1-*N*-allylthiocarbamoyl-3,5-di(2-furyl)-2-pyrazoline (**11**) significantly reduced the duration of immobility times at 10 mg $kg^{-1}$ dose level when compared to control ($p < 0.05$, Table 2).

The anticonvulsant activities of the synthesized compounds were also investigated and results from these experiments are shown in Table 3. 1,5-Diphenyl-3-(2-furyl)-2-pyrazoline (**2**) and 1-*N*-allylthiocarbamoyl-3-(2-furyl)-5-phenyl-2-pyrazoline (**7**) were found protective only against MES-induced seizures. 1-Thiocarbamoyl-3,5-di(2-furyl)-2-pyrazoline (**4**), 1-*N*-ethylthiocarbamoyl-3,5-di(2-furyl)-2-pyrazoline (**10**) and 1-*N*-phenylthiocarbamoyl-3,5-di(2-furyl)-2-pyrazoline (**12**) only exhibited activity against *sc*Met.-induced seizures, however, 1-*N*-methylthiocarbamoyl-3,5-di(2-furyl)-2-pyrazoline (**9**) and 1-*N*-allylthiocarbamoyl-3,5-di(2-furyl)-2-pyrazoline (**11**) were found to be protective against MES and *sc*Met.-induced seizures. 1-Thiocarbamoyl-3,5-di(2-furyl)-2-pyrazoline (**4**) and 1-*N*-ethylthiocarbamoyl-3,5-di(2-furyl)-2-pyrazoline (**10**) were found to be protective against *sc*Met.-induced seizures at 30–300 mg $kg^{-1}$ dose levels at half an hour. Neurotoxicity was observed in none of the synthesized compounds in the dose range of 30–300 mg $kg^{-1}$ (Table 3).

Table 2
Antidepressant activities of the compounds

| Compounds | Antidepressant activities | |
|---|---|---|
| | Duration of immobility (s) (mean ± S.E.M.) | Change from control (%) |
| **1** | 213 ± 5.7 | 1.42 |
| **2** | 169 ± 9.9 | −19.52 |
| **3** | 202 ± 9.8 | 3.81 |
| **4** | 182 ± 17.2 | −13.33 |
| **5** | 201 ± 12.9 | −4.28 |
| **6** | 139 ± 12 | −33.80* |
| **7** | 190 ± 18 | −9.52 |
| **8** | 184 ± 16.4 | −12.38 |
| **9** | 186 ± 22 | −11.42 |
| **10** | 211 ± 9.8 | 0.48 |
| **11** | 144 ± 21.4 | −31.42* |
| **12** | 181 ± 16.7 | −13.81 |
| Tranylcypromine sulfate (10 mg $kg^{-1}$, *ip*) | 57 ± 11.6 | −72.85* |
| Control | 210 ± 7.3 | – |

Values represent the mean ± S.E.M. ($n = 6$).
*Significantly compared to control (Dunnet's test; $p < 0.05$).

## 5. Conclusion

Only two of the synthesized compounds (**6** and **11**) have shown significant antidepressant activity, but generally, the synthesized compounds having a 2-furyl substituent at the fifth position of the pyrazoline ring (**2**, **4**, **9**–**12**) possess remarkable anticonvulsant activity. Therefore, they seem to be really promising compounds for their anticonvulsant activities. The synthesis studies should be continued concerning this group of compounds followed with further in vivo studies.

## 6. Experimental protocols

### 6.1. Chemistry

All chemicals used in this study were supplied by E. Merck, Aldrich Chemical Co. and Fluka AG. Melting points were taken in a Thomas Hoover capillary melting point apparatus and are uncorrected. UV spectra were obtained on Agilent 8453 UV–vis spectrophotometer in methanol. IR spectra were recorded in a Bruker Vector 22 IR Opus Spectroscopic Software Version 2.0 using KBr pellets. $^1H$ NMR spectra were recorded on a Bruker Avance 400 MHz FT spectrometer in $CDCl_3$ using TMS as internal standard. Mass spectra were recorded on Scientific Instrument Service HPP7-M direct insertion probe spectrometer using Agilent 5973 network mass selective electron impact detector. Microanalyses of the compounds were performed at ATAL The Laboratory of Instrumental Analyses—The Scientific and Technical Research Council of Turkey (Instrument: Leco CHNS-932).

Table 3
Phase I anticonvulsant screening of the compounds

| Compounds | MES | | | | | | *sc*Met. | | | | | | Toxicity | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 1/2 h | | | 4 h | | | 1/2 h | | | 4 h | | | 1/2 h | | | 4 h | | |
| | mg kg$^{-1}$ | | | mg kg$^{-1}$ | | | mg kg$^{-1}$ | | | mg kg$^{-1}$ | | | mg kg$^{-1}$ | | | mg kg$^{-1}$ | | |
| | 30 | 100 | 300 | 30 | 100 | 300 | 30 | 100 | 300 | 30 | 100 | 300 | 30 | 100 | 300 | 30 | 100 | 300 |
| **1** | 0/1 | 0/1 | 0/1 | 0/1 | 0/1 | 0/1 | 0/1 | 0/1 | 0/1 | 0/1 | 0/1 | *1/1* | 0/4 | 0/4 | 0/4 | 0/2 | 0/2 | 0/2 |
| **2** | 0/1 | *1/1* | *1/1* | 0/1 | 0/1 | 0/1 | 0/1 | 0/1 | 0/1 | 0/1 | 0/1 | 0/1 | 0/4 | 0/4 | 0/4 | 0/2 | 0/2 | 0/2 |
| **3** | 0/1 | 0/1 | 0/1 | 0/1 | 0/1 | 0/1 | 0/1 | 0/1 | 0/1 | 0/1 | 0/1 | 0/1 | 0/4 | 0/4 | 0/4 | 0/2 | 0/2 | 0/2 |
| **4** | 0/1 | 0/1 | 0/1 | 0/1 | 0/1 | *1/1* | *1/1* | *1/1* | *1/1* | 0/1 | 0/1 | 0/1 | 0/4 | 0/4 | 0/4 | 0/2 | 0/2 | 0/2 |
| **5** | 0/1 | 0/1 | 0/1 | 0/1 | 0/1 | 0/1 | 0/1 | 0/1 | 0/1 | 0/1 | 0/1 | 0/1 | 0/4 | 0/4 | 0/4 | 0/2 | 0/2 | 0/2 |
| **6** | 0/1 | 0/1 | 0/1 | 0/1 | 0/1 | 0/1 | 0/1 | 0/1 | *1/1* | 0/1 | 0/1 | 0/1 | 0/4 | 0/4 | 0/4 | 0/2 | 0/2 | 0/2 |
| **7** | 0/1 | *1/1* | *1/1* | 0/1 | 0/1 | 0/1 | 0/1 | 0/1 | 0/1 | 0/1 | 0/1 | 0/1 | 0/4 | 0/4 | 0/4 | 0/2 | 0/2 | 0/2 |
| **8** | 0/1 | 0/1 | 0/1 | 0/1 | 0/1 | *1/1* | 0/1 | 0/1 | 0/1 | 0/1 | 0/1 | 0/1 | 0/4 | 0/4 | 0/4 | 0/2 | 0/2 | 0/2 |
| **9** | 0/1 | 0/1 | 0/1 | *1/1* | *1/1* | *1/1* | 0/1 | 0/1 | 0/1 | 0/1 | *1/1* | *1/1* | 0/4 | 0/4 | 0/4 | 0/2 | 0/2 | 0/2 |
| **10** | 0/1 | 0/1 | 0/1 | 0/1 | 0/1 | 0/1 | *1/1* | *1/1* | *1/1* | 0/1 | 0/1 | *1/1* | 0/4 | 0/4 | 0/4 | 0/2 | 0/2 | 0/2 |
| **11** | 0/1 | 0/1 | 0/1 | 0/1 | *1/1* | *1/1* | 0/1 | 0/1 | 0/1 | 0/1 | *1/1* | *1/1* | 0/4 | 0/4 | 0/4 | 0/2 | 0/2 | 0/2 |
| **12** | 0/1 | 0/1 | 0/1 | 0/1 | 0/1 | 0/1 | 0/1 | *1/1* | *1/1* | 0/1 | 0/1 | 0/1 | 0/4 | 0/4 | 0/4 | 0/2 | 0/2 | 0/2 |

MES: maximal electroshock seizure test, *sc*Met.: subcutaneous pentylenetetrazole (metrazol) seizure test, toxicity: rotarod test.
0/1: no activity at dose level, 1/1: noticeable activity at dose level (given in italics).

*6.1.1. 1-(2-Furyl)-3-phenyl/(2-furyl)-2-propen-1-ons (chalcones)*

Chalcone derivatives were obtained from 2-acetylfuran (0.01 mol) and appropriate aldehydes (0.01 mol) by known methods [17–20].

*6.1.2. 1-Phenyl-3-(2-furyl)-5-phenyl/(2-furyl)-2-pyrazolines*

The solution of appropriate chalcone (0.01 mol) and phenylhydrazine (0.02 mol) in ethanolic sodium hydroxide (0.025 mol, 20 ml) was refluxed for 4 h. The product was poured into ice water and the crude product which was separated out was filtered and crystallised from proper solvent.

*6.1.2.1. 1,5-Diphenyl-3-(2-furyl)-pyrazoline (**1**).* Yield 63.88%. m.p. 125–126 °C (EtOH). UV $\lambda_{Maks}^{MeOH}$ 202 (log $\varepsilon$: 4.75), 244 (log $\varepsilon$: 4.44), 353 nm (log $\varepsilon$: 4.63). IR $\nu$ (KBr) 1501, 1365, 1119, 1065 cm$^{-1}$. $^1$H NMR $\delta$ ($CDCl_3$) 3.05 (1H; dd; $H_A$, $J_{AB}$: 17.47 Hz, $J_{AX}$: 7.19 Hz), 3.75 (1H; dd; $H_B$, $J_{AB}$: 17.07 Hz, $J_{BX}$: 12.38 Hz), 5.18 (1H; dd; $H_X$, $J_{AX}$: 7.18 Hz, $J_{BX}$: 12.35 Hz), 6.30 (1H; m; furan $H^4$), 6.40 (1H; d; furan $H^3$, $J_{AB}$: 3.36 Hz), 6.60–7.60 ppm (11H; m; furan $H^5$, benzene). MS *m/e* 288 ($M^+$, %100), 259 (M − CHO), 211 (M − $C_6H_5$), 115 (M − $C_{10}H_9N_2O$), 91 (M − $C_{12}H_9N_2O$), 77 (M − $C_{13}H_{11}N_2O$).

*6.1.2.2. 1-Phenyl-3,5-di(2-furyl)-2-pyrazoline (**2**).* Yield 78.42%. m.p. 92–93 °C (EtOH–$H_2O$). UV $\lambda_{Maks}^{MeOH}$ 201 (log $\varepsilon$: 4.82), 244 (log $\varepsilon$: 4.63), 349 nm (log $\varepsilon$: 4.83). IR $\nu$ (KBr) 1501, 1362, 1103, 1070 cm$^{-1}$. $^1$H NMR $\delta$ ($CDCl_3$) 3.22 (1H; dd; $H_A$, $J_{AB}$: 16.94 Hz, $J_{AX}$: 6.59 Hz), 3.65 (1H; dd; $H_B$, $J_{AB}$: 16.62 Hz, $J_{BX}$: 12.10 Hz), 5.25 (1H; dd; $H_X$, $J_{AX}$: 6.60 Hz, $J_{BX}$: 12.08 Hz), 6.15 (1H; d; 5-furan $H^3$, $J$: 3.22 Hz), 6.20 (1H; m; 5-furan $H^4$), 6.40 (1H; m; 3-furan $H^4$), 6.55 (1H; d; 3-furan $H^3$, $J$: 3.36 Hz), 6.75 (1H; t; phenyl $H^4$, $J$: 7.21 Hz), 7.05 (2H; d; phenyl $H^{3,5}$, $J$: 22.48 Hz), 7.20 (2H; m; phenyl $H^{2,6}$), 7.25 (1H; m; 5-furan $H^5$), 7.45 ppm (1H; m; 3-furan $H^5$). MS *m/e* 278 ($M^+$, %100), 186 (M − $C_5H_2N_2O$), 91 (M − $C_{11}H_9NO_2$), 77 (M − $C_{11}H_9N_2O_2$).

*6.1.3. 1-Thiocarbamoyl-3-(2-furyl)-5-phenyl/(2-furyl)-2-pyrazolines*

1-Thiocarbamoyl-3-(2-furyl)-5-phenyl/(2-furyl)-2-pyrazolines were obtained by heating (2 h) thiosemicarbazide (0.012 mol) with appropriate chalcone (0.01 mol) and sodium hydroxide (0.025 mol in 5 ml water) in ethanol (50 ml). The product was poured into ice water and the crude product which was separated out was filtered and crystallised from proper solvent.

*6.1.3.1. 1-Thiocarbamoyl-3-(2-furyl)-5-phenyl-2-pyrazoline (**3**).* Yield 63.46%. m.p. 176–177 °C (EtOH). UV $\lambda_{Maks}^{MeOH}$ 206 (log $\varepsilon$: 4.68), 327 nm (log $\varepsilon$: 4.88). IR $\nu$ (KBr) 3481, 1614, 1465, 1376, 1357, 1074 cm$^{-1}$. $^1$H NMR $\delta$ ($CDCl_3$) 3.25 (1H; dd; pyrazoline $H_A$, $J_{AB}$: 17.6 Hz, $J_{AX}$: 3.61 Hz), 3.80 (1H; dd; pyrazoline $H_B$, $J_{AB}$: 17.67 Hz, $J_{BX}$: 11.47 Hz), 6.05 (1H; dd; pyrazoline $H_X$, $J_{AX}$: 3.55 Hz, $J_{BX}$: 11.48 Hz), 6.10 (1H; b; NH), 6.55 (1H; m; furan $H^4$), 6.80 (1H; d; $J_{AB}$: 3.49 Hz, furan $H^3$), 7.10 (1H; b; NH), 7.20–7.60 ppm (6H; m; furan $H^5$ and benzene). MS *m/e* 273 (M + 2, %4.5 $M^+$), 271 ($M^+$, %100), 238 (M − SH), 211 (M − $CSNH_2$), 177 (M − $C_6H_6O$), 103 (M − $C_6H_6N_3OS$), 77 (M − $C_8H_8N_3OS$). Calcd. for $C_{13}H_{12}N_2OS$ % C 61.97, H 4.83, N 15.49, S 11.82; found C 61.82, H 4.26, N 15.47, S 11.50.

*6.1.3.2. 1-Thiocarbamoyl-3,5-di(2-furyl)-2-pyrazoline (**4**).* Yield 56.70%. m.p. 162–163 °C (EtOH). UV $\lambda_{Maks}^{MeOH}$ 213 (log $\varepsilon$: 4.68) and 325 nm (log $\varepsilon$: 4.94). IR $\nu$ (KBr) 3483, 1576, 1464, 1349, 1083, 1055 cm$^{-1}$. $^1$H NMR $\delta$ ($CDCl_3$) 3.40 (1H; dd; $H_A$, $J_{AB}$: 17.53 Hz, $J_{AX}$: 3.21 Hz), 3.60 (1H; dd; $H_B$, $J_{AB}$: 17.51 Hz, $J_{BX}$: 11.42 Hz), 6.10 (1H; dd; $H_X$, $J_{AX}$: 3.45 Hz, $J_{BX}$: 11.27 Hz), 6.15 (1H; b; NH), 6.35 (1H; m; 3-furan $H^4$), 6.42 (1H; d; $J$: 3.26 Hz, 3-furan $H^3$), 6.57 (1H; m; 5-furan $H^4$), 6.85 (1H; d; $J$: 3.46 Hz, 5-furan $H^3$),

7.00 (1H; b; NH), 7.35 (1H; d; *J*: 1.65 Hz, 3-furan $H^5$), 7.60 ppm (1H; d; *J*: 1.51 Hz, 5-furan $H^5$). MS *m/e* 263 (M + 2, %4.5 $M^+$), 261 ($M^+$), 244 (M − $NH_3$), 201 (M − $CH_2NS$), 185 (M − $CH_4N_2S$), 173 (M − $CH_2N_3S$), 115 (M − $C_9H_6O_2$), 94 (M − $C_7H_7N_2OS$), 81 (M − $C_7H_6N_3OS$), 60 (M − $C_{11}H_9N_2O_2$, %100). Calcd. for $C_{14}H_{13}N_3O_2S$ % C 55.16, H 4.24, N 16.08, S 12.27; found C 55.16, H 3.86, N 16.02, S 11.93.

### 6.1.4. 1-N-Substituted thiocarbamoyl-3-(2-furyl)-5-phenyl/(2-furyl)-2-pyrazolines

Hydrazine hydrate (0.02 mol) was added to an ethanolic solution of appropriate chalcone (0.01 mol, 10 ml ethanol) and refluxed for 2 h. The solvent was evaporated at reduced pressure. The residue was dissolved in dry ether. Isothiocyanate (0.01 mol) and 4 drops of triethylamine were added and stirred for 4 h at room temperature. The mixture was evaporated to dryness and the residue was crystallised from proper solvent.

*6.1.4.1. 1-N-Methylthiocarbamoyl-3-(2-furyl)-5-phenyl-2-pyrazoline (**5**).* Yield 57.89%. m.p. 133–134 °C (EtOH–$H_2O$). UV $\lambda_{Maks}^{MeOH}$ 202 (log ε: 4.39), 329 nm (log ε: 4.51). IR ν (KBr) 3401, 1528, 1439, 1345, 1112, 1057 $cm^{-1}$. $^1H$ NMR δ ($CDCl_3$) 2.98 (1H; dd; $H_A$, $J_{AB}$: 17.57 Hz, $J_{AX}$: 3.71 Hz), 3.10 (3H; d; $J_{AB}$: 4.77 Hz, $CH_3$), 3.72 (1H; dd; $H_B$, $J_{AB}$: 17.57 Hz, $J_{BX}$: 11.66 Hz), 5.98 (1H; dd; $H_X$, $J_{AX}$: 3.68 Hz, $J_{BX}$: 11.63 Hz), 6.41 (1H; m; furan $H^4$), 6.67 (1H; d; $J_{AB}$: 3.48 Hz, furan $H^3$), 7.10–7.55 (6H; m; furan $H^5$ and benzene), 7.38 ppm (1H; b; NH). MS *m/e* 287 (M + 2, %4.5 $M^+$), 285 ($M^+$) (%100), 252 (M − SH), 242 (M − $CH_3N_2$), 212 (M − $C_2H_4NS$), 177 (M − $C_6H_6NO$), 91 (M − $C_8H_8N_3OS$), 74 (M − $C_{13}H_{11}N_2O$). Calcd. for $C_{15}H_{15}N_3OS$ % C 63.13, H 5.30, N 14.73, S 11.24; found C 63.30, H 5.53, N 14.76, S 10.91.

*6.1.4.2. 1-N-Ethylthiocarbamoyl-3-(2-furyl)-5-phenyl-2-pyrazoline (**6**).* Yield 60.86%. m.p. 99–100 °C (EtOH–$H_2O$). UV $\lambda_{Maks}^{MeOH}$ 202 (log ε: 4.52), 330 nm (log ε: 4.65). IR ν (KBr) 3375, 1522, 1454, 1363, 1332, 1180, 1075 $cm^{-1}$. $^1H$ NMR δ ($CDCl_3$) 1.17 (3H; t; $J_{AB}$: 5.62 Hz, $CH_3$), 3.00 (1H; dd; $H_A$, $J_{AB}$: 17.55 Hz, $J_{AX}$: 3.63 Hz), 3.50–3.70 (3H; m; $H_B$ and $CH_2$), 5.97 (1H; dd; $H_X$, $J_{AX}$: 3.6 Hz, $J_{BX}$: 11.63 Hz), 6.45 (1H; m; furan $H^4$), 6.65 (1H; d; $J_{AB}$: 3.41 Hz, furan $H^3$), 7.05–7.55 (6H; m; furan $H^5$ and benzene), 7.30 ppm (1H; b; NH). MS *m/e* 301 (M + 2, %4.5 $M^+$), 299 ($M^+$), 266 (M − SH), 212 (M − $C_3H_5NS$), 104 (M − $C_8H_{11}N_3OS$), 77 (M − $C_{10}H_{12}N_3OS$), 44 (M − $C_{14}H_{11}N_2OS$). Calcd. for $C_{16}H_{17}N_3OS$ % C 64.19, H 5.72, N 14.04, S 10.71; found C 64.18, H 5.34, N 14.04, S 10.35.

*6.1.4.3. 1-N-Allylthiocarbamoyl-3-(2-furyl)-5-phenyl-2-pyrazoline (**7**).* Yield 46.94%. m.p. 116–117 °C (EtOH–$H_2O$). UV $\lambda_{Maks}^{MeOH}$ 202 (log ε: 4.64), 330 nm (log ε: 4.75). IR ν (KBr) 3372, 1516, 1453, 1371, 1332, 1120, 1048 $cm^{-1}$. $^1H$ NMR δ ($CDCl_3$) 3.06 (1H; dd; $H_A$, $J_{AB}$: 17.59 Hz, $J_{AX}$: 3.61 Hz), 3.66 (1H; dd; $H_B$, $J_{AB}$: 17.58 Hz, $J_{BX}$: 11.61 Hz), 4.10–4.30 (2H; m; $-CH_2$), 5.10–5.25 (2H; m; $=CH_2$), 5.80–6.00 (1H; m; =CH), 6.01 (1H; dd; $H_X$, $J_{AX}$: 3.56 Hz, $J_{BX}$: 11.60 Hz), 6.45 (1H; m; furan $H^4$), 6.70 (1H; d; $J_{AB}$: 3.44 Hz, furan $H^3$), 7.05–7.50 (6H; m; furan $H^5$ and benzene), 7.42 ppm (1H; s; NH). MS *m/e* 313 (M + 2, %4.5 $M^+$), 311 ($M^+$), 296 (M − $CH_3$), 278 (M − SH), 255 (M − $C_3H_6N$, %100), 211 (M − $C_4H_6NS$), 196 (M − $C_4H_7N_2S$), 104 (M − $C_9H_{13}N_3OS$), 91 (M − $C_{10}H_{14}N_3OS$), 77 (M − $C_{11}H_{12}N_3OS$), 56 (M − $C_{14}H_{11}N_2OS$), 41 (M − $C_{14}H_{12}N_3OS$). Calcd. for $C_{17}H_{17}N_3OS$ % C 65.57, H 5.50, N 13.49, S 10.30; found C 65.63, H 5.15, N 13.41, S 10.20.

*6.1.4.4. 1-N-Phenylthiocarbamoyl-3-(2-furyl)-5 phenyl-2-pyrazoline (**8**).* Yield 76.94%. m.p. 126–127 °C (EtOH). UV $\lambda_{Maks}^{MeOH}$ 202 (log ε: 4.47), 335 nm (log ε: 4.50). IR ν (KBr) 3212, 1547, 1483, 1445, 1337, 1189, 1071 $cm^{-1}$. $^1H$ NMR δ ($CDCl_3$) 3.07 (1H; dd; $H_A$, $J_{AB}$: 17.66 Hz, $J_{AX}$: 3.46 Hz), 3.75 (1H; dd; $H_B$, $J_{AB}$: 17.65 Hz, $J_{BX}$: 11.56 Hz), 6.45 (1H; m; furan $H^4$), 6.50 (1H; dd; $H_X$, $J_{AX}$: 3.39 Hz, $J_{BX}$: 11.52 Hz), 6.75 (1H; d; $J_{AB}$: 3.38 Hz, furan $H^3$) 7.05–7.60 (11H; m; furan $H^5$ and benzene), 9.10 ppm (1H; s; NH). MS *m/e* 349 (M + 2, %4.5 $M^+$), 347 ($M^+$), 270 (M − $C_6H_5$), 255 (M − $C_6H_6N$) 212 (M − $C_7H_5NS$, %100), 183 (M − $C_7H_6N_3S$), 135 (M − $C_{13}H_{12}N_2O$), 77 (M − $C_{14}H_{12}N_3OS$). Calcd. for $C_{20}H_{17}N_3OS$ % C 69.14, H 4.93, N 12.09, S 9.23; found C 69.37, H 5.06, N 12.13, S 9.04.

*6.1.4.5. 1-N-Methylthiocarbamoyl-3,5-di(2-furyl)-2-pyrazoline (**9**).* Yield 35.63%. m.p. 164–165 °C (EtOH–$H_2O$). UV $\lambda_{Maks}^{MeOH}$ 201 (log ε: 4.39), 216 (log ε: 4.45), 327 nm (log ε: 4.68). IR ν (KBr) 3291, 1529, 1483, 1370, 1315, 1105, 1059 $cm^{-1}$. $^1H$ NMR δ ($CDCl_3$) 3.05 (3H; d; $J_{AB}$: 4.78 Hz, $CH_3$), 3.25 (1H; dd; $H_A$, $J_{AB}$: 17.43 Hz, $J_{AX}$: 3.55 Hz), 3.55 (1H; dd; $H_B$, $J_{AB}$: 17.43 Hz, $J_{BX}$: 11.48 Hz), 6.08 (1H; dd; $H_X$, $J_{AX}$: 3.47 Hz, $J_{BX}$: 11.43 Hz), 6.22 (1H; m; 5-furan $H^4$), 6.32 (1H; d; $J_{AB}$: 3.19 Hz; 5-furan $H^3$), 6.48 (1H; m; 3-furan $H^4$), 6.72 (1H; d; $J_{AB}$: 3.47 Hz; 3-furan $H^3$), 7.20–7.50 (2H; m; 3- and 5-furan $H^5$), 7.30 ppm (1H; b; NH). MS *m/e* 277 (M + 2, %4.5 $M^+$), 275 ($M^+$, %100), 246 (M − $CH_3N$), 201 (M − $C_2H_4NS$), 173 (M − $C_2H_4N_3S$), 109 (M − $C_7H_6N_2OS$), 81 (M − $C_8H_8O$). Calcd. for $C_{13}H_{13}N_3O_2S$ % C 56.71, H 4.76, N 15.26, S 11.65; found C 56.86, H 4.47, N 15.22, S 11.35.

*6.1.4.6. 1-N-Ethylthiocarbamoyl-3,5-di(2-furyl)-2-pyrazoline (**10**).* Yield 47.06%. m.p. 135–136 °C (MeOH). UV $\lambda_{Maks}^{MeOH}$ 200 (log ε: 4.35), 217 (log ε: 4.41), 328 nm (log ε: 4.63). IR ν (KBr) 3350, 1518, 1420, 1390, 1179, 1071 $cm^{-1}$. $^1H$ NMR δ ($CDCl_3$) 1.25 (3H; t; $CH_3$, $J_{AB}$: 7.24 Hz), 3.21 (1H; dd; $H_A$, $J_{AB}$: 17.41 Hz, $J_{AX}$: 3.46 Hz), 3.45 (1H; dd; $H_B$, $J_{AB}$: 17.43 Hz, $J_{BX}$: 11.42 Hz), 3.62 (2H; m; $CH_2$), 6.10 (1H; dd; $H_X$, $J_{AX}$: 3.39 Hz, $J_{BX}$: 11.41 Hz), 6.22 (1H; m; 5-furan $H^4$), 6.34 (1H; d; 5-furan $H^3$, $J_{AB}$: 3.20 Hz), 6.47 (1H; m; 3-furan $H^4$), 6.72 (1H; d; 3-furan $H^3$, $J_{AB}$: 3.42 Hz), 7.15–7.55 (2H; m; 3- and 5-furan $H^5$), 7.23 ppm (1H; b; NH). MS *m/e* 291 (M + 2, %4.5 $M^+$), 289 ($M^+$, %100), 260 (M − $C_2H_5$), 202 (M − $C_3H_5NS$), 173 (M − $C_3H_6N_3S$), 94 (M − $C_9H_{11}N_2OS$).

Calcd. for $C_{14}H_{15}N_3O_2S$ % C 58.51, H 5.23, N 14.52, S 11.08; found C 58.31, H 5.58, N 14.13, S 10.78.

*6.1.4.7. 1-N-Allylthiocarbamoyl-3,5-di(2-furyl)-2-pyrazoline (**11**).* Yield 48.84%. m.p. 113 °C (MeOH). UV $\lambda_{Maks}^{MeOH}$ 201 (log $\varepsilon$: 4.39), 217 (log $\varepsilon$: 4.42), 328 nm (log $\varepsilon$: 4.62). IR $\nu$ (KBr) 3382, 1517, 1483, 1368, 1326, 1069, 1050 $cm^{-1}$. $^1H$ NMR $\delta$ ($CDCl_3$) 3.25 (1H; dd; $H_A$, $J_{AB}$: 17.44 Hz, $J_{AX}$: 3.43 Hz), 3.55 (1H; dd; $H_B$, $J_{AB}$: 17.44 Hz, $J_{BX}$: 11.41 Hz), 4.10–4.30 (2H; m; $-CH_2$), 5.05–5.20 (2H; m; $=CH_2$), 5.80–6.00 (1H; m; $-CH=$), 6.23 (1H; dd; $H_X$, $J_{AX}$: 3.40 Hz, $J_{BX}$: 11.38 Hz), 6.25 (1H; m; 5-furan $H^4$), 6.30 (1H; d; 5-furan $H^3$, $J_{AB}$: 3.21 Hz), 6.45 (1H; m; 3-furan $H^4$), 6.73 (1H; d; 3-furan $H^3$, $J_{AB}$: 3.46 Hz), 7.20–7.50 (2H; m; 3- and 5-furan $H^5$), 7.33 ppm (1H; s; NH). MS *m/e* 303 ($M+2$, %4.5 $M^+$), 301 ($M^+$), 286 ($M-CH_3$), 272 ($M-C_2H_5$), 245 ($M-C_3H_6N$), 202 ($M-C_4H_5NS$), 187 ($M-C_4H_6N_2S$, %100), 173 ($M-C_4H_6N_3S$), 115 ($M-C_{11}H_8NO_2$), 94 ($M-C_9H_9N_2OS$), 81 ($M-C_{10}H_{10}N_2OS$), 65 ($M-C_{11}H_{14}N_3OS$), 41 ($C_{12}H_{10}N_3O_2S$). Calcd. for $C_{15}H_{15}N_3O_2S$ % C 59.78, H 5.02, N 13.94, S 10.64; found C 59.74, H 5.32, N 13.89, S 10.63.

*6.1.4.8. 1-N-Phenylthiocarbamoyl-3,5-di(2-furyl)-2-pyrazoline (**12**).* Yield 67.95%. m.p. 149–150 °C (EtOH). UV $\lambda_{Maks}^{MeOH}$ 201 (log $\varepsilon$: 4.58), 333 nm (log $\varepsilon$: 4.70). IR $\nu$ (KBr) 3450, 1541, 1448, 1389, 1320, 1075, 1050 $cm^{-1}$. $^1H$ NMR $\delta$ ($CDCl_3$) 3.30 (1H; dd; $H_A$, $J_{AB}$: 17.52 Hz, $J_{AX}$: 3.35 Hz), 3.49 (1H; dd; $H_B$, $J_{AB}$: 17.51 Hz, $J_{BX}$: 11.34 Hz), 6.15 (1H; dd; $H_X$, $J_{AX}$: 3.31 Hz, $J_{BX}$: 11.32 Hz), 6.25 (1H; m; 5-furan $H^4$), 6.40 (1H; d; 5-furan $H^3$, $J_{AB}$: 3.13 Hz), 6.50 (1H; m; 3-furan $H^4$), 6.82 (1H; d; 3-furan $H^3$, $J_{AB}$: 3.40 Hz), 7.05–7.55 (7H; m; 3- and 5-furan $H^5$ and benzene), 9.00 ppm (1H; s; NH). MS *m/e* 339 ($M+2$, %4.5 $M^+$), 337 ($M^+$, %100), 308 ($M-CHO$), 202 ($M-C_7H_5NS$), 173 ($M-C_7H_6N_3S$), 152 ($M-C_{11}H_9NO_2$), 135 ($M-C_{11}H_{10}N_2O_2$), 93 ($M-C_{13}H_{12}N_2OS$), 77 ($M-C_{12}H_{10}N_3O_2S$).

### 6.2. Pharmacology

The present study was approved by the Ethics Committee of Hacettepe University, School of Medicine (# 04/1-1).

*6.2.1. Antidepressant activity*

Local breed, male albino mice (20–24 g) were used in the forced swimming test under standard conditions with free access to food and water. They were housed in groups of six. On test day mice were dropped one at a time into a Plexiglass cylinder (height 25 cm, diameter 10 cm) containing 10 cm of water at 23–25 °C [10]. On the testing day, mice were assigned into different groups ($n = 6$–9 for each group). Tranylcypromine sulfate was supplied by Sigma Chemical Co.

*6.2.2. Anticonvulsant activity*

Stimulator (Grass S88, Astro-Med. Inc.), constant current unit (Grass CCU1A, Grass Medical Instruments), and corneal electrode were used for the evaluation of anticonvulsant activity. The rotarod used in the neurotoxicity test was made by Hacettepe University Technical Department. Pentylenetetrazole was supplied by Sigma Chemical Co. Twelve albino male mice (20–24 g) in our laboratory according to the NINCDS-ADD programme [11,12] were used for each compound.

*6.2.2.1. Maximal electroshock seizure (MES) test.* Maximal electroshock seizures are elicited with a 60-cycle alternating current of 50 mA intensity (5–7 times that is required to elicit minimal electroshock seizures) delivered for 0.2 s via corneal electrodes. A drop of 0.9% saline is instilled in the eye prior to application of the electrodes in order to prevent the death of the animal. Abolition of the hind limb tonic extension component of the seizure is defined as protection.

*6.2.2.2. Subcutaneous pentylenetetrazole (metrazol) (scMet.) test.* Pentylenetetrazole (85 mg $kg^{-1}$) (produces seizures in greater than 95% of mice) is administered as a 0.5% solution *sc* in the posterior midline. The animal was observed for 30 min, failure to observe even a threshold seizure (a single episode of clonic spasms of at least 5 s duration) was defined as protection.

*6.2.2.3. Neurotoxicity.* The rotarod test was used to evaluate neurotoxicity. The animal was placed on a 1 inch diameter knurled wooden rod rotating at 6 rpm. Normal mice remain on a rod rotating at this speed indefinitely. Neurologic toxicity was defined as the failure of the animal to remain on the rod for 1 min.

*6.2.3. Statistical analysis*

Results are expressed as mean ± S.E.M.; $n$ represents the number of animals. Data obtained from pharmacological experiments were analyzed by one way analysis of variance (ANOVA) followed by Dunnet's post hoc test and used to evaluate the results, employing Pharmacologic Calculation System Version 4.1. (Microcomputer Specialists). A $p$-value of less than 0.05 was considered statistically significant.

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## References

[1] S.S. Parmar, B.R. Pandey, C. Dwivedi, R.D. Harbison, J. Pharm. Sci. 63 (1974) 1152–1155.
[2] N. Soni, K. Pande, R. Kalsi, T.K. Gupta, S.S. Parmar, J.P. Barthwal, Res. Commun. Chem. Pathol. Pharmacol. 56 (1987) 129–132.
[3] F. Chimenti, E. Maccioni, D. Secci, A. Bolasco, P. Chimenti, A. Granese, O. Befani, P. Turini, S. Alcaro, F. Ortuso, R. Cirilli, F. La Torre, M.C. Cardia, S. Distinto, J. Med. Chem. 48 (2005) 7113–7122.
[4] A.A. Bilgin, E. Palaska, R. Sunal, B. Gümüşel, Pharmazie 49 (1994) 67–69.
[5] A.A. Bilgin, E. Palaska, R. Sunal, Arzneimittel-forschung/Drug Res. 43 (1993) 1041–1044.

[6] A.A. Bilgin, A. Yeşilada, E. Palaska, R. Sunal, Arzneimittel-forschung/Drug Res. 42 (1992) 1271–1273.
[7] N. Gökhan, A. Yeşilada, G. Uçar, K. Erol, A.A. Bilgin, Arch. Pharm. Med. Chem. 336 (2003) 362–371.
[8] O. Ruhoğlu, Z. Özdemir, Ü. Çalış, B. Gümüşel, A.A. Bilgin, Arzneimittel-forschung/Drug Res. 55 (2005) 431–436.
[9] P. İyidoğan, Z. Özdemir, B. Kandilci, B. Gümüşel, Ü. Çalış, A.A. Bilgin, J. Fac. Pharm. İstanbul, in press.
[10] R.D. Porsolt, A. Bertin, M. Jalfre, Arch. Int. Pharmacodyn. Ther. 229 (1977) 327–336.
[11] H. Schäfer, Handbook of Experimental Pharmacology: Antiepileptic Drugs, in: H.H. Frey, D. Janz (Eds.), Springer-Verlag, Berlin, 1985, pp. 199–210.
[12] R.L. Krall, J.K. Penry, B.G. White, H.J. Kupferberg, E.A. Swinyard, Epilepsia 19 (1978) 409–428.
[13] W. Ried, G. Dankert, Chem. Ber. 90 (1957) 2707–2711.
[14] A.S. Angeloni, A. Bellotti, E. Coghi, Ann. Chim. 53 (1963) 1392–1398.
[15] R.D. Porsolt, Antidepressants: Neurochemical, Behavioural and Clinical Perspectives, in: S.J. Enna, J.B. Malick, E. Richelson (Eds.), Raven Press, New York, 1981, pp. 129–139.
[16] P. Willner, P.J. Mitchell, Behav. Pharmacol. 13 (2002) 169–188.
[17] St.v. Kostanecki, L. Podrajansky, Chem. Ber. 29 (1896) 2248–2250.
[18] W.E. Kaufmann, R. Adams, J. Am. Chem. Soc. 45 (1923) 3029–3044.
[19] C. Weygand, F. Strobelt, Chem. Ber. 68B (1935) 1839–1847.
[20] W.S. Emerson, T.M. Patrick, J. Org. Chem. 14 (1949) 790–797.