

## Synthesis, anticonvulsant and toxicity evaluation of 2-(1*H*-indol-3-yl)acetyl-*N*-(substituted phenyl)hydrazine carbothioamides and their related heterocyclic derivatives

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A series of new 5-(1*H*-indol-3-yl)methyl-4-(substituted aryl)-2,4-dihydro-3*H*-1,2,4-triazole-3-thiones (**4a-g**), 5-(1*H*-indol-3-yl)methyl-*N*-(substituted aryl)-1,3,4-oxadiazol-2-amines (**5a-g**) and 5-(1*H*-indol-3-yl)methyl-*N*-(substituted aryl)-1,3,4-thiadiazol-2-amines (**6a-g**) were prepared by treating 2-(1*H*-indol-3-yl)acetyl-*N*-(substituted phenyl)hydrazine carbothioamides (**3a-g**) with suitable reagents. All the newly synthesized compounds were screened for their anticonvulsant activity in the MES model and were compared with the standard drugs phenytoin sodium and carbamazepine. Out of the twenty-one compounds studied, **4b**, **4e**, **4f**, **5b**, **5d**, **5g**, **6b**, **6d** and **6e** showed comparable MES activity to phenytoin and carbamazepine after 0.5 h. Compound **5b** showed to be more potent than carbamazepine after 4 h. Compounds **4a**, **4c**, **4d**, **5a**, **5c**, **5e**, **5f**, **6f** and **6g** showed lower neurotoxicity than phenytoin.

**Keywords:** indoles, triazoles, thiadiazoles, oxadiazoles, anticonvulsants, neurotoxicity

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In recent years, indole derivatives have acquired conspicuous significance due to their wide spectrum of biological activities. The anticonvulsant drug design is based on the presumption (1) that for the activity in maximal electroshock seizure (MES) evaluation, at least one phenyl or similar aromatic group in close proximity to a two electron donor atom is required. For activity in pentylenetetrazole (PTZ) evaluation, an alkyl group close to a two electron donor atom is needed.

Several five-membered aromatic systems such as triazoles, oxadiazoles and thiadiazoles having three heteroatoms at symmetrical positions have been evaluated for their anticonvulsant activity (2, 3). New 3-aryl/alkylimino-indol-2-ones were synthesized and screened for their anticonvulsant and anti-inflammatory activities. Compounds having 1-naphthyl and 4-chlorophenyl substituents were most potent compounds of the series (4). A series of 3-aryl/alkylimino-indol-2-ones were synthesized and screened for anti-

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convulsant activity by electroshock and chemoshock methods. The compound having a naphthyl moiety showed 100% protection (5).

As part of the programme on the synthesis of bi-heterocyclic compounds containing indole as one of the heterocyclic units, we undertook the synthesis of heterocycles wherein the two potentially active moieties are present together and to explore the anticonvulsant activity associated with these nuclei.

## EXPERIMENTAL

The chemicals and solvents used for the experimental work were commercially procured from E. Merck, India, CDH, s.d. Fine Chem. and Qualigens, India. Silica gel G (160–120  $\mu\text{m}$ ) used for analytical chromatography (TLC) was obtained from E. Merck.

Melting points were determined in an open glass capillary using a Kjeldahl flask containing paraffin and are uncorrected. The proton magnetic resonance spectra ( $^1\text{H}$  NMR) were recorded on a Bruker 300 MHz instrument (Bruker, Germany) in  $\text{DMSO-}d_6/\text{CDCl}_3$  using tetramethylsilane  $[(\text{CH}_3)_4\text{Si}]$  as internal standard. Chemical shifts ( $\delta$ ) are expressed in ppm. The infrared spectra of compounds were recorded in KBr on a Bio-Rad FTIR (Browser Morner, USA) spectrometer. Elemental analyses were performed on a Perkin-Elmer model 240c analyzer (Perkin Elmer, USA). The physicochemical and spectral data of the compounds are listed in Tables I and II, respectively.

### Syntheses

*Ethyl-(1H-indol-3-yl) acetate* (1). – Indole-3-acetic acid (0.05 mol) was dissolved in absolute ethanol (10 mL). Conc.  $\text{H}_2\text{SO}_4$  (1 mL) was added and the reaction mixture was refluxed for 28 h. Reaction mixture gave on processing ethyl ester (1). The solid obtained was washed with sodium bicarbonate solution (10%, 50 mL) and crystallized from methanol.

*2-(1H-indol-3-yl)acetohydrazide* (2). – Hydrazine hydrate (10 mL) was placed in a round bottom flask, and compound 1 (0.004 mol) was added. Contents were diluted with a sufficient quantity of dry ethanol till clear solution was obtained and the reaction mixture was refluxed for 20–22 h. After completion of the reaction, ethanol was distilled off till a small volume was left. On cooling, crystals of acid hydrazides (2) were formed and were filtered and recrystallized from ethanol.

*2-(1H-indol-3-yl-acetyl)-N-(substituted phenyl)hydrazinecarbothioamides* (3a-g). – A mixture of 2-(1*H*-indol-3-yl)acetohydrazide (2, 0.01 mol, 2 g) and substituted phenylisothiocyanates (0.01 mol) in 20 mL of absolute ethanol was refluxed for 5–6 h. After completion of the reaction the reaction mixture was concentrated and kept overnight at room temperature. The needle shaped crystals thus obtained were purified by repeated washing with petroleum ether (6).

*5-(1H-indol-3-yl methyl)-4-(substituted aryl)-2,4-dihydro-3H-1,2,4-triazole-3-thiones* (4a-g). – A mixture of substituted hydrazinecarbothioamides (3, 0.004 mol, 1.23 g) and 30 mL of 2% NaOH solution was refluxed for 6 h. After completion of the reaction, the reaction mixture was filtered and the filtrate was neutralized with conc. HCl dropwise till pH

was adjusted to 7. The mixture was kept aside for a few minutes. The distinctive precipitate thus obtained was filtered, washed with water, and recrystallized from a mixture of ethanol/water (80:20) (6).

*5-(1H-indol-3-yl)methyl-N-(substituted aryl)-1,3,4-oxadiazol-2-amines (5a-g)*. – A solution of substituted hydrazinecarbothioamides (**3**, 0.004 mol, 1.23 g) and sodium hydroxide (5 mol L<sup>-1</sup>, 2 mL) in 25 mL of absolute ethanol was cooled under continuous stirring for 30 min. To this mixture, iodine in KI (5%) was added dropwise till the color of iodine persisted at room temperature. After that the mixture was refluxed for 2 h. After completion of the reaction, the reaction mixture was poured onto crushed ice. The solid thus obtained was washed with sodium thiosulphate solution and recrystallized from absolute ethanol (6).

*5-(1H-indol-3-yl)methyl-N-(substituted aryl)-1,3,4-thiadiazol-2-amines (6a-g)*. – Concentrated sulphuric acid (5 mL) was placed in a conical flask, and substituted hydrazinecarbothioamides (**3**, 0.004 mol, 1.23 g) were added in small portions over a period of 2 h under stirring while maintaining the temperature at about 0–5 °C. When the reaction was completed, the mixture was poured onto crushed ice. Precipitated solid thus obtained was filtered, washed with water, dried at room temperature and recrystallized from absolute ethanol (6).

### Pharmacology

*Anticonvulsant screening*. – Albino mice (Swiss, 18–25 g) of either sex were used as experimental animals. The animals were kept at room temperature (25–30 °C) on an adequate diet and allowed free access to food and water except during the short time they were removed from the cages for testing. All the experimental protocols were carried out with the permission from Institutional Animal Ethics Committee. Animals were obtained from the Central Animal House Facility, Hamdard University, New Delhi, India.

Initial anticonvulsant evaluations of the test compounds were undertaken by following the anticonvulsant drug development (ADD) program protocol (7, 8). Albino mice were stimulated through corneal electrodes to 50 mA current at a pulse of 60 Hz applied for 0.25 s. Animals were previously given the test drug *i.p.* Abolition of the hind limb tonic extension spasm was recorded as the anticonvulsant activity. The test compounds were suspended in a 0.5% methyl cellulose-water mixture or in polyethylene glycol (PEG). In preliminary screening, each compound was administered through an *i.p.* injection at three dose levels (30, 100 and 300 mg kg<sup>-1</sup> body mass) and the anticonvulsant activity was assessed after 0.5 h and 4 h intervals of administration (9). The anticonvulsant efficacy was evaluated by the maximal electroshock-induced seizure (MES) and data are presented in Table III.

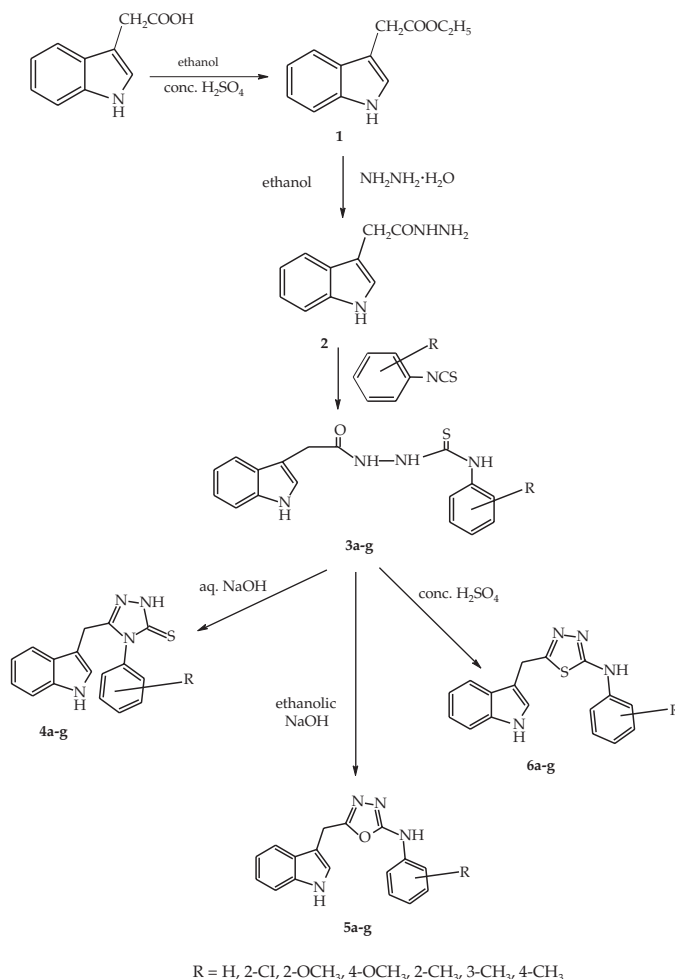
*Neurotoxicity screening*. – Activity of the drug interfering with motor coordination was checked by the rotorod test (10). In that test, mice were trained to stay on the knurled plastic rod. Rod was rotated by 10 rotations min<sup>-1</sup> and its diameter was 3.2 cm. Normal mice could maintain equilibrium on the rotating rod for long periods of time. The test compounds were injected *i.p.* at doses of 30, 100, 300 mg kg<sup>-1</sup> body mass and tested at the time of the peak drug effect to measure the effect of the drug.

Neurotoxicity of compounds was indicated by the inability of the animal to maintain equilibrium on the rod for at least one minute in each of the three trials. Mice lost

their balance due to their skeletal muscle relaxation effect of the drug. The dose at which 50% of the animals were disabled to balance and fell off the rotating rod was determined.

## RESULTS AND DISCUSSION

The synthetic pathway is presented in Scheme 1. All the title compounds were newly synthesized and their structures were confirmed on the basis of IR and  $^1\text{H}$  NMR spectra (Tables I and II).



Scheme 1

Table I. Physicochemical data of synthesized compounds

Compd. No.	R	Mol. formula ( $M_r$ ) <sup>a</sup>	M.p. (°C) <sup>b</sup>	$R_f/R_m$ value <sup>c</sup>	log $P_d$	Yield (%)	Elemental analysis Calcd./found (%)		
							C	H	N
4a	H	C <sub>17</sub> H <sub>14</sub> N <sub>4</sub> S (306.38)	138–141	0.73/–0.43	3.69	85	66.64	4.61	18.29
							67.04	5.00	18.56
4b	2-Cl	C <sub>17</sub> H <sub>13</sub> ClN <sub>4</sub> S (340.83)	250–253	0.68/–0.32	4.02	89	59.91	3.84	16.44
							60.43	4.15	16.81
4c	2-OCH <sub>3</sub>	C <sub>18</sub> H <sub>16</sub> N <sub>4</sub> OS (336.41)	205–208	0.71/–0.38	3.99	90	64.26	4.79	16.65
							64.56	5.02	17.01
4d	4-OCH <sub>3</sub>	C <sub>18</sub> H <sub>16</sub> N <sub>4</sub> OS (336.41)	270–273	0.74/–0.45	3.89	86	64.26	4.79	16.65
							64.67	5.11	17.02
4e	2-CH <sub>3</sub>	C <sub>18</sub> H <sub>16</sub> N <sub>4</sub> S (320.41)	136–139	0.69/–0.34	4.01	75	67.47	5.03	17.49
							67.55	5.42	17.69
4f	3-CH <sub>3</sub>	C <sub>18</sub> H <sub>16</sub> N <sub>4</sub> S (320.41)	167–170	0.72/–0.41	3.89	78	67.47	5.03	17.49
							67.73	5.45	17.66
4g	4-CH <sub>3</sub>	C <sub>18</sub> H <sub>16</sub> N <sub>4</sub> S (320.41)	268–271	0.70/–0.36	2.81	76	67.47	5.03	17.49
							67.02	4.76	17.05
5a	H	C <sub>17</sub> H <sub>14</sub> N <sub>4</sub> O (290.31)	265–268	0.68/–0.32	2.89	65	70.33	4.86	19.30
							70.62	5.26	19.41
5b	2-Cl	C <sub>17</sub> H <sub>13</sub> ClN <sub>4</sub> O (324.76)	235–238	0.71/–0.38	2.53	68	62.87	4.03	17.25
							62.75	4.43	17.32
5c	2-OCH <sub>3</sub>	C <sub>18</sub> H <sub>16</sub> N <sub>4</sub> O <sub>2</sub> (320.34)	238–241	0.69/–0.34	1.99	70	67.49	5.03	17.49
							67.77	5.31	17.76
5d	4-OCH <sub>3</sub>	C <sub>18</sub> H <sub>16</sub> N <sub>4</sub> O <sub>2</sub> (320.34)	282–285	0.72/–0.41	1.87	72	67.49	5.03	17.49
							67.75	5.41	17.64
5e	2-CH <sub>3</sub>	C <sub>18</sub> H <sub>16</sub> N <sub>4</sub> O (304.34)	278–281	0.74/–0.45	2.58	73	71.04	5.30	18.41
							71.42	5.65	18.55
5f	3-CH <sub>3</sub>	C <sub>18</sub> H <sub>16</sub> N <sub>4</sub> O (304.34)	265–268	0.66/–0.28	2.67	74	71.04	5.30	18.41
							71.31	5.63	18.74
5g	4-CH <sub>3</sub>	C <sub>18</sub> H <sub>16</sub> N <sub>4</sub> O (304.34)	278–281	0.73/–0.43	2.69	71	71.04	5.30	18.41
							71.41	5.74	18.83
6a	H	C <sub>17</sub> H <sub>14</sub> N <sub>4</sub> S (306.38)	136–139	0.66/–0.28	2.56	82	66.64	4.61	18.29
							66.30	4.35	18.73
6b	2-Cl	C <sub>17</sub> H <sub>13</sub> ClN <sub>4</sub> S (340.83)	152–155	0.68/–0.32	3.19	75	59.91	3.84	16.44
							59.35	3.51	16.11
6c	2-OCH <sub>3</sub>	C <sub>18</sub> H <sub>16</sub> N <sub>4</sub> OS (336.41)	140–143	0.69/–0.34	2.57	72	64.26	4.79	16.65
							64.53	4.53	16.31
6d	4-OCH <sub>3</sub>	C <sub>18</sub> H <sub>16</sub> N <sub>4</sub> OS (336.41)	170–173	0.72/–0.41	2.43	68	64.26	4.79	16.65
							64.35	4.34	16.32
6e	2-CH <sub>3</sub>	C <sub>18</sub> H <sub>16</sub> N <sub>4</sub> S (320.41)	168–171	0.71/–0.38	3.74	65	67.47	5.03	17.49
							67.65	5.31	17.16

<b>6f</b>	3-CH <sub>3</sub>	C <sub>18</sub> H <sub>16</sub> N <sub>4</sub> S (320.41)	120–123	0.70/–0.36	3.68	71	67.47 67.75	5.03 5.21	17.49 17.06
<b>6g</b>	4-CH <sub>3</sub>	C <sub>18</sub> H <sub>16</sub> N <sub>4</sub> S (320.41)	142–145	0.73/–0.43	3.23	72	67.47 67.65	5.03 5.41	17.49 17.17

<sup>a</sup> Solvent for crystallization – ethanol.

<sup>b</sup> Melting point of the compounds at their decomposition.

<sup>c</sup> Solvent system – benzene/acetone (8:2),  $R_m$  – lipophilicity parameter;  $R_m = \log\left(\frac{1}{R_f} - 1\right)$

<sup>d</sup>  $\log P$  was calculated from absorbance data using chloroform/phosphate buffer at 28 °C.

<sup>e</sup> Elemental analysis for C, H, N were within  $\pm 0.4\%$  of the theoretical value.

Table II. Spectral characterization of synthesized compounds

Compd.	FT-IR (KBr, cm <sup>-1</sup> )	<sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> , $\delta$ ppm)
<b>4a</b>	3671 (NH str.), 3396 (Ar-CH), 2361 (CH <sub>2</sub> ), 1641 (C=N), 1563 (C=C), 1224 (C=S), 1010 (N-N)	10.64 (s, 1H, NH triazole), 7.96 (s, 1H, NH indole), 6.83–7.52 (m, 9H, Ar-H), 6.47 (s, 1H, CH indole), 4.14 (s, 2H, CH <sub>2</sub> )
<b>4b</b>	3883 (NH str.), 3461 (Ar-CH), 2351 (CH <sub>2</sub> ), 1639 (C=N), 1551 (C=C), 1082 (N-N), 797 (C-Cl)	10.53 (s, 1H, NH triazole), 8.33 (s, 1H, NH indole), 6.70–7.52 (m, 8H, Ar-H), 6.35 (s, 1H, CH indole), 3.71 (s, 2H, CH <sub>2</sub> )
<b>4c</b>	3634 (NH str.), 3463 (Ar-CH), 2394 (CH <sub>2</sub> ), 1638 (C=N), 1551 (C=C), 1446 (C=S), 1388 (COCH <sub>3</sub> ), 1100 (N-N)	10.56 (s, 1H, NH triazole), 8.33 (s, 1H, NH indole), 6.51–8.04 (m, 8H, Ar-H), 6.51 (s, 1H, CH indole), 3.84 (s, 3H, OCH <sub>3</sub> ), 1.19 (s, 2H, CH <sub>2</sub> )
<b>4d</b>	3678 (NH Str.), 3489 (Ar-CH), 2215(CH <sub>2</sub> ), 1645 (C=N), 1496 (C=C), 1483 (C=S), 1359 (COCH <sub>3</sub> ), 1083 (N-N)	10.48 (s, 1H, NH triazole), 8.29 (s, 1H, NH indole), 6.44–8.39 (m, 8H, Ar-H), 6.47 (s, 1H, CH indole), 3.61 (s, 3H, OCH <sub>3</sub> ), 1.23 (s, 2H, CH <sub>2</sub> )
<b>4e</b>	3580 (NH str.), 3417 (Ar-CH), 2349 (CH <sub>3</sub> ), 1643 (C=N), 1550 (C=C), 1449 (C=S), 1024 (N-N)	10.53 (s, 1H, NH triazole), 7.53 (s, 1H, NH indole), 6.81–7.33 (m, 8H, Ar-H), 6.35 (s, 1H, CH indole), 4.14 (s, 2H, CH <sub>2</sub> ), 3.71 (s, 3H, CH <sub>3</sub> )
<b>4f</b>	3556 (NH str.), 3401 (Ar-CH), 2398 (CH <sub>3</sub> ), 1601 (C=N), 1567 (C=C), 1487 (C=S), 1032 (N-N)	10.51 (s, 1H, NH triazole), 7.48 (s, 1H, NH indole), 6.78–7.41 (m, 8H, Ar-H), 6.41 (s, 1H, CH indole), 4.23 (s, 2H, CH <sub>2</sub> ), 3.75 (s, 3H, CH <sub>3</sub> )
<b>4g</b>	3573 (NH str.), 3415 (Ar-CH), 2382 (CH <sub>3</sub> ), 1634 (C=N), 1543 (C=C), 1476 (C=S), 1056 (N-N)	10.49 (s, 1H, NH triazole), 7.50 (s, 1H, NH indole), 6.84–7.65 (m, 8H, Ar-H), 6.29 (s, 1H, CH indole), 4.27 (s, 2H, CH <sub>2</sub> ), 3.63 (s, 3H, CH <sub>3</sub> )
<b>5a</b>	3556 (NH str.), 3261 (Ar-CH), 2356 (CH <sub>2</sub> ), 1642 (C=N), 1568 (C=C), 1093 (N-N), 1009 (C-O-C)	10.83 (s,1H, NH), 8.70 (s, 1H, NH indole), 6.54–7.46 (m, 9H, Ar-H), 5.66 (s, 1H, CH indole), 4.13 (s, 2H, CH <sub>2</sub> )
<b>5b</b>	3660 (NH str.), 3426 (Ar-CH), 2348 (CH <sub>2</sub> ), 1665 (C=N), 1638 (C=C), 1386 (N-N), 1089 (C-O-C), 746 (C-Cl)	8.93 (s,1H, NH), 8.24 (s, 1H, NH indole), 6.96–8.22 (m, 8H, Ar-H), 6.96 (s, 1H, CH indole), 2.72 (s, 2H, CH <sub>2</sub> )
<b>5c</b>	3745 (NH str.), 3447 (Ar-CH), 2366 (CH <sub>2</sub> ), 1646 (C=N), 1517 (COCH <sub>3</sub> ), 1096 (C-O-C), 793 (N-N)	10.70 (s, 1H, NH), 8.36 (s, 1H, NH indole), 6.83–7.52 (m, 8H, Ar-H), 6.54 (s, 1H, CH indole), 3.85 (s, 3H, OCH <sub>3</sub> ), 3.77 (s, 2H, CH <sub>2</sub> )

<b>5d</b>	3751 (NH str.), 3456 (Ar-CH), 2398 (CH <sub>2</sub> ), 1676 (C=N), 1534 (COCH <sub>3</sub> ), 1112 (C-O-C), 780 (N-N)	10.74 (s, 1H, NH), 8.41 (s, 1H, NH indole), 6.78-7.76 (m, 8H, Ar-H), 6.49 (s, 1H, CH indole), 3.81 (s, 3H, OCH <sub>3</sub> ), 3.60 (s, 2H, CH <sub>2</sub> )
<b>5e</b>	3671 (NH str.), 3423 (Ar-CH), 2367 (CH <sub>2</sub> ), 1640 (C=N), 1563 (C=C), 1230 (N-N), 1014 (C-O-C)	10.69 (s, 1H, NH), 8.31 (s, 1H, NH indole), 6.82-7.75 (m, 8H, Ar-H), 6.35 (s, 1H, CH indole), 3.02 (s, 3H, CH <sub>3</sub> ), 2.72 (s, 2H, CH <sub>2</sub> )
<b>5f</b>	3676 (NH str.), 3414 (Ar-CH), 2356 (CH <sub>2</sub> ), 1667 (C=N), 1565 (C=C), 1245 (N-N), 1023 (C-O-C)	10.74 (s, 1H, NH), 8.46 (s, 1H, NH indole), 6.76-7.87 (m, 8H, Ar-H), 6.23 (s, 1H, CH indole), 3.15 (s, 3H, CH <sub>3</sub> ), 2.63 (s, 2H, CH <sub>2</sub> )
<b>5g</b>	3692 (NH str.), 3456 (Ar-CH), 2360 (CH <sub>2</sub> ), 1630 (C=N), 1565 (C=C), 1243 (N-N), 1002 (C-O-C)	10.54 (s, 1H, NH), 8.27 (s, 1H, NH indole), 6.78-7.62 (m, 8H, Ar-H), 6.20 (s, 1H, CH indole), 3.23 (s, 3H, CH <sub>3</sub> ), 2.69 (s, 2H, CH <sub>2</sub> )
<b>6a</b>	3568 (NH str.), 3211 (Ar-CH), 2340 (CH <sub>2</sub> ), 1630 (C=N), 1594 (C=C), 1032 (N-N), 604 (C-S-C)	10.22 (s, 1H, NH), 9.52 (s, 1H, NH indole), 6.66-8.70 (m, 9H, Ar-H), 6.66 (s, 1H, CH indole), 4.25 (s, 2H, CH <sub>2</sub> )
<b>6b</b>	3694 (NH str.), 2921 (Ar-CH), 2283 (CH <sub>2</sub> ), 1585 (C=N), 1503 (C=C), 943 (N-N), 743 (C-S-C), 699 (C-Cl)	10.22 (s, 1H, NH), 8.31 (s, 1H, NH indole), 6.50-8.91 (m, 8H, Ar-H), 6.50 (s, 1H, CH indole), 4.03 (s, 2H, CH <sub>2</sub> )
<b>6c</b>	3519 (NH str.), 3296 (Ar-CH), 2365 (CH <sub>2</sub> ), 1649 (C=N), 1598 (C=C), 1149 (C-S-C), 1030 (N-N), 605 (C-S-C)	11.07 (s, 1H, NH), 8.41 (s, 1H, NH indole), 7.08-7.52 (m, 8H, Ar-H), 5.34 (s, 1H, CH indole), 4.39 (s, 2H, CH <sub>2</sub> ), 3.81 (s, 3H, OCH <sub>3</sub> )
<b>6d</b>	3523 (NH str.), 3287 (Ar-CH), 2350 (CH <sub>2</sub> ), 1640 (C=N), 1587 (C=C), 1154 (COCH <sub>3</sub> ), 1046 (N-N), 615 (C-S-C)	11.13 (s, 1H, NH), 8.23 (s, 1H, NH indole), 7.16-7.67 (m, 8H, Ar-H), 5.12 (s, 1H, CH indole), 4.43 (s, 2H, CH <sub>2</sub> ), 3.78 (s, 3H, OCH <sub>3</sub> )
<b>6e</b>	3633 (NH str.), 3263 (Ar-CH), 2921 (CH <sub>3</sub> ), 2386 (CH <sub>2</sub> ), 1614 (C=N), 1585 (C=C), 1030 (N-N), 616 (C-S-C)	11.02 (s, 1H, NH), 9.23 (s, 1H, NH indole), 7.84 (s, 1H, CH indole), 6.98-7.81 (m, 8H, Ar-H), 4.33 (s, 2H, CH <sub>2</sub> ), 1.51 (s, 3H, CH <sub>3</sub> )
<b>6f</b>	3627 (NH str.), 3255 (Ar-CH), 2943 (CH <sub>3</sub> ), 2378 (CH <sub>2</sub> ), 1623 (C=N), 1598 (C=C), 1043 (N-N), 632 (C-S-C)	11.15 (s, 1H, NH), 9.29 (s, 1H, NH indole), 7.81 (s, 1H, CH indole), 6.82-7.98 (m, 8H, Ar-H), 4.45 (s, 2H, CH <sub>2</sub> ), 1.43 (s, 3H, CH <sub>3</sub> )
<b>6g</b>	3643 (NH str.), 3271 (Ar-CH), 2934 (CH <sub>3</sub> ), 2390 (CH <sub>2</sub> ), 1623 (C=N), 1590 (C=C), 1043 (N-N), 665 (C-S-C)	11.23 (s, 1H, NH), 9.34 (s, 1H, NH indole), 7.98 (s, 1H, CH indole), 6.78-7.89 (m, 8H, Ar-H), 4.25 (s, 2H, CH <sub>2</sub> ), 1.65 (s, 3H, CH <sub>3</sub> )

s – singlet, m – multiplet, str – stretching

The anticonvulsant activity and neurotoxicity of all compounds were examined using reported procedures (7-10). The anticonvulsant evaluation of compounds **4a-g**, **5a-g** and **6a-g** in mice at 30, 100 and 300 mg kg<sup>-1</sup> by *i.p.* MES (maximal electroshock seizure) and NT (neurotoxicity screening) are summarized in Table III together with the literature data on the drugs used as standards, phenytoin and carbamazepine.

Compounds **4b**, **4e**, **4f**, **5b**, **5d**, **5g**, **6b**, **6d** and **6e** exhibited fifty percent or more protection at a dose of 30 mg kg<sup>-1</sup> after 0.5 h and have shown activity comparable to phenytoin and carbamazepine. Among these compounds, **4b**, **4e**, **4f**, **5d**, **5g**, **6d** and **6e** were also active after 4 h at a dose of 100 mg kg<sup>-1</sup> body mass. This shows the rapid onset and long duration of action of these compounds at a comparatively low dose. Compound **5b**

Table III. Anticonvulsant activity and minimal motor impairment (mg kg<sup>-1</sup>) of synthesized compounds

Compd. No.	Intraperitoneal injection in mice			
	MES screen after injection (h) <sup>a</sup>		Neurotoxicity screen after injection (h) <sup>a</sup>	
	0.5	4	0.5	4
Control	–	–	–	–
<b>4a</b>	100	300	300	–
<b>4b</b>	30	100	30	–
<b>4c</b>	300	300	300	–
<b>4d</b>	100	100	300	–
<b>4e</b>	30	100	100	300
<b>4f</b>	30	100	100	300
<b>4g</b>	100	300	100	100
<b>5a</b>	100	300	300	300
<b>5b</b>	30	30	30	300
<b>5c</b>	100	300	300	–
<b>5d</b>	30	100	100	300
<b>5e</b>	–	300	300	300
<b>5f</b>	–	300	300	300
<b>5g</b>	30	100	100	300
<b>6a</b>	100	100	30	100
<b>6b</b>	30	300	100	300
<b>6c</b>	100	300	100	300
<b>6d</b>	30	100	100	300
<b>6e</b>	30	100	30	100
<b>6f</b>	300	–	300	300
<b>6g</b>	100	300	300	300
Phenytoin <sup>b</sup>	30	30	100	100
Carbamazepine <sup>b</sup>	30	100	300	300

MES – maximal electroshock seizure

<sup>a</sup> Doses of 30, 100 and 300 mg kg<sup>-1</sup> were administered *i.p.* Test compounds were suspended in 0.5% methylcellulose/water mixture or in polyethylene glycol (PEG). Figures in the table indicate the minimum dose with bio-activity demonstrated in half or more of the mice. The dash (–) indicates the absence of activity at maximum dose administered (300 mg kg<sup>-1</sup>).

<sup>b</sup> Data from references 11 and 12.

was found to be the most active in the series that showed protection against seizures both after 0.5 h and 4 h at 30 mg kg<sup>-1</sup> body mass.

Compounds **4a**, **4d**, **4g**, **5a**, **5c**, **6a**, **6c** and **6g** showed protection at a dose of 100 mg kg<sup>-1</sup> body mass after 0.5 h. These compounds were also active after 4 h but at a higher dose, 300 mg kg<sup>-1</sup> body mass, except compounds **4d** and **6a** which were active after 4 h at the same dose, 100 mg kg<sup>-1</sup> body mass. This shows the ability of these compounds to



prevent spreading of seizures. All the remaining compounds, except **5e** and **5f**, were active at 300 mg kg<sup>-1</sup>.

In the rotorod test, compounds **4a**, **4c**, **4d**, **5a**, **5c**, **5e**, **5f**, **6f** and **6g** showed neurotoxicity comparable to carbamazepine and were less toxic than phenytoin.

Compounds with the electron withdrawing chloro substituent at the *ortho* position to the amino group led to considerable increase in the activity but were relatively more toxic. The presence of a bulkier electron donating methoxy group at *para* position of the amino group resulted in an increase in activity. This may be due to the increase in lipophilicity of the compound. The effect of the methyl group was found to be different in the three groups of compounds. In the case of triazole derivatives, the activity was as follows:  $o \sim m > p$ , with no effect on toxicity. In the case of oxadiazole derivatives, only *p*-substituted compound was active, and in thiadiazole derivatives it followed the order of  $o \sim p > m$ .

## CONCLUSIONS

Indole based heterocyclic derivatives were found to have encouraging anticonvulsant activity. Some are promising and need to be further investigated to get better agents. These may act as lead molecules for the future.

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## S A Ž E T A K

### Sinteza 2-(1*H*-indol-3-il)acetil-*N*-(supstituiranih fenil)hidrazinkarbotioamida i srodnih heterocikličkih spojeva te procjena njihovog antikonvulzivnog djelovanja i toksičnosti

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Reakcijom 2-(1*H*-indol-3-il)acetil-*N*-(supstituiranih fenil)hidrazinkarbotioamida (**3a-g**) s odgovarajućim reaktantom sintetizirana je serija novih 5-(1*H*-indol-3-il)metil-4-(supstituiranih aril)-2,4-dihidro-3*H*-1,2,4-triazol-3-tiona (**4a-g**), 5-(1*H*-indol-3-yl)metil-*N*-(supstituiranih aril)-1,3,4-oksadiazol-2-amina (**5a-g**) i 5-(1*H*-indol-3-il)metil-*N*-(supstituiranih aril)-1,3,4-tiadiazol-2-amina (**6a-g**). Ispitano je antikonvulzivno djelovanje sintetiziranih spojeva na MES modelu i uspoređeno s djelovanjem fenitoin natrija i karbamazepina. Spojevi **4b**, **4e**, **4f**, **5b**, **5d**, **5g**, **6b**, **6d** i **6e** pokazali su MES djelovanje usporedivo s djelovanjem fenitoina i karbamazepina nakon 0,5 h, dok je spoj **5b** nakon 4 sata imao snažnije djelovanje od karbamazepina. Osim toga, spojevi **4a**, **4c**, **4d**, **5a**, **5c**, **5e**, **5f**, **6f** i **6g** su manje neurotoksični od fenitoina.

*Ključne riječi:* indoli, triazoli, tiadiazoli, oksadiazoli, antikonvulzivi, neurotoksičnost

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