

## SYNTHESIS AND ANTICONVULSANT ACTIVITY OF 2-SUBSTITUTED-5-CHLOROBENZOXAZOLE

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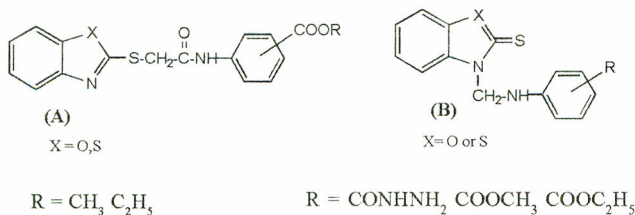
(Received 9 May 2000; accepted 24 April 2001)

The potassium salt (**1**) of 5-chlorobenzoxazole-2-thione was prepared and allowed to react with alkyl chloroacetate and alkyl 3-chloro-propionate to afford **II**<sub>1-10</sub>. Compound **II**<sub>2</sub> was allowed to react with ammonia and hydrazine hydrate to afford **III**<sub>11</sub> and **III**<sub>12</sub> respectively. The compound **III**<sub>12</sub> was also reacted with the appropriate aldehydes to afford compounds **IV**<sub>13-19</sub>. The potassium salt (**1**) was also reacted with chloro-acetanilides to afford compounds **V**<sub>20-39</sub>. Preliminary pharmacological testing of some of these compounds showed that they exhibit anticonvulsant activity. The structure of these compounds was confirmed by elemental analysis IR, <sup>1</sup>HNMR and in some cases by MS spectral data.

**Key words:** Anticonvulsant activity, Alkylchloroacetate, Hydrazine hydrate.

## Introduction

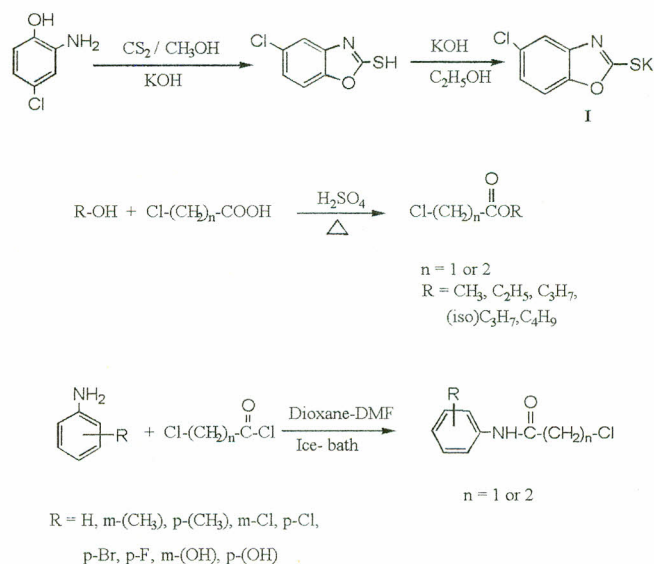
Benzoxazole-2-thione derivatives had been prepared and reported to possess anticonvulsant and CNS depressant activities which is reflected by the 30-100% protection afforded by these compounds against pentylenetetrazole induced convulsions (Misra *et al* 1974 and 1976; Dalkara *et al* 1988, Ucar *et al* 1996; Ucar *et al* 1998a and 1998b) synthesized some new derivatives of the general formula A and B for screening the anticonvulsant activities of these compounds



Consequently, a decision was made to synthesize some new derivatives of 5-substituted benzoxazole-2-thione with the aim to obtain some new derivatives, with potential CNS depressant activity as shown in scheme 1 and 2. For the preparation of such compounds, the schemes 1-2 were adopted.

## Experimental

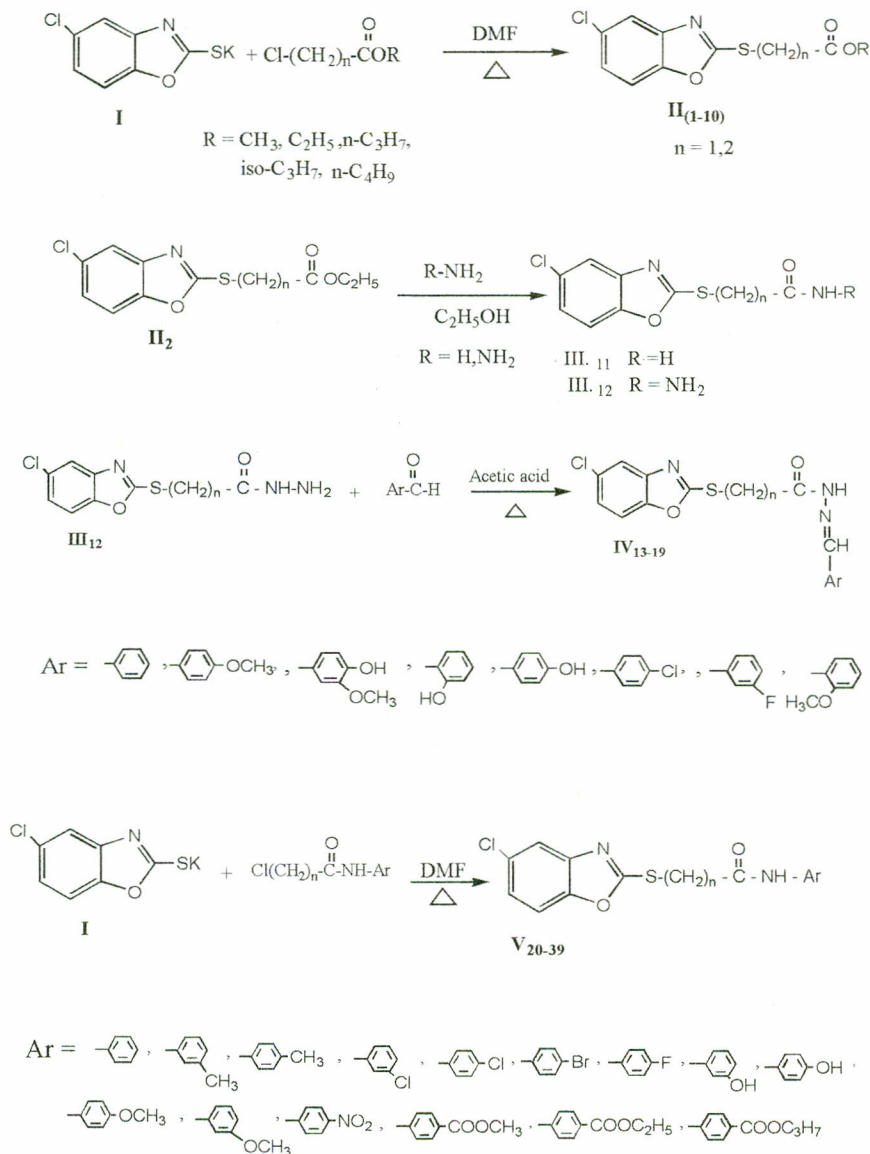
Melting points were recorded on a Griffin melting point apparatus and are uncorrected, IR spectra were recorded on a Buck scientific 500 IR spectrophotometer using KBr disc. <sup>1</sup>HNMR spectra were recorded on a Varian Gemini 300 MHz NMR spectrometer using CDCl<sub>3</sub> as solvent and TMS as an Internal reference. Elemental analyses were performed on a Perkin-Elmer CHN 240.



Scheme 1

2-Amino-4-chlorophenol was refluxed with carbon disulfide and KOH in methanol to afford 5-chlorobenzoxazole-2-thiol (Parmar *et al* 1972; Misra *et al* 1974 and 1976; Kolasa *et al* 1979; Diouf *et al* 1995; Ucar *et al* 1996; Ucar *et al* 1998 a and b). The latter derivative was treated with alcoholic potassium hydroxide to afford the potassium salt (**I**). Many chloroacetanilides were obtained through the reaction of chloroacetyl chloride with the appropriate N-substituted anilines (Agronov and Shabaror 1974). Several alkyl chloroacetate and alkyl 3-chloropropionate were obtained by the standard method (El-Moghazy 1992) (Scheme 1).

The potassium salt (**I**) was allowed to react with alkyl chloroacetate and alkyl 3-chloropropionate to afford com-



Scheme 2

pounds **II**<sub>(1-10)</sub> (Table 1). The ethyl ester (**II**<sub>2</sub>) was allowed to react with liquid ammonia and hydrazine hydrate to give compounds (**III**<sub>11</sub>) and (**III**<sub>12</sub>). Compound (**III**<sub>12</sub>) was allowed to react with the appropriate aldehydes in glacial acetic acid to give the azomethine derivatives (**IV**<sub>13-19</sub>) Table 2. Reaction of potassium salt (**I**) with different chloroacetanilides in DMF afforded 5-chloro-2 (substituted phenylaminocarbonylalkylthio) benzoxazoles (**V**<sub>20-39</sub>) (Table 3) (Scheme 2)

The structures of the newly synthesized compounds (Tables 1-3) were substantiated by microanalyses, IR, PMR and in some cases with MS spectral data.

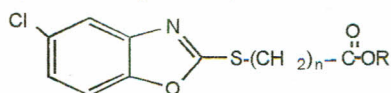
*\*Synthesis of potassium salt of 5-chloro benzoxazole-2-thiol (**I**).* A mixture of alcoholic solution of benzoxazole-2-

thiol (0.01 mol) and alcoholic potassium hydroxide solution (0.01 mol, 0.56g) was stirred for 2 h. Potassium thiobenzoxazole-2-thiolate (**I**) so separated, was filtered, washed with absolute ethanol and then dried. m.p. > 300, yield: quantitative.

*\*Synthesis of alkyl 2-[5-chloro-benz-1,3-oxazolythio] acetate and alkyl 2-[5-chloro-benz 1,3-oxazolythio] propionate **II**<sub>(1-10)</sub>.* The potassium salt **I** (0.01 mol) was treated with alkyl chloroacetate and alkyl chloropropionate (0.01 mol) in 50 ml DMF, heated on water bath for 4 h. The reaction mixture was poured onto water, the precipitated esters were filtered, and recrystallized from ethanol (Table 1).

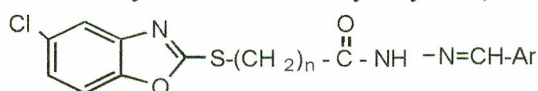
*\*Synthesis of 2-(5-chloro benz-1,3-oxazolythio) acetamide **III**<sub>(11)</sub>.* The ethyl ester **II**<sub>2</sub> (0.01 mol) was treated with

**Table 1**  
Aky 2-(5-chloro-benz 1, 3-oxazoly-2-thio) acetates and propionates (II)<sub>1-10</sub>



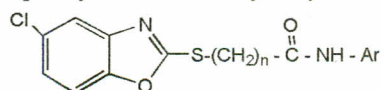
Comp.	R	(n)	Yield %	M.P. °C	M.Formula	Analysis Calced / Found		
					M. wt.	C%	H%	N%
II <sub>1</sub>	CH <sub>3</sub>	1	73	69	C <sub>10</sub> H <sub>8</sub> ClNO <sub>3</sub> S	46.56	3.10	5.43
					257.5	46.20	3.00	5.60
2	C <sub>2</sub> H <sub>5</sub>	1	75	64	C <sub>11</sub> H <sub>10</sub> ClNO <sub>3</sub> S	44.20	3.68	5.15
					271.5	44.60	3.70	5.30
3	n-C <sub>3</sub> H <sub>7</sub>	1	65	64	C <sub>12</sub> H <sub>12</sub> ClNO <sub>3</sub> S	50.43	4.20	4.90
					285.5	50.60	4.30	5.20
4	iso-C <sub>3</sub> H <sub>7</sub>	1	55	91	C <sub>12</sub> H <sub>13</sub> ClNO <sub>3</sub> S	50.43	4.20	4.90
					285.5	50.30	4.50	4.70
5	n-C <sub>4</sub> H <sub>9</sub>	1	60	60	C <sub>13</sub> H <sub>14</sub> ClNO <sub>3</sub> S	52.08	4.57	4.67
					299.5	52.10	4.70	4.30
6	CH <sub>3</sub>	2	75	91	C <sub>11</sub> H <sub>10</sub> ClNO <sub>3</sub> S	48.61	3.68	5.15
					271.5	48.80	3.70	4.90
7	C <sub>2</sub> H <sub>5</sub>	2	80	82	C <sub>12</sub> H <sub>12</sub> ClNO <sub>3</sub> S	50.43	4.20	4.90
					285.5	50.90	4.60	5.10
8	n-C <sub>3</sub> H <sub>7</sub>	2	62	75	C <sub>13</sub> H <sub>14</sub> ClNO <sub>3</sub> S	52.08	4.57	4.67
					299.5	52.20	4.90	4.90
9	iso-C <sub>3</sub> H <sub>7</sub>	2	55	72	C <sub>13</sub> H <sub>14</sub> ClNO <sub>3</sub> S	52.08	4.57	4.67
					299.5	52.30	4.70	4.70
10	n-C <sub>4</sub> H <sub>9</sub>	2	61	66	C <sub>14</sub> H <sub>16</sub> ClNO <sub>3</sub> S	53.58	4.10	4.46
					313.5	53.70	4.90	4.60

**Table 2**  
5-Chloro 2-(substituted benzylidenaminocarbonylalkyl thio) benzoxazole(IV)<sub>13-19</sub>



Comp.	Ar	(n)	Yield %	M.P. °C	M.Formula	Analysis Calced / Found		
					M. wt.	C%	H%	N%
IV <sub>13</sub>		1	78	251	C <sub>16</sub> H <sub>12</sub> ClN <sub>3</sub> O <sub>2</sub> S	55.57	3.47	12.15
					345.5	55.10	3.70	11.80
14		1	60	250	C <sub>17</sub> H <sub>14</sub> ClN <sub>3</sub> O <sub>3</sub> S	54.32	3.72	11.18
					375.5	54.70	3.70	10.70
15		1	66	230	C <sub>17</sub> H <sub>15</sub> ClN <sub>3</sub> O <sub>4</sub> S	52.12	3.57	10.72
					391.5	52.00	4.10	10.30
16		1	67	258	C <sub>16</sub> H <sub>12</sub> ClN <sub>3</sub> O <sub>3</sub> S	53.11	3.31	11.61
					361.5	53.50	3.50	11.30
17		1	70	265	C <sub>16</sub> H <sub>11</sub> Cl <sub>2</sub> N <sub>3</sub> O <sub>2</sub> S	50.52	2.98	11.05
					380	50.50	2.40	11.00
18		1	71	213	C <sub>16</sub> H <sub>11</sub> ClN <sub>3</sub> O <sub>2</sub> S	52.81	3.02	11.55
					363.5	53.10	3.02	11.90
19		1	73	248	C <sub>17</sub> H <sub>14</sub> ClN <sub>3</sub> O <sub>3</sub> S	54.32	3.72	11.18
					375.5	54.70	4.00	11.00

**Table 3**  
5-Chloro-2-(substituted phenylaminocarbonylalkyl-2- thio)benzoxazole (V)<sub>20-39</sub>



Comp	Ar	(n)	Yield %	M.P °C	M.Formula M.wt.	Analysis		
						Calced/Found		
						C%	H%	N%
V <sub>20</sub>		1	77	155-7	C <sub>15</sub> H <sub>11</sub> ClN <sub>2</sub> O <sub>2</sub> S 318.5	56.51, 56.40	3.45, 3.60	8.79, 9.00
21		2	76	150	C <sub>16</sub> H <sub>13</sub> ClN <sub>2</sub> O <sub>2</sub> S 332.5	57.79, 58.00	3.90, 4.00	8.42, 8.60
21		1	66	134	C <sub>16</sub> H <sub>13</sub> ClN <sub>2</sub> O <sub>2</sub> S 332.5	57.79, 57.90	3.90, 4.00	8.42, 8.60
22		2	60	123	C <sub>17</sub> H <sub>13</sub> ClN <sub>2</sub> O <sub>2</sub> S 346.5	58.87, 58.60	3.75, 3.70	8.08, 8.50
23		2	77	160	C <sub>17</sub> H <sub>15</sub> ClN <sub>2</sub> O <sub>2</sub> S 346.5	58.87, 59.00	4.32, 4.40	8.08, 7.90
24		1	76	196	C <sub>15</sub> H <sub>10</sub> Cl <sub>2</sub> N <sub>2</sub> O <sub>2</sub> S 353	51.99, 51.10	2.83, 3.00	7.93, 8.00
25		1	78	184-6	C <sub>15</sub> H <sub>10</sub> Cl <sub>2</sub> N <sub>2</sub> O <sub>2</sub> S 352	51.13, 51.00	2.84, 3.00	7.95, 7.60
26		2	60	211	C <sub>16</sub> H <sub>12</sub> Cl <sub>2</sub> N <sub>2</sub> O <sub>2</sub> S 366	52.45, 52.50	3.27, 3.30	7.65, 8.00
27		1	61	132	C <sub>15</sub> H <sub>10</sub> BrClN <sub>2</sub> O <sub>2</sub> S 397.5	45.28, 45.30	2.51, 2.90	7.07, 7.40
28		2	77	167	C <sub>16</sub> H <sub>12</sub> BrClN <sub>2</sub> O <sub>2</sub> S 411.5	46.65, 46.30	2.91, 3.00	6.80, 7.00
29		1	55	200	C <sub>15</sub> H <sub>10</sub> ClFN <sub>2</sub> O <sub>2</sub> S 336.5	53.49, 53.70	2.97, 3.00	8.32, 8.00
30		1	61	175-7	C <sub>15</sub> H <sub>11</sub> ClN <sub>2</sub> O <sub>3</sub> S 334.5	53.81, 53.90	3.28, 3.50	8.37, 8.30
31		2	66	166	C <sub>16</sub> H <sub>13</sub> ClN <sub>2</sub> O <sub>3</sub> S 348.5	55.09, 54.90	3.73, 4.00	8.03, 7.90
32		1	85	160	C <sub>15</sub> H <sub>11</sub> ClN <sub>2</sub> O <sub>3</sub> S 334.5	53.81, 54.00	3.28, 3.50	8.37, 8.60
33		2	65	197-200	C <sub>16</sub> H <sub>13</sub> ClN <sub>2</sub> O <sub>3</sub> S 348.5	55.09, 55.30	3.73, 4.00	8.03, 8.40
34		1	67	163-5	C <sub>16</sub> H <sub>13</sub> ClN <sub>2</sub> O <sub>3</sub> S 348.5	55.09, 55.40	3.73, 3.50	8.03, 8.30
35		1	71	215	C <sub>16</sub> H <sub>13</sub> ClN <sub>2</sub> O <sub>3</sub> S 348.5	55.09, 54.90	3.73, 3.80	8.03, 8.20
36		1	61	272	C <sub>15</sub> H <sub>10</sub> ClN <sub>3</sub> O <sub>4</sub> S 363.5	49.52, 50.00	2.75, 3.20	11.55, 11.30
37		1	60	249	C <sub>17</sub> H <sub>13</sub> ClN <sub>2</sub> O <sub>4</sub> S 376.5	49.79, 50.00	2.76, 2.80	11.06, 11.20
38		1	60	234-6	C <sub>18</sub> H <sub>15</sub> ClN <sub>2</sub> O <sub>4</sub> S 390.5	54.18, 54.30	3.45, 3.40	7.43, 7.50
39		1	56	215	C <sub>19</sub> H <sub>17</sub> ClN <sub>2</sub> O <sub>4</sub> S 404.5	56.36, 56.30	4.20, 4.30	6.92, 7.00

ammonia solution in ethanol (50 ml). The reaction mixture was stirred for two h and then poured onto water. The solid product was recrystallized from ethanol. Mp, 180; Yield, 70%; M. Formula ( $C_9H_7ClN_2O_2S$ ; found C%, 44.00; H%, 3.00; N%, 11.70 the calcd. value for  $C_9H_7ClN_2O_2S$ , C%, 43.81, H%, 2.83; N%, 11.35.

\*Synthesis of 2-(5-chlorobenz-1,3-oxazolylthio)acetic acid hydrazide **III**<sub>(12)</sub>. The ethyl ester **II**<sub>2</sub> (0.01 mol) was treated with hydrazine hydrate in ethanol (50 ml), the reaction mixture was heated under reflux for 2 h cool, poured onto water, the solid product was recrystallized from ethanol. M.p.

195; Yield, 77%; M. Formula,  $C_9H_8ClN_3O_2S$ ; found C%, 41.50; H%, 3.40; N%, 16.70 the calcd value for  $C_9H_8ClN_3O_2S$ , C%, 41.94, H%, 3.10; N%, 16.31.

\*Synthesis of 5-chloro-2-(substituted benzylideneaminocarbonylalkyl-2-thiobenzoxazole) (**IV**)<sub>(13-19)</sub> (0.01 mol) of compound **III**<sub>12</sub> was treated with treated with the appropriate aromatic aldehyde in 100 ml glacial acetic acid, the reaction mixture was refluxed for 6 h allowed to cool, poured onto water, the solid product obtained was recrystallized from glacial acetic acid (Table 2).

**Table 4**  
IR <sup>1</sup>HNMR and MS spectral data of compounds **II,III, IV and V**.

Comp. No		Spectral data
<b>II</b> <sub>2</sub>	IR	2979 cm <sup>-1</sup> (CH stretching), 1739 cm <sup>-1</sup> (carbonyl ester)
	<sup>1</sup> HNMR ppm	1.25 (t, 3H, CH <sub>3</sub> ), 4.10 (q, -CH <sub>2</sub> -CH <sub>3</sub> ), 4.20 (s, 2H, S-CH <sub>2</sub> -COO) 7.20-7.70 (m, 3H, aromatic protons)
	MS	271 (C <sub>11</sub> H <sub>10</sub> ClNO <sub>3</sub> S, 6.15, M <sup>+</sup> ), 185 (C <sub>7</sub> H <sub>4</sub> ClNOS, 100, base peak)
<b>II</b> <sub>4</sub>	IR	2979 cm <sup>-1</sup> (CH stretching) 1734 cm <sup>-1</sup> (carbonyl ester)
	<sup>1</sup> HNMR ppm	1.50 (d, 6H, CH(CH <sub>3</sub> ) <sub>2</sub> ), 4.20 (m, 1H, CH(CH <sub>3</sub> ) <sub>2</sub> ), 4.40 (s, 2H, S-CH <sub>2</sub> ), 7.30-8.60 (m, 3H, aromatic protons).
<b>II</b> <sub>7</sub>	IR	1734 cm <sup>-1</sup> (carbonyl ester).
	<sup>1</sup> HNMR ppm	1.60 (t, 3H, CH <sub>2</sub> -CH <sub>3</sub> ), 4.00 (q, 2H, CH <sub>2</sub> -CH <sub>3</sub> ), 4.00 (t, 2H, CH <sub>2</sub> -CH <sub>2</sub> -COO), 3.70 (t, 2H, CH <sub>2</sub> -CH <sub>2</sub> -COO), 7.6-8.60 (m, 3H, aromatic protons)
<b>III</b> <sub>11</sub>	<sup>1</sup> HNMR ppm	4.60 (s, 2H, -S-CH <sub>2</sub> -), 7.20-8.20 (m, 3H, aromatic H), 10.0 (s, 2H, CONH <sub>2</sub> )
<b>III</b> <sub>12</sub>	IR	3305 cm <sup>-1</sup> (CO-NH-NH <sub>2</sub> ), 3178 cm <sup>-1</sup> (CO-NH-NH <sub>2</sub> ), 1656 cm <sup>-1</sup> (CH <sub>2</sub> -CO-NH)
<b>IV</b> <sub>13</sub>	<sup>1</sup> HNMR ppm	4.10 (s, 2H, SCH <sub>2</sub> CO), 6.70-7.80 (m, 8H, aromatic protons), 10.00 (s, 1H, CONHC <sub>6</sub> H <sub>5</sub> )
<b>IV</b> <sub>14</sub>	<sup>1</sup> HNMR ppm	4.30 (s, 2H, S-CH <sub>2</sub> -), 3.50 (s, 1H, NCHC <sub>6</sub> H <sub>5</sub> ), 4.00 (s, 3H, -OCH <sub>3</sub> ), 9.80 (s, 1H, NH-NCHC <sub>6</sub> H <sub>5</sub> ), 7.20, 8.20 (m, 7H, aromatic protons).
	MS	375 (C <sub>17</sub> H <sub>14</sub> ClN <sub>3</sub> O <sub>3</sub> S, 12.5M <sup>+</sup> ), 185 (C <sub>7</sub> H <sub>4</sub> ClNOS 100 base peak)
<b>V</b> <sub>20</sub>	<sup>1</sup> HNMR ppm	4.10 (s, 2H, S-CH <sub>2</sub> -CO), 6.8-7.7 (m, 8H, aromatic protons), 10.00 (s, 1H, CONH-ph)
<b>V</b> <sub>21</sub>	<sup>1</sup> HNMR ppm	4.30 ppm (d, 2H, S-CH <sub>2</sub> -CH <sub>2</sub> ) 4.00 ppm (d, 2H, S-CH <sub>2</sub> CH <sub>2</sub> ), 7.20-8.20 (m, 8H, aromatic protons).
<b>V</b> <sub>32</sub>	IR	2930cm <sup>-1</sup> (CH strech.) 1670 cm <sup>-1</sup> (-COO-NH) 3310 cm <sup>-1</sup> (COO-NH), (3400-3500 cm <sup>-1</sup> ) (broad band of OH group)
	MS	334 (C <sub>15</sub> H <sub>11</sub> ClN <sub>2</sub> O <sub>3</sub> S, 10.5, M <sup>+</sup> ), 185 (C <sub>7</sub> H <sub>4</sub> ClNOS, 100, base peake).
<b>V</b> <sub>38</sub>	IR	1670 cm <sup>-1</sup> (CONH), 1760 cm <sup>-1</sup> (COOC <sub>2</sub> H <sub>5</sub> ), 2930cm <sup>-1</sup> (CH-strech.), 3283 cm <sup>-1</sup> (NH stretching),
	<sup>1</sup> HNMR ppm	1.20 (t, 3H, COOCH <sub>2</sub> -CH <sub>3</sub> ), 4.20 (q, 2H, COO-CH <sub>2</sub> -CH <sub>3</sub> ), 4.70 (s-2H, S-CH <sub>2</sub> ), 9.80 (s, 1H, NH-NCHC <sub>6</sub> H <sub>5</sub> ), 7.20-8.40 (m, 7H, aromatic protons).

**Table 5**  
Anticonvulsant activity of compounds II-V

Compd	Dose mgkg <sup>-1</sup>	Dose mgkg <sup>-1</sup>	ED <sub>50</sub>	Relative potency	Compd	Dose mgkg <sup>-1</sup>	Dose mgkg <sup>-1</sup>	ED <sub>50</sub>	Relative potency
II <sub>1</sub>	200	100			V <sub>24</sub>	150	100		
	100	50	82	1.2		100	50	75	1.3
	50	16.5				50	33.3		
II <sub>2</sub>	150	100			V <sub>25</sub>	200	100		
	100	66.5	75	1.3		100	50	82	1.2
	50	33.5				50	16.6		
II <sub>3</sub>	200	100			V <sub>26</sub>	200	100		
	100	66.5	75	1.3		100	50	87.5	1.14
	50	33.5				50	16.5		
II <sub>7</sub>	200	100			V <sub>27</sub>	150	100		
	100	50	82	1.2		100	50	75	1.3
	50	16.6				50	33.3		
II <sub>8</sub>	200	100			V <sub>28</sub>	300	100		
	100	50	82	1.2		200	50	175	0.57
	50	16.5				100	33.5		
II <sub>9</sub>	150	100			V <sub>29</sub>	150	100		
	100	66.6	75	1.3		100	50	75	1.3
	50	50				50	16.6		
IV <sub>13</sub>	200	100			V <sub>31</sub>	300	100		
	100	66.6	82	1.2		200	50	175	0.57
	50	33.3				100	33.5		
IV <sub>14</sub>	200	100			V <sub>32</sub>	150	100		
	100	50	112	0.89		100	50	75	1.3
	50	16.6				50	16.6		
IV <sub>15</sub>	300	100			V <sub>33</sub>	200	100		
	200	66.6	160	0.62		100	66.6	87.5	1.14
	100	33.3				50	33.5		
IV <sub>19</sub>	300	100			V <sub>34</sub>	300	100		
	200	50	175	0.57		200	50	175	0.57
	100	16.6				100	16.6		
V <sub>20</sub>	150	100			V <sub>35</sub>	150	100		
	100	66.6	75	1.3		100	66.6	75	1.3
	50	33.3				50	33.3		
phenobarbitone					V <sub>38</sub>	150	100		
						100	50	75	1.3
						50	16.5		
						175	100		
						125	66.6	100	1.00
					75	33.3			

\**Synthesis of 5-chloro-2-(substituted phenylaminocarbonylalkyl thio) benzoxazole. (V)*<sub>20-39</sub>. The potassium salt (I) (0.01 mol) and chloroacetanilides (0.01 mol) in DMF 50 ml were heated on water bath for 3 h, the reaction mixture was poured onto water, the separated solid product was filtered and recrystallized from dioxane (Table 3).

The structure of these compounds were confirmed by IR <sup>1</sup>HNMR, MS and elemental analyses. (Table 1-4).

*Pharmacological testing.* Some new compounds were tested for their anticonvulsant activity using phenobarbitone as reference compound, following the method reported by Soaje-Echaque and Lim (1962) Chaturvedi *et al* (1975). The results are illustrated in Table 5.

### Results and Discussion

A preliminary, blind and randomized pharmacological test for evaluation of the anticonvulsant activity of some newly synthesized compounds II, III, IV and V against pentylenetetrazole-induced convulsions was performed. Phenobarbitone was used as a standard anticonvulsant drug. The data obtained showed that, some of the tested compounds produced significant anticonvulsant activity at a dose range of 50-300 mg kg<sup>-1</sup>. The ester compounds (II<sub>1-10</sub>) and the para substituted derivatives showed higher activity than that produced by ortho derivatives.

Elongation of the alkyl chain showed no effect on the activity, while the nitro compounds revealed toxic effects. None of the tested compounds were found to exhibit loss of righting reflex i.e., no hypnotic effect.

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