Acta Poloniae Pharmaceutica – Drug Research, Vol. 68 No. 5 pp. 657–663, 2011 ISSN 0001-6837
Polish Pharmaceutical Society

DRUG SYNTHESIS

SYNTHESIS, ANTICONVULSANT AND NEUROTOXICITY SCREENING OF SOME NOVEL 1,2,4-TRISUBSTITUTED-1*H*-IMIDAZOLE DERIVATIVES

ASIF HUSAIN[1*], NADEEM SIDDIQUI[1], MD SARAFROZ[1], YASMIN KHATOON[1], MOHD RASID[1] and NIYAZ AHMAD[2]

[1] Department of Pharmaceutical Chemistry, [2]Department of Pharmaceutics, Faculty of Pharmacy, Jamia Hamdard University, Hamdard Nagar, New Delhi-110062, India

Abstract: A series of 1,2,4-trisubstituted-1*H*- imidazole derivatives (**4a**-**o**) was synthesized by reacting 2,4-disubstituted-1*H*-imidazoles (**3a**-**o**) with chlorobenzene in the presence of triethylamine. Phenylglyoxal (2) was reacted with different aromatic aldehydes in the presence of ammonium acetate and glacial acetic acid to afford the disubstituted imidazoles (**3a**-**o**). The structures of the synthesized compounds were confirmed on the basis of their elemental analysis and spectral data results. Anticonvulsant activity was shown by majority of the synthesized compounds in the maximal electroshock (MES) and subcutaneous pentylenetetrazole (scPTZ) screens when given *i.p*. to mice. In anticonvulsant screening, only one compound **4k** showed potent activity comparable to that of standard drugs phenytoin and carbamazepine. Compounds **4a, 4c, 4e, 4l** and **4n** passed the rotorod test successfully without any sign of neurological deficit.

Keywords: trisubstituted imidazoles, anticonvulsant, neurotoxicity and lipophilicity.

Epilepsy is a common neurological disorder characterized by unprovoked seizures that affects at least 0.5 to 1% of the population worldwide (45–100 million people) (1). Although conventional antiepileptic drugs (AEDs): phenobarbital, primidone, phenytoin, carbamazepine, ethosuximide and benzodiazepine, are already in clinical use, some types of seizures are still not adequately treated with current therapy and have limitations or intolerable side effects (1–3). In response to these limitations several new drugs like oxcarbazepine, lamotrigine, topiramate, gabapentin, zonisamide, tiagabine, fosphenytoin, vigabatrin and felbamate have been strongly advocated to optimally manage seizures (3). However, there is a significant group of patients (up to 40%) who are resistant to the available antiepileptic drugs (4–7). Hence, there is an urgent need to develop new antiepileptic compounds with a more selectivity and lower toxicity (8) which continues to be an area of investigation in medicinal chemistry.

In recent years, the field of antiepileptic drug development (ADD) has become quite dynamic, affording many promising research opportunities. Mechanistic approaches are increasingly being facilitated by the new wave of research in epileptics (9). Recent studies revealed that the substituted imidazole derivatives have attracted much attention due to their broad spectrum of pharmacological activities such as anti-inflammatory, analgesic, antimicrobial, antiviral, antifungal, antitubercular, anticancer and anticonvulsant (10–16).

Literature survey shows that imidazole-heterocyclic compounds could be new classes of anticonvulsant agents by virtue of their potential anticonvulsant properties (17–19). Here, we present the synthesis, anticonvulsant and neurotoxicity activity of a series of unpublished trisubstituted imidazole derivatives (**4a-o**).

EXPERIMENTAL

All the chemicals and solvents used were mostly of AR grade obtained from Merck, CDH and S.D. Fine Chem Ltd.. The melting points were determined in open glass capillary tubes using Kjeldahl flask containing liquid paraffin and are uncorrected. Purity of the compounds was checked

* Corresponding author: e-mail: drasifhusain@yahoo.com

Table 1. Physical data of the title compounds (**4a-o**).

Compd.	R	Mol. formula[a] (Mol. Wt.)	M.p.[b] (^{o}C)	Yield (%)	log P[c]	R_f[d]
4a	H	$C_{23}H_{20}N_3O_2$ (370.41)	140–142	60	0.97	0.67
4b	3-Cl	$C_{23}H_{18}ClN_3O_2$ (403.86)	135–136	45	1.69	0.74
4c	4-Cl	$C_{23}H_{18}ClN_3O_2$ (403.86)	145–147	71	1.64	0.60
4d	4-F	$C_{23}H_{18}ClN_3O_2$ (387.40)	150–152	50	1.74	0.68
4e	2-OH	$C_{23}H_{19}N_3O_3$ (385.41)	161	70	1.17	0.61
4f	4-OH	$C_{23}H_{19}N_3O_3$ (385.41)	120–122	65	1.78	0.58
4g	3-NO_2	$C_{23}H_{18}N_4O_4$ (414.41)	145–148	39	1.45	0.58
4h	4-NO_2	$C_{23}H_{18}N_4O_4$ (414.41)	154	60	1.51	0.70
4i	4-OCH_3	$C_{24}H_{21}N_3O_3$ (399.44)	156–158	55	1.84	0.71
4j	4-$N(CH_3)_2$	$C_{25}H_{24}N_4O_2$ (412.48)	122	74	0.65	0.55
4k	3,4-$(OCH_3)_2$	$C_{25}H_{23}N_3O_4$ (429.46)	140	40	1.81	0.68
4l	4-OCH_3, 3-OH	$C_{24}H_{21}N_3O_4$ (415.44)	171–173	47	1.74	0.60
4m	4-OCH_3, 3-OCH_2COOH	$C_{26}H_{23}N_3O_6$ (473.47)	155–157	55	0.85	0.60
4n	4-OC_2H_5, 3-OH	$C_{25}H_{23}N_3O_4$ (429.46)	152–153	40	1.85	0.75
4o	4-OC_2H_5, 3-OCH_2COOH	$C_{27}H_{25}N_3O_6$ (487.50)	148–150	60	0.91	0.65

[a]Solvent of crystallization – ethanol, [b]Melting point of the compounds at their decomposition, [c]Log P was calculated by using absorbance data, Chloroform/phosphate buffer at 28^{o}C, [d]Solvent system – toluene:ethyl acetate:formic acid (5:4:1, v/v/v) and benzene:acetone (8:2, 7:3 v/v) . Elemental analysis for C, H, N were within ± 0.4% of the theoretical value.

on thin layer chromatography (TLC) plates using silica gel G (Merck) and the solvent system benzene–acetone (9:1 and 8:2, v/v) and toluene–ethyl acetate–formic acid (TEF) (5:4:1, v/v/v); the spots were visualized under iodine vapors or UV light. The FT-IR spectra were obtained in KBr pellets on BIO-RAD FTS FT-IR spectrophotometer. The ^{1}H-NMR spectra were recorded on DPX-300 NMR spectrometer and BRUKER-400 Ultra Shield™ spectrometer using tetramethylsilane (TMS) as an internal standard in DMSO/$CDCl_3$. Chemical shifts (δ) are expressed in ppm. Mass spectrometry was recorded on UPLC-MS/MS (WATERS, Mass Lynx version 4.1) spectrometer. Microanalysis of the compounds was done on Perkin-Elmer model 240 analyzer and the values were found within ± 0.4% of the theoretical values. The synthetic protocol of the title compounds is presented in Scheme 1. The physical constants, spectral data and anticonvulsant screening of the synthesized compounds are presented in Tables 1, 2 and 3, respectively.

Synthesis of *N*-[4-hydroxy-3-(2-oxoacetyl) phenyl] acetamide (2)

It was synthesized from *N*-(3-acetyl-4-hydroxyphenyl) acetamide **(1)** according to the literature method (20).

Synthesis of 2,4-disubstituted-1*H*-imidazoles (3a-o)

A mixture of *N*-[4-hydroxy-3-(2-oxoacetyl) phenyl] acetamide **(2)** (0.025 mol), aromatic aldehyde (0.025 mol) and ammonium acetate (10 g) in glacial acetic acid (50 mL) was refluxed in round bottom flask for 5 h. After completion of the reaction, the reaction mixture was cooled to room temperature and the content was poured into the cold water (250 mL). The precipitates so obtained were filtered, washed with water, dried and recrystallized from acetone to get the desired products **3**. The compounds were found pure on TLC examination (TEF 5:4:1, v/v/v).

Table 2. Spectral data of the title compounds **(4a-o)**.

Compd.	IR (KBr), cm^{-1}	^{1}H-NMR (DMSO-d_6), δ (ppm)† / MS data
4a	3309 (OH), 3227 (NH), 3008 (CH), 1685 (C=O),1602 (C=N), 1458 (C=C), 1341 (C-N).	2.55 (3H, s, CH_3), 6.73–8.11 (13H, m, Ar-H), 9.01 (1H, s, imidazole), 9.49 (1H, s, OH), 9.91 (1H, s, CONH) / 371 (M+1).
4b	3321 (OH), 3233 (NH), 3011 (CH), 1676 (C=O), 1590, (C=N), 1440 (C=C), 1344 (C-N),709 (C-Cl).	2.53 (3H, s, CH_3), 7.01-8.11 (12H, m, Ar-H), 9.11 (1H, s, imidazole), 9.51 (1H, s, OH), 10.10 (1H, s, CONH).
4c	3324 (OH), 3210 (NH), 3022 (CH), 1677 (C=O), 1589 (C=N), 1444 (C=C), 1344 (C-N), 696 (C-Cl).	2.48 (3H, s, CH_3), 6.44–8.03 (12H, m, Ar-H), 9.04 (1H, s, imidazole), 9.63 (1H, s, OH), 9.85 (1H, s, CONH) / 403 (M^+).
4d	3339 (OH), 3201 (NH), 2995 (CH), 1660 (C=O), 1575 (C=N), 1450 (C=C), 1349 (C-N), 1105 (C-F).	2.51 (3H, s, CH_3), 7.05–7.80 (12H, m, Ar-H), 9.13 (1H, s, imidazole), 9.32 (1H, s, OH), 10.25 (1H, s, CONH).
4e	3311 (OH), 3244 (NH), 3020 (CH), 1688 (C=O), 1571 (C=N), 1419 (C=C), 1333 (C-N).	2.47 (3H, s, CH_3), 7.15–7.71 (12H, m, Ar-H), 9.04 (1H, s, imidazole), 9.54 (2H, s, 2 × OH), 10.23 (1H, s, CONH) / 385 (M^+).
4f	3324 (OH), 3210 (NH), 3022 (CH), 1677 (C=O), 1589 (C=N), 1444 (C=C), 1341 (C-N).	2.48 (3H, s, CH_3), 6.74–7.90 (12H, m, Ar-H), 9.07 (1H, s, imidazole), 9.51 (2H, s, 2 × OH), 10.30 (1H, s, CONH).
4g	3330 (OH), 3232 (NH), 3001 (CH), 1680 (C=O), 1589 (C=N), 1482 (C=C), 1336 (C-N).	2.45 (3H, s, CH_3), 7.00–7.81 (9H, m, Ar-H), 8.30-8.60 (4H, m, Ar-H), 8.91 (1H, s, imidazole), 9.25 (1H, s, OH), 10.55 (1H, s, CONH) / 414 (M^+).
4h	3309 (OH), 3229 (NH), 3018 (CH), 1681 (C=O), 1558 (C=N), 1449 (C=C), 1331 (C-N).	2.51 (3H, s, CH_3), 7.00–7.58 (8H, m, Ar-H), 8.01-8.32 (4H, m, Ar-H), 9.01 (1H, s, imidazole), 9.35 (1H, s, OH), 10.47 (1H, s, CONH).
4i	3341 (OH), 3226 (NH), 3013 (CH), 1686 (C=O), 1587 (C=N), 1464 (C=C), 1349 (C-N).	2.49 (3H, s, CH_3), 3.85 (3H, s, OCH_3), 7.14–7.91 (12H, m, Ar-H), 8.95 (1H, s, imidazole), 9.44 (1H, s, OH), 10.55 (1H, s, CONH) / 399 (M^+).
4j	3317 (OH), 3220 (NH), 3010 (CH), 1646 (C=O), 1556 (C=N), 1452 (C=C), 1338 (C-N).	2.53 (3H, s, CH_3), 2.95 (6H, s, -$N(CH_3)_2$), 6.84–7.98 (12H, m, Ar-H), 9.01 (1H, s, imidazole), 9.45 (1H, s, OH), 10.53 (1H, s, CONH) / 413 (M^{+1}).
4k	3312 (OH), 3208 (NH), 3019 (CH), 1685 (C=O), 1579 (C=N), 1451 (C=C), 1323 (C-N).	2.50 (3H, s, CH_3), 3.83 (6H, s, 2 × OCH_3), 6.91–7.85 (11H, m, Ar-H), 9.13 (1H, s, imidazole), 9.50 (1H, s, OH), 10.70 (1H, s, CONH) / 429 (M^+).
4l	3339 (OH), 3206 (NH), 3014 (CH), 1665 (C=O), 1569 (C=N), 1444 (C=C), 1334 (C-N).	2.46 (3H, s, CH_3), 3.85 (3H, s, OCH_3), 6.90–7.85 (11H, m, Ar-H), 8.94 (1H, s, imidazole), 9.45 (2H, s, 2 × OH), 10.49 (1H, s, CONH) / 415 (M^+).
4m	3311 (OH), 3215 (NH), 3061 (CH), 1686 (C=O), 1560 (C=N), 1432 (C=C), 1320 (C-N).	2.31 (3H, s, CH_3), 3.83 (3H, m, OCH_3), 4.70 (2H, s, OCH_2), 6.95–7.61 (11H, m, Ar-H), 9.02 (1H, s, imidazole), 9.25 (1H, s, OH), 10.44 (1H, s, CONH), 11.15 (1H, s, COOH).
4n	3334 (OH), 3202 (NH), 3001 (CH), 1687 (C=O), 1569 (C=N), 1458 (C=C), 1334 (C-N).	2.48 (3H, s, CH_3), 3.85 (3H, s, OCH_3), 6.90–7.85 (11H, m, Ar-H), 8.94 (1H, s, imidazole), 9.45 (2H, s, 2 × OH), 10.50 (1H, s, CONH) / 429 (M^+).
4o	3348 (OH), 3214 (NH), 2998 (CH), 1668 (C=O), 1559 (C=N), 1431 (C=C), 1328 (C-N).	1.32 (3H, m, CH_3 of C_2H_5), 2.45 (3H, s, CH_3), 4.13 (2H, m, CH_2 of C_2H_5), 4.60 (2H, s, CH_2 of OCH_2), 6.95–7.55 (11H, m, Ar-H), 9.01(1H, s, imidazole) 9.41 (1H, s, OH), 10.50 (1H, s, CONH), 11.23 (1H, s, COOH).

†s = singlet; d = doublet; m = multiplet; Ar-H = aromatic protons.

Table 3. Anticonvulsant and neurotoxicity screening of the title compounds **(4a-o)**.

Compd.	*i.p.* injection in mice[a]				Neurotoxicity screening[b]	
	(MES screen)		(scPTZ)			
	0.5 h	4 h	0.5 h	4 h	0.5 h	4 h
4a	–	–	–	300	–	–
4b	100	300	–	300	–	300
4c	100	–	–	–	–	–
4d	100	300	300	–	300	300
4e	300	–	×	×	–	–
4f	100	300	–	300	300	–
4g	300	–	300	–	300	300
4h	300	–	–	–	300	–
4i	100	300	300	–	–	300
4j	–	–	–	–	×	×
4k	30	300	300	–	300	–
4l	100	300	–	300	–	–
4m	300	–	300	–	–	300
4n	100	300	×	×	–	–
4o	300	–	–	300	–	300
Phenytoin	30	30	–	–	100	100
CBZ	30	100			300	300

[a]Doses of 30, 100 and 300 mg/kg were administered; the figures in the table indicate the minimum dose whereby activity was demonstrated in half or more of the mice (n = 6). The animals were examined 0.5 and 4 h after injections. The dash (–) indicates an absence of activity at maximum dose administered (300 mg/kg). The cross (×) indicates not tested. [b]Data from references (29, 30). CBZ = carbamazepine.

Synthesis of 1, 2, 4-trisubstituted-1*H*-imidazoles (4a-o)

Compound **3** (0.01mol) was suspended in tetrahydrofuran (20 mL) and refluxed with chlorobenzene (2 mL) in the presence of 2–3 drops of triethylamine for 8 h. The reaction was monitored by using TLC. After completion of the reaction, acetone was added to the reaction mixture and left at room temperature overnight. A precipitate **(4)** was formed, which was filtered, dried and recrystallized from ethanol. The compounds were found pure on TLC examination (B:A, 9:1, v/v).

PHARMACOLOGY

Anticonvulsant activity

The anticonvulsant screening of the final compounds was done according to the protocols of National Institute of Neurological Disorders and Stroke, NIH (USA). Swiss albino mice (25–30 g) of either sex were used as experimental animals. The mice were kept under standard conditions at an ambient temperature of 25 ± 2°C and allowed free access to food and water except at the time they were brought out of the cage. The tested compounds and standard drugs were suspended in 0.5% (CMC) carbomethoxycellulose water mixture or in PEG (polyethylene glycol).

Maximal electroshock seizure test (MES)

Maximal electroshock seizure was elicited with a current intensity of 50 mA, 60Hz for 0.2 s *via* ear clip electrodes, with the doses of test compounds (30, 100, 300 mg/kg). The maximal seizure typically consists of a short period of tonic extension of the hind limbs and a final clonic episode. The abolition of the hind limb tonic extensor component of the seizure due to the drug treatment is defined as anticonvulsant activity (21, 22).

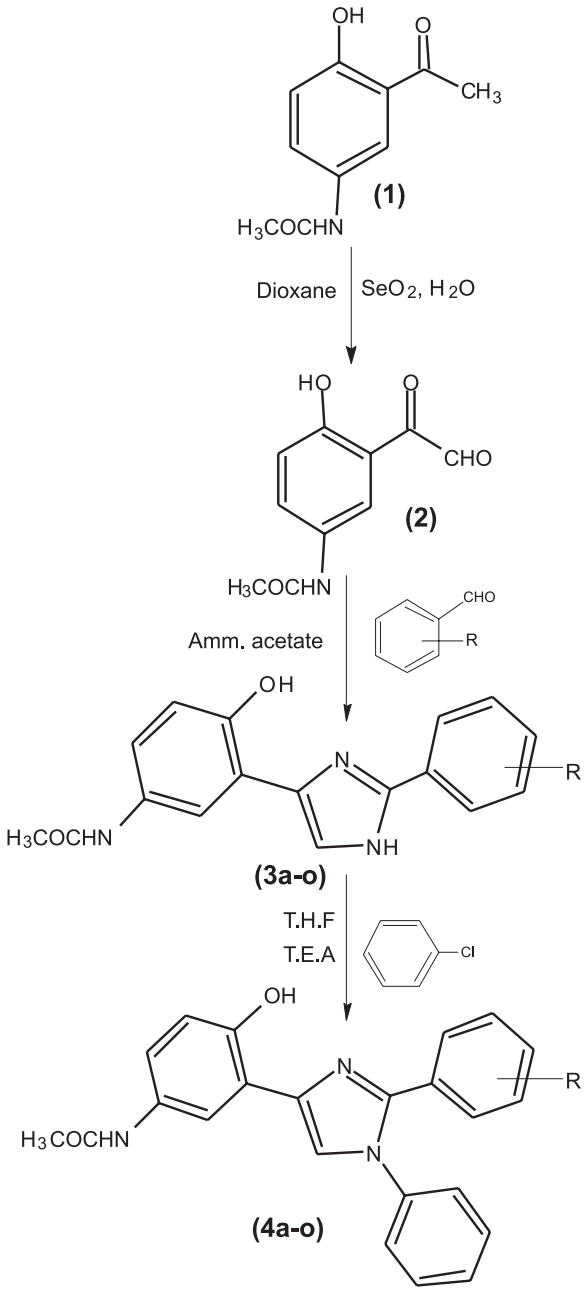
Subcutaneous pentylenetetrazole induced seizure test (scPTZ)

The subcutaneous pentylenetetrazole test was performed according to the known protocol (23, 24).

This method utilizes pentylenetetrazole (75 mg/kg) administered as a 0.5% solution subcutaneously in the posterior midline that produces seizures in > 95% of animals. The animals were 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.

Neurotoxicity screening (NT)

The minimal motor impairment was measured by the rotorod test (25). The mice (20–25 g) were trained to stay on an accelerating rotorod that rotates at 6 rpm, and its diameter was 3.2 cm. Only those mice were taken for the test which could stay on the revolving rod for at least one minute. Trained ani-



Scheme 1. Synthesis of the title compounds (**4a-o**). R substituents are the same as in Table 1

mals were injected *i.p.* with the test compounds at doses of 300 mg/kg. The inability of the animal to maintain equilibration on the rod for at least one minute indicated neurotoxicity.

Log P determination

Biological activity is dependent on lipophilic character of the drug. In particular, the reports by Lien et al. indicated that anticonvulsant activity of different types of compounds was correlated with lipophilicity (26). However, it has been observed that the maximum potency of the drugs which act on the central nervous system (CNS) is obtained with congeners having an optimum lipophilicity (log P_0) near 2. In this study, an attempt was made to correlate the anticonvulsant activity of the 1,2,4-trisubstituted-1*H*-imidazole analogues with the calculated log P value (CLOGP) (27). The experimental log P values of the compounds were obtained using chloroform/phosphate buffer method (28).

RESULTS AND DISCUSSION

The new derivatives (**4a-o**) were injected *i.p.* into mice at doses of 30, 100 and 300 mg/kg for anticonvulsant activity (Table 3). All the compounds except **4a** and **4j** showed anti-MES activity indicative of their ability to prevent seizure spread. Compounds that showed protection against MES model at 100 mg/kg include **4b, 4c, 4d, 4f, 4i, 4l** and **4n**. Compounds **4b, 4d, 4f, 4i, 4k, 4l** and **4n** showed activity both at 0.5 and 4.0 h. Thus, only one compound **4k** showing activity at a lower dose of 30 mg/kg seems to be very potent in anticonvulsant MES screening. Some of the compounds showed activity only at 0.5 h, indicating that they have rapid onset and shorter duration of action.

In scPTZ screening, compounds **4d, 4g, 4i, 4k** and **4m** showed 100% protection at a dose of 300 mg/kg at 0.5 h. So these compounds have quick onset but for shorter duration of action. Some compounds (**4a, 4b, 4f, 4l** and **4o**) were also active after 4.0 h extended period of activity.

In the neurotoxicity screening, compounds **4a, 4c, 4e, 4l** and **4n** do not show any toxicity at the dose of 300 mg/kg. Compounds **4d** and **4g** were toxic at 0.5 and 4.0 h, whereas compounds **4f, 4h** and **4k** showed toxicity only after 0.5 h and do not show toxicity after 4.0 h. Four compounds (**4b, 4i, 4m** and **4o**) showed delayed toxicity i.e., toxicity only after 4.0 h, which is comparable with that of carbamazepine (300 mg/kg). However, all the compounds were less toxic than phenytoin (100 mg/kg).

Compounds **4b, 4c, 4d, 4f, 4i, 4k, 4l** and **4n** were found to be more lipophilic having potent anticonvulsant activity. The other compounds (**4e, 4g** and **4h**) were also lipophilic having some potency. Compounds **4a, 4m and 4o** were less lipophilic and were less active in MES test.

CONCLUSION

The present work indicates that halo and alkoxy substituted phenyl ring of imidazole moiety have given impetus to the present investigation and showed favored MES activity as compared to hydroxyl or unsubstituted rings. Thus, a number of 1,2,4-trisubstituted-1*H*-imidazole derivatives exhibited anticonvulsant activity in MES screen. Some compounds (**4b, 4c, 4d, 4f, 4i, 4k, 4l** and **4n**) showed more lipophilic character and were more active. The compounds **4a, 4e, 4g, 4h, 4m** and **4o** were also lipophilic but were less active in MES test. Some of the above mentioned compounds have shown high degree of protection and obviously may have future commitment.

Acknowledgments

We are thankful to the UGC, New Delhi for providing financial support. Thanks are also due to IIT, Delhi, CIF, Faculty of Pharmacy and Science, Jamia Hamdard New Delhi for providing ^{1}H-NMR, MS and IR spectra of the compounds.

REFERENCES

1. Deckers C.L.P., Genton P., Sills G.J., Schmidt D.: Epilepsy Res. 53, 1 (2003).
2. Kwan P., Brodie M.J.: N. Engl. J. Med. 342, 314 (2000).
3. Mc-Namara O.J.: Drugs effective in the therapy of the epilepsies. In The Pharmacological Basis of Therapeutics, Brunton L.L., Lazo J.S., Parker K.L. Eds., p. 501. McGraw-Hill, New York 2006.
4. Lima L.J.M.: Curr. Pharm. Design 6, 873 (2000).
5. Berk M., Segal J., Janet L., Vorster M.: Drugs 61, 1407 (2001).
6. Duncan J.S.: Br. J. Clin. Pharmacol. 53, 123 (2002).
7. Eadie M.J.: CNS Drugs 15, 679 (2001).
8. Szelenyi I., Horvath K., Howes J.F., Mazarati A.M.: Drugs Fut. 28, 925, (2003).
9. Delgado-Escueta A.V.: Ann. Neurol. 16, 145 (1984).

10. Navidpour L., Shadnia H., Shafaroodi H., Amini M., Dehpour A.R., Shafiee A.: Bioorg. Med. Chem. 15, 1976 (2007).
11. Schiaffella F., Macchiarulo A., Milanese L., Vecchiarelli A., Fringuelli R.: Bioorg. Med. Chem. 14, 5196 (2006).
12. Zhang P., Liu X., Zhu J., Fang Z., Li Z., Pannecouque C., Clercq E.D.: Bioorg. Med. Chem. 17, 5775 (2009).
13. Zampieri D., Mamolo M.G., Laurini E., Scialino G., Banfi E., Vio L.: Bioorg. Med. Chem. 16, 4516 (2008).
14. Khoshneviszadeh M., Edraki N., Javidnia K., Alborzi K., Pourabbas P., Mardaneh J., Miri R.: Bioorg. Med. Chem. 17, 1579 (2009).
15. Kahlon D.K., Lansdell T.A., Fisk J.S., Tepe J.J.: Bioorg. Med. Chem. 17, 3093 (2009).
16. Ustunes L., Pabuccuoglu V., Berkan T., Ozer A.: J. Fac. Pharm. Ankara 19, 124 (2005).
17. Hempel A., Camerman N., Camerman A., Mastropaolo D.: Acta. Cryst. 61, 1387 (2005).
18. Thenmozhiyal J.C., Peter T.S.W., Wai-Keung C.: J. Med. Chem. 47, 1527 (2004).
19. Rostom S.A.F., Ashour H.M.A., El Razik H.A.A., El Fattah A.E.F.H.A., El-Din N.N.: Bioorg. Med. Chem. 17, 2410 (2009).
20. Husain A., Drabu S., Kumar N.: Acta Pol. Pharm. Drug Res. 66, 243 (2009).
21. Stables J.P., Kupferberg H.J.: National Institute of Neurological Disorders and Stroke. Anticonvulsant Screening Project Report. Chapter 16. www.ninds.nih.gov/ anticonvulsant_screening_project.htm.
22. White H.S., Woodhead J.H., Franklin M.R.: General principles, experimental selection, quantification, and evaluation of antiepileptic drugs. In: Antiepileptic Drugs, 4th edn., Levy, R.H., Mattson, R.H., Meldrum, B.S. Eds., p. 99, Raven Press, New York 1995.
23. Chen J., Sun X-Y., Chai K-Y., Lee J-S., Song M-S., Quan Z-S.: Bioorg. Med. Chem. 15, 6775 (2007).
24. Kucukguzel I., Kucukguzel S.G., Rollas S., Ozdemir O., Bayrak I., Altug T., Stables J.P.: Farmaco 59, 893 (2004).
25. Kucukgzuel I., Kucukgzuel S.G., Roller S., Sanis G.O., Ozdemir O., Bolyrek I., Altug T., Stables J.P.: J. Med. Chem. 49, 1212 (2006).
26. Lien E.J., Liuo R.C.H., Shinoucla H.G.: J. Pharm. Sci. 68, 463 (1979).
27. Leo A., Weininger D., Weininger A.: CLOGP, CMR. Med. Chem. Project, Pomona College: Claremont C.A. Release 4.20, Distributed by Daylight Chemical Information Systems (1992).
28. Farrar V.A., Grochowski J., Serda P., Pilati T., Filippini G., Hinko C.N., El-Assadi A. et al.: J. Med. Chem. 36, 3517 (1993).
29. Dimmock J.R., Puthucode R.N., Smith J.M., Hetherington M., Quail J.W., Pugazhenthi U., Lechler T., Stables J.P.: J. Med. Chem. 39, 3984 (1996).
30. Porter R.J., Cereghino J.J., Gladding G.D., Hessie B.J., Kupferberg H.J., Scotville B., White B.: Cleveland Clin. Quart. 51, 293 (1984).

Received: 18. 07. 2010