Asian Journal of Chemistry; Vol. 23, No. 4 (2011), 1861-1862

ASIAN JOURNAL OF CHEMISTRY

www.asianjournalofchemistry.co.in

NOTE

Synthesis and Anticonvulsant Activity of Prodrug of Gabapentin

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(*Received*: 25 September 2009; *Accepted*: 27 December 2010) AJC-9434

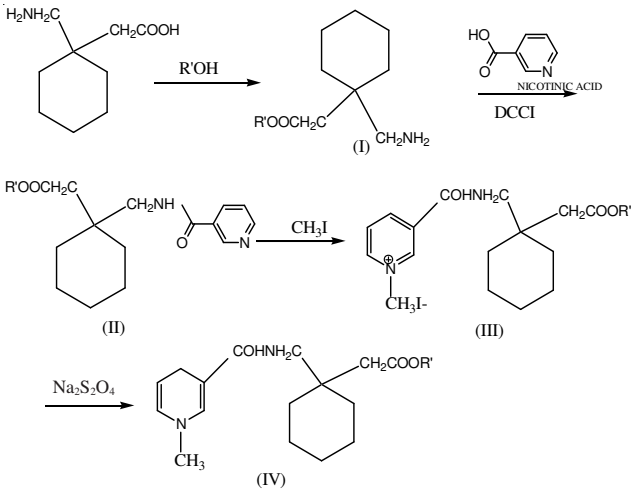
The synthesis and evaluation of anticonvulsant activity of prodrugs of gabapentin are reported by taking the dihydropyridine compound as carrier molecules, in redox delivery approach. A redox system of drug delivery based on an interconvertible dihydropyridine ⇌ pyridinium salt carrier. Anticonvulsant activity of all the compounds were tested by chemo-convulsion method and all the compounds found active. All the compounds were also studied for oxidation in various biological fluids and found to be stable and shows sustained release profile which follow first order kinetics. Oxidized form of the conjugate inside the brain act as prodrug, which on hydrolysis yields parent drug.

Key Words: Synthesis, Prodrug, Gabapentin, Anticonvulsant activity, Release of drug.

The epilepsies or convulsions are a group of disorders characterized by chronic, recurrent, paroxymal changes in neurologic function caused by abnormalities in electrical activity of the brain. They are one of the common neurologic disorders estimated to affect 0.5-2.0 % of the population and can occur at any age. The epileptic attack is initiated by an abnormal focus of the electric discharge, originated either in grey matter or other part of the brain[1].

Gabapentin is a broad spectrum anticonvulsant. Gabapentin doesnot interact indirectly with $GABA_A$ and $GABA_B$ recptor inspite of its similarity to GABA. It also has no effect on the enzyme of GABA pathway. Although it does enhances aminoxy acetic acid induced GABA accumulation in several region in the brain. In brain slices, gabapentin has been shown to inhibit the release of dopamine but not that of acetyl choline. Gabapentin has also been shown to inhibit the release of GABA from slices of rat neostriatum. It is tempting to speculate that its mechanisms involve action on the release of transmitters as well as the activation of the new receptor site in the CNS[1].

The synthesis of nicotinyl-gabapentin prodrug was followed according to Bodor *et al.*[1,2]. The procedure involves esterification of gabapentin with various alcohols (MeOH, EtOH, isopropanol, BuOH and benzyl alcohol) get (**I**) then amidation with nicotinic acid or coupling of esterified gabapentin with carrier molecule to found (**II**) followed by quaternization using methyl iodide produced (**III**) and then reduced with sodium dithionite to get 1,4-dihydropyridine derivatives (**IV**) (**Scheme-I**).

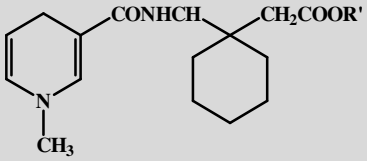


Scheme-I

All the structure of synthesized compounds were confirmed by UV, IR and NMR Spectroscopy and on the basis of C, H and N analysis (Table-1).

Evaluation: The anticonvulsant activity of the synthesized compounds were evaluated by following the chemo-convulsion method using strychnine HCl to produce convulsion in rats, in which animal were weighed and divide into two groups, each comprising of six animals. One group was injected with only strychnine HCl (control) and the second group was also received strychnine HCl but after 4 h of injection of the synthesized

TABLE-1
LIST OF THE SYNTHESIZED COMPOUNDS AND ANTICONVULSANT ACTIVITY



Compd. Code	R'	m.f. (m.w.)	m.p. (ºC)	Average wt. of animal (g)	Dose (i.p.) (mg/kg)	Anticonvulsant activity (%) Inhibition	N % calcd. (found)	Lipophilicity Rm (R_f)
X21	CH_3	$C_{17}H_{26}O_3N_2$ (320)	205	200 ± 10	25	65	8.75/8.50	1.70 (0.0200)
X22	CH_3CH_2	$C_{18}H_{28}O_3N_2$ (334)	225	175 ± 10	25	70	8.38/7.89	1.06 (0.0140)
X23	$(CH_3)_2CH$	$C_{19}H_{30}O_3N_2$ (348)	232	190 ± 10	25	80	8.05/8.00	1.90 (0.0125)
X24	$CH_3CH_2CH_2CH_2$	$C_{20}H_{32}O_3N_2$ (362)	240	190 ± 10	25	90	7.73/7.50	2.97 (1.0700)
X25	$C_6H_5CH_2$	$C_{23}H_{30}O_3N_2$ (396)	189	190 ± 10	25	65	7.07/6.95	1.98 (0.0100)
DPH Na^+	–	–	–	190 ± 10	25	80	–	–

All the compounds having mortality (24 h) was nil.

TABLE-2
THE HALF-LIVE ($t_{½}$) OF THE DERIVATIVES IN VARIOUS BIOLOGICAL FLUID

Compd.	Blood		Plasma		Liver		Brain	
	K (min^{-1})	t½ (min^{-1})	K (min^{-1})	t½ (min^{-1})	K (min^{-1})	t½ (min^{-1})	K (min^{-1})	t½ (min^{-1})
X21	0.0495	14.00	0.0247	28	0.124	5.6	0.0447	15.5
X22	0.1610	4.30	0.0256	27	0.2038	3.4	0.1174	5.9
X23	0.2388	2.90	0.033	21	0.577	1.2	0.0778	8.9
X24	0.0385	180	0.01824	38	0.0575	12	0.0385	18
X25	0.6549	1.05	0.02887	24	0.5747	1.2	0.0778	8.9

compounds (or phenytoin sodium). The severity of convulsions in these groups[3] was noted and compared the activity of the synthesized compounds to the standard drug.

Lipophilicity: Lipophilicity is a essential feature for a chemical delivery system having brain delivery properties. Lipophilicity of the synthesized compounds was determined using the formula Rm = log ($1/R_f$ -1). The chromatographic Rm value was correlated with penetrating substance in biological cells and calculated Rm value of these synthesized derivative were compared to that of respective parent drugs[4].

Oxidation of synthesized compounds: the synthesized derivatives were studied for the rate of oxidation in various biological fluids (like whole human blood, plasma liver and brain tissue homogenates). The methanolic solution of these derivatives were prepared and added to the media. The mixture was kept at 37 ºC and scanned using UV spectrophotometer from 400-250 nm for every 10 min till 2 h. Then the percentage of the dihydropyridine derivatives and the quaternary compounds were determined in these biological media and was calculated the half lives of these dihydropyridine derivatives (Table-2).

All the synthesized compounds had shown a comparable anticonvulsant activity and almost equal % mortality with that of phenytoin sodium (25 mg/kg). In the synthesized compounds **X24** has shown high activity even more than standard followed by **X23**, **X22**, and **X25**, **X25** and **X21** having equal activity.

The lipophilicity of synthesized compounds were determined using Rm value and it appear that all of them can be able to penetrate the blood brain barrier, the order (most lipophilic → least lipophilic) being **X24 > X25 > X23 > X21 > X22**. The lipophilicity of synthesized compounds was found to be superior to its parent drug.

The oxidation of synthesized compounds was examined in various tissue homogenates as well as human blood. All the compounds were found quite reactive in these biological media among which **X24** was stable. However, **X24** ($t_{1/2}$ = 18) was shown to oxidized to its pyridinium derivatives in brain homogenate. The other dihydropyridine in tissues other than brain did not show any accumulation of it corresponding pyridinium compounds during the incubation period, so no peripheral toxicity.

The redox delivery pro-pro-drug approach has been applied to several potential gabapentin for solving the site and organ delivery problem. So this approach has been used in this work and prepare the nicotinyl derivatives, which were screened for is anticonvulsant activity and release of drug in brain. From the prepared derivatives all the compounds were shown a comparable anticonvulsant activity to that of phenytoin sodium but the compound **X24** has high activity and more lipophilicity.

In oxidation studied all the compounds were shown stability in various biological media. The *in vivo* study reveals that there is in an appearance and disappearance of quaternary compound in blood and brain after the administration of dihydropyridine derivative in sustained manner. These studies showed that this type of chemical delivery system of drug (gabapentin) producing significant and sustained brain specific GABAnergic activity.

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