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Synthesis and anticonvulsant activity of 4-(2-(2,6-dimethylphenylamino)-2-oxoethylamino)-*N*-(substituted)butanamides: A pharmacophoric hybrid approach

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Abstract—A series of pharmacophoric hybrids of ameltolide-γ-aminobutyric acid (GABA)-amides was designed, synthesized, and evaluated for their anticonvulsant and neurotoxic properties. Initial anticonvulsant screening was performed using intraperitoneal (ip) maximal electroshock-induced seizure (MES), subcutaneous pentylenetetrazole (scPTZ), and subcutaneous picrotoxin (scPIC)-induced seizure threshold tests. All the compounds had improved lipophilicity and the pharmacological activity profile confirmed their blood–brain barrier penetration. The titled compounds showed promising activity in scPIC screen indicating the involvement of GABA-mediation. Compound 4-(2-(2,6-dimethylaminophenylamino)-2-oxoethylamino)-*N*-(2,6-dimethylphenyl) butanamide (**7**) emerged as the most potent derivative effective in all the three animal models of seizure with no neurotoxicity at the anticonvulsant dose.

Epilepsy is a disorder characterized by recurrent seizures of cerebral origin, presenting with episodes of sensory, motor or autonomic phenomenon with or without loss of consciousness. Epilepsy is the second most common chronic neurological condition reported by neurologists.[1] Despite the optimal use of available antiepileptic drugs (AED), many patients with epilepsy fail to experience seizure control and others do so only at the expense of significant toxic side effects.[2] In recent years, the field of antiepileptic drug development is quite dynamic, affording many promising research opportunities. γ-Aminobutyric acid (GABA) is the major inhibitory neurotransmitter in the mammalian brain.[3] It has been well documented that the reduction of GABAergic neuronal activity plays an important role in a number of neurological disorders, including epilepsy.[4,5] The peripheral administration of GABA cannot be usefully performed since this neurotransmitter is able to cross the blood–brain diffusion barrier (BBB) only at extremely high doses, which produce severe adverse side effects.[6] Hence, over the past few decades, research aimed at achieving successful delivery of GABA into the CNS has resulted in the discovery of various GABA analogs with improved pharmacological activities.[7] We undertook a drug discovery program on designing newer GABA derivatives and recently two series of pharmacophoric hybrids of phthalimide-GABA-anilides/hydrazones were reported as anticonvulsants in which the most active compound was found to be 4-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-*N*-(2,6-dimethyl phenyl) butanamide.[8] 4-Amino-*N*-(2,6-dimethylphenyl)phthalimide was previously designed from the models of ameltolide and thalidomide.[9] In view of the above results, the present work is aimed at combining the pharmacophoric features of ameltolide, a 2,6-dimethylanilide, GABA, and amide as novel class of GABA derivatives.

The synthesis of pharmacophoric hybrids of ameltolide-GABA-amides was accomplished as presented in Scheme 1. The coupling of the 2,6-dimethylphenyl amino group with GABA was achieved via an intermediate acetanilide obtained by chloroacetylation reaction in dichloromethane and the latter was condensed with

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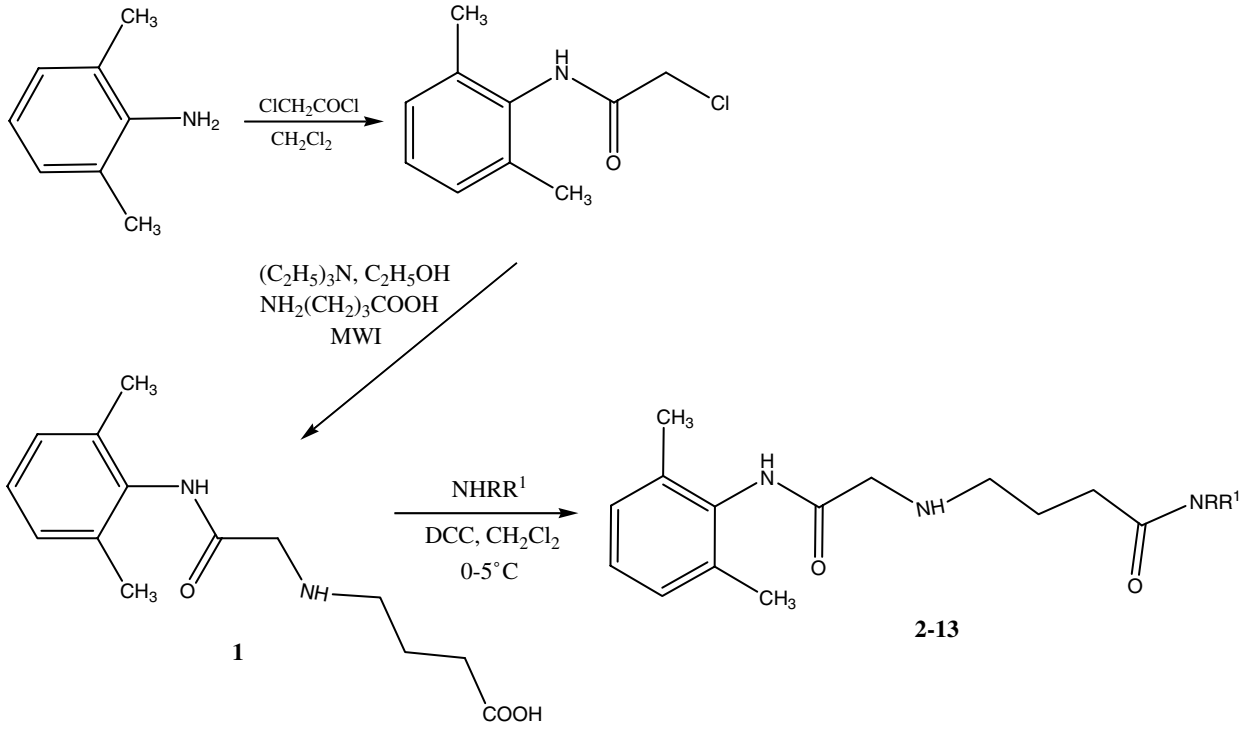

Scheme 1. Synthetic protocol of the titled compounds.

GABA in ethanol in the presence of triethylamine under microwave[10] for 30 s at 60% intensity to yield 75% of 4-(2-(2,6-dimethylphenylamino)-2-oxoethylamino)butanoic acid (**1**).[14] The 4-(2-(2,6-dimethylaminophenylamino)-2-oxoethylamino)-*N*-(aryl/alkyl/heteroalkyl) butanamides (**2**–**13**) were obtained by reaction of **1** with respective anilines or alkyl amines or secondary amines at ice cold condition (0–5 °C) in presence of *N*,*N*′-dicyclohexyl carbodiimide (DCC) (Table 1). The purity was assessed by TLC; and the assignments of the structures were based on elemental and spectroscopic methods of analysis. The IR spectral data of the synthesized compounds (**1**–**13**) were identical in the following aspects, 3200–3100, 3030, 1640, 1400, 780 cm^{-1}. In the ^1H NMR spectra the signals of the respective protons of the prepared butanamides were verified on the basis of their chemical shifts, multiplicities, and coupling constants. The spectra showed a signal at $\delta \sim 2.0$ ppm correlated to be the amino group at γ carbon of GABA; NH proton attached to aromatic nucleus appeared at $\delta \sim 10.02$ ppm in addition to a singlet signal at $\delta \sim 3.49$ ppm corresponding to the methylene proton of $COCH_2N$ group. Elemental analysis results were within ±0.4% of the theoretical values. log *P* for all the synthesized compounds were calculated using chemdraw ultra 9.0 (Cambridge software).

The anticonvulsant activity of the synthesized compounds (**1**–**13**) was determined using three animal models of seizure which included maximal electroshock seizure[11] (MES), subcutaneous pentylenetetrazole[12] (scPTZ), and intraperitoneal picrotoxin[13] (ipPIC)-induced seizure threshold tests. The acute neurological toxicity was determined in the rotorod test. The results are summarized along with the data for standard drugs in Table 2. All of the compounds except **4**, **8**, **12**, and **13** showed activity in the MES screen at 100 mg/kg except **10** at 300 mg/kg after 0.5 h of drug administration indicative of their ability to prevent seizure spread. In the subcutaneous pentylenetetrazole (scPTZ) screen, a test used to identify compounds that elevate seizure threshold, only two compounds with dimethyl phenyl group (**6** and **7**) showed protection at 300 and 30 mg/kg, respectively. In the scPIC-induced seizure threshold test, all of the compounds exhibited activity indicative of the possible involvement of GABA-mediation in the anticonvulsant action. The compound 2,6-dimethylanilide (**7**) showed pronounced activity at 10 mg/kg and compounds that showed protection at 30 mg/kg include **1**, **3**, **4**, **9**, and **13**. All other compounds showed activity at 100 mg/kg. In general, it appears that except compounds **4**, **8**, **12**, and **13**, all other compounds were found to be effective in at least two models of seizure with compounds **6** and **7** effective in three animal models of seizures. In the acute neurological toxicity screen, the compounds **1**–**5**, **7**–**9**, and **13** emerged as promising anticonvulsants with less or no neurotoxicity. There was no separation between the anticonvulsant dose and the neurotoxic dose (300 mg/kg) for compounds **6**, and **10**–**12**. Compound 4-(2-(2,6-dimethylaminophenylamino)-2-oxoethylamino)-*N*-(2,6-dimethylphenyl) butanamide (**7**)[15] emerged as the most potent derivative effective in all the three animal models of seizure with no neurotoxicity at the anticonvulsant dose when compared to the standard drugs.

In the present study, we have demonstrated that combination of ameltolide-GABA-amide pharmacophores