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Pyridazinone hybrids: Design, synthesis and evaluation as potential anticonvulsant agents

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ABSTRACT

A series of new hybrid benzothiazole containing pyridazinones derivatives were designed and synthesized fulfilling all the pharmacophoric requirements essential for the anticonvulsant activity. *In-silico* and *in vitro* studies revealed that some of these hybrid derivatives demonstrated admirable GABA AT inhibitory activity. An attempt has also been made to validate the results of *in vitro* GABA AT inhibition of the most potent compound SPS-5F (IC_{50} 9.10 μM) through *in vivo* anticonvulsant screening. Compound SPS-5F administration significantly increases the whole brain GABA level, might be through the inhibition of GABA AT enzyme.

1. Introduction

Epilepsy is a serious and common neurological condition which is characterized by seizures due to hyper synchronous discharges in the brain. According to an epidemiological study, epilepsy is the third most destructive neurological disorder, affecting>50 million people worldwide with almost 90% of these patients being in developing countries [1]. Antiepileptic drugs (AEDs) act by different mechanism mainly through enhancement of γ-amino butyric acid (GABA) mediated inhibitory neurotransmission, modulation of voltage-gated ion channels (Na^+, Ca^{2+}) and reduction of excitatory, particularly glutamate-mediated neurotransmitter [2]. Despite the large numbers medicines available for treatment of epilepsy, still there is no complete cure for epilepsy. Unfortunately, current AEDs suppress the seizure of 70% epileptic patients and rest of the epileptic patients suffers from refractory epilepsy. Moreover, all available AEDs suffer from serious disorder, such as minimal brain impairment, anemia and hepatic failure [3]. Thus, there is an urgent demand for development of more efficacious, safe and non-toxic agents in the area of Antiepileptic drug development.

Pyridazinone is an important pharmacophore possessing the wide range of biological applications. A number of pyridazinone analogue have been reported as anticonvulsant lead compounds [4]. Apart from antiepileptic activity of pyridazinone nucleus, other activity includes antidepressant [5], antihypertensive [6–8], antithrombotic [9], cardiotonic [10], antibacterial [11] and diuretics, etc. [12]. Moreover, several benzothiazole derivatives are also shown to have seizure protective effects [13]. In continuation with previous work [14], some new benzothiazole-pyridazinone hybrids were further synthesized and evaluated for their anticonvulsant activity. The designed benzothiazole-pyridazinone derivatives possess all the essential pharmacophoric elements necessary for anticonvulsant activity [15]. These are hydrogen bonding domain (HBD), electron donor moiety (D) and distal hydrophobic domain (R) which influence on blood brain barrier (BBB) diffusion and pharmacokinetic properties of the anticonvulsants. Pyridazinone are cyclized derivatives of β-aroyl propionic acids which contains GABA like pharmacophore [16]. Thus benzothiazole pharmacophore is being introduced to the pyridazinone nucleus (cyclized GABA) as molecular hybrid, in search of potent anticonvulsant agents (Fig. 1).

The replacement, refinement, and reduction of animals in preclinical research have gained much attention in recent years. Reducing candidate drug attrition through better predictive *in silico* and *in vitro* assays, can effectively reduce overall animal use (Fig. 2) [17]. Therefore, the present work describes the design, synthesis, *in silico* and *in vitro* anticonvulsant activity of pyridazinone derivatives. All the compounds were subjected to prediction of

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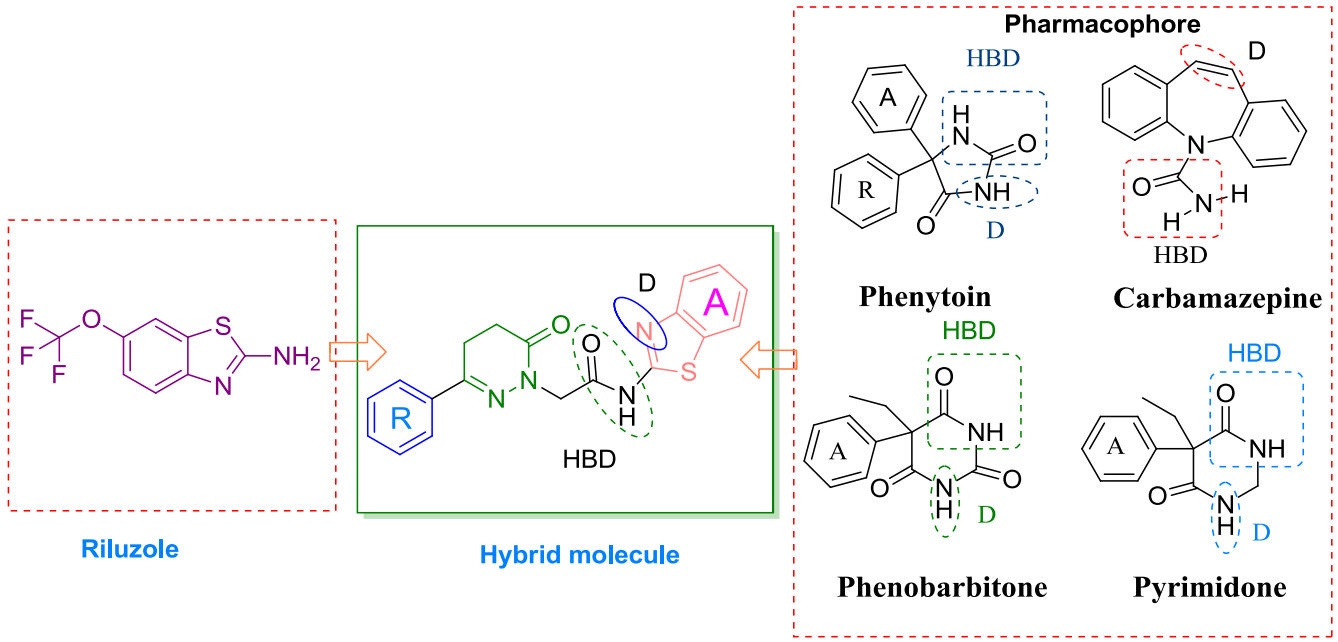

Fig. 1. Design of titled compounds bearing all the essential anticonvulsant pharmacophoric groups.

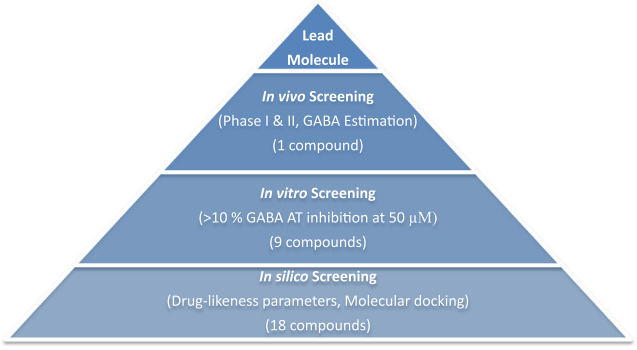

Fig. 2. Approach for minimizing animal use in pharmaceutical development of anticonvulsants.

drug-likeness parameters so as to avoid the late stage clinical failures followed by virtual screening and *in vitro* GABA transaminase (GABA AT) inhibition studies. The most potent compound was finally assessed for its *in vivo* efficacy in phase I & II anticonvulsant screenings.

2. Result and discussion

2.1. Chemistry

Various β-aroyl propionic acids (SPS-1a to SPS-18a) were initially synthesized according to the Lewis acid-catalyzed Friedel-Crafts acylation of appropriate hydrocarbon with succinic anhydride [18]. The condensation of above synthesis acids (SPS1a-SPS18a) with hydrazine hydrate afforded different 6-substitued-4,5-dihydropyridazine-3(2H)-one(SPS1b-SPS18b) [19]. The synthetic route of synthesized derivatives is outlined in Scheme 1. The reaction mixture of 6-substitued-4,5-dihydropyridazine-3(2H)-one and *N*-(benzo[*d*]thiazol-2-yl)-2-chloroacetamide was carried out in dry DMF in the presence of potassium carbonate for 5 h and completion reaction was confirmed by TLC. The final mixture was poured over ice cooled 10% aqueous ammonium chloride solution. Insoluble compound thus obtained was filtered and recrystallized.

The completion of reactions and purity of synthesized compounds was confirmed by TLC using ethyl acetate:hexane (4:6) as solvent system and melting points were recorded. The structures were characterized by elemental and spectral data analyses. The SPS-5F recorded IR spectra in the range of 1632 and 3320 cm^{-1} which shows the appearance of C═O and N—H absorption bands respectively. A broad singlet proton signal (-NHD_2O exchangeable) was shown by ^1H NMR spectra at δ 9.66 ppm. SPS-5F having methylene proton displayed a characteristic singlet signal at δ 3.89 ppm and the triplet peaks at δ 2.92 and 2.43 ppm confirmed the pyridazinone proton. Compound SP-5F with ^{13}C NMR spectra as a prototype revealed two upfield peaks at δ 54.6 ppm of methylene carbons and the carbonyl carbon appeared downfield at δ 165.8 ppm.

2.2. In silico studies

2.2.1. Drug-likeness parameters

An *in silico* studies of drug-likeness parameters has always been critical filter for drugs with poor pharmacokinetic properties. Therefore, in present investigation all the compounds were subjected to prediction of molecular properties and drug-likeness parameters so as to minimize perturbing preclinical *in vivo* studies and late stage clinical failures. CNS bioavailability of a drug is greatly affected by physicochemical descriptors such as logP (partition coefficient), molecular weight (MW), hydrogen bond acceptors and donors counts in a molecule. Therefore, partition coefficient of all the compounds were determined experimentally using octanol-phosphate buffer method and the data were presented in Table 1. All the compounds were found to be lipophilic enough (>2) and have potential to cross the blood brain barrier to have potent anticonvulsant action. Rapid onset and shorter duration of action may be reasoned due to high lipophilicity of the drugs. More importantly, the logP values were found to be in the optimal range of 2.95–4.63 (≤5), otherwise it may cause CNS toxicities like motor impairment, etc. The topological polar surface area (TPSA) was calculated with Molinspiration and the results