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Design, synthesis and anticonvulsant evaluation of *N*-(benzo[*d*]thiazol-2-ylcarbamoyl)-2-methyl-4-oxoquinazoline-3(4*H*)-carbothioamide derivatives: A hybrid pharmacophore approach

Sachin Malik [a], Radhe Shyam Bahare [b], Suroor Ahmad Khan [a,*]

[a] Department of Pharmaceutical Chemistry, Faculty of Pharmacy Jamia Hamdard, New Delhi 110062, India
[b] Department of Pharmaceutical Sciences, Birla Institute of Technology, Mesra, Ranchi, Jharkhand 835215, India

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ABSTRACT

Novel *N*-(benzo[*d*]thiazol-2-ylcarbamoyl)-2-methyl-4-oxoquinazoline-3(4*H*)-carbothioamide derivatives were synthesized and evaluation of their anticonvulsant effects was done using various models of experimental epilepsy. Initial anticonvulsant activities of the compounds were investigated using intraperitoneal (i.p.) maximal electroshock shock (MES), subcutaneous pentylenetetrazole (*sc*PTZ) seizure models in mice. The quantitative assessment after oral administration in rats showed that the most active was 2-methyl-4-oxo-*N*-(6-(trifluoromethoxy)benzo[*d*]thiazol-2-ylcarbamoyl)quinazoline-3(4*H*)-carbothioamide (**SA 24**) with ED_{50} values of 82.5 μmol/kg (MES) and 510.5 μmol/kg (*sc*PTZ). This molecule was more potent than phenytoin and ethosuximide which were used as reference antiepileptic drugs. To explain the possible mechanism for anticonvulsant action, some of the selected active compounds were subjected to GABA (γ-amino butyric acid) assay and AMPA ((*S*)-2-amino-3-(3-hydroxyl-5-methyl-4-isoxazolyl) propionic acid) induced seizure test.

1. Introduction

Epilepsy is a heterogeneous group of disorders characterized by neuronal hyperexcitability and hypersynchronous neuronal firing presented with episodes of sensory, motor or autonomic phenomenon with or without loss of consciousness [1]. Epilepsy is one of the most common disorders of the brain, affecting more than 50 million individuals worldwide [2,3]. Lamotrigine, tiagabine, felbamate, pregabalin, stiripentol and topiramate are recent antiepileptic drugs (AEDs) which are effective toward only 60–80% of patients companioned with undesirable side effects, such as headache, nausea, anorexia, ataxia, hepatotoxicity, drowsiness, gastrointestinal disturbance, gingival hyperplasia, and hirsutism [4–8]. In many cases the clinical use of AEDs is restricted by their side effect. Therefore, a substantial need remains to discover novel chemical entities for the development of new effective and safer AEDs. Quinazolin-4(3*H*)-one **1** and their derivatives constitute a significant class of heterocyclic compounds and are shown to have potent central nervous system (CNS) activities such as anticonvulsant and CNS depressant [9–14]. 2-Aminobenzothiazoles and derivatives like 2-benzothiazolamines, benzothiazoles containing sulphonamide and guanidines emerged as new classes of anticonvulsant agents and one of its derivatives, riluzole (2-amino-6-trifluoromethoxy benzothiazole) **4** is clinically available drug reported to diminish sensitivity of one of the sub types from the family of ionotropic glutamate receptors (iGluRs) (*S*)-2-amino-3-(3-hydroxyl-5-methyl-4-isoxazolyl)propionic acid (AMPA) and also reported to show no effect on pentylenetetrazole (PTZ) induced convulsions in moderate doses [15–17]. Over activities of iGluRs are linked to mediate excitatory synaptic transmission. In particular AMPA antagonists have shown anticonvulsant and neuroprotective activity in various animal models [18]. They also offer therapeutic innervations without side effects associated with inhibition of *N*-methyl-D-aspartate (NMDA) receptors [19].

A literature survey revealed that the presence of a substituted aromatic ring at position 3 and a methyl group at position 2 on quinazolin-4(3*H*)-one nucleus is a necessary requirement for CNS depression and anticonvulsant activities [20]. Methaqualone **2a** (2-methyl-3-*o*-tolyl-4(3*H*)-quinazolinone) is a well known anticonvulsant and sedative-hypnotic containing quinazolin-4(3*H*)-one nucleus responsible for its activity and its 3-(2-chlorophenyl)-2-methyl-4(3*H*)-quinazolinone analog (Mecloqualone) **2c** was found to be 1.5 times more potent than phenytoin in maximal electroshock (MES) induced convulsions and 10 times more potent than

* Corresponding author. Tel.: +91 11 26059681x5612, +91 11 26059688x5613, +91 8860135605 (Mob); fax: +91 11 6988874.
E-mail address: sakhanpchem@gmail.com (S.A. Khan).

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troxidone against PTZ induced seizure [21–23]. It has been reported that convulsant induced seizure by inhibiting γ-amino butyric acid (GABA) neurotransmission (such as PTZ) and $GABA_A$ antagonist [24]. $GABA_A$ agonist shows therapeutic effects by increasing chloride influx via brain chloride channel or directly antagonizes the inhibitory spinal reflex of glycine. Quinazolin-4(3*H*)-one derivatives reported to control seizure induced by MES and PTZ *i.e.* exhibited broad spectrum of activity in animal models possibly via GABA activation [25–27].

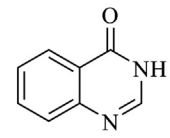
In view of the above mentioned knowledge based facts of different pharmacophores and in continuation of our research program we have synthesized benzothiazole moiety, quinazolinone nucleus along with incorporated urea and electronic environment to get single molecular framework in the form of titled compounds **5** comprising the four pharmacophoric elements that are necessary for good anticonvulsant activity as suggested by Pandeya et al. (Fig. 1) [28]. These elements are present in many currently used antiepileptic drugs. These are hydrophobic domain (A), hydrogen bonding domain (HBD), electron donor moiety (D), and distal hydrophobic domain (R). The attachment of a second aryl ring designated as the distal ring to the proximal aryl ring to increase the van der waal's bonding at the binding site and to increase potency have also been reported [28,29].

Intrigued by the above observations, and in an attempt to design and develop new potential anticonvulsant agents, a hybrid pharmacophoric approach was adopted in which the quinazolin-4(3*H*)-one and benzothiazole nuclei were hybridized in one structure hoping to synergize the anticonvulsant potential of both groups. The validity of this design was assessed through anticonvulsant screening of the target compounds.

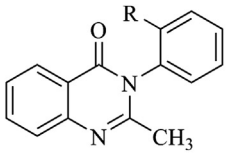
2. Result and discussion

2.1. Chemistry

The titled compounds (**SA 1**–**30**) described in this study were prepared as outlined in Scheme 1. Synthesis of substituted-benzothiazol-2yl-amines (**1a**–**j**) and substituted benzothiazol-2yl-



Quinazol-4(3H)-one
(1)



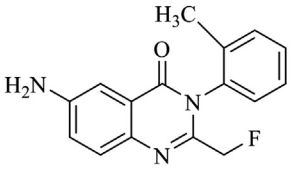
(2)

R - CH_3 = Methaqualone (2a)

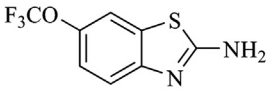
R - C_2H_5 = Etaqualone (2b)

R - Cl = Mecloqualone (2c)

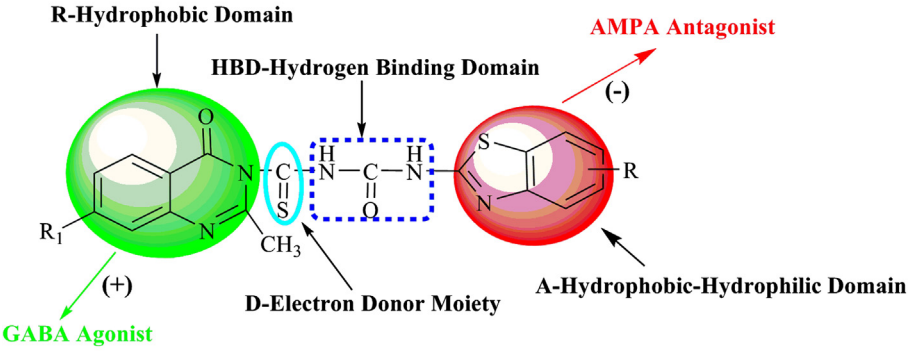
R - Br = Mebroqualone (2d)



Afloqualone
(3)



Riluzole
(4)



Overlay of pharmacophores and biological targets in titled compounds SA(1-30)
(5)

Fig. 1. Chemical structure of (1) quinazol-4(3*H*)-one, (2) reported quinazolinones as anticonvulsants, (3) afloqualone, (4) riluzole, (5) titled compounds **SA** (**1**–**30**).