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Short communication

Synthesis of novel bioactive derivatives of 3-(4-chlorophenyl)-2-hydrazino-5,6,7,8-tetrahydrobenzo(*b*)thieno[2,3-*d*]pyrimidine-4(3*H*)-ones

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ABSTRACT

A series of triazolo[4,3-*a*]tetrahydrobenzo(*b*)thieno[3,2-*e*]pyrimidine-5(4*H*)-ones (**12a**–**n**) were synthesized and evaluated for CNS depressant, skeletal muscle relaxant and anticonvulsant activities by photoactometer, Rotarod and pentylenetetrazole induced the convulsions method respectively in Swiss albino mice. Diazepam was used as standard drug. The five derivatives **12b**, **12c**, **12d**, **12i** and **12m** showed the CNS depressant and skeletal muscle relaxant activities comparable to those of diazepam at a dose of 5 mg/kg. These derivatives also exhibited good activity when tested for anticonvulsant activity in mice at different dose levels. The ED_{50} values for these derivatives are in the range of 4.40–9.33 mg/kg.

1. Introduction

Central nervous system (CNS) depressant agents are an important class of drugs, which are useful in the treatment of anxiety and related emotional disorders. Among the different classes of CNS depressant agents, benzodiazepines were found to have good activity and well accepted by patients. They are acting through benzodiazepine receptors, which are adjacent to γ-amino butyric acid (GABA) receptors. GABA is the major inhibitory neurotransmitter in the brain. It controls excitability of many central nervous system pathways. The intimate relationship between the benzodiazepine sites and GABA binding sites has been studied [1]. GABA exerts its physiological effects by binding to the different receptor types in the neuronal membrane: $GABA_A$, $GABA_B$ and $GABA_C$ receptors. The $GABA_B$ receptor belongs to the G-protein-coupled receptors super family, while the $GABA_A$ [2] and $GABA_C$ [3] are ligand gated chloride ion channel complexes. $GABA_A$ receptors, which are responsible for the majority of neuronal inhibition in the mammalian CNS, mediate the action of many pharmacological useful agents, including benzodiazepines, barbiturates, neuroactive steroids, anesthetics and convulsants [4,5]. At least two classes of compounds have been identified by their ability to modulate GABA neurotransmission by interacting with receptor complex. Positive modulation, which leads to an increase in GABA-induced chloride ion flux, is produced by agonist class-1 i.e. benzodiazepine type e.g. diazepam (**1**), and triazolum (**2**) [6,7] and class-2 i.e. non-benzodiazepine type cyclopyrones, e.g. zopiclone (**3**), triazolopyridazine like compound (**4**) [8] suriclone (**5**) [9] and CL 218,872 (**6**), imidazopyridines e.g. zolpidem (**7**) [10] as shown in Fig. 1. Some non-benzodiazepine ligands are apparently selective for $GABA_A$ receptors, which have reduced sedation. All these non-benzodiazepine ligands were found to contain common polyaza system. The condensed triazole and 1,2,4-triazole are also found to contain polyaza ring system and which is present in a potent CNS depressant agent alprazolam.

The literature survey reveals that triazoles were reported for analgesic, anti-inflammatory, anti-allergic and CNS depressant activities. A large number of references [11–17] showed that condensed 1,2,4-triazoles are having excellent CNS depressant and anticonvulsant activities. Significant CNS depressant activity was reported for triazoles especially triazoloquinazoline [18], triazolopyrimidines [19], triazolothienopyrimidine [20], 1,3,4-thiadiazolotetrahydrobenzothienopyrimidine [21] and 1,3,4-thiadiazole-quinazoline [22] has given an impetus to synthesize some non-benzodiazepine ligands (bioisosteric triazolotetrahydrobenzo(*b*)thienopyrimidines), which are devoid of typical

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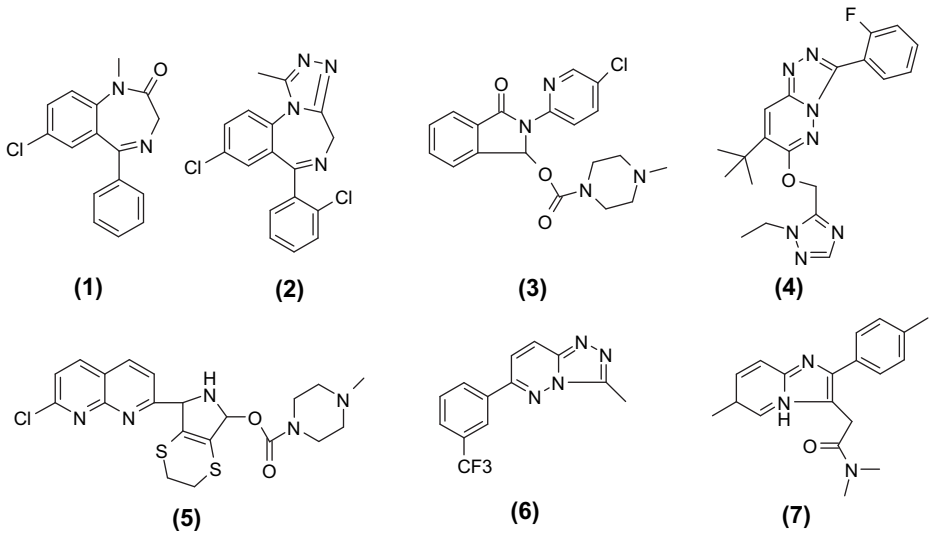


Fig. 1.

benzodiazepine mediated side effect such as physical dependence, amnesia, over sedation.

A series of 14 novel derivatives of triazolo[4,3-*a*]tetrahydrobenzo(*b*)thieno[3,2-*e*]pyrimidine-5(4*H*)-ones were synthesized and evaluated for CNS depressant, skeletal muscle relaxant and anticonvulsant activities.

2. Chemistry

Compound 3-(4-chlorophenyl)-2-hydroxy-5,6,7,8-tetrahydro benzo(*b*)thiophene[2,3-*d*]pyrimidine-4(3*H*)-one (**9**) was synthesized from 2-amino-3-carbethoxy-4,5,6,7-tetrahydrobenzo(*b*)thiophene (**8**) [23] on treatment with solution of *p*-chlorophenyl isocyanate at 120 °C and followed by cyclization with potassium hydroxide solution. The compound (**9**) on treatment with mixture of phosphorus oxychloride and phosphoruspentachloride yielded the 2-chloro-3-(4-chlorophenyl)-5,6,7,8-tetrahydrobenzo(*b*)thiophene[2,3-*d*]pyrimidine-4(3*H*)-one (**10**) at refluxing condition. The chloro derivative (**10**) on treatment with hydrazine hydrate in methanol yielded 3-(4-chlorophenyl)-2-hydrazino-5,6,7,8-tetrahydrobenzo(*b*)thiophene[2,3-*d*]pyrimidine-4(3*H*)-one (**11**) as shown in Scheme 1. The title compounds (**12a**–**n**) were prepared by treating hydrazino derivative (**11**) with various one carbon donors such as triethyl orthoformate, triethyl orthoacetate, propionic acid, butyric acid, isobutyric acid, chloroacetyl chloride, benzoyl chloride, cyanogen bromide, ammonium thiocyanate and benzoyl chloride, methyl isothiocyanate, ethyl isocyanate, phenyl isothiocyanate, carbon disulphide. The title compounds (**12a**–**n**) were synthesized by the route depicted in Scheme 2.

3. Biological activity

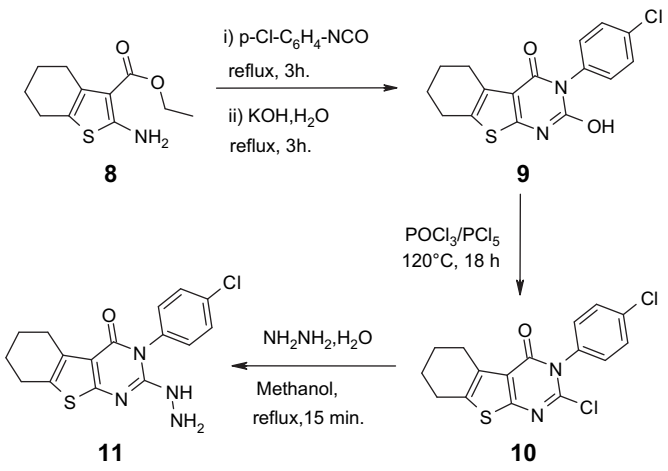
The title derivatives (**12a**–**n**) were evaluated for CNS depressant activity by photoactometer and skeletal muscle relaxant activity (motor coordination) by Rotarod method at a dose of 5 mg/kg in Swiss albino mice. The activity was compared with diazepam as a standard drug. Of the various compounds tested for CNS depressant and skeletal muscle relaxant activities, the most active five derivatives **12b**, **12c**, **12d**, **12i** and **12m** were evaluated for anticonvulsant activity at different dose levels. The results of the various activities are presented in Tables 1–4.

4. Result and discussion

Fourteen derivatives were synthesized and their structure was confirmed by IR, NMR, mass spectroscopy and elemental analysis. All the fourteen derivatives tested for CNS depressant activity by photoactometer (Table 1) shown a decrease in locomotor activity between 46.15% and 90.40%.

The five derivatives (**12b**, **12c**, **12d**, **12i** and **12m**) showed comparable CNS depressant activity at a dose of 5 mg/kg *i.p.* after 60 min of administration to that of standard drug diazepam (89.32%) at a dose of 5 mg/kg. All the compounds except **12h** exhibited more than 50% decrease in locomotor activity after 60 min.

The title derivatives were also tested for skeletal muscle relaxant activity (motor coordination) by Rotarod method (Table 2). In this model, the five derivatives (**12b**, **12c**, **12d**, **12i** and **12m**) showed the superior activity in the range from 102.75% to 116.62% when compared with diazepam (100%) at a dose of 5 mg/kg. The other derivative showed the activity in the range of 49.02–92.60%



Scheme 1. Synthesis of hydrazino intermediate (**11**).