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Original Article

Synthesis and anticonvulsant activity of some newer dihydro-pyrimidine-5-carbonitrile derivatives: Part II

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الملخص

أهداف البحث: تكوين مشتقات دايهيدرو- بايريميدين -٥-كاربونيترايل (٥-٢٣)، كامتداد من السلسلة السابقة وتقييم قدراتها كمضادات للصرع.

طرق البحث: تم تجميع وتمييز المركبات المصممة باستخدام الأشعة تحت الحمراء، والرنين المغناطيسي النووي والكتلة، وتم تقييمها لمعرفة نشاطها كمضادات للصرع باستخدام الصدمات الكهربية القصوى المسببة لنوبات الصرع، وطرق بنتيالنتيترازول تحت الجلد. كما تم فحص المركبات ذات النشاط الملحوظ للسمية العصبية بواسطة اختبار روتورد.

النتائج: وجد أن المركبان ١٧ و ٢٣ هما الأكثر نشاطا بجرعة ٣٠ مجم كجم$^{-1}$ بين النصف ساعة و ٤ساعات في كلا النموذجين، ولم تظهر ضعفا النشاط الحركي حتى بجرعات عالية.

الإستنتاجات: وجد أن المركبات المصممة حديثا هي أفضل بالمقارنة بالمركبات المعروفة سابقا. كما أظهرت هذه الدراسة أيضا أن زيادة الانجذاب يعطي علاقة مباشرة مع نشاط مضادات الصرع،

الكلمات المفتاحية: الصرع؛ مضاد الصرع؛ السمية العصبية؛ الرنين المغناطيسي النووي؛ الأشعة تحت الحمراء

Abstract

Objectives: To synthesize dihydro-pyrimidine-5-carbonitrile derivatives (**5–23**), as an extension of the previous series, and to evaluate their anticonvulsant potential.

Methods: The designed compounds were synthesized and characterized using infrared (IR), nuclear magnetic resonance (NMR) and mass spectroscopy and were evaluated for anticonvulsant activity using the maximal electroshock seizure (MES) and *subcutaneous* pentylenetetrazole (*sc*PTZ) methods. Compounds with appreciable activity were investigated for their neurotoxicity using the rotarod test.

Results: Compounds **17** and **23** were found to be most active at a dose of 30 mg kg^{-1} at 0.5 h and 4 h in both models and did not exhibit motor impairment activity, even at higher doses.

Conclusion: The newer designed compounds were found to be better than previously reported compounds. This study also shows that increased lipophilicity is directly related to the anticonvulsant activity.

Keywords: Anticonvulsant; Epilepsy; Infrared; Neurotoxicity; Nuclear magnetic resonance

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Introduction

Hybrid molecules, an emerging trend containing two or more structural domains, acting on the same or different targets have been reported to exhibit diverse pharmacological activities, including anticonvulsant activity. Recently, following the hybrid approach, compounds containing a combination of pyridines and pyrrolidones[1] (**I**) and thiazoles coupled to an oxoquinazoline moiety (**II**) have been synthesized, some of which exhibit comparable or even higher anticonvulsant activity[2] than the standard drug phenytoin (Figure 1).

Among various heterocycles, pyrimidine derivatives are quite significant because they have been found to possess diverse pharmacological activities.[3–5] The well-known anticonvulsant drugs phenobarbitone (**III**) and primidone (**IV**) possess a dihydropyrimidine ring (Figure 2).

Similarly, Schiff bases have been reported to elicit such activities.[6,7]

Due to the anticonvulsant activities of pyrimidine and Schiff bases, synergistic activity was expected upon attaching the two moieties. In this context, we previously synthesized 6-oxo-4-(4-methoxy-phenyl)-1,6-dihydropyrimidine-5-carbonitrile derivatives as anticonvulsants. Among these derivatives, compounds with bromo (**V**) and nitro substitution (**VI**) on ring **C** were found to be the most active (Figure 3) with lower neurotoxicity.[8]

Following this,[8] we have now synthesized newer derivatives (**5–23**) by replacing the methoxy group with hydrogen and chloro groups on ring **A** (Figure 4) to examine the effect of increasing the lipophilicity on anticonvulsant activity using the MES[9,10] and *sc*PTZ[11] methods. Compounds with appreciable activity were investigated for neurotoxicity using the rotarod[12] test.

Materials and Methods

Chemistry

The reagents/chemicals/solvents used during the course of these studies were procured from Merck (India), SD Fine and CDH Laboratories as 'synthesis grade' and were used without purification. Melting points (mp) were recorded in open glass capillaries using a Kjeldahl flask containing liquid paraffin. The purity of the compounds was investigated by thin layer chromatography (TLC) on silica gel G plates using benzene:acetone (7:3) as the solvent system. Spots were located either under ultraviolet (UV) light or through exposure to iodine vapours.

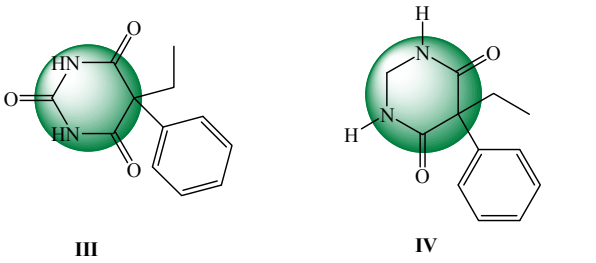

Figure 2: Anticonvulsant drugs bearing dihydropyrimidine ring.

IR spectra were recorded using a Bruker alpha-T spectrophotometer. ^{1}H-NMR spectra were recorded on a Bruker Avance 400 MHz instrument in $CDCl_3$ or DMSO-d_6 using tetramethylsilane [$(CH_3)_4Si$] (TMS) as an internal standard. The ^{13}C-NMR spectra of the compounds were recorded on a Bruker Avance 100 MHz instrument in DMSO-d_6. Chemical shifts (δ) are reported in parts per million (*ppm*) downfield from TMS, and coupling constants (*J*) are reported in hertz. Mass spectra were recorded using a Waters SYNAPT UPLC-MS/MS operating with Mass Linux V4.1 software. Elemental analysis (C, H, N) was performed using a PerkinElmer model 240 analyser, and elements were found within $\pm$ 0.4% of the theoretical values.

General procedure for the synthesis of 2-mercapto-6-oxo-4-aryl-1,6-dihydropyrimidine-5-carbonitrile derivatives ***(1–2)***

These derivatives were synthesized following the previously reported method.[13]

2-Mercapto-6-oxo-4-phenyl-1,6-dihydropyrimidine-5-carbonitrile ***(1)*****:**. mp: 299–300°C[13]

4-(4-Chlorophenyl)-2-mercapto-6-oxo-1,6-dihydropyrimidine-5-carbonitrile ***(2)***. mp: 281–282°C[13]

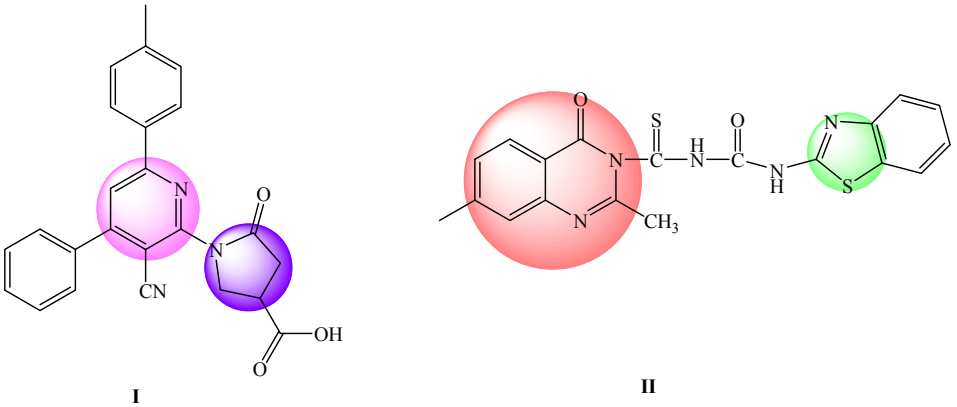

Figure 1: Hybrid molecules reported as anticonvulsant agents.