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ORIGINAL ARTICLE

Synthesis, characterization and biological behavior of some Schiff's and Mannich base derivatives of Lamotrigine

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Abstract A series of various Schiff's and Mannich base derivatives (N1–2 & ND1–6) of Lamotrigine with isatin and substituted isatin were synthesized to get more potent anticonvulsant agents. The starting material for the synthesis of various new Schiff's and Mannich base derivatives was isatin (1H-indole- 2, 3-dione) which in turn was prepared from substituted isonitrosoacetanilide using aniline. Lamotrigine reacts with isatin & substituted isatin gave Schiff's bases (N1–2) which on reaction with various secondary amines (dimethylamine, diethylamine, morpholine) produced Mannich bases (ND1–6). The structures of newly synthesized compounds were characterized by using TLC, UV, FT-IR, 1HNMR and studied for their anticonvulsant activity. Anticonvulsant activity of all the derivatives was evaluated by MES method using phenobarbitone sodium & Lamotrigine as standard drugs and % reduction of time spent by animals in extension, flexion, clonus, and stupor phase were noted. Compounds ND-4 and ND-6 showed significant anticonvulsant activity when compared with that of standard drugs. The remaining all compounds show moderate activity. Biological activity data of the synthesized derivatives revealed that, the synthesized derivatives are good anticonvulsant agents as compared to Lamotrigine.

1. Introduction

Lamotrigine is a member of drug class of phenyltriazine, used for the adjunctive treatment of partial seizures in epilepsy and generalized seizures of Lennox–Gastaut syndrome (Lebre et al., 2003; Qian et al., 2009; Sagud et al., 2008; Calabrese et al., 1999). It is also used for the maintenance treatment of bipolar I disorder and depression. (Barbee and Jamhour,

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2002; Botts and Raskind, 1999). Isatin is an endogenous molecule identified in human beings which has anticonvulsant (Bhattacharya and Chakrobarti,1998; Gursoy and Karali, 1996; Popp and Donogn, 1979), antimicrobial, tuberculostatic, analgesic and various other pharmacological activities. Extensive literature review has been made regarding the activities of the isatin, especially for its anticonvulsant, antimicrobial, analgesic and anti-inflammatory activities (Silva et al., 2001; Sridhar et al., 2001). Schiff's bases and Mannich bases of isatin (Pandeya et al., 2000) were reported to possess anticonvulsant activity and various other pharmacological activities (Aboul-fadl and Aboul-wafa, 2010; Agarwal et al., 2006; Chakraborty et al., 2010; Liu et al., 2005; Pandeya et al., 2002; Verma et al.,2004).

Literature review indicates that, Lamotrigine is less potent and shows side effects. In order to increase the potency and reduce the side effects of Lamotrigine, we have considered isatin as one of the conjugate which can be coupled with Lamotrigine due to its structural similarities with already known anticonvulsants such as Mephobarbital, Phenytoin. Herein we report the synthesis, characterization and in vivo anticonvulsant activity of Lamotrigine derivatives (Scheme 1).

2. Materials and methods

2.1. Materials

All the reagents used for synthesis were obtained from Sigma Aldrich and Loba Chem Ltd. (India). All the solvents used in these studies were dried and distilled before use. Melting points were determined by using Veego digital melting point apparatus (VMP-PM, 32/1104) and are uncorrected. All the reactions were monitored by thin layer chromatography (TLC) using Silica gel G (60 mesh). The solvent system used includes Acetone: Toluene: Ammonia (7:3:1). The IR spectra (KBr) were recorded on a FTIR spectrophotometer with Diffuse Reflectance attachment (Shimadzu 8400S). UV studies were carried out on a UV Visible spectrophotometer (Shimadzu 1700) and the λ_{max} of the respective synthesized compounds was determined using ethanol as the solvent. ^{1}H NMR spectra were recorded on NMR spectrometer (Varian Mercury YH 300) with DMSO as a solvent with TMS as an internal standard.

2.2. Methods

2.2.1. Synthesis of 3,3′{[6-(2,3-dichlorophenyl)-1,2,4-triazine-3,5 diyl]dinitrolo}bis-(1,3-dihydro-2H-indol-2-one) N-1

To 20 ml of hot ethanol, 0.735 gm (0.005 mol) of isatin and 0.640 gm (0.0025 mol) of Lamotrigine were dissolved. To this mixture 1.0 ml of glacial acetic acid was added. The reaction mixture was then refluxed on a water bath in a 250 ml round bottomed flask for 8 h. Completion of the reaction was monitored by TLC. The mixture was allowed to stand for 24 h at room temperature. The product was collected and recrystallized with ethanol-chloroform mixture.

N-1: Yield: 76%; m.p.: 145–148 °C. IR (KBr) (cm^{-1}): 3444 (NH), 3088 (Ar-CH), 1731 (C═O), 1616(C═N), 771 (C-Cl); ^{1}H NMR (DMSO) δ (ppm): 6.6–7.7 (m, Ar-H), 10.29 (s, 2H, NH); Anal. Calcd for $C_{25}H_{13}Cl_2N_7O$: C, 58.38; H, 2.55; N, 19.06; Found: C, 58.31; H, 2.48; N, 19.01%.

2.2.2. Synthesis of 3,3′{[6-(2,3-dichlorophenyl)-1,2,4-triazine-3,5-diyl]dinitrolo}bis-(5-chloro-1,3-dihydro-2H-indol-2-one) N-2

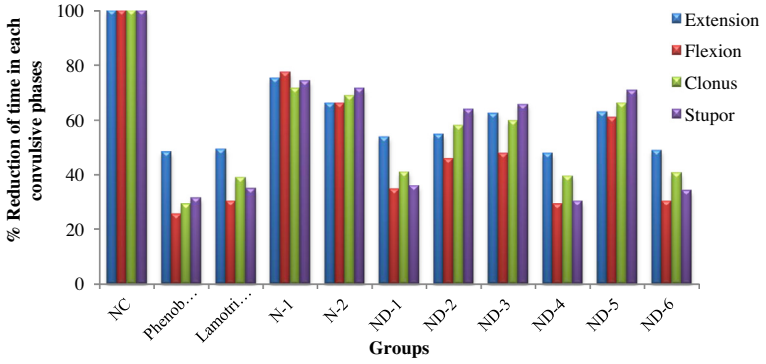
N-2 obtained from 5-choroisatin (0.90 gm, 0.005 mol) under the same conditions as describe above for N-1.

N-2: Yield: 73%; m.p.: 162–165 °C. IR (KBr) (cm^{-1}): 3309 (NH), 3070 (Ar-CH), 1741 (C═O), 1612 (C═N), 798 (C-Cl); ^{1}H NMR (DMSO) δ (ppm): 6.9–7.9 (m, 9H, Ar-H), 10.29 (s, 2H, NH); Anal. Calcd for $C_{25}H_{11}Cl_4N_7O$: C, 51.49; H, 1.90; N, 16.81; Found: C, 51.35; H, 1.78; N, 16.75%.

2.2.3. Synthesis of 3,3′{[6-(2,3-dichlorophenyl)-1,2,4-triazine-3,5-diyl]dinitrolo}bis-{1-[(dimethylamino)methyl]1,3-dihydro-2H-indol-2-one} ND-1

A slurry consisting of the N-1 (0.0025 mol), THF (5 ml) and 37% formalin (2 ml) was made. To this dimethylamine (0.005 mol) was added drop wise with cooling and shaking. The reaction mixture was allowed to stand at room temperature for 1 h with occasional shaking after which it was warmed on a steam bath for 15 min. At the end of the period the contents were cooled and the product was obtained, which was further recrystallized from ethanol.

ND-1: Yield: 80%; m.p.: 94–97 °C. IR (KBr) (cm^{-1}): 2887 (N-CH_2-N), 3064 (Ar-CH), 1735 (C═O), 1610 (C═N), 757 (C-Cl); ^{1}H NMR ($CDCl_3$) δ (ppm): 2.19 (s, 12H, CH_3), 4.00 (s, 4H, N-CH_2-N), 6.6–8.0 (m, 11H, Ar-H); Anal. Calcd for



NC: Distill water, Phen: Phenobarbitone sodium, Lamo: Lamotrigine

Scheme 1 Scheme of synthesis. Step 1: Synthesis of Schiff's bases (imines) from Lamotrigine and substituted isatin. Step 2: Synthesis of Mannich bases of synthesized Schiff's bases.