Asian Journal of Chemistry; Vol. 23, No. 1 (2011), 127-131

ASIAN JOURNAL OF CHEMISTRY

www.asianjournalofchemistry.co.in

Synthesis and Anticonvulsant Activity 6-Alkoxy-[1,2,4]triazolo[3,4-a]phthalazin-3(2*H*)-ones

WEI CHENG-XI, GUO ZHOU, LI FU-NAN and QUAN ZHE-SHAN*

College of Pharmacy, Yanbian University, Yanji, Jilin 133000, P.R. China

*Corresponding author: Fax: +86 433 2660606; Tel: +86 433 2660606; E-mail: zsquan@ybu.edu.cn

(*Received*: 31 December 2009; *Accepted*: 21 August 2010) AJC-9003

A new series of 6-alkoxy-[1,2,4]triazolo[3,4-a]phthalazin-3(2*H*)-one derivative was synthesized by condensation of appropriate 1-chloro-4-alkoxy phthalazine with methyl hydrazine carboxylate. All the compounds **5a-5r**, characterized by IR, ^{1}H NMR and MS, have been evaluated for their anticonvulsant activity against MES-induced seizure. The result illustrats that 6-pentyloxy-[1,2,4]triazolo[3,4-a]phthalazin-3(2*H*)-one (**5b**) possessed the most potential anticonvulsant activity.

Key Words: 1,2,4-Triazolo[3,4-a]phthalazine-3(2*H*)-one, Triazolone, Phthalazine, Anticonvulsant, Maximal electroshock.

INTRODUCTION

Epilepsy, one of the most common neurologic diseases, is characterized by epileptic seizures, which are evoked by unexpected, high-level neuronal discharges in the brain[1]. For epilepsy treatment, nearly 95 % of clinically available drugs were approved before 1985 and they could provide satisfactory seizure control for 60-70 % of patients. These drugs, however, also cause notable adverse side effects such as drowsiness, ataxia, gastrointestinal disturbance, hepatotoxicity and megaloblastic anemia[2-4] and even life threatening conditions[5]. Therefore the development of new antiepileptic drugs with approved therapeutic properties is an important challenge for medicinal chemists.

In our search for new compounds with anticonvulsant activity, a series of derivatives of 6-alkoxy-3,4-dihydro-2(1*H*)-quinoline[6] were first found to have some weak anticonvulsant activities. On the basis of the derivatives of 1,2,4-triazol-3-one (triazolone) found to be associated with anticonvulsant activity[7,8], introduction of triazolone ring to the first and second position of this compound **I** (Fig. 1) caused a remarkable increase in the anticonvulsant activity, as seen in 7-benzyloxy-4,5-dihydro-[1,2,4]triazolo[4,3-a]quinolin-1(2*H*)-one (compound **II**)[9] and 8-hexyl oxy-4,5-dihydro-[1,2,4]triazolo[4,3-a]quinolin-1(2*H*)-one (compound **III**)[10]. There were aslo some similar design reports[11,12], which demonstrated that 1,2,4-triazol-3-one has been incorporated into the functional nucleus of anticonvulsant durgs.

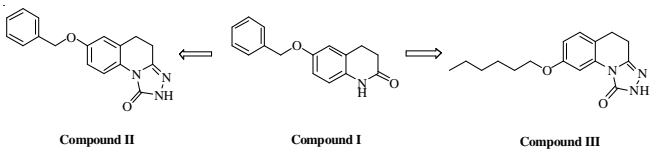


Fig. 1. Introduction of triazolone ring to compound **I**

Phthalazine derivatives were shown to possess a variety of activities such as antimicrobial[13,14], antifugal[14,15], antitumor[16,17], antibacterial[18,19] and anticonvulsant[20-22]. It is reported that 11*H*-[1,2,4]triazolo[4,5-c][2,3]benzodiazepin-3(2*H*)-ones (compound **IV**)[11,12], the agents likely to be mainly responsible for the anticonvulsant properties observed, shows strong anticonvulsant activity. Prompted by the above observation and the ring contraction of 11*H*-[1,2,4]triazolo[4,5-c][2,3]benzodiazepin-3(2*H*)-ones, the title compounds **5a-5r** (Fig. 2) were synthesized by combining triazolone with the lead compound V, which exhibited significant anticonvulsant activity[22].

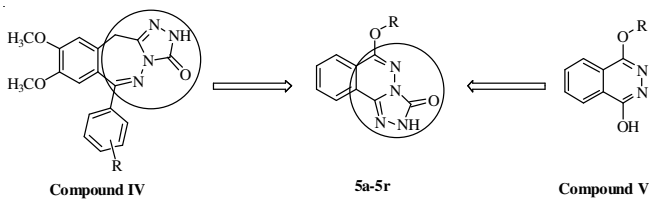


Fig. 2. Design of **5a-5r** from compounds **IV** and **V**

The structural assignments of new compounds **5a-5r** were based on their spectral datas (IR, ^{1}H NMR and MS). And the novel compounds have been screened for their anticonvulsant activity in the maximal electroshock test (MES).

EXPERIMENTAL

Melting points were determined in open capillary tubes and were uncorrected. IR spectra were recorded (in KBr) on a FTIR 1730. ^{1}H NMR spectra were measured on a AV-300 (Bruker, Switzerland) and all chemical shifts were given in ppm relative to tetramethysilane. Mass spectra were measured on an HP1100LC (Agilent Technologies, USA). The major chemicals were purchased from Alderich Chemical Corporation. All other chemicals were of analytical grade.

General procedure for the synthesis of compounds 5a-5r

Synthesis of 2,3-dihydrophthalazine-1,4-dione (2): The starting compound phthalic anhydride (**1**) (20 g, 67.6 mmol) was dissolved in 100 mL ethanol in 0.5 h, then to the mixture 6.80 g hydrazine hydrate was added. The reaction mixture was stirred at room temperature for 2 h and cooled down to 0 ºC. The white solid was collected through filtration and dried in a vacuum to produce the compound 2,3-dihydrophthalazine-1,4-dione 19.80 g. M.p. 181-183 ºC, yield = 90.5 %. ^{1}H NMR (DMSO, 300 MHz) δ 7.59-7.63 (m, 2H, H-6, H-7), 8.14 (d, *J* = 7.92 Hz, 2H, H-5, H-8), 9.04 (s, 2H, -CO-NH-NH-CO-).

Synthesis of 1,4-dichlorophthalazine (3): 2,3-Dihydrophthalazine-1,4-dione (**2**) (19.80 g, 0.12 mol)) was dissolved in phosphorus oxychloride (100 mL) and stirred under reflux for 4 h. Then the solvent was removed under vacuum. The residue was dissolved in dichloromethane (200 mL) and stirred rapidly and the solution was neutralized by the addition of solid and aqueous sodium hydrogen carbonate (cautiously). When effervescence had ceased, the organic layer was separated and the aqueous layer was extracted with dichloromethane (2 × 200 mL). The combined organic layers were dried over $MgSO_4$, filtered and evaporated; the residue was purified by silica gel column chromatography with ethyl acetate:petroleum ether (1:8) and yield obtained 19.58 g. M.p. 192-194 ºC, yield = 81.99 %. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.08 (d, *J* = 7.89 Hz, 2H, H-6, H-7), 8.32-8.36 (m, 2H, H-5, H-8).

General procedure for the synthesis of 1-chloro-4-alkoxyphthalazine (4a-4r): A solution of compound **3** (1.99 g, 10 mmol) and appropriate alkanol (13 mmol) in 20 mL dichloromethane was mixed with 10 mL sodium hydroxide (15 mmol) solution, then added triethyl benzyl ammonium chloride (TEBAC, 3 mmol). The mixture solution was stired for several days at room temperature untill the reaction was completed by TLC monitoring. Then the organic layer was separated and the aqueous layer was extracted with dichloromethane (2 × 10 mL). The combined organic layers were dried with anhydrous $MgSO_4$, filtered and concentrated the solvent. The residue was recrystallized in ethannol to afford compounds **4a-4f** with yields 50-80 %.

Compound **3** (1.99 g, 10 mmol) and appropriate substituted phenol (11 mmol) were added to a solution of potassium carbonate (10 mmol) in dimethyl formamide with stirring and heating at the temperature of 120 ºC *ca.* 2-12 h, monitoring the reaction finished with TLC. After the mixture solution cooled and then poured into 100 mL of ice-water, compounds **4g-4r** were obtained through filtration, which were dried in a vacuum with yields 60-90 %.

General procedure for the synthesis of 6-alkoxy-[1,2,4]-triazolo[3,4-a]phthalazin -3(2*H*)-one (5a-5r): A solution of compounds **4a-4f** (5 mmol) and methyl hydrazine carboxylate (0.62 g, 6.5 mmol) in 30 mL dimethyl sulfoxide was stired and heated at the temperature of 150 ºC for 6 h. The solution was evaporated to dryness under reduced pressure and the soil residue was purified by silica gel column chromatography with dichloromethane:methanol (40:1) to gain compounds **5a-5f**. The melting point, yield, spectral data of each compound is given below.

6-Butoxy-[1,2,4]triazolo[3,4-a]phthalazin-3(2*H*)-one (5a): M.p. 198-200 ºC, yield = 51.7 %. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.02 (t, 3H, *J* = 7.35 Hz, -CH_3), 1.52-1.59 (m, 2H, -CH_2-), 1.84-1.92 (m, 2H, -CH_2-), 4.55 (t, 2H, *J* = 6.45 Hz, -OCH_2-), 7.71-7.84 (m, 2H, H-8, H-9), 8.11 (d, 1H, *J* = 7.50 Hz, H-10), 8.22 (d, 1H, *J* = 7.20 Hz, H-7), 9.97 (s, 1H, H-2). IR (KBr, ν_{amx}, cm^{-1}): 3159 (N-H), 1714 (C=O), 1574, 1558 (C=N), 1254, 1026 (C-O-C), 1175 (N-N). MS m/z 259 (M+1).

6-Pentyloxy-[1,2,4]triazolo[3,4-a]phthalazin-3(2*H*)-one (5b): M.p. 162-164 ºC, yield = 54.2 %. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.98 (t, 3H, *J* = 7.03 Hz, -CH_3), 1.41-1.52 (m, 4H, -CH_2-CH_2-), 1.88-1.93 (m, 2H, -CH_2-), 4.54 (t, 2H, *J* = 6.60 Hz, -OCH_2-), 7.70-7.83 (m, 2H, H-8, H-9), 8.10 (d, 1H, *J* = 7.80 Hz, H-10), 8.24 (d, 1H, *J* = 7.80 Hz, H-7), 10.94 (s, 1H, H-2). IR (KBr, ν_{amx}, cm^{-1}): 3162 (N-H), 1710 (C=O), 1572, 1558 (C=N), 1269, 1032 (C-O-C), 1179 (N-N). MS m/z 273 (M+1).

6-Hexyloxy-[1,2,4]triazolo[3,4-a]phthalazin-3(2*H*)-one (5c): M.p. 201-203 ºC, yield = 60.1 %. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.93 (t, 3H, *J* = 6.83 Hz, -CH_3), 1.36-1.39 (m, 4H, -CH_2-CH_2-), 1.52-1.53 (m, 2H, -CH_2-), 1.88-1.93 (m, 2H, -CH_2-), 4.55 (t, 2H, *J* = 6.67 Hz, -OCH_2-), 7.74-7.82 (m, 2H, H-8, H-9), 8.12 (d, 1H, *J* = 7.80 Hz, H-10), 8.23 (d, 1H, *J* = 7.80 Hz, H-7), 10.21 (s, 1H, H-2). IR (KBr, ν_{amx}, cm^{-1}): 3159 (N-H), 1713 (C=O), 1572, 1553 (C=N), 1267, 1029 (C-O-C), 1179 (N-N). MS m/z 287 (M+1).

6-Heptyloxy-[1,2,4]triazolo[3,4-a]phthalazin-3(2*H*)-one (5d): M.p. 196-198 ºC, yield = 58.4 %. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.92 (t, 3H, *J* = 6.80Hz, -CH_3), 1.33-1.38 (m, 6H, -CH_2-CH_2-CH_2-), 1.52-1.54 (m, 2H, -CH_2-), 1.88-1.97 (m, 2H, -CH_2-), 4.57 (t, 2H, *J* = 6.60 Hz, -OCH_2-), 7.73-7.89 (m, 2H, H-8, H-9), 8.13 (d, 1H, *J* = 7.50 Hz, H-10), 8.26 (d, 1H, *J* = 7.50 Hz, H-7), 10.90 (s, 1H, H-2). IR (KBr, ν_{amx}, cm^{-1}): 3160 (N-H), 1717 (C=O), 1572, 1553 (C=N), 1258, 1019 (C-O-C), 1165 (N-N). MS m/z 301 (M+1).

6-Octyloxy-[1,2,4]triazolo[3,4-a]phthalazin-3(2*H*)-one (5e): M.p. 184-186 ºC, yield = 50.9 %. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.92 (t, 3H, *J* = 6.70 Hz, -CH_3), 1.28-1.35 (m, 8H, -CH_2-CH_2-CH_2-CH_2-), 1.63-1.65 (m, 2H, -CH_2-),1.91-1.96 (m, 2H, -CH_2-), 4.57 (t, 2H, *J* = 6.60 Hz, -OCH_2-), 7.74-7.87 (m, 2H, H-8, H-9), 8.14 (d, 1H, *J* = 7.50 Hz, H-10), 8.26 (d, 1H, *J* = 7.50 Hz, H-7), 10.33 (s, 1H, H-2). IR (KBr, ν_{amx}, cm^{-1}): 3187 (N-H), 1712 (C=O), 1569, 1548 (C=N), 1246, 1015 (C-O-C), 1180 (N-N). MS m/z 315 (M+1).

6-Decyloxy-[1,2,4]triazolo[3,4-a]phthalazin-3(2*H*)-one (5f): M.p. 158-160 ºC, yield = 48.9 %. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.87 (t, 3H, *J* = 6.90 Hz, -CH_3), 1.28-1.45 (m, 12H, -$(CH_2)_3$-), 1.49-1.52 (m, 2H, -CH_2-), 1.85-1.92 (m, 2H, -CH_2-), 4.54 (t, 2H, *J* = 6.45 Hz, -OCH_2-), 7.71-7.84 (m, 2H, H-8, H-9), 8.11 (d, 1H, *J* = 7.50 Hz, H-10), 8.23 (d, 1H, *J* = 7.50 Hz, H-7), 10.41 (s, 1H, H-2). IR (KBr, ν_{amx}, cm^{-1}): 3167 (N-H), 1712 (C=O), 1579, 1550 (C=N), 1226, 1008(C-O-C), 1152 (N-N). MS m/z 343 (M+1).

6-Phenoxy-[1,2,4]triazolo[3,4-a]phthalazin-3(2*H*)-one (5g): M.p. 218-220 ºC, yield = 81.5 %. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 7.30-7.37 (m, 3H, Ar-H), 7.47-7.52 (m, 2H, Ar-H), 7.86-8.25 (m, 2H, H-8, H-9), 8.19-8.25 (m, 2H, H-7, H-10), 12.49 (s, 1H, H-2). IR (KBr, ν_{amx}, cm^{-1}): 3170 (N-H), 3065, 1719 (C=O), 1571, 1506 (C=N), 1212, 1019 (C-O-C), 1173 (N-N). MS m/z 279 (M+1).

6-(4-Fluorophenoxy)-[1,2,4]triazolo[3,4-a]phthalazin-3(2*H*)-one (5h): M.p. 252-254 ºC, yield = 78.2 %. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 6.80-6.86 (m, 2H, Ar-H), 6.99-7.03 (m, 2H, Ar-H), 7.49-7.62 (m, 2H, H-8, H-9), 7.95-7.97 (m, 2H, H-7, H-10), 11.98 (s, 1H, H-2). IR (KBr, ν_{amx}, cm^{-1}): 3175 (N-H), 1716 (C=O), 1574, 1558 (C=N), 1271, 1023 (C-O-C), 1175 (N-N). MS m/z 297 (M+1).

6-(2-Chlorophenoxy)-[1,2,4]triazolo[3,4-a]phthalazin-3(2*H*)-one (5i): M.p. 278-280 ºC, yield = 68.9 %. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 7.37-7.68 (m, 4H, Ar-H), 7.92-8.01 (m, 2H, H-8, H-9), 8.21-8.29 (m, 2H, H-7, H-10), 12.55 (s, 1H, H-2). IR (KBr, ν_{amx}, cm^{-1}): 3176 (N-H), 1719 (C=O), 1578, 1555 (C=N), 1272, 1029 (C-O-C), 1180 (N-N). MS m/z 313 (M+1).

6-(3-Chlorophenoxy)-[1,2,4]triazolo[3,4-a]phthalazin-3(2*H*)-one (5j): M.p. 248-250 ºC, dec., yield = 63.6 %. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 7.39-7.42 (m, 2H, Ar-H), 7.51-7.54 (m, 1H, Ar-H), 7.59 (s, 1H, Ar-H), 7.90-7.99 (m, 2H, H-8, H-9), 8.21-8.23 (m, 2H, H-7, H-10), 12.52 (s, 1H, H-2). IR (KBr, ν_{amx}, cm^{-1}): 3183 (N-H), 1715 (C=O), 1575, 1558 (C=N), 1270, 1025 (C-O-C), 1172 (N-N). MS m/z 313 (M+1).

6-(4-Chlorophenoxy)-[1,2,4]triazolo[3,4-a]phthalazin-3(2*H*)-one (5k): M.p. 248-250 ºC, yield = 73.4 %. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 7.45 (d, 2H, *J* = 8.25 Hz, Ar-H), 7.57 (d, 2H, *J* = 8.79 Hz, Ar-H), 7.90-7.99 (m, 2H, H-8, H-9), 8.20-8.25 (m, 2H, H-7, H-10), 12.47 (s, 1H, H-2). IR (KBr, ν_{amx}, cm^{-1}): 3180 (N-H), 1720 (C=O), 1574, 1558 (C=N), 1261, 1020 (C-O-C), 1168 (N-N). MS m/z 313 (M+1).

6-(2,4-Dichlorophenoxy)-[1,2,4]triazolo[3,4-a]-phthalazin-3(2*H*)-one (5l): M.p. > 300 ºC, yield = 71.8 %. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 7.58-7.66 (m, 2H, Ar-H), 7.88-7.95 (m, 2H, H-8, H-9), 7.90-7.99 (m, 2H, H-8, H-9), 8.00-8.05 (t, 1H, *J* = 7.53 Hz, Ar-H), 8.22-8.29 (m, 2H, H-7, H-10), 12.54 (s, 1H, H-2). IR (KBr, ν_{amx}, cm^{-1}): 3175 (N-H), 1719 (C=O), 1574, 1558 (C=N), 1251, 1014 (C-O-C), 1168 (N-N). MS m/z 347 (M+1).

6-(4-Bromophenoxy)-[1,2,4]triazolo[3,4-a]phthalazin-3(2*H*)-one (5m): M.p. > 300 ºC, yield = 85.6 %. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 7.38 (d, 2H, *J* = 8.70 Hz, Ar-H), 7.68 (d, 2H, *J* = 8.70 Hz, Ar-H), 7.86-8.01 (m, 2H, H-8, H-9), 8.19-8.21 (m, 2H, H-7, H-10), 12.49 (s, 1H, H-2). IR (KBr, ν_{amx}, cm^{-1}): 3180 (N-H), 1719 (C=O), 1580, 1549 (C=N), 1276, 1018 (C-O-C), 1170 (N-N). MS m/z 357 (M+1).

6-(2-Tolyloxy)-[1,2,4]triazolo[3,4-a]phthalazin-3(2*H*)-one (5n): M.p. 264-266 ºC, yield = 72.4 %. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 2.20 (s, 3H, -CH_3), 7. 26-7.39 (m, 4H, Ar-H), 7.91-8.00 (m, 2H, H-8, H-9), 8.21-8.31 (m, 2H, H-7, H-10), 12.47 (s, 1H, H-2). IR (KBr, ν_{amx}, cm^{-1}): 3164 (N-H), 1715 (C=O), 1574, 1558 (C=N), 1201, 1017 (C-O-C), 1165 (N-N). MS m/z 293 (M+1).

6-(3-Tolyloxy)-[1,2,4]triazolo[3,4-a]phthalazin-3(2*H*)-one (5o): M.p. 228-230 ºC, yield = 70.5 %. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 2.35 (s, 3H, -CH_3), 7.12-7.19 (m, 3H, Ar-H), 7.37 (s, 1H, Ar-H), 7.89-8.01 (m, 2H, H-8, H-9), 8.21-8.23 (m, 2H, H-7, H-10), 12.48 (s, 1H, H-2). IR (KBr, ν_{amx}, cm^{-1}): 3170 (N-H), 1717 (C=O), 1578, 1555 (C=N), 1204, 1020 (C-O-C), 1169 (N-N). MS m/z 293 (M+1).

6-(4-Tolyloxy)-[1,2,4]triazolo[3,4-a]phthalazin-3(2*H*)-one (5p): M.p. 290-292 ºC, yield = 73.8 %. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 2.35 (s, 3H, -CH_3), 7.23-7.28 (m, 4H, Ar-H), 7.89-7.98 (m, 2H, H-8, H-9), 8.19-8.25 (m, 2H, H-7, H-10), 12.47 (s, 1H, H-2). IR (KBr, ν_{amx}, cm^{-1}): 3165 (N-H), 1715 (C=O), 1574, 1558 (C=N), 1202, 1032 (C-O-C), 1157 (N-N). MS m/z 293 (M+1).

6-(2-Methoxyphenoxy)-[1,2,4]triazolo[3,4-a]-phthalazin-3(2*H*)-one (5q): M.p. 258-260 ºC, dec., yield = 69.6 %. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 3.73 (s, 3H, -OCH_3), 7.03-7.37 (m, 4H, Ar-H), 7.89-8.03 (m, 2H, H-8, H-9), 8.21-8.28 (m, 2H, H-7, H-10), 12.50 (s, 1H, H-2). IR (KBr, ν_{amx}, cm^{-1}): 3180 (N-H), 1720 (C=O), 1573, 1558 (C=N), 1242, 1053 (C-O-C), 1180 (N-N). MS m/z 309 (M+1).

6-(4-Methoxyphenoxy)-[1,2,4]triazolo[3,4-a]-phthalazin-3(2*H*)-one (5r): M.p. 218-220 ºC, dec., yield = 65.2 %. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 3.80 (s, 3H, -OCH_3), 7.28 (d, 2H, *J* = 8.04 Hz, Ar-H), 7.29 (d, 2H, *J* = 7.98 Hz, Ar-H), 7.85-8.00 (m, 2H, H-8, H-9), 8.21-8.29 (m, 2H, H-7, H-10), 12.50 (s, 1H, H-2). IR (KBr, ν_{amx}, cm^{-1}): 3175 (N-H), 1721 (C=O), 1574, 1557 (C=N), 1261, 1060 (C-O-C), 1175 (N-N). MS m/z 309 (M+1).

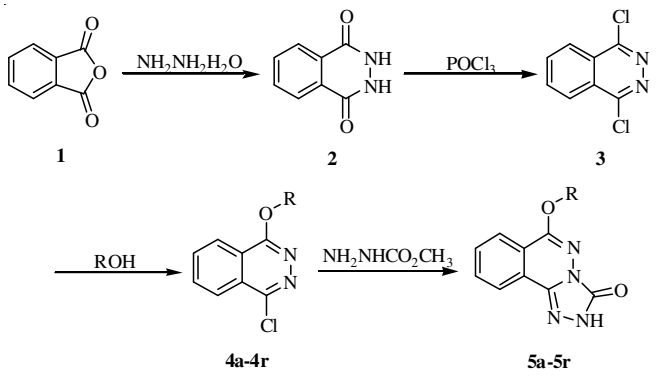
Pharmacology: Pharmacological test of the 6-alkoxy-[1,2,4]triazolo[3,4-a]phthalazin-3(2*H*)-one derivatives (**5a-5r**) were conducted at the Epilepsy Branch of the National Institute of Neurological Disorders and Stroke (NINDS) following the Protocol adopted by the Antiepileptic Drug Development (ADD) program[23,24].

All target compounds **5a-5r** were tested for anticonvulsant activity with KunMing mice in the 18-22 g weight range purchased from the Laboratory of Animal Research, College of Pharmacy, Yanbian University. The tested compounds were dissolved in polyethylene glycol 400. In pharmacological screening each compound was administered at two dose levels (100 and 300 mg/kg i.p., to a total of 6 mice, using 3 for each dose) with anticonvulsant activity and neurotoxicity assessed at 0.5 h and 4 h intervals after administration.

Anticonvulsant efficacy of the target compounds was measured in the MES test. In the MES test, seizures were elicited with a 60 Hz alternating current of 50 mA intensity in mice. The current was applied *via* corneal electrodes for 0.2 s. Protection against the spread of MES-induced seizures was defined as the abolition of the hind leg and tonic maximal extension component of the seizure. At 0.5 h after the administration of the compounds, the activities were evaluated in MES test.

RESULTS AND DISCUSSION

As shown in **Scheme-I**, starting material phthalic anhydride reacted with hydrazine hydrate in ethanol to yield 2,3-dihydrophthalazine-1,4-dione, which reacted further with refluxing $POCl_3$ to yield 1,4-dichlorophthalazine (**3**)[25,26]. Compound **3** reacted further with appropriate alkanol and substituted phenol in dimethyl formamide to afford compounds **4a-4r** and then compounds **4a-4r** reacted with methyl hydrazine carboxylate in dimethyl sulfoxide to gain target compounds 6-alkoxy-[1,2,4]triazolo[3,4-a]phthalazin-3(2*H*)-one derivatives (**5a-5r**)[27].



5a = n-C_4H_9	**5h** = -C_6H_5	**5m** = -C_6H_4(4-Br)
5b = n-C_5H_{11}	**5h** = -C_6H_4(4-F)	**5n** = -C_6H_4(2-CH_3)
5c = n-C_6H_{13}	**5i** = -C_6H_4(2-Cl)	**5o** = -C_6H_4(3-CH_3)
5d = n-C_7H_{15}	**5j** = -C_6H_4(3-Cl)	**5p** = -C_6H_4(4-CH_3)
5e = n-C_8H_{17}	**5k** = -C_6H_4(4-Cl)	**5q** = -C_6H_4(2-OCH_3)
5f = n-$C_{10}H_{21}$	**5l** = -C_6H_3(2,4-Cl2)	**5r** = -C_6H_4(4-OCH_3)

Scheme-I: Synthesis route of compounds **5a-5r**

Pharmacological evaluation: The results of preliminary screening of **5a-5r** are summarized in Table-1. As shown in Table-1, the results of pharmacological experiments indicated that that the anticonvulsant activity of the title compounds was not good as the previously designed expectation.

Most of the synthesized compounds exhibited moderate anticonvulsant activity against MES-induced seizure at the concentration of 300 mg/kg, while only **5b**, **5c**, **5j**, **5n** and **5p** displayed the potency of anticonvulsant at 100 mg/kg in MES test. Among all the compounds, 6-pentyloxy-[1,2,4]triazolo-[3,4-a]phthalazin-3(2*H*)-one (**5b**) unfolded the most potential anticonvulsant activity against MES-induced seizure and showed potency of anticonvulsant after administrated 4 h.

Analyzing the activities of the synthesized compounds **5a-5f**, the length of the alkoxyl chain appeared to have impact on anticonvulsant activity of the derivatives. From **5b** to **5f**, as the alkoxyl chain length increased, anticonvulsant activity gradually decreased with the compound **5b** (with the 6-pentyloxy group) being the most active compound. Among the alkoxyl chain-substituted derivatives, the potency of compound **5c** (with the 6-hexyloxy group) was less than that of compound **5b**. In a series of aryloxy group substitutions, the derivatives of the fluorophenoxy, chlorophenoxy and tolyloxy group substituted showed the better potency of anticonvulsant at at the concentration of 100 mg/kg, while compounds

TABLE-1
QUANTITATIVE ANTICONVULSANT DATA IN MICE
(TEST DRUG ADMINISTERED i.p.)[a]

Compd.	MES[b]			
	100 mg/kg		300 mg/kg	
	0.5 h	4.0 h	0.5 h	4.0 h
5a	0/3	-[c]	1/3	0/3
5b	3/3	1/3	3/3	0/3
5c	1/3	0/3	2/3	0/3
5d	0/3	-	1/3	1/3
5e	0/3	-	0/3	-
5f	0/3	-	0/3	-
5g	0/3	-	1/3	0/3
5h	0/3	-	3/3	1/3
5i	0/3	-	3/3	0/3
5j	1/3	0/3	3/3	0/3
5k	0/3	-	3/3	0/3
5l	0/3	-	1/3	0/3
5m	0/3	-	1/3	1/3
5n	1/3	0/3	2/3	0/3
5o	0/3	-	2/3	0/3
5p	1/3	0/3	2/3	0/3
5q	0/3	-	1/3	0/3
5r	0/3	-	1/3	0/3

[a]All of tested compounds were dissolved in polyethylene glycol-400.
[b]Anticonvulsant activity was determined by maximal electroshock test (MES) 30 min and 4 h after the tested compounds were administrated.
[c]Not tested.

5j, **5n** and **5p**, which were substituted by 3-Cl, 2-CH_3, 4-CH_3, respectively, displayed the anticonvulsant activity at 100 mg/kg.

Conclusion

Most of these compounds possessed the weak or moderate anticonvulsant effect even under the large dose of 300 mg/kg, which went beyond the previously designed expectation. It is possible that triazolone incorporation into the substituted phthalazine led to dramatic reduction in the lipophilicity of the compounds and made it difficult for the target compounds to pass biological membranes.

ACKNOWLEDGEMENTS

This work was supported by the National Natural Science Foundation of China (No. 30760290 and No. 30860340) and Important Item Foundation of Ministry of Education P.R. China (No. 20070422029).

REFERENCES

1. W. Löscher, *Eur. J. Pharmacol.*, **342**, 1 (1998).
2. D. Schmidt and K. Stavem, *Epilepsia*, **50**, 1301 (2009).
3. E. Perucca, *Br. J. Clin. Pharmacol.*, **42**, 531 (1996).
4. Z. Lin and P.K. Kadaba, *Med. Res. Rev.*, **17**, 537 (1997).
5. Y.A. Al-Soud, N.A. Al-Masoudi and Ael-R. Ferwanah, *Bioorg. Med. Chem.*, **11**, 1701 (2003).
6. Z.S. Quan, J.M. Wang, J.R. Rho, K.C. Kwak, H.C. Kang, C.S. Jun and K.Y. Chai, *Bull. Korean Chem. Soc.*, **26**, 1757 (2005).
7. J.H. Kehne, J.M. Kane, S.F. Chaney, G. Hurst, T.C. McCloskey, M.A. Petty, Y. Senyah, H.H. Wolf, R. Zobrist and H.S. White, *Epilepsy Res.*, **27**, 41 (1997).
8. L. Le Campion, M. Delaforge, J.P. Noel, J. Ouazzani, *Eur. J. Biochem.*, **248**, 401 (1997).
9. H.G. Jin, X.Y. Sun, K.Y. Chai, H.R. Piao and Z.S. Quan, *Bioorg. Med. Chem.*, **14**, 6868 (2006).

10. X.Y. Sun, Y.Z. Jin, F.N. Li, G. Li, K.Y.Chai and Z.S. Quan, *Arch. Pharm. Res.*, **29**, 1080 (2006).
11. M. Zappalà, R. Gitto, F. Bevacqua, S. Quartarone, A. Chimirri, M. Rizzo, G. De Sarro and A. De Sarro, *J. Med. Chem.*, **43**, 4834 (2000).
12. R. Gitto, V. Orlando, S. Quartarone, G. De Sarro, A. De Sarro, E. Russo, G. Ferreri and A. Chimirri, *J. Med. Chem.*, **46**, 3758 (2003).
13. E.M. Kassem, M.M. Kamel and M.el-Zahar, *Pharmazie*, **45**, 215 (1990).
14. S. Dima, M. Caprosu, M. Ungureanu, G. Grosu and M. Petrovanu, *Ann. Pharm. Fr.*, **57**, 415 (1999).
15. C.K. Ryu, R.E. Park, M.Y. Ma and J.H. Nho, *Bioorg. Med. Chem. Lett.*, **17**, 2577 (2007).
16. C.A. Gandolfi, G. Beggiolin, E. Menta, M. Palumbo, C. Sissi, S. Spinelli and F. Johnson, *J. Med. Chem.*, **38**, 526 (1995).
17. J. Li, Y.F. Zhao, X.Y. Yuan, J.X. Xu and P. Gong, *Molecules*, **11**, 574 (2006).
18. L. Heinisch, E. Roemer, P. Jütten, W. Haas, W. Werner and U. Möllmann, *J. Antibiot (Tokyo)*, **52**, 1029 (1999).
19. A.M. Khalil, M.A. Berghot and M.A. Gouda, *Eur. J. Med. Chem.*, **44**, 4434 (2009).
20. K. Go, K. Tsurumi and H. Fujimura, *Jpn. J. Pharmacol.*, **28**, 93 (1978).
21. S. Grasso, G. De Sarro, A. De Sarro, N. Micale, M. Zappalà, G. Puja, M. Baraldi and C. De Micheli, *J. Med. Chem.*, **43**, 2851 (2000).
22. R. Sivakumar, S. Kishore, Gnanasam, S. Ramachandran and J.T. Leonard, *Eur. J. Med. Chem.*, **37**, 793 (2002).
23. R.L. Krall, J.K. Penry, B.G. White, H.J. Kupferberg and E.A. Swinyard, *Epilepsia*, **19**, 409 (1978).
24. R.J. Porter, J.J. Cereghino, G.D. Gladding, B.J. Hessie, H.J. Kupferberg, B. Scoville and B.G. White, *Cleve. Clin. Q.*, **51**, 293 (1984).
25. L.J. Street, F. Sternfeld, R.A. Jelley, A.J. Reeve, R.W. Carling, K.W. Moore, R.M. McKernan, B. Sohal, Cook, S.A. Pike, G.R. Dawson, F.A. Bromidge, K.A. Wafford, G.R. Seabrook, S.A. Thompson, G. Marshall, G.V. Pillai, J.L. Castro, J.R. Atack and A.M. MacLeod, *J. Med. Chem.*, **47**, 3642 (2004).
26. X.Y. Sun, L.P. Guan, L. Zhang, C.X. Wei, H.R. Piao and Z.S. Quan, *J. Brazil. Chem. Soc.*, **20**, 826 (2009).
27. J.B. Jr. Hester, A.D. Rudzik and P. Von Voigtlander, *J. Med. Chem.*, **23**, 402 (1980).