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# Synthesis and Sedative-Hypnotic Activity of Novel N-[3-(3-Aminomethylpyrazolo[1,5-a]pyrimidin-7-yl)phenyl]-N-ethylacetamide Derivatives

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N-[3-(3-Aminomethylpyrazolo[1,5-a]pyrimidin-7-yl)phenyl]-N-ethylacetamide derivatives were synthesized and evaluated for sedative-hypnotic activity *in vivo*. These derivatives contain sulfa, amine and amide three series. The structures of these newly prepared compounds were confirmed by melting point, IR, $^1$H NMR spectroscopy and HRMS. The sedative-hypnotic activity of the synthesized compounds was evaluated by testing their effects on the locomotor activity of mice. Compounds **3h**, **4d** and **5c** were found to have more smoothly and lastingly activity and these products can be recognized as lead compounds for further optimization. The structure-activity relationship (SAR) showed that derivatives containing electron-withdrawing group or conjugation structure on C7 position were the most effective compounds. These findings not only preliminary screened few good target compounds, but also provided useful structural information for rational design and synthesis.

**Key Words: Synthesis, Zaleplon derivatives, Vivo assay, Sedative-hypnotic.**

## INTRODUCTION

Insomnia is the subjective complaint of poor sleep or an inadequate amount of sleep that adversely affects daily functioning[1]. Approximately 1/4 adults experiences insomnia at some time; at least 10 % of the general population consider the problem to be chronic[2]. Insomnia is not only a leading cause of mental impairment[3], it is also the major reason that leads to a higher incidence of psychiatric disturbances including depression and anxiety[4]. Therefore, the emergence of a new medicine that has safety and effective treatments for insomnia has great realistic significance.

Zaleplon (Fig. 1), a pyrazolopyrimidine derivative with high affinity and selectivity for the $\alpha_1$-subunit of the GBAA-A receptor, which has extremely rapid absorption and onset of effect as a kind of the most common prescribed hypnotic. It has been used in patients for many years without rebound, tolerance and withdrawal. However, it also has some adverse effects, such as dizziness, headache, somnolence and fatigue. Nitriles have been reported to possess various therapeutic activities, but the toxicity of cyanide is well known and the potential for cyanide release from nitriles is paramount concern to the medicinal chemist when designing compounds containing the nitrile group[5]. Because of the potential toxicity, nitriles have low therapeutic importance in drug design. Meanwhile, the growing potent literatures of recent years demonstrate that the sulphonamide derivatives are used due to their many therapeutic properties[6-10]. Additionally, numerous compounds containing amide moiety have been shown to exhibit many pharmacological activities, including psychotropic[11], anticancer[12], antiallergic[13], anticonvulsant and antagonist activity[14,15]. Moreover the pyrimidine substructure and their amino substituted congeners are frequently occurring motifs in commercially available drugs[16]. In order to preliminary screen some compounds that have less potential undesirable side effects, we report the design and synthesis of a novel zaleplon derivatives that contain sulfa, amine and amide three series.

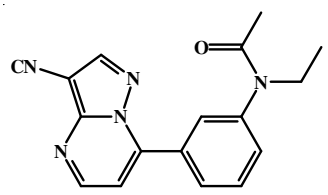
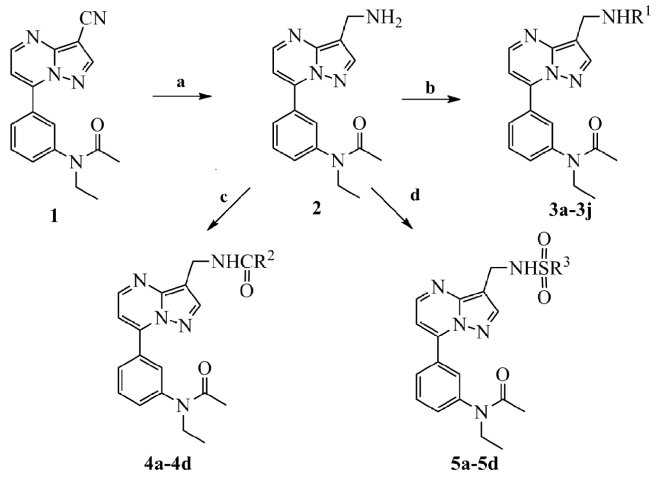



Fig. 1. Zaleplon

## EXPERIMENTAL

The synthesis is outlined in **Scheme-I**. Initially, zaleplon **1** was treated with $NaBH_4$ and $FeCl_3 \cdot 6H_2O$ in N,N-dimethylformamide at 65 ºC to yield intermediate **2**.

Synthesis of other target compounds was carried out according to the reagents and conditions presented in **Scheme-I**



**Scheme-I:** Reagents conditions: (a) $FeCl_3 \cdot 6H_2O$, $NaBH_4$, DMF, 65 ºC; (b) $R^1X$, NaH, THF, rt; (c) $R^2COCl$, $Et_3N$, THF, rt; (d) $R^3SO_2Cl$, NaH, THF, rt

and thin layer chromatography (TLC) was run throughout the reaction to optimize the reaction for purity and completion.

All synthesized compounds were obtained as solid crystalline forms in good yields, which were showed IR, $^1$H NMR and HRMS spectra according to the assigned structures and were not reported in literatures.Melting points (uncorrected) were recorded on a XT-4 microscope melting point apparatus. $^1$H NMR spectra were measured with a BRUKER AV II-400 MHz spectrometer, using TMS as an internal reference. Chemical shifts are expressed as d units (parts per million) relative to the solvent peak . Coupling constants *J* are valued in Hertz (Hz). HRMS spectra were determined on Bruker Daltonics ESI-Bio TOF-Q mass spectroscopy.

Synthesis procedure of N-[3-(3-amino-pyrazolo[1,5-a]pyrimidin-7-yl)phenyl]-N-ethyl-acetamide **2**. To a solution of zaleplon (0.31 g, 1 mmol) in DMF (5 mL) under ice bath were added a solution of $FeCl_3 \cdot 6H_2O$ (0.55 g, 2 mmol) in $H_2O$ (1.0 mL). After the resulting solution was stirred for 10 min, $NaBH_4$ (0.38 g, 10 mmol) were slowly added. Then the mixture was stirred at 65 ºC for 8 h. The resulting mixture was extracted with ethyl acetate, washed with water in many times and dried over anhydrous $Na_2SO_4$, then evaporation of the solvent under reduced pressure obtained product as a solid. The crude product was purified by chromatograph on silica gel with appropriate solvent to afford **2**.

**N-[3-(3-Amino-pyrazolo[1,5-a]pyrimidin-7-yl)phenyl]-N-ethyl-acetamide (2):** IR (KBr, $\nu_{max}$, cm$^{-1}$): 3287, 2979, 2866, 2207, 1653, 1606, 1404, 1220, 713. $^1$H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.09 (t, *J* = 7.2 Hz, 3H), 1.81 (s, 3H), 2.20 (m, 1H), 2.51 (m, 1H), 3.23 (m, 2H), 3.40 (d, *J* = 12.0 Hz, 3H), 3.72 (q, *J* = 7.2 Hz, 2H), 5.51 (t, *J* = 4.0 Hz, 1H), 6.23 (s, 1H), 6.85 (s, 1H), 7.01-7.51 (m, 4H, PhH).

**N-Ethyl-N-[3-(3-methylamino-pyrazolo[1,5-a]-pyrimidin-7-yl)phenyl]acetamide (3a):** IR (KBr, $\nu_{max}$, cm$^{-1}$): 3432, 2974, 2868, 2209, 1652, 1584, 1522, 1419, 704. $^1$H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.09 (t, *J* = 7.2 Hz, 3H), 1.79 (s, 3H), 2.24 (m, 1H), 2.59 (m, 1H), 3.18 (m, 2H), 3.30 (s, 3H), 3.72 (m, 2H), 5.46 (t, *J* = 4.4 Hz, 1H), 6.80 (s, 1H), 6.97-7.53(m, 4H, PhH).

**N-Ethyl-N-[3-(3-ethylamino-pyrazolo[1,5-a]pyrimidin-7-yl)phenyl]acetamide (3b):** IR (KBr, $\nu_{max}$, cm$^{-1}$): 3560, 2976, 2867, 2208, 1671, 1566, 1528, 1422, 708. $^1$H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.08 (t, *J* = 7.2 Hz, 3H), 1.29 (t, *J* = 7.2 Hz, 3H), 1.79 (s, 3H), 2.26 (m, 1H), 2.57 (m, 1H), 3.20 (m, 2H), 3.57 (m, 1H), 3.74(m, 2H), 5.49 (t, *J* = 4.0 Hz, 1H), 6.75 (s, 1H), 6.99-7.53(m, 4H, PhH).

**N-Ethyl-N-[3-(3-propylamino-pyrazolo[1,5-a]pyrimidin-7-yl)phenyl]acetamide (3c):** IR (KBr, $\nu_{max}$, cm$^{-1}$): 2979, 2937 2868, 2210, 1656, 1585, 1525, 1406, 1305, 703. $^1$H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.00 (t, *J* = 7.2 Hz, 3H), 1.08 (t, *J* = 7.0 Hz, 3H), 1.73 (m, 2H), 1.79 (s, 3H), 2.23 (m, 1H), 2.55 (m, 1H), 3.20 (m, 2H), 3.47 (m, 1H), 3.64 (m, 1H), 3.69 (m, 2H), 5.48 (t, *J* = 4.0 Hz, 1H), 6.75 (s, 1H), 6.98-7.52 (m, 4H, PhH).

**N-Ethyl-N-[3-(3-isopropylamino-pyrazolo[1,5-a]-pyrimidin-7-yl)phenyl]acetamide (3d):** IR (KBr, $\nu_{max}$, cm$^{-1}$): 3431, 2978, 2210, 1651, 1584, 1523, 1410, 1296, 1181, 715. $^1$H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.08 (t, *J* = 7.2 Hz, 3H), 1.26 (d, *J* = 6.8 Hz, 3H), 1.30 (d, *J* = 6.4 Hz, 3H), 1.79 (s, 3H), 2.23 (m, 1H), 2.49 (m, 1H), 3.00 (td, *J* = 11.6 Hz, 2.8 Hz, 1H), 3.25 (dt, *J* = 12 Hz, 4 Hz, 1H), 3.71 (m, 2H), 4.58 (m, 1H), 5.49 (t, *J* = 4.0 Hz, 1H), 6.74 (s, 1H), 6.99-7.52 (m, 4H, PhH).

**N-[3-(3-Butylamino-pyrazolo[1,5-a]pyrimidin-7-yl)-phenyl]-N-ethyl-acetamide (3e):** IR (KBr, $\nu_{max}$, cm$^{-1}$): 2954, 2875, 2207, 1658, 1586, 1567, 1432, 1295, 708. $^1$H NMR (400 MHz, $CDCl_3$) δ (ppm): 0.98 (t, *J* = 7.2 Hz, 3H), 1.08 (t, *J* = 6.8 Hz, 3H), 1.40 (m, 2H), 1.68 (m, 2H), 1.79 (s, 3H), 2.22 (m, 1H), 2.55 (m, 1H), 3.19 (dd, *J* = 4.0 Hz, 8.0 Hz, 2H), 3.49 (m, 3H), 3.70 (m, 3H), 5.48 (t, *J* = 4.0 Hz, 1H), 6.74 (s, 1H), 6.97-7.53 (m, 4H, PhH).

**N-[3-(3-Benzylamino-pyrazolo[1,5-a]pyrimidin-7-yl)-phenyl]-N-ethyl-acetamide (3f):** IR (KBr, $\nu_{max}$, cm$^{-1}$): 3089, 3034, 2845, 2207, 1646, 1596, 1388, 1293, 1171, 705. $^1$H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.04 (t, *J* = 7.2 Hz, 3H), 1.72 (s, 3H), 2.16 (m, 1H), 2.51 (m, 1H), 3.10 (m, 2H), 3.66 (m, 2H), 4.69 (d, *J* = 16.0 Hz, 1H), 4.93 (d, *J* = 16.0 Hz, 1H), 5.48 (t, *J* = 4.0 Hz, 1H), 6.68 (s, 1H), 6.93-7.58 (m, 9H, PhH).

**N-Ethyl-N-{3-[3-(4-methyl-benzylamino)pyrazolo-[1,5-a]pyrimidin-7-yl]phenyl}acetamide (3g):** IR (KBr, $\nu_{max}$, cm$^{-1}$): 3434, 2933, 2863, 2205, 1647, 1592, 1400, 1136, 697. $^1$H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.04 (t, *J* = 7.2 Hz, 3H), 1.72 (s, 3H), 2.14 (m, 1H), 2.34 (s, 3H), 2.50 (m, 1H), 3.07 (m, 2H), 3.66 (m, 2H), 4.65 (d, *J* = 16.0 Hz, 1H), 4.88 (d, *J* = 16.0 Hz, 1H), 5.47 (t, *J* = 4.4 Hz, 1H), 6.68 (s, 1H), 6.93-7.58 (m, 8H, PhH).

**N-Ethyl-N-{3-[3-(4-nitro-benzylamino)pyrazolo[1,5-a]pyrimidin-7-yl]phenyl}acetamide (3h):** IR (KBr, $\nu_{max}$, cm$^{-1}$): 3435, 2930, 2856, 2210, 1654, 1588, 1345,707. $^1$H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.07 (t, *J* = 6.8 Hz, 3H), 1.78 (s, 3H), 2.22 (m, 1H), 2.59 (m, 1H), 3.17 (m, 2H), 3.70 (q, *J* = 7.2 Hz, 2H), 4.92 (q, *J* = 16.0 Hz, 2H), 5.53 (t, *J* = 4.4 Hz, 1H), 6.80 (s, 1H), 6.93-8.24 (m, 8H, PhH).

**N-{3-[3-(2-Chloro-benzylamino)pyrazolo[1,5-a]-pyrimidin-7-yl]phenyl}-N-ethyl-acetamide (3i):** IR (KBr, $\nu_{max}$, cm$^{-1}$): 2935, 2211, 1650, 1593, 1524, 1437, 1303, 762. $^1$H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.07 (t, *J* = 7.2 Hz, 3H), 1.72 (s, 3H), 2.19 (m, 1H), 2.54 (m, 1H), 3.14 (m, 2H), 3.70 (q, *J* = 7.2 Hz, 2H), 4.96 (q, *J* = 16.0 Hz, 2H), 5.52 (t, *J* = 4.0 Hz, 1H), 6.76 (s, 1H), 6.99-7.59 (m, 8H, PhH).

**{7-[3-(Acetyl-ethyl-amino)phenyl]pyrazolo[1,5-a]-pyrimidin-3-ylamino}acetic acid ethyl ester (3j):** IR (KBr, $\nu_{max}$, $cm^{-1}$): 3435, 2977, 2208, 1743, 1641, 1583, 1407, 1199,702. $^1H$ NMR (400 MHz, $CDCl_3$) δ (ppm): 1.00 (t, *J* = 7.2 Hz, 3H), 1.22 (t, *J* = 7.2 Hz, 3H), 1.72 (s, 3H), 2.14 (m, 1H), 2.58 (m, 1H), 3.08 (td, *J* = 12.0 Hz, 4.0 Hz, 2H), 3.35 (td, *J* = 12.0 Hz, 2.8 Hz, 2H), 3.66 (m, 2H), 3.98 (d, *J* = 18.8 Hz, 1H), 4.18 (m, 2H), 4.59 (d, *J* = 18.8 Hz, 1H), 5.49 (t, *J* = 3.2 Hz, 1H), 6.84 (s, 1H), 7.04-7.46 (m, 4H, PhH).

**N-{7-[3-(Acetyl-ethyl-amino)phenyl]pyrazolo[1,5-a]-pyrimidin-3-yl}acetamide (4a):** IR (KBr, $\nu_{max}$, $cm^{-1}$): 3096, 2978, 2230, 1688, 1654, 1507, 1381,946, 781. $^1H$ NMR (400 MHz, $CDCl_3$) δ (ppm): 1.09 (t, *J* = 7.2 Hz, 3H), 1.79 (s, 3H), 2.30 (m, 1H), 2.41 (s, 3H), 2.62 (m, 1H), 3.71 (q, *J* = 7.2 Hz, 2H), 3.92 (s, 2H), 5.59 (t, *J* = 6.0 Hz, 1H), 6.81 (s, 1H), 6.84-7.78(m, 4H, PhH).

**N-{7-[3-(Acetyl-ethyl-amino)phenyl]pyrazolo[1,5-a]pyrimidin-3-yl}benzamide (4b):** IR (KBr, $\nu_{max}$, $cm^{-1}$): 3105, 2993, 2231, 1660, 1496, 1356, 1056, 709. $^1H$ NMR (400 MHz, $CDCl_3$) δ (ppm): 1.09 (t, *J* = 4.8 Hz, 3H), 1.81 (s, 3H), 2.24 (m, 1H), 2.61 (m, 1H), 3.72 (q, *J* = 7.2 Hz, 2H), 3.96 (m, 2H), 5.62 (t, *J* = 6.0 Hz, 1H), 6.90 (s, 1H), 7.04-8.05 (m, 9H, PhH).

**N-{7-[3-(Acetyl-ethyl-amino)phenyl]pyrazolo[1,5-a]pyrimidin-3-yl}-2-phenyl-acetamide (4c):** IR (KBr, $\nu_{max}$, $cm^{-1}$): 3466, 2972, 2228, 1694, 1652, 1495, 1356, 942, 710. $^1H$ NMR (400 MHz,$CDCl_3$) δ (ppm): 1.06 (t, *J* = 6.8 Hz, 3H), 1.75 (s, 3H), 2.24 (m, 1H), 2.59 (m, 1H), 3.68 (q, *J* = 7.2 Hz, 2H), 3.75 (m, 1H), 4.05 (m, 2H), 5.43 (t, *J* = 6.4 Hz, 1H), 6.78 (m, 1H), 7.10-7.77 (m, 9H, PhH).

**N-{7-[3-(Acetyl-ethyl-amino)phenyl]pyrazolo[1,5-a]pyrimidin-3-yl}-2-trifluoro-acetamide (4d):** IR (KBr, $\nu_{max}$, $cm^{-1}$): 3385, 2928, 2857, 2217, 1726, 1606, 1505, 1186, 704. $^1H$ NMR (400 MHz, $CDCl_3$) δ (ppm): 1.18 (t, *J* = 7.2 Hz, 3H), 1.83 (s, 3H), 2.13 (m, 1H), 2.49 (m, 1H), 3.72 (q, *J* = 7.2 Hz, 2H), 3.94 (m, 1H), 4.32 (m,1H), 5.48 (t, *J* = 6.0 Hz, 1H), 6.61 (s, 1H), 7.09-7.98 (m, 4H, PhH).

**N-[3-(3-Benzenesulfonylamino-pyrazolo[1,5-a]-pyrimidin-7-yl)phenyl]-N-ethyl-acetamide (5a):** IR (KBr, $\nu_{max}$, $cm^{-1}$):3443, 2933, 2234, 1660, 1559, 1378, 1174, 719. $^1H$ NMR (400 MHz, $CDCl_3$) δ (ppm): 0.98 (t, *J* = 7.2 Hz, 3H), 1.66 (s, 3H), 1.89 (m, 1H), 2.25 (m, 1H), 3.59 (q, *J* = 7.2 Hz, 2H), 3.74 (m, 1H), 3.88 (m, 1H), 5.26 (t, *J* = 6.8 Hz, 1H), 6.43 (s, 1H), 6.68-7.89 (m, 9H, PhH).

**N-Ethyl-N-{3-[3-(toluene-4-sulfonylamino)pyrazolo-[1,5-a]pyrimidin-7-yl]phenyl}acetamide (5b):** IR (KBr, $\nu_{max}$, $cm^{-1}$): 3436, 2935, 2232, 1646, 1559, 1404, 1166, 804, 670. $^1H$ NMR (400 MHz, $CDCl_3$) δ (ppm): 0.97 (t, *J* = 6.8 Hz, 3H), 1.66 (s, 3H), 1.87 (m, 1H), 2.22 (m, 1H), 2.38 (s, 3H), 3.59 (m, 2H), 3.75 (m, 2H), 5.28 (t, *J* = 6.4 Hz, 1H), 6.57 (s, 1H), 6.62-7.74 (m, 8H, PhH).

**N-Ethyl-N-{3-[3-(4-nitro-benzenesulfonylamino)-pyrazolo[1,5-a]pyrimidin-7-yl]phenyl}acetamide (5c):** IR (KBr, $\nu_{max}$, $cm^{-1}$): 3424, 2930, 2218, 1704, 1555, 1335, 1109, 851, 751. $^1H$ NMR (400 MHz, $CDCl_3$) δ (ppm): 1.08 (t, *J* = 7.2 Hz, 3H), 1.90 (s, 3H), 2.22 (m, 1H), 2.39 (m, 1H), 2.72 (dd, *J* = 13.6 Hz, 6.4 Hz, 3H), 3.74 (m, 2H), 3.86 (m, 2H), 5.54 (t, *J* = 6.0 Hz, 1H), 6.89 (s, 1H), 7.08-8.30 (m, 8H, PhH).

**N-{3-[3-(4-Bromo-benzenesulfonylamino)pyrazolo-[1,5-a]pyrimidin-7-yl]phenyl}-N-ethyl-acetamide (5d):** IR (KBr, $\nu_{max}$, $cm^{-1}$): 3440, 2970, 2234, 1643, 1486, 1173, 1068, 817, 631. $^1H$ NMR (400 MHz, $CDCl_3$) δ (ppm): 1.08 (t, *J* = 7.2 Hz, 3H), 1.75 (s, 3H), 1.87 (m, 1H), 2.13 (m, 1H), 2.43 (dd, *J* = 13.6 Hz, 6.4 Hz, 3H), 3.70 (m, 2H), 3.82 (m, 2H), 5.41 (t, *J* = 6.0 Hz, 1H), 6.68 (s, 1H), 6.70-7.87 (m, 8H, PhH).

Physico-chemical properties of compounds **2**, **3a-3g**, **4a-4d** and **5a-5d** are given in Table-1.

**Sedative-hypnotic activity experiments:** Testing the effects on the locomotor activity of mice is a classical experimental method for evaluating the function of a drug on the central nervous system. The experiment that tested the sedative-hypnotic activity of compounds were performed on Kunming mice, consisting of both males and females, amount to 114, which were randomly arranged in 19 groups, 6 in each. Sponta-

TABLE-1
STRUCTURE, YIELD, MELTING POINT AND HRMS OF DERIVATIVES **2**, **3a-3j**, **4a-4d**, **5a-5d**

| Compounds | $R^1$ or $R^2$ or $R^3$ | Yield (%) | m.p. (ºC) | HRMS (calcd/found) (%) |
|---|---|---|---|---|
| **2** | – | 58 | 145-147 | 310.1666/310.1662 |
| **3a** | $CH_3$ | 98 | 80-82 | 324.1825/324.1819 |
| **3b** | $C_2H_5$ | 89 | 73-74 | 338.1981/338.1985 |
| **3c** | *n*-$C_3H_7$ | 96 | 115-116 | 374.1955/374.1951 |
| **3d** | *iso*-$C_3H_7$ | 92 | 179-180 | 352.2139/352.2132 |
| **3e** | *n*-$C_4H_9$ | 94 | 87-88 | 366.2303/366.2288 |
| **3f** | $C_6H_5CH_2$ | 90 | 97-99 | 400.2133/400.2132 |
| **3g** | 4-$CH_3C_6H_4CH_2$ | 86 | 75-77 | 414.2289/414.2288 |
| **3h** | 4-$NO_2C_6H_4CH_2$ | 91 | 125-127 | 352.1776/352.1768 |
| **3i** | 2-$ClC_6H_4CH_2$ | 93 | 123-124 | 434.1757/434.1742 |
| **3j** | $CH_2CO_2C_2H_5$ | 89 | 120-122 | 396.2035/396.2030 |
| **4a** | $CH_3CO$ | 92 | 152-154 | 352.1776/352.1768 |
| **4b** | $C_6H_4CO$ | 92 | 179-180 | 414.1928/414.1925. |
| **4c** | $C_6H_4CH_2CO$ | 85 | 179-180 | 428.2084/428.2081 |
| **4d** | $CF_3CO$ | 95 | 67-69 | 406.1489/406.1485 |
| **5a** | $C_6H_4SO_2$ | 92 | 160-161 | 450.1602/450.1594 |
| **5b** | 4-$CH_3C_6H_4SO_2$ | 89 | 159-160 | 486.1577/486.1570 |
| **5c** | 4-$NO_2C_6H_4SO_2$ | 89 | 69-71 | 495.1441/495.1445 |
| **5d** | 4-$BrC_6H_4SO_2$ | 89 | 137-139 | 528.0712/528.0699 |

neous locomotor activity was measured with the use of YLS-1A locomotion recording apparatus. The tested compounds, zaleplon and the synthesized compounds which were made into suspensions using 5 % CMC-Na were administered orally (0.4 mL/20 g) to the dose group. While the base control group was treated with only 5 % CMC-Na. The compound preparation was administered intragastrically in mice. All mice were habituated in the locomotion recording cage for 10min before the experiment, then the locomotor activity of each mouse was recorded for 5 min and the data was served as a control. By the same method above, the locomotor activity of each mouse was recorded when the mouse was given a compound after 30, 60, 90 and 120 min.

## RESULTS AND DISCUSSION

The results of these screenings are summarized in Table-2. The structure-activity relationship (SAR), as revealed by the sedative-hypnotic activity from animal experiments associated with the test compounds, may be analyzed as follows.

The pharmacological test shows that compounds **3d**, **3e**, **3f**, **3g**, **3h**, **3i**, **4d** and **5c** can significantly inhibit the locomotor activity of mice. Compared with base control, some of them have obvious effect at different points in time.

Comparison of compounds **3d**, **3e**, **3f**, **3g**, **3i** with **3a**, **3b**, **3c**, **3h** in Table-2 shows that benzylamino substituted compounds are more effective than alkylamino substituted compounds. Meanwhile, **4d** and **5c** that are substituted by strong electron-withdrawing groups also have remarkable activity. However, as shown in Table-2, zaleplon is still one of the most active compounds. The fact may prove that the cyano group should be an important structure of zaleplon. The structure reveals that all effective compounds have strong electron-withdrawing or conjugate substituent. It is probable that the interaction between the compound and corresponding target receptor belong to the intercalative mode or the formed hydrogen bonds. The negative induction effect and π-π conjugation reduce the electron density of matrix structure and all these may be the favorable factors that affect the activity of these compounds.

Compared to zaleplon, the efficacy of compounds **3h**, **4d** and **5c** showed more smoothly and lastingly. Zaleplon, as a fat-soluble drug, has low absolute bioavailability for its strong first-pass effect. The induction of polar groups has enhanced the water-solubility of these compounds and the improved lipid-water partition coefficient may be more beneficial for the absorption of these compounds.

### Conclusion

In general, three series of N-[3-(3-aminomethylpyrazolo-[1,5-a]pyrimidin-7-yl). Phenyl]-N-ethylacetamide derivatives were prepared, including some sulfa, amine and amide derivatives. The synthesized compounds were characterized and evaluated for sedative-hypnotic activity. Most of the assayed compounds showed attractive activity against insomnia. In particular, compounds **3h**, **4d** and **5c** afford quite potent activity. They could be the leading compounds for further beneficial modification. This finding suggested that negative induction effect or π-π conjugation of the substituent groups may contribute to the effective combination with receptors. Therefore, our future work should be directed by this general trend, or we can replace the cyano group with strong election-withdrawing groups such as trifluoromethyl. On the other hand, combining with the deficiency and undesirable effects of zaleplon, further evaluation of these compounds is required to determine their long-term efficacy and safety profile.

TABLE-2
EFFECTS OF COMPOUNDS ON THE LOCOMOTOR ACTIVITY OF MICE ($\bar{x}$ ± s, n = 6)

| Compounds | Dose mg/kg | Locomotor activity/times | | | | |
|---|---|---|---|---|---|---|
| | | Basline | 30' | 60' | 90' | 120' |
| Contrl | – | 112.0 ± 32.3 | 80.0 ± 43.7 | 92.5 ± 44.5 | 98.6 ± 48.8 | 94.7 ± 47.6 |
| Zaleplon | 138 | 118.0 ± 23.9 | 4.1 ± 5.9** | 3.33 ± 4.4*** | 3.0 ± 2.7*** | 9.5 ± 8.8** |
| **2** | 140 | 126.8 ± 15.0 | 51.8 ± 44.6 | 34.2 ± 32.2 | 41.2 ± 43.9 | 51.3 ± 44.8 |
| **3a** | 146 | 126.8 ± 7.8 | 64.1 ± 28.7 | 49.2 ± 46.2 | 59.8 ± 46.7 | 51.7 ± 42.5 |
| **3b** | 153 | 126.1 ± 17.9 | 52.3 ± 59.1 | 51.8 ± 52.2 | 53.7 ± 60.2 | 37.0 ± 41.1 |
| **3c** | 159 | 121.0 ± 21.7 | 69.3 ± 38.6 | 60.7 ± 46.9 | 73.2 ± 56.9 | 67.2 ± 46.8 |
| **3d** | 159 | 126.2 ± 19.2 | 31.8 ± 32.6 | 29.5 ± 37.2* | 46.8 ± 31.6 | 57.6 ± 52.9 |
| **3e** | 165 | 114.0 ± 42.4 | 14.6 ± 11.1* | 46.8 ± 30.0 | 17.8 ± 31.8** | 28.8 ± 24.9* |
| **3f** | 181 | 123.0 ± 28.5 | 20.8 ± 39.0 | 38.8 ± 33.4 | 23.8 ± 39.4* | 25.6 ± 37.9* |
| **3g** | 187 | 101.6 ± 30.2 | 35.3 ± 46.8 | 17.8 ± 24.8** | 22.2 ± 33.2** | 24.3 ± 31.0* |
| **3h** | 195 | 117.2 ± 32.2 | 22.3 ± 16.7 | 22.8 ± 19.6* | 23.7 ± 39.2* | 13.7 ± 14.3* |
| **3i** | 223 | 118.7 ± 29.2 | 57.6 ± 50.0 | 65.8 ± 37.0 | 34.1 ± 38.8* | 53.8 ± 47.1 |
| **3j** | 179 | 107.8 ± 34.5 | 116.3 ± 34.2 | 94.8 ± 50.2 | 60.7 ± 46.1 | 80.0 ± 55.6 |
| **4a** | 159 | 123.0 ± 22.3 | 85.6 ± 44.5 | 77.2 ± 22.1 | 62.5 ± 36.3 | 73.5 ± 36.7 |
| **4b** | 187 | 103.2 ± 27.8 | 68.5 ± 39.4 | 46.7 ± 46.0 | 41.0 ± 33.2 | 48.8 ± 40.6 |
| **4c** | 193 | 98.0 ± 30.1 | 64.3 ± 43.3 | 56.0 ± 46.8 | 42.2 ± 30.7 | 42.3 ± 35.8 |
| **4d** | 183 | 125.5 ± 26.9 | 36.2 ± 35.2 | 14.5 ± 20.8** | 7.0 ± 9.4*** | 12.7 ± 20.1* |
| **5a** | 203 | 119.8 ± 20.1 | 67.5 ± 49.0 | 66.1 ± 37.4 | 73.8 ± 40.9 | 73.2 ± 44.8 |
| **5b** | 219 | 120.1 ± 26.5 | 109.0 ± 66.5 | 96.5 ± 54.5 | 101.5 ± 64.1 | 102 ± 66.6 |
| **5c** | 195 | 117.2 ± 32.2 | 22.3 ± 16.7 | 22.8 ± 19.6* | 23.7 ± 39.2* | 13.7 ± 14.3* |
| **5d** | 239 | 114.0 ± 25.4 | 45.7 ± 31.9 | 42.3 ± 38.8 | 58.3 ± 35.9 | 42.1 ± 29.1 |

*$p < 0.05$ **$p < 0.01$ ***$p < 0.001$ compared with the control group.

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