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Design, Synthesis, and Hypnotic Activity of Pyrazolo[1,5-a]pyrimidine Derivatives

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Abstract: On the basis of the Zaleplon structure, novel pyrazolo[1,5-a]pyrimidines were designed and prepared for studies on their hypnotic activity. This paper reported the synthesis of twelve new 5-methyl-7-substituted–pyrazolo[1,5-a]pyrimidine-3-carbonitrile derivatives by using simple starting materials such as propane dinitrile and triethyl orthoformate. The structures of the derived target compounds were confirmed by their IR and ^{1}H-NMR spectroscopic data. The preliminary pharmacological evaluations indicated that some compounds showed hypnotic activity, while derivative **1c** was the most potent one.

Keywords: GABA, hypnotic drug, synthesis, pyrazolo[1,5-a]pyrimidines.

One important class of inhibitory neurotransmitters in the central nervous system is the gamma aminobutyric acid (GABA). The receptors for GABA have been defined pharmacologically as $GABA_A$, $GABA_B$, and $GABA_C$, and some related pharmacological therapy has played an important role in the management of insomnia. Several traditional drugs are highly effective for initiating and maintaining sleep, but their common limitations are tolerance, withdrawal effects, and impairment of daytime performance. With the increased knowledge of GABA, new hypnotic sedatives have been developed to be selective for the various subunits of the GABA receptors. This development has resulted in the discovery of new agents with very favorable hypnotic and side-effect profiles. These agents are expected to provide improved treatment options for medical practitioners. This fact has led to launch three novel sedative-hypnotic drugs Zolpidem, Zopiclon, and Zaleplon[1-4], in which Zaleplon contains the structure of pyrazolo[1,5-a]pyrimidine ring. We designed an efficient synthetic route for new derivatives of pyrazolo[1,5-a]pyrimidine-3-carbonitrile for screening.

Design and Synthesis

The newly designed target compounds resemble the structural feature of Zaleplon with carbonitrile substituent at the position of pyrazolo[1,5-a]pyrimidine ring. The 7-substitueted derivatives of [1,5-a]pyrimidine 3-carbonitriles **1** were synthesized 3-carbonitriles **1** were synthesized through an efficient route.

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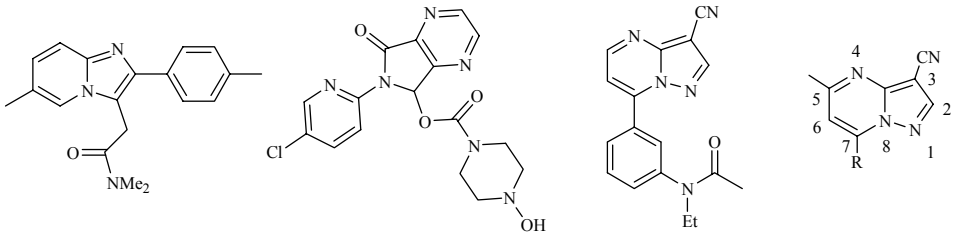
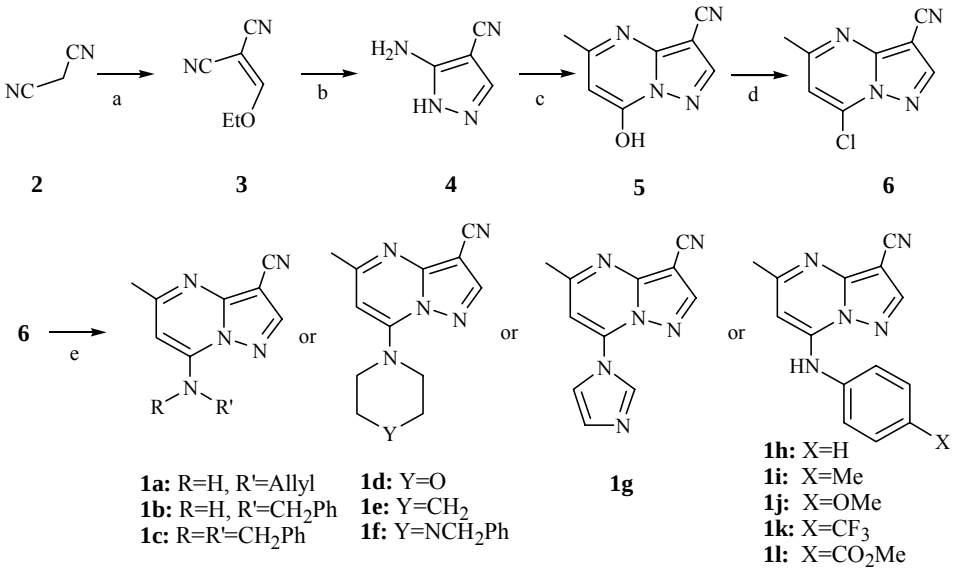


Zolpidem **Zopiclon** **Zaleplon** **1**

The general method for the preparation of pyrazolo[1,5-a]pyrimidine-3-carbonitrile derivatives (**1a-l**) is outlined in **Scheme 1**[5-7]. Reaction of propane dinitrile **2** with triethyl orthormate in acetic anhydride gave the condensation product **3**, which was reacted with hydrazine for the formation of cyclic compound **4**. The second ring was easily constructed by reacting **4** with ethyl acetoacetate to give **5**, which was converted to chloride **6**. Replacement the halide of **6** with amines produced the desired products **1a-l** in good yield.

Scheme 1 5-Methyl-7-substitutied-pyrazolo[1,5-a]pyrimidine-3-carbonitrile derivatives **1a-l**



2 **3** **4** **5** **6**

1a: R=H, R'=Allyl
1b: R=H, R'=CH_2Ph
1c: R=R'=CH_2Ph

1d: Y=O
1e: Y=CH_2
1f: Y=NCH_2Ph

1g

1h: X=H
1i: X=Me
1j: X=OMe
1k: X=CF_3
1l: X=CO_2Me

a: $HC(OEt)_3$, Ac_2O b: H_2NNH_2 H_2O/HOAc c: $CH_3COCH_2CO_2Et$ d: $POCl_3$ e: Amine

The typical procedure for the synthesis of 5-methyl-7-N,N-diphenylmethylamino-pyrazolo[1,5-a]pyrimidine-3-carbonitrile 1c

To a solution of anhydrous potassium carbonate (0.40 g, 3 mmol) in absolute EtOH (15 mL) were added the 5-methyl-7-chloropyrazolo[1,5-a]pyrimidine-3-carbonitrile (0.6 g, 3 mmol) and N, N-dibenzylamine (0.41 g, 4.5 mmol). This solution was stirred at room temperature about 12 h. The precipitate was filtrated off and EtOH was removed.Water (30 mL) was then added to the residue and extracted with EtOAc (3 x 30 mL). The

combined organic layers were dried over $MgSO_4$ and concentrated to yield a crude solid. The solid was then purified with silica gel column chromatography, eluting with ethyl acetate/petroleum ether (1/1) to afford pure product **1c** as a gray solid, m.p. 137-138℃, yield 77.2%. IR (KBr) cm^{-1}: 3421.1, 3001.6, 2222.3 (υ_{CN}), 1612.9, 1586.8, 1554.3, 1451.6, 1368.1, 1339.1, 1296.6, 1195.4, 987.9, 712.4, 696.6; ^{1}H-NMR in **Table 1**; MS (EI) (MS spectra were taken on a Finnigan MAT/USA spectrometer.) *m/z*: 353, Calcd. for $C_{22}H_{19}N_5$ 353.42; Anal. Calcd. C 74.77%,H 5.42%,N 19.81%; found: C 74.75%, H 5.42%, N 19.80%.

Table 1 The HNMR and other physical data of compounds **1a-l***

Cpd	m.p. (°C)	Yield (%)	^{1}H-NMR ppm ($CDCl_3$)
1a	158-160	90.1	8.21 (s, 1H, pyrazole-2-**H**), 6.16 (s, 1H, pyrimidine-6-**H**), 6.03 (s, 1H, -N**H**CH_2-), 5.96 (m, 1H, -C**H**=CH_2), 5.39 (m, 2H, -CH=C**H$_2$**), 4.1 (m, 2H, -NHC**H$_2$**-), 2.57 (s, 3H, pyrimidine-5-C**H$_3$**) ($CDCl_3$)
1b	176-178	57.6	8.17 (s, 1H, pyrazole-2-**H**), 7.41~7.37 (m, 5H, -C_6**H$_5$**), 6.79 (s, 1H, -N**H**), 6.05 (s, 1H, pyrimidine-6-**H**), 4.62 (d, 2H, J=7.8Hz, -C**H$_2$**), 2.56 (s, 3H, -**CH$_3$**) ($CDCl_3$)
1c	137-138	77.2	8.23 (1s, H, pyrazole-2-**H**), 7.36~7.21 (m, 10H, 2×-C_6**H$_5$**), 6.09 (s, 1H, pyrimidine-6-**H**), 5.0 (s, 4H, 2×C_6H_5C**H$_2$**-), 2.50 (s, 3H, pyrimidine-5-C**H$_3$**) ($CDCl_3$)
1d	241-243	70.9	8.23 (s, 1H, pyrazole-2-**H**), 6.17 (s, 1H, pyrimidine-6-**H**), 3.95 (t, 4H, J=4.7Hz, morpholine-C**H$_2$**-), 3.76 (t, 4H, J=4.7Hz, morpholine-C**H$_2$**-), 2.61 (s, 3H, pyrimidine-5-C**H$_3$**) ($CDCl_3$)
1e	158-160	64.4	8.21 (s, 1H, pyrazole-2-**H**), 6.17 (1H, s, pyrimidine-6-**H**), 3.77 (m, 4H, 7-piperidine-C**H$_2$**-), 2.61 (s, 3H, pyrimidine-5-C**H$_3$**), 1.80 (m, 6H, piperidine-C**H$_2$**-) ($CDCl_3$)
1f	202-204	80.7	8.61 (s, 1H, pyrazole-2-**H**), 7.34-7.27 (m, 5H, -CH_2C_6**H$_5$**), 6.60 (s, 1H, pyrimidine-6-**H**), 3.78 (m, 5H, piperazine-C**H$_2$**- and -C**H$_2$**C_6-**H$_5$**), 3.55 (m, 5H, piperazine-C**H$_2$**- and C_6H_5C**H$_2$**-), 2.51 (s, 3H, -C**H$_3$**) (DMSO-d_6)
1g	240-241	56.8	8.74 (s, 1H, pyrazole-2-**H**), 8.44 (s, 1H, imidazole-2-**H**), 7.81 (s, 1H, imidazole-5-**H**), 7.35 (s, 1H, imidazole-4-**H**), 6.99 (s, 1H, pyrimidine-6-**H**), 2.79 (s, 3H, pyrimidine-5-C**H$_3$**) ($CDCl_3$)
1i	190-192	82.2	8.25 (s, 1H, pyrazole-2-**H**), 7.80 (s, 1H, -N**H**-), 7.31 (d, 2H, J=8.3Hz, 7- C_6**H$_4$**CH_3), 7.25 (d, 2H, J=8.7Hz, 7-C_6**H$_4$**CH_3), 6.28 (s, 1H, pyrimidine- 6-**H**), 2.54 (s, 3H, -C**H$_3$**), 2.43 (s, 3H, C_6H_4C**H$_3$**) ($CDCl_3$)
1h	181-183 (decompose)	85.5	8.26 (s, 1H, pyrazole-2-**H**), 8.06 (s, 1H, -N**H**), 7.55~7.36 (m, 5H, -C_6**H$_5$**-), 6.36 (s, 1H, pyrimidine-6-**H**), 2.56 (s, 3H, -C**H$_3$**) ($CDCl_3$)
1j	179-181	89.0	8.23 (s, 1H, pyrazole-2-**H**), 7.92 (s, 1H, -N**H**), 7.29 (d, 2H, -C_6**H$_4$** OCH_3), 7.02 (d, 2H, -C_6**H$_4$**OCH_3), 6.14 (s, 1H, pyrimidine- 6-**H**), 3.87 (s, 3H, -OC**H$_3$**), 2.52 (s, 3H, -C**H$_3$**) ($CDCl_3$)
1k	207-208	66.4	8.70 (1s, H, pyrazole-2-**H**), 7.83 (d, 2H, -C_6**H$_5$**CF_3), 7.70 (d, 2H, -C_6**H$_5$**CF_3), 6.67 (s, 1H, pyrimidine-6-**H**), 2.49 (s, 3H, pyrimidine-5-C**H$_3$**) ($CDCl_3$)
1l	245-246	65.8	10.12 (s, 1H, -N**H**), 8.64 (s, 1H, pyrazole-2-**H**), 7.36 (d, 2H, J=8.2Hz, -C_6**H$_4$**$COOCH_3$), 7.32 (d, 2H, J=8.5Hz, -C_6**H$_4$**$COOCH_3$), 6.15 (s, 1H, pyrimidine-6-**H**), 3.76 (s, 3H, -OC**H$_3$**), 2.37 (s, 3H, -C**H$_3$**) (DMSO-d_6)

* ^{1}H-NMR spectra were taken on a Bruker ARX-300 spectrometer. Tetramethylsilane was used as an internal standard. Melting points were determined with the capillary tube method and the thermometer was uncorrected.

Hypnotic Activities

The hypnotic activities of pyrazolo[1,5-a]pyrimidine derivatives (**1a-l**) were tested and evaluated at pentobarbital sodium test[8] by measuring the sleeping time taken for loss and regaining of righting reflex. All data were analyzed using a non-parametric analysis of variance, followed by Mann-Whitney's *U*-test. The criterion of statistical significance were expressed as $p < 0.05$, comparing with the control group. The results showed that compound **1c** had the best activity among the all tested compounds.

Table 2 The pentobarbital sodium-induced hypnosis test in mice ($\bar{X} \pm SD$)

Group	Number of Animals	Sleeping Time (min)
Zaleplon	10	78.6±14.23 to 92.1±17.41
1c	10	69.5±17.39 to 95.1±24.1
1a	10	68.9±25.08 to 87.0±25.92
1b	10	67.5±26.57 to 79.1±24.17
1d	10	65.8±16.68 to 67.85±15.01
1e	10	60.1±24.46 to 67.1±18.06
1f	10	63.9±15.98 to 67.6±14.85
1g	10	66.2±15.26 to 68.1±15.53
1h	10	66.4±16.48 to 80.3±23.23
1i	10	67.1±20.46 to 70.6±16.84
1j	10	66.2±18.86 to 79.0±18.89
1k	10	58.0±14.86 to 66.0±18.89
1l	10	52.7±18.22 to 55.8±19.83

Pentobarbital sodium 40.0 mg/kg, ***i.p.***

References and Notes

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8. Compared drug: Zaleplon was obtained from Batch Pharmaceutical Co, USA, 010118; Positive control drug: Estazolam was obtained from Tianjin Haiguang Pharmaceutical factory, 2 mg/Kg.

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