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Synthesis and Vasodilatory Activities of New Pyrazolo[3,4-d] pyrimidin-4-one Derivatives

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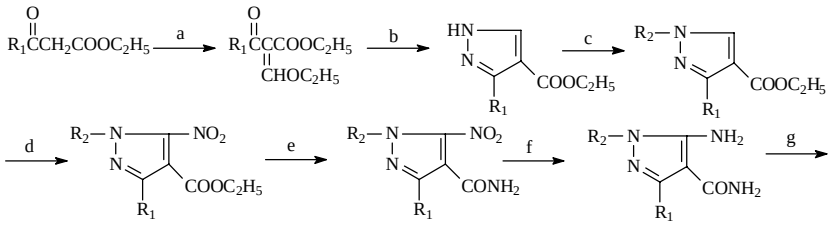
Abstract: A series of pyrazolo[3,4-d]pyrimidin-4-one derivatives were synthesized and tested for vasodilatory activities. All of them were new compounds and their structures were confirmed by IR, ^{1}H NMR, MS and elemental analysis.

Keywords: Pyrazolo [3,4-d] pyrimidin-4-ones, synthesis, vasodilatory activity.

Selective cyclic guanosine 3′,5′-monophosphate phosphodiesterase (cGMP PDE) inhibitors have utility in the treatment of various cardiovascular disorders such as angina, hypertension, congestive heart failure and so on. Pyrazolo[4,3-d]pyrimidin-7-ones have been reported as potent and selective inhibitors of cGMP PDE[1,2]. In order to find new type of cGMP PDE inhibitors, we turned our attention to the synthesis of pyrazolo [3,4-d]pyrimidin-4-one derivatives and their pharmacological activities. All of them were new compounds and their structures were confirmed by IR, ^{1}H NMR, MS and elemental analysis.

Herein, pyrazolo[3,4-d]pyrimidin-4-ones XI**a~h** were synthesized in ten steps starting with 3-oxoalkanoic acid ethyl ester I and triethyl orthoformate (**Scheme 1**). The substituents of compound XI were shown in **Table 1**. The data of melting points, elemental analyses, MS and yields for compounds XI**a~h** were shown in **Table 2**.

Scheme 1 The synthetic route of pyrazolo[4,3-d]pyrimidin-7-ones



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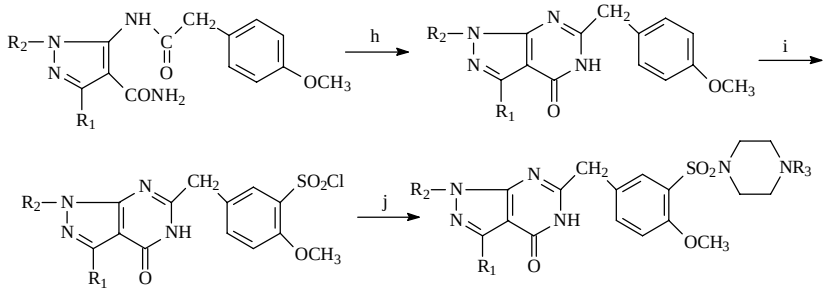

Reagents and conditions: a. $HC(OEt)_3$, Ac_2O, $ZnCl_2$, reflux 6 h; b. $H_2NNH_2H_2O$, EtOH, reflux 4 h, 58~69% (for a, b steps); c. Me_2SO_4 or Et_2SO_4, 80~90°C 4 h, 82~90%; d. HNO_3, H_2SO_4, 60°C 6 h, 75~84%; e. NH_4OH, 80°C 5 h, 80~87%; f. $H_2NNH_2H_2O$, EtOH, Raney Ni, reflux 10 h, 90~95%; g. *p*-methoxyphenyl acetyl chloride, pyridine, dimethylaminopyridine, CH_2Cl_2, reflux 4 h, 60~76%; h. NaOH, H_2O_2, EtOH, reflux 3 h, 68~80%; i. $ClSO_3H$, rt 10 h, 90~95%; j. 1-methylpiperazine or piperazine, CH_3OH, rt 24 h, 80~92%.

Table 1 The Substituents of compound **XI**

Compd.	R_1	R_2	R_3	Compd.	R_1	R_2	R_3
XIa	*n*-C_3H_7	CH_3	CH_3	**XIe**	*iso*-C_3H_7	C_2H_5	H
XIb·HCl	*n*-C_3H_7	C_2H_5	CH_3	**XIf**	*iso*-C_4H_9	C_2H_5	CH_3
XIc·HCl	*n*-C_3H_7	C_2H_5	H	**XIg**	*iso*-C_4H_9	CH_3	CH_3
XId	*iso*-C_3H_7	C_2H_5	CH_3	**XIh**	*iso*-C_4H_9	CH_3	H

Table 2 Data of melting point, elemental analysis, MS and yields for compound **XI**[4]

Compd.	mp (°C)	Elemental Analysis				$[MH^+]$	Yields
		C%	H%	N%	S%	(*m/z*)	(%)
XIa	208~210	55.68	6.37	17.71	6.76	475.3	15.6
		(55.61)*	(6.26)	(17.85)	(6.81)		
XIb·HCl	210~212	52.61	6.33	16.01	6.11	489.4	12.9
		(52.59)	(6.21)	(16.17)	(6.20)		
XIc·HCl	223~225	51.71	6.11	16.44	6.27	475.4	11.8
		(51.62)	(6.22)	(16.58)	(6.38)		
XId	192~195	56.54	6.60	17.20	6.56	489.4	10.8
		(56.68)	(6.78)	(17.06)	(6.48)		
XIe	230~232	55.68	6.37	17.71	6.76	475.1	11.3
		(55.52)	(6.36)	(17.59)	(6.81)		
XIf	190~192	57.35	6.82	16.72	6.38	503.3	9.6
		(57.50)	(6.76)	(16.89)	(6.39)		
XIg	163~165	56.54	6.60	17.20	6.56	489.7	8.9
		(56.54)	(6.76)	(17.09)	(6.52)		
XIh	229~231	55.68	6.37	17.71	6.76	475.6	9.6
		(55.73)	(6.31)	(17.59)	(6.68)		

*Data in Parentheses represent the found data

The effects of the above compounds on the contractions induced by arterenol bitartrate (Shanghai Hefeng Co.Ltd.) were examined on the rabbit aortic strips. Helically cut strips of rabbit thoracic aorta were prepared as described by Xu Shuyun[3]. Contractions were measured isometrically with a force-displacement transducer. Title

compounds were dissolved in flesh distilled water, and their final concentrations were 1.0×10^{-5} Mol/L. Verapamil (Shanghai Hefeng Co.Ltd.) was used as control and its final concentration was 1.7×10^{-5} Mol/L. The results were summarized in **Table 3**.

Table 3 The vasodilatory effects of compounds XI**a~h** on the isolated rabbit thoracic aorta (n=10)

Compd.	Vasodilatory effects (%) ($\bar{x} \pm s$)	Compd.	Vasodilatory effects (%) ($\bar{x} \pm s$)
verapamil	10.50±5.58		
XIa	8.56±6.11	**XIe**	7.85±6.03
XIb·HCl	4.56±3.08	**XIf**	9.06±3.89
XIc·HCl	15.19±5.32	**XIg**	3.02±4.05
XId	7.31±4.02	**XIh**	2.21±5.10

Compounds XI**a~h** all showed vasodilatory activities on the isolated rabbit thoracic aorta, and XI**c·HCl** was probably more potent than control compound verapamil.

Further experiments and pharmacological evaluations of these compounds are in progress.

General procedures for the preparation of compounds XI were as follows:

The appropriately substituted compound I (0.1mol), triethyl orthoformate (0.25 mol), and a catalytic amount of zinc chloride (0.01 mol) were dissolved in acetic anhydride (50 mL) and the mixture refluxed for 6 h. Solvents were evaporated, then hydrazine hydrate (0.12 mol) and ethanol (50 mL) were added. The resulting mixture was stirred 4 h at reflux. The solution was concentrated to dryness in *vacuo* to give Ⅲ (58~69%).

The substituted pyrazole III (0.1 mol) reacted with dimethyl sulphate or diethyl sulphate (0.12 mol) at 80~90°C for 4 h. The mixture was dissolved in dichloromethane and the solution washed with sodium carbonate solution. The organic phase was separated, dried and evaporated in *vacuo* to give IV (82~90%).

The resulting substituted pyrazole IV (0.2 mol) was added portionwise to a mixture of sulfuric acid (0.56 mol) and fuming nitric acid (0.60 mol), keeping the temperature below 60°C, then, the mixture was heated at 60°C for 6 h and cooled to room temperature. Filtration of the precipitate gave V (75~84%).

V (0.1 mol) was added to concentrated aqueous ammonium hydroxide solution (100 mL) and the resulting mixture was stirred for 5 h at 80°C. The solution was cooled to room temperature. The precipitate was collected by filtration to provide VI (80~87%).

The mixture of VI (0.05 mol), Raney nickel (1 g) and hydrazine hydrate (0.4 mol) in ethanol (20 mL) was refluxed for 10 h. The resulting mixture was cooled to room temperature and filtrated. The filtrate was basified to pH 9 by addition of 2 mol/L aqueous sodium hydroxide and extracted with dichloromethane (3×80 mL). The organic extracts were combined, dried and evaporated in *vacuo*. Recrystallization from acetic acetate and acetone to give VII (90~95%).

A solution of *p*-methoxyphenyl acetyl chloride (0.10 mol) in dichloromethane (50 mL) was added to a stirred solution of the substituted pyrazoloaminoamide VII

(0.05 mol), pyridine (0.15 mol), and dimethylaminopyridine (0.005 mol) in dichloromethane (50 mL) at 0°C. The resulting mixture was refluxed for 4 h. The solution was washed with 14% aqueous ammonium hydroxide, and then with 2 mol/L hydrochoride acid and brine, dried and evaporated in *vacuo*. The crude material was recrystallized from ethyl acetate and hexane to give VIII (60~76%).

VIII (0.05 mol) was added portionwise to a solution of sodium hydroxide (0.1 mol) and hydrogen peroxide solution (0.2 mol) in water (150 mL). Ethanol (50 mL) was added and the resulting mixture heated under reflux for 3 h, cooled, then evaporated in *vacuo*. The resulting residue was treated with 2 mol/L hydrochloric acid (40 mL), and the mixture was extracted with dichloromethane (3×50 mL). The combined organic extracts were washed with aqueous sodium carbonate solution and brine, then dried and evaporated in *vacuo* to give IX (68~80%).

IX (0.03 mol) was added portionwise to chlorosulphonic acid (0.27mol) at 0°C. After being stirred 10 h at room temperature, the reaction solution was added to ice-water and then filtrated. The resulting solid was washed with water to give X (90~95%).

1-Methylpiperazine or piperazine (0.03mol) was added to a stirred suspension of X (0.01 mol) in methanol (50 mL) at room temperature. The resulting mixture was stirred for 24 h. The solvent was removed by evaporation in *vacuo*. The residue was dissolved in chloroform (50 mL) and the solution washed with saturated aqueous sodium carbonate solution. The organic phase was dried and evaporated under vacuum to give a solid. Crystallization from ethanol gave the title compounds XI**a~h** [4] (80~92%).

References and Notes

1. A. S. Bell, D. Brown, N. K. Terrett, *Preparation of pyrazolo[4,3-d]pyrimidin-7-ones as cardiovascular agents*, EP 463,756, **1991**.
2. A. S. Bell, N. K. Terrett, *Preparation of pyrazolopyrimidinones as cGMP phosphodiesterase inhibitors*, EP 526,004, **1992**.
3. S. Y. Xu, R. L. Bian, X. Chen. *Pharmacological experimental methods*. People health press. Beijing, **1991**, 984.
4. XIc·HCl: IR (KBr, cm^{-1}): 1681.3 ($_{C=O}$), 1603.7, 1488.1 ($_{C=C}$), 1315.6, 1156.4 ($_{SO2}$). ^{1}H NMR ($CDCl_3$): ppm: 1.01 (t, 3 H, J=7.3 Hz, $CH_2CH_2CH_3$), 1.50 (t, 3 H, J=7.1 Hz, CH_2CH_3), 1.82 (m, 2 H, J=7.4, 7.3 Hz, $CH_2CH_2CH_3$), 2.90 (t, 2 H, J=7.4 Hz, $CH_2CH_2CH_3$), 2.96 (m, 4 H, piperazine), 3.29 (m, 4 H, piperazine), 3.88 (s, 3 H, OCH_3), 4.03 (s, 2 H, CH_2), 4.62(q, 2 H, N**C**$\mathbf{H_2}$$CH_3$), 6.96 (d, 1 H, J=8.5 Hz, Ph H-5), 7.58 (dd, 1 H, J=8.5, 1.5 Hz, Ph H-6), 7.95 (d, 1 H, J=1.5 Hz, Ph-2-H), 12.29 (s, 1 H, CONH)
Other compounds were also confirmed by IR and ^{1}H NMR.

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