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SYNTHESIS OF SOME NEW PYRAZOLO [1,5-A] PYRIMIDINES AND THEIR CNS ACTIVITY

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Abstract:

3-amino-4-phenylpyrazole condenses with appropriate fluorinated 1,3-diketone in absolute ethanol in presence of piperidine to give pyrazolo [1,5-a] pyrimidines. The structures of all these compounds have been confirmed by their IR, ^{1}H NMR, ^{19}F NMR, mass spectral data and elemental analysis. Compounds have been found to possess CNS depressant activity.

Introduction

Pyrazolo-pyrimidine and their derivatives have significant therapeutic and biological properties. They possess potent anxiolytic properties, which are comparable to diazepam and chlordiazepoxide[1]. Pyrazolo [1,5-a] pyrimidines have been found to possess wide variety of biological properties like: antagonistic[2], antimicrobial[3], potent inhibitors of hepatitis C virus[4].

In continuation of our work on heterocyclic compounds[5-8], we have synthesized new substituted pyrazolo [1,5-a] pyrimidines from 3-amino-4-phenylpyrazoles.

Experimental

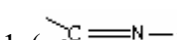
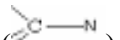
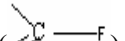
Melting points were determined in open capillaries and are uncorrected. The IR spectra (cm^{-1}) were recorded on a SHIMADZU 8400S FT-IR spectrometer in KBr pellets. ^{1}H NMR spectra were recorded on JEOL DRX-300 SPECTROMETER (300 MHz) using TMS as an internal standard (chemical shifts are reported in δ scale). Purity of compounds was checked by TLC on silica gel plate.

Synthesis of 5,7-Disubstituted-3-phenylpyrazolo [1,5-a] pyrimidine

It was prepared by the method of Novinson et al. equimolar quantities of 3-Amino-pyrazole and appropriate 1,3-diketone were heated under reflux in absolute ethanol in presence of piperdine (one drop) for 24 hrs. Excess of solvent was removed under reduced pressure. The solid was washed with petroleum ether and recrystallized from ethanol/methanol.

The details of amount taken of different reactants, m.p.'s, yield and physical data are given in **Table-I**.

Result and Discussion

IR spectra in KBr pellet showed characteristic absorption bands in the region of 1600-1680 cm-1 (); 1440-1520 cm^{-1} (); 1030-1210 cm^{-1} () and 1240-1380 cm^{-1} ($-CF_3$).

^1H NMR spectra were recorded in trifluoroacetic acid as a solvent. ^1H NMR spectra showed characteristic resonance signals in the range of δ 1.6-2.5 ppm (3H, C-C<u>H</u>$_3$); δ 3.0-3.5 ppm (3H, C-OC<u>H</u>$_3$); and δ 7.0-8.1 ppm (aromatic protons). Disappearance of amino proton (-N<u>H</u>$_2$) signal and methine proton (=C<u>H</u>) signal of 3-amino-4-phenylpyrazole provides strong evidence for the formation of pyrazolo [1,5-a] pyrimidines.

^{19}F NMR spectra of fluorine containing pyrazolo [1,5-a] pyrimidines showed a sharp singlet at δ 32-43 ppm and confirmed the presence of single fluorine in benzene ring in compound numbers 1, 5 and 7. Another resonance signal at δ -10 to -8 ppm is due to the presence of $–CF_3$ group in compound numbers 2 and 6.

CNS Activity

Compound Numbers 1, 2, 5 and 6 were screened for their CNS activities and tabulated in **Table-II**.

1 Behavioural activity –

At a dose of 464 mg/kg (i.p.), in test animals, respiration decreases, slight writhing is present. Reactivity towards sound and touch decrease. Catalepsy, pineal, corneal and writhing activities is present in compound Number 2. Mortality is NIL within 24 hrs.

At a dose level of 1000 mg/kg (i.p.), writhing is present, respiration decreases and reactivity towards sound and touch decrease. Mortality is 25, 100, 75 and 50 percent in compound Numbers 1, 2, 5 and 6 respectively within 24 hrs.

Compounds have been found to possess CNS ***depressant activity***.

2 Acute toxicity –

Compound Number 2 has been found to possess significant acute toxicity, test animal dies immediately after administration of drug at a dose of 1000 mg/kg (i.p.) due to failure of respiratory system.

3 Analgesic activity –

None of the screened compounds showed significant analgesic activity.

4 Anticonvulsant activity –

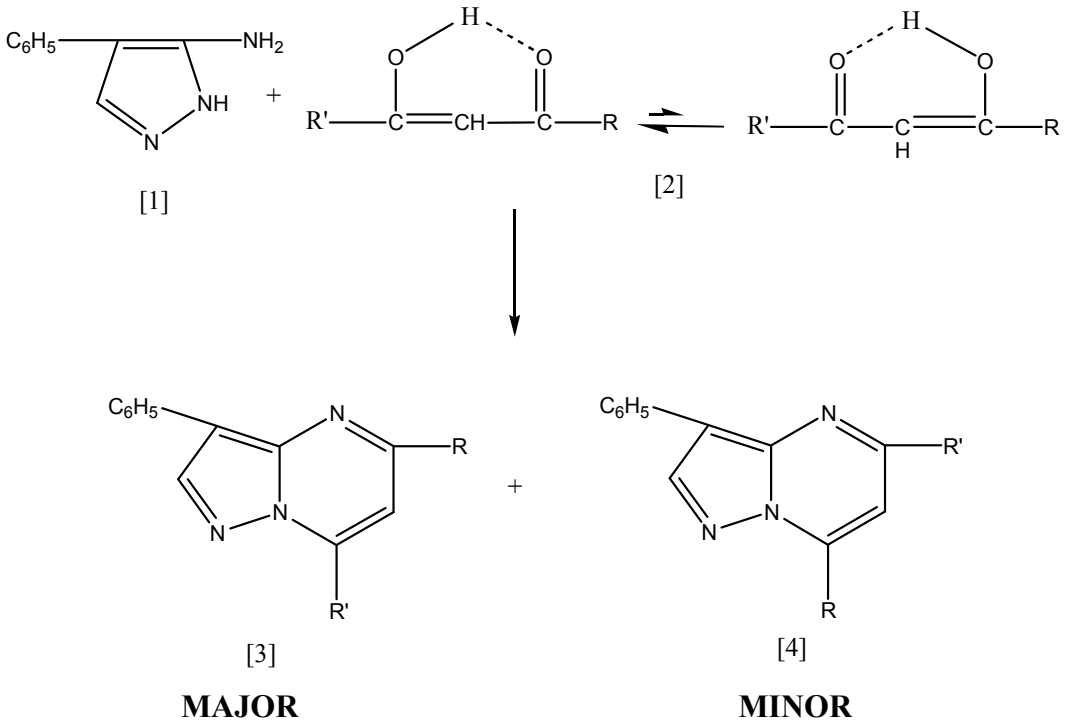
Compound Number 2 exhibited 60 percent protection of electric shock at a dose of 136.2 mg/kg.

5 Anti-inflammatory activity –

Compound Numbers 1, 2 and 6 exhibited significant anti-inflammatory activity with indomethacin as reference compound.

Table – I Pyrazolo [1,5-a] pyrimidines

Compound No.	3-Amino-4-phenyl-pyrazole (in gm)	1,3-Diketones (in gm)	Yield, %	M.P., in ºC	R	R'	Molecular Formula	Analysis of N, %	
								Calculated	Found
1	1.5	2.1	59	119	CH_3	3-F, 4-OCH_3.C_6H_3	$C_{20}H_{16}FN_3O$	12.61	12.58
2	1.5	2.6	63	160	CF_3	3-F, 4-OCH_3.C_6H_3	$C_{20}H_{13}F_4N_3O$	10.85	10.65
3	1.5	2.7	58	157	C_6H_5	3-F, 4-OCH_3.C_6H_3	$C_{25}H_{18}FN_3O$	10.63	10.58
4	1.5	3.2	67	145	C_2F_5	3-F, 4-OCH_3.C_6H_3	$C_{21}H_{13}F_6N_3O$	09.61	09.43
5	1.5	2.1	54	154	CH_3	3-Cl, 4-F.C_6H_3	$C_{19}H_{13}ClFN_3$	12.44	12.39
6	1.5	2.6	69	171	CF_3	3-Cl, 4-F.C_6H_3	$C_{19}H_{10}ClF_4N_3$	10.72	10.60
7	1.5	2.7	50	168	C_6H_5	3-Cl, 4-F.C_6H_3	$C_{24}H_{15}ClFN_3$	10.51	10.48



SCHEME

R=CH_3,CF_3,C_2F_5,C_6H_5
R'= 3-F-4-OCH_3.C_6H_3, 3-Cl-4-F.C_6H_3

Table-II CNS SCREENING

Compd No.	Dose mg/kg (i.p.)	Respi-ration	Writhing	Reactivity		Catalepsy, pineal, corneal	Mortality	LD_{50}	Body temp in °C	Anal-gesic activity (i.p.)	Anti-convul-sant activity (i.p.)
				Sound	Touch						
1	464	↓	+	↓	↓	–	Nil	□1000	0.3↓	–	–
	1000	↓	+	↓	↓	–	25				
	200	↓	+	↓	↓	–	Nil				
2	464	↓	+	↓	↓	+	Nil	681	1.1↓	–	60
	1000	–	–	–	–	–	100				
	136.2	↓	+	↓	↓	+	Nil				
5	464	↓	+	↓	↓	–	Nil	825	0.7↓	–	–
	1000	↓	+	↓	↓	–	75				
	165	↓	+	↓	↓	–	Nil				
6	464	↓	+	↓	↓	–	Nil	1000	0.5↓	–	–
	1000	↓	+	↓	↓	–	50				
	200	↓	+	↓	↓	–	Nil				

ABBREVIATIONS:	↑↓	=	Increase or decrease in reactivity.
	+	=	Mild effect.
	–	=	No effect.

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