RESEARCH PAPER

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Synthesis of 3-[4[4,5-Dihydro-5-(substituted aryl)-1H-pyrazol-3- yl]phenyl]sydnones as Antiinflammatory and Analgesic agents

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3-[4-(3-(Substituted aryl)-1-oxo-2-propenyl]phenyl]sydnones were condensed with hydrazine to yield fifteen 3-[4-(4,5-Dihydro-5- (substituted aryl)-1H-pyrazol-3-yl]phenyl]sydnones. Three compounds have shown antiinflammatory activity in carrageenan induced edema assay in rats and five compounds have shown analgesic activity in acetic acid-induced writhing assay in mice at 100 mg/kg dose p.o. respectively. Compound 24 exhibited both antiinflammatory and analgesic activity, which appeared to be similar to those produced by the standards phenylbutazone and aspirin. However compound 21 showed more analgesic activity than aspirin (ED_{50}, 25.0mg/kg, 81.4mg/kg)

SYDNONES (1,2,3,-oxadiazolium-5-olates) are mesoionic compounds[1]. Some sydnones derivatives are reported to possess antinflammatory activity in adjuvant-induced arthritics[2,3] and carrageenan-induced edema assays[4]. In search of potential antiinflammatory sydnones, we have synthesized a number of sydnone derivatives[5-8]. Some of these sydnones have shown significant antiinflammatory activity in carrageenan-induced edema and adjuvant-induced arthritis assays. Some compounds have also exhibited appreceiable analgesic activity in acetic acid-induced writhing test. As an extension of our studies on sydnones, we describe the synthesis of 3-[4-(4,5-Dihydro-5-(substituted aryl)-1H-pyrazol-3-yl) phenyl] sydnones, and their antiinflammatory, antiarthritic, and analgesic activities in this paper.

EXPERIMENTAL

Materials

Melting points were determined in an open capillary on a Toshniwal melting point apparatus and were uncorrected.Elemental analysis (C,H, and N) was carried out on a Carlo Erba 1108. UV spectra in chloroform, ehtanol, or methanol were recorded on a Shimadzu 240 spectrometer. Infrared (IR) spectra were recorded on a Perkin Elmer R-32 spectrometer. ^{1}H-NMR spectra in $CDC1_3$, or DMSO-d_6 were recorded on a Perkin-Elmer R- 3L spectrometer using TMS as internal standard. Progress of the reactions and purity of the products were analyzed by TLC using glass slides coated with silica gel G, and were detected by iodine vapor.

Methods

Synthesis of 3-[4-['3-(Substituted aryl)-1—oxo-2-propenyl] phenyl]sydnones(1-15)

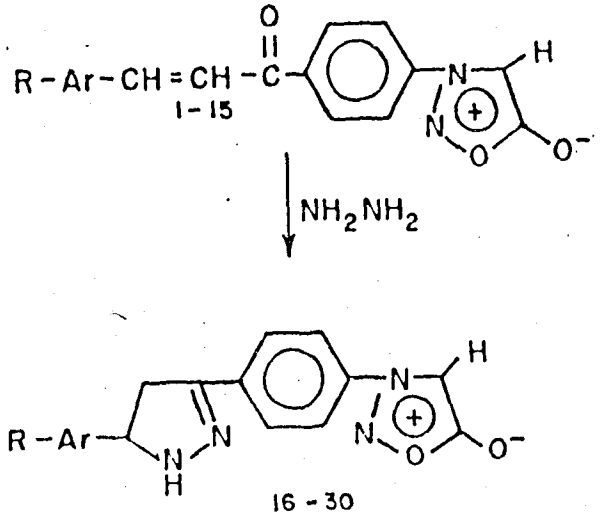
Compounds 1-15 were synthesized as reported earlier[7] in yields of 25-70%. The physical data were in complete agreement with those cited[7].

Synethesis of 3-[4-[4,5-Dihydro-5-(4-dimethylamino phenyl)-1H- pyrazol-3-yl]phenyl]sydnone (21)

3-[4-[3(4-Dimethylaminophenyl)-1-oxo-2-propenyl]phenyl]sydnone (6)(2.3g, 0.0066mol), and hydrazine hydrate (2.0ml, 80%, 0.02mol) in 30ml ethanol

were refluxed on a water bath for 6 hours. The precipitated title compound was filtered and thoroughly washed with ethanol. It was purified by repeated ethanol water crystalization (yield 1.7g, 0.005mol, 75%): m.p. 169-70°C; R_f(3:13 ethyl acetate-benzene) 0.44; C, 64.93(65.32), H, 5.40(5.48), N, 20.10(20.04); UV($CHCl_3$), 255 nm(E, 30,360), 330(26,866); IR(KBr), 3360(NH,Pyrazoline), 3160(CH,sydnone), 1770(C=O,sydnone), 1620(C=N,pyrazoline), 1470(CH_2, pyrazoline) cm^{-1}; ^{1}H-NMR, δ 2.9(s,6H,Ar-N(CH_3)$_2$), 3.2-3.5(m,2H,CH_2,Pyrazoline), 5.0(t,1H,NH,pyrazoline), 6.6(s,1H,NH,pyrazoline),6.7(s,1H,CH,sydnone), 7.1-7.9(m,9H,Ar-H),

Scheme -I



Pharmacological Evaluation

Albino rats (Charles Foster Strain) of either sex (150-180g) and Swiss albino mice of either sex (18-25g), obtained from the animal house of the College of Pharmaceutical Sciences, were used. The compounds were given p.o. using a feeding tube, as homogenized suspensions in 0.5% sodium carboxymethyl cellulose; 0.5% sodium carboxymethyl cellulose was administered as the vehicle control.

Carrageenan-Induced Edema[9]

Groups of four rats were administered 100 mg/kg p.o. of each of the respective test compounds, 1h before 0.05 ml of a 1% suspension of TypeIV Lambda(Sigma) carrageenan was injected into the subplantar region of the right hind paw; additional groups of four rats were similarly pretreated with 100 mg/kg phenylbutazone or ibuprofen (positive control) or 10 ml/kg 0.5% sodium carboxymethyl cellulose (vehicle controls). Paw volumes were measured by water displacement in a plenthysmograph immediately after carrageenan injection, and again 3h later. Edema volumes for test compound-treated and positive control rats were compared statistically with those for the vehicle-treated control rats; data were reported as percent edema inhibition. The test was repeated on additional groups containing four rats each, treated, respectively, with those compounds for which edema inhibition had been calculated to be > 10%; these results are shown in **Table 2.**

Adjuvant Arthritis[10]

Adjuvant arthritis was induced in groups containing six rats each, by subcutaneous injection of 0.13 ml Freund's adjuvant containing dead **Mycobacterium butyrium** (1mg/ml) in liquid paraffin(Sigma) into the plantar surface of their right hind paws. Paw volumes were measured on the day of injection and again 17 days later, by means of a plethysmograph. Compounds 21 and 24, and phenylbutazone were given at a dose of 33 mg/kg/day for 18 days beginning one day before the adjuvant injection; an additional group was treated similarly with 3 mg/kg indomethacin. Edema volumes for the test compound-treated and positive control rats were compared with those for vehicle-treated control rats; the data are reported as percent edema inhibition.

Analgesic Activity[11]

This method is based on acetic acid-induced writhings in mice. Groups of six mice each were

Table I: Physical Data and Yields of 3-[4-{4,5-dihydro-5(substituted aryl)-1H-ptrazol-3-yl}phenyl]sydnomes(16-30)

Compound	Ar	R	mp[a] °C	Yield (%)	Formula[b]
16	Ph	H	162-63(160)[14]	51	$C_{17}H_{14}N_4O_2$
17	Ph	4-CH_3	182-84(178)[14]	53	$C_{18}H_{16}N_4O_2$
18	Ph	4-$CH(CH_3)2$	135-37	46	$C_{20}H_{20}N_4O_2$
19	Ph	4-OCH_3	125-28(127)[14]	52	$C_{18}H_{16}N_4O_3$
20	Ph	2,4-$(OCH_3)3$	188-90	58	$C_{19}H_{16}N_4O_3$
21	Ph	4-$N(CH_3)2$	169-71	73	$C_{19}H_{19}N_4O_2$
22	Ph	4-$NHCOCH_3$	208-11	48	$C_{19}H_{17}N_5O_3$
23	Ph	4-Br	179-80	43	$C_{17}H_{13}BrN_4O_2$
24	Ph	4-C1	169-71(168)[14]	43	$C_{17}H_{13}C1N_4O_2$
25	Ph	3-C1	158-60	41	$C_{17}H_{13}C1N_4O_2$
26	Ph	2,4-$C1_2$	225-28	43	$C_{17}H_{12}C1_2N_4O_2$
27	Ph	2,6,$C1_2$	213-16	51	$C_{17}H_{12}C1_2N_4O_2$
28	Ph	4-F	175-78	57	$C_{17}H_{13}FN_4O_2$
29	2-furyl H		145-48	47	$C_{15}H_{12}N_4O_3$
30	2-thienyl H		197-98	38	$C_{15}H_{12}N_4O_28$

a. Purification from repeated ethanol-water system crystallization.
b. all the compounds were analyzed for C, H, and N, and results agreed to ± 0.4% of theoretical values.

dosed with the test compounds or with aspirin, at a dose of 100 mg/kg p.o., 1h before the i.p. injection of 0.6% acetic acid (10 ml/kg). Mice were observed for 15 min beginning 5 min after the acetic acid injection, and the total number of writhes recorded. The mean value of writhes for each group was calculated and compared statistically with that for the vehicle-treated control group (n=6); data were reported as percent inhibition of the number of writhes. The test was repeated on additional groups containing six mice each, treated respectively, with those compounds for which the reduction in writhes had been calculated to be > 10%; these results are shown in **Table 4.**

Yeast-Induced Pyrexia[12]

Male rats were injected subcutaneously with a 15% (dose 10 ml/kg) aqueous suspension of locally purchased dried yeast. Those developing a 1°C-2.5°C rise in rectal temperature 18 h after injection, measured using an Elico telethermometer, were divided into groups of five. They were dosed at 100 mg/kg p.o. with compounds 21 and 24 or with aspirin; rectal temperatures were recorded at 1, 2, and 3 h, and compared with correspondingly recorded temperatures for the vehicle-treated control animals.

Acute Toxicity

Compounds 21,24 and 27 were administered p.o. to groups containing four mice each, at doses

Table II Antiinflammatory Activity of 16-30

Compound	Edema vol. ml. (± SD)[a]	Edema inhibition (%)[b]
16	0.52(0.06)[c]	NA[f]
17	0.41(0.08)[d]	21.2
18	0.55(0.05)[c]	NA
19	0.50(0.04)[c]	NA
20	0.51(0.03)[c]	NA
21	0.22(0.05)[d]	57.6*
22	0.36(0.03)[d]	30.7*
23	0.38(0.08)[d]	26.9
24	0.17(0.04)[d]	67.3*
25	0.54(0.08)[e]	NA
26	0.59(0.10)[e]	NA
27	0.50(0.09)[e]	NA
28	0.52(0.06)[e]	NA
29	0.54(0.07)[e]	NA
30	0.55(0.04)[e]	NA
Phenylbutazone	0.17(0.050[d]	67.3*
ibuprofen	0.16(0.06)[e]	71.4*

a At 100 mg/kg, p.o, edema volume measured 3h after carrageenan injection, and expressed as mean ± standard deviation (N=4).

b Percent edema inhibition calculated by comparing with the vehicle treated control animals.

c Control edema volume = 0.54(0.0); d Control edema volume = 0.52(0.04); e Control edema volume = 0.56(0.05)

f Not active (activity ≥ 10 %) : * Statistically significant ($p \leq 0.05$, Mann-Whitney).

of 250, 500, 750, and 1000 mg/kg respectively. The mice were observed for lethality over a period of seven days.

Statistical Analysis[13]

All values are expressed as mean ± standard deviation. Data were analyzed by Mann-Whitney or ANOVA.

Results and Discussion

3-[4-{3-(Substituted aryl) -1-oxo-2-propenyl}phenyl]sydnone (1- 15), synthesized according to a previosuly described procedure[7], were condensed with hydrazine hydrate to yield 3-[4-{4,5,-dihydro-5-(substituted aryl)-1H-pyrazol-3- yl}phenyl]sydnones(16-30, Table 1.). All the compounds were characterized by elemental and spectral analysis.

All the compounds were tested at 100 mg/kg, p.o. for Antiinflammatory activity in the carrageenan-induced edema assay in rats (Table 2). Amongst fifteen compounds, three compounds (21,22,24) showed significant ($p \leq 0.05$) activity. Compounds 24 showed highest activity (67.3%), which was equal to that of phenylbutazone. Compounds 21 has also showed appreciable activity (57.6%). Hence these two compounds were tested at lower doses (Table 3). Compound 21 was significantly active at 10 mg/kg and 30 mg/kg doses, whereas compound 24 was significantly active at 30 mg/kg dose only. These two compounds were also tested for antiarthritic activity in adjuvant-induced arthritis assay and antipyretic activity in yeast-induced pyrexia assay in rats. Both compounds showed no activity in these assays (data not shown). All these compounds were also tested for analgesic activity in acetic acid-induced writhing assay in mice at a dose of 100 mg/kg, p.o. (Table 4). Five compounds (21,23,24,27 and 29) showed significant activity. The highest activity (79.7%) was shown by 21, which was higher than that of aspirin (58.1%). Compound 24 and 27 also showed more activity than aspirin. It is further interesting to note that 21 and 24 showed significant activity in carrageenan model too. **Table 5** gives the activities of 21,24 and 27 at lower doses. From ED_{50} values it is clear that 21 possess appreciable anal-

Table III: Antiinflammatory Activity of Compounds 21 and 24 at Different doses

Compound	Edema inhibition (%)[a]			ED_{50} mg/kg[b]
	10mg/kg	30mg/kg	100 mg/kg	
21	29.3(5.1)*	53.4(6.8)*	57.6(9.6)*	47.0
24	10.3(3.4)	25.2(8.9)*	67.3(7.6)*	58.9
Phenylbutazone	25.8(7.3)*	51.6(6.8)*	67.3(9.6)*	34.8

a Given p.o.; percent edema inhibition compared to control 3h after carrageenan injection, men ± standard deviation (N = 4).
b ED_{50} in mg/kg calculated from the refression equation.
* Statistically significant ($p \leq 0.05$, Mann-Whitney test).

Table IV: Analgesic Activity of 16-30

Compound	No. of writhes in 15 minutes (± SD)[a]	% Reduction from control[b]
16	65(8)[c]	NA[f]
17	63(6)[c]	NA
18	72(10)[c]	NA
19	66(9)[c]	NA
20	66(8)[c]	NA
21	15(6)[d]	79.7*
22	60(12)[d]	18.9
23	46(4)[d]	37.8*
24	30(7)[d]	59.5*
25	70(8)[d]	NA
26	60(9)[e]	NA
27	21(3)[e]	68.2*
28	52(6)[e]	22.7
29	36(5)[e]	45.5*
30	51(10)[e]	22.7
aspirin	31(4)[d]	58.1*

a At 100 mg/kg, p.o. number of writhes in 15 min beginning 5 min after acetic acid injection, expressed as mean ± standard deviation (N=6).
b Percent writhing inhibition calculated by comparing with vehicle treated control animals.
c Control no. of writhes = 70(6); d Control no. of writhes = 74(5); e Control no. of writhes = 66(6);
f Not active (activity ≤ 10%)
* Statistically significant (ANOVA ≤ 0.05).

Table V: Analgesic Activity of 21, 24, and 27 at Different Doses

Compound	Writhing inhibition % (± SE)[a]			ED_{50}[b]
	10 mg/kg	30 mg/kg	100 mg/kg	
21	32.2(7.1)*	51.5(3.4)*	79.7(8.1)*	25.0
24	21.1(3.8)*	24.1(5.2)*	59.5(9.4)*	73.5
27	3.0(4.1)	30.6(6.2)*	68.2(5.4)*	54.5
aspirin	6.6.(5.1)	20.0(3.5)*	58.1(5.4)*	81.4

a Given p.o. percent writhing inhibition compared to control, mean ± Standard deviation (N=6)
b ED_{50} in mg/kg, calculated from regression equation.
* Statistically significant ($p \leq 0.05$, ANOVA)

gesic activity, which is much higher than that of aspirin. Compounds 21,24 and 27 were tested for acute toxicity in mice. No deaths were seen over a period of seven days following the dose unto 500 mg/kg p.o. with 21 and 1000 mg/kg with 24 and 27.

In summary the present study shows that out of fifteen title pyrazolinyl phynyl sydnones studied, significant dose-dependent activity was shown by compound 21 and 24 (antiinflammatory) and by compounds 21, 24 and 27 (analgesic). Compounds 21 showed both potent analgesic activity, more than that of aspirin, and significant antiinflammatory activity.

REFERENCES

1. Newton, C.G., Ramsdon, C.A., **Tetrahedron**, 1982, 38, 2965.
2. Wagner, H., Hill, J.B., **J. Med.Chem.**, 1974, 17, 1337.
3. Hill, J.B., Ray,R.E., Wagner, H., Aspinall R.L.,**J. Med.Chem.**, 1975, 18, 50.
4. Upadhya, K.G., Badami, B.V., Puranik, G.S.,Birader, V.N., Nagappa, S., **Arch. Pharm.(weinheim).**, 1980, 313, 684.
5. Satyanarayana, K., Rao, M.N.A., **Indian Drugs.**, 1993, 30, 313.
6. Satyanarayana, K., Rao, M.N.A., **Indian J. Pharm.Sci.**, 1993, 55, 230.
7. Satyanarayana, K., Rao, M.N.A., **J. Pharm. Sci.**, 1995, 84, 263.
8. Satyanarayana, K., Rao, M.N.A. **Eur.J. Med. Chem.**, 1995, **30**, 641.
9. Winter, C.A., Risley, E.A., Nuss, G.W., **Proc. Soc. Exp. Biol. Med.**, 1962, 111, 544.
10. Newbould, B.B., **Br. J. Pharmacol. Chemother.**, 1963, 21, 127.
11. Koster, R., Anderson, M., dee Beer, E.J., **Fed. Proc.**, 1952, 18, 412.
12. Loux, J.J., Depalma, P.D., Yankell, S.L., **Toxicol. Appl. Pharmacol.**, 1972, 22, 672.
13. Tallarada, R.J., Murray, R.B, **Manual of Pharmacological Calculations with Computer Programs**, Springer-Verlag, New York. (1981)
14. Dambal, D.B., Pattanashetti, P., Tikare, R.K., Badami, B.V., Puranik, G.S., **Indian J. Chem.**, 1984, 23B, 186.