Synthesis of 1-(2-arylindol-3yl) 2-[3-(p-morpholinophenyl) 6,8-disubstituted-quinazolin-4(3H)-one-2yl] ethenes as CNS active and anti-inflammatory agents

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Summary: Sixteen new title styryl quinazolinones have been synthesised by Knoevenagel condensation of 2-methyl-3-(p-morpholinophenyl)6,8-disubstituted-quinazolin-4(3H)-ones with 2-aryl-indol-3-aldehydes in the presence of gl. AcOH. The intermediates, 2-methyl-3-(p-morpholinophenyl) 6,8-disubstituted quinazolin-4(3H)-ones, were prepared by the direct fusion of 6,8-disubstituted-acetyl anthranils with p-morpholinoaniline. Some of the title compounds have shown significant inhibition against carrageenin induced oedema. A definite SAR has also been established.In addition, the compounds were found to be psychotropic (stimulants and depressants) and quite nontoxic. The structures of the unknown compounds were confirmed by elemental and spectral (IR & PMR) analysis.

Quinazolones comprise a very significant group of inflammation inhibitors, specially 3-amino-propylcyclohexyl-2-methyl-6,8-halo substituted quinazolones have been reported to possess significant anti-inflammatory activity, similar to phenyl butazone at 10 mg/kg i.p.[1]. A number of quinazolones with potent anti-inflammatory and antipyretic activities have also been reported[2,3]. Moreover, some styryl quinazolones were also reported to possess remarkable anti-inflammatory activity. Recently, 2-styryl-3,6,8-trisubstituted quinazolin-4(3H) ones have been found to be significant anti-inflammatory agents against carrageenin induced rat paw oedema [4]. Further, 2-styryl-3, 6,8-trisubstituted quinazolinones have been reported to possess a good MAO inhibitor and anticholinergic activity [5].

On the other hand, different indole derivatives constitute an important group of anti-inflammatory agents. Some of these compounds viz: Sinmetacin[6], Indolcarboxanilides [7] and Indomethacin [8] are reported in patent literature as anti-inflammatory agents. Furthermore, serotonin, an indole derivative, is a chemical neurotransmitter. The results of researches on the effects of serotonin on the CNS disorders showed that serotonin is related to anti-inflammatory agents as the level of serotonin in brain is increased by various anti-inflammatory agents [9].

Visualising the aforesaid valid findings, the main theme of the present paper was to incorporate a quinazolinone with indole moiety for obtaining the new title compounds and to subject them to anti-inflammatory screening against carrageenin induced oedema along with toxicity tests and gross CNS screenings.

The unknown intermediates 2-methyl-3-(p-morpholinophenyl)-6,8-disubstituted quinazolin-4(3H)-ones (IV) have been synthesised by the direct fusion of 6,8-disubstituted acetyl anthranils (I) and p-morpholino-aniline (II) in an oil bath. The title compounds viz. 1-

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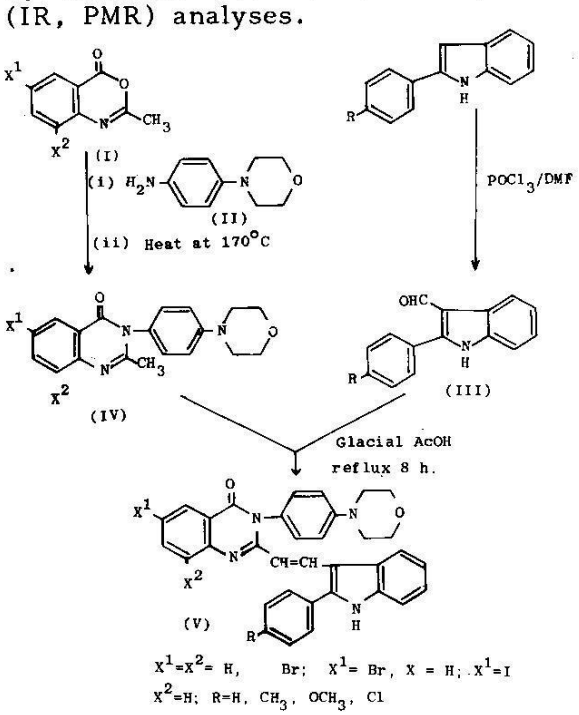
(2-aryl-indol-3yl)-2-[3-(p-morpholino-phenyl)-6,8-disubstituted quinazolin-4(3H)-one-2yl]-ethenes (V) were then obtained by the Knoevenagel condensation of the precursors (IV) with 2-aryl indole-3-aldehydes (III) in the presence of gl. AcOH, via the route shown in scheme. The structures of all the newly synthesised precursors and final compounds were established by elemental (C, H, N) and spectral (IR, PMR) analyses.



Pharmacological Activity

All the final 1,2-disubstituted ethenes have been tested for their gross CNS screening and lethal test on the albino mice. The anti-inflammatory activity against carrageenin induced mice paw oedema has also been evaluated for all the final compounds.

For the toxicity test the compounds were administered at the doses of 464 and 1000 mg/kg weight of mice intraperitoneally as gum acacia suspension and their ALD_{50} in 50% of the tested animals was noted by the method of Weil [10].

Regarding their CNS activity, these compounds were finally injected at 1/5 of their ALD_{50} in the same manner, and the changes in SMA and reactivities to sound and touch were noted. The effect of compounds on the body temperature was also measured.

The anti-inflammatory activity on the albino mice was evaluated by adopting the method of Winter [11] by measuring the percentage protection of animals against carrageenin induced oedema.

All the compounds were found to be quite nontoxic having the ALD_{50} values in the range of 681 to > 1000 mg/kg (i.p). In gross CNS observations, eight of the sixteen tested compounds were found to be CNS stimulants whereas the remaining eight have been found to be CNS depressant, as they increased and decreased the spontaneous motor activity (SMA) and reactivities to sound and touch respectively, at the doses of 464, 1000 and 1/5th of ALD_{50} mg/kg (mice). Negligible hypothermia was also observed in the range of 0.1 - 0.9°C. All the depressant compounds have also shown writting showing their muscle-relaxant nature.

In their anti-inflammatory activity only seven compounds have shown significant effect in the range of 3.2 to 35.6% as compared to the 36% inhibition shown by indomethacin, against carrageenin induced paw oedema. A study of the percentage anti-inflammatory activity data of table-1 reveals that;

(i) Only mono-substituted compounds(at position-6 of the quinazolone moiety by bromo or iodo group) were found to be active except compound No.9.

(ii) Visualising the data of compound nos. 5 to 8, it is also noteworthy that the compounds without any substitution or with methyl substitution at para position of the phenyl ring present at

Table-1: Gross CNS observations, ALD_{50} and anti-inflammatory activity of the compounds, described in Table-3.

Compound No	Gross CNS Observations: SMA and reactivity	Writhing	Hypothermia (°C) (i.p)	ALD_{50} mg/mg	Anti-inflammatory activity (% protection)
1.	↑	(-)	0.4	681	-
2.	↑	(-)	0.4	681	-
3.	↑	(-)	0.6	825	-
4.	↓	(+)	0.4	681	18.6
5.	↓	(+)	0.1	> 1000	35.6
6.	↓	(+)	0.4	> 1000	20.3
7.	↓	(+)	0.2	> 1000	3.9
8.	↓	(+)	0.2	> 1000	3.2
9.	↑	(-)	0.4	681	-
10.	↓	(+)	0.6	1000	10.00
11.	↓	(+)	0.4	681	33.3
12.	↓	(+)	0.2	681	28.8
13.	↑	(-)	0.4	> 1000	-
14.	↑	(-)	0.8	> 1000	-
15.	↑	(-)	0.9	> 1000	-
16.	↑	(-)	0.9	> 1000	-
Indomethacin					33.8 at 10 mg/kg (mice)

↑= Increased, ↓= Decreased, (+) = Present (-) = Absent

position 2 of indole, were more active than their methoxy or chloro substituted congeners. Whereas, in compound nos. 9 to 12, a reverse finding was observed.

(iii) It is also worth mentioning that the compounds with either mono-bromo or dibromo substitutions in the quinazolinone ring were comparatively more nontoxic (ALD_{50} > 1000) than the compounds without any substitution or with iodo substitution in the same ring (ALD_{50} 681 to 1000).

Experimental

M.Ps were determined in open capillaries using A.R. H_2SO_4 bath, and are uncorrected, IR spectra in KBr phase were recorded on a Perkin-Elmer 157 spectrophotometer ν max in cm^{-1}. The PMR spectra were recorded in TFA on a Varian A60D instrument using TMS as an internal standard (chemical shifts in δ ppm). The purity of the compounds was checked by TLC using silica-gel G coated plates (0.25 mm) and the solvent system: benzene-methanol 100:5. 5-Bromo or 3,5-dibromoanthranilic acid [12] and 5-iodoanthranilic acid [13] - were prepared by the well known literature method.

p-Morphilonoaniline[14] and 2-Aryl indole-3-aldehydes[15,16] were also prepared by the known methods.

2-Methyl-3-(p-morpholinophenyl)quinazolin-4(3H) one (IV) (Table-2)

A mixture of anthranilic acid (0.01 mole) and acetic anhydride (50 ml) was

Table-2: Physical data of 2-methyl-3(p-morpholinophenyl) 6,8-disubstituted quinazolin-4(3H)-ones (IV)

Compound No.	X^1	X^2	Molecular formula	M.P.*(°C)	Yield(%)	% Elemental Analysis C Calcd.	C Found	H Calcd.	H Found	N Calcd.	N Found
1.	H	H	$C_{19}H_{19}N_3O_2$	252	70	71.20	71.00	5.91	6.12	13.08	13.10
2.	Br	H	$C_{19}H_{18}N_3O_2Br$	201	68	57.00	57.26	4.50	4.50	10.50	10.46
3.	Br	Br	$C_{19}H_{17}N_3O_2Br_2$ >	270	75	45.51	45.38	3.54	3.48	8.76	8.85
4.	I	H	$C_{19}H_{18}N_3O_2I$	230	72	52.90	53.01	4.17	4.20	9.74	9.62

*All the intermediates were recrystallised from ethanol.

refluxed for two hours on a sand bath, thereafter the excess of anhydride was distilled off under reduced pressure. The residue was grinded thoroughly in a pestle-mortar and washed with pet .ether (40-60°C).

The acetyl anthranil thus prepared was mixed with p-morpholinoaniline (0. 01 mole) and fused in an oil bath at 170°c for half an hour. Thereafter it was cooled and left aside overnight after the addition of 10 ml of methanol. The separated solid was filtered, washed with little ethanol and finally recrystallised from ethanol, m.p. 252°C, yield 70%. IR: 3050-2900 (C-H, Ar and Ali.), 1680 (N-C=O), 1620 (C=N), 1510, 1560, 1380 etc; PMR (TFA): 7.60-6.65 (complex multiplet, 8H, Ar-H), 4.00 (t,J 4.5 Hz, 4H, $C\underline{H}_2$-N-$C\underline{H}_2$), 3.65 (t, J=4.5 Hz, 4H, $C\underline{H}$-O-$C\underline{H}_2$) and 2.93 (s, 3H, $C\underline{H}_3$).

Similarly, other compounds having structure IV have been synthesised by fusing different 6,8-disubstituted acetyl anthranils with p-morpholinoaniline.

1-(2-Phenylindol-3yl) 2-[3-(p-morpholinophenyl)quinazolin-4(3H) one-2-yl] ethene (V) (Table 3).

An equimolar (0.0025 mole) mixture of 2-methyl-3-(p-morpholinophenyl) quinazolin-4(3H) one and 2-phenyl-indol-3aldehyde in gl. AcOH (20 ml) was refluxed on a sand bath for 8 hrs. Thereafter, the reaction mixture was cooled and the solid separated was filtered, washed with methanol and finally recrystallised from ethyl acetate, m.p. 245°C; yield 60% IR: 3250 (N-H), 3050, 2910 (C-H Ar and Aliph.), 1670 (N-C=O), 1640 (CH=CH), 1620 (C=N), 1520, 1470, 1380 etc; PMR (TFA): 9.62 (s, 1H, N-H of indole), 8.18-6.65 (complex multiplet 19H, 17 Ar-H and 2-CH = CH-), 4.02 (t, J=4.5 Hz, 4H, $C\underline{H}$-N-$C\underline{H}_2$) and 3.65 (t, J=4.5 Hz 4H, $C\underline{H}_2$-O-$C\underline{H}_2$).

Similarly, all the other compounds having structure V have been synthesised by using approriate IV and diffrent indole-aldehydes. Their relevant data are noted in table-3, whereas the spectral data of some of them are as:

Compd.No.6

PMR (TFA): 9.60 (s,1H, N-H), 8.20-6.62 (m, 17H, 15 Ar-H and 2-CH=CH-), 4.00 (t, J=4.5 Hz, 4H, $C\underline{H}_2$-N-$C\underline{H}_2$), 3.65 (t, J = 4.5 Hz, 4H, $C\underline{H}_2$-O-$C\underline{H}_2$) and 1.96 (s, 3H, -$C\underline{H}_3$).

Compd. No.11

PMR(TFA): 9.60 (s,1H, N-H), 8.24-6. 68 (m, 17H, 15 Ar-H and 2-CH=CH-),

Table-3: Physical data of 1-(2-phenylindol-3yl)-2-[3-(p-morpholinophenyl)-quinazolin-4(3H)-one-2 yl] ethenes (V)

Compound No	R	X^1	X^2	Molecular formula	M.P.*(°C)	Yield	% Elemental Analysis C Calcd.	C Found	H Calcd.	H Found	N Calcd.	N Found
1.	H	H	H	$C_{34}H_{28}N_4O_2$	245	60	77.86	77.90	5.34	5.41	10.68	10.72
2.	CH_3	H	H	$C_{35}H_{30}N_4O_2$	230	58	78.06	77.98	5.57	5.62	10.40	10.49
3.	OCH_3	H	H	$C_{35}H_{30}N_4O_3$	> 260	67	75.81	75.62	5.41	5.60	10.10	10.00
4.	Cl	H	H	$C_{34}H_{27}N_4O_2Cl$	246	65	73.05	73.00	4.83	4.66	10.02	10.25
5.	H	Br	H	$C_{34}H_{27}N_4O_2Br$	250	63	67.67	67.51	4.47	4.40	9.28	9.30
6.	CH_3	Br	H	$C_{35}H_{29}N_4O_2Br$	170	70	68.08	68.00	6.70	6.45	9.07	8.97
7.	OCH_3	Br	H	$C_{35}H_{29}N_4O_3Br$	> 270	71	66.36	66.49	4.58	4.50	8.84	8.67
8.	Cl	Br	H	$C_{34}H_{26}N_4O_2ClBr$	> 280	59	64.01	64.12	4.07	4.14	8.78	8.80
9.	H	I	H	$C_{34}H_{27}N_4O_2I$	225	62	62.76	62.55	4.15	4.20	8.61	8.52
10.	CH_3	I	H	$C_{35}H_{29}N_4O_2I$	217	64	63.25	63.19	4.36	4.60	8.43	8.56
11.	OCH_3	I	H	$C_{35}H_{29}N_4O_3I$	250	59	61.76	61.80	4.26	4.31	8.23	8.19
12.	Cl	I	H	$C_{34}H_{26}N_4O_2ClI$	265	67	69.60	59.65	3.79	3.85	8.18	8.29
13.	H	Br	Br	$C_{34}H_{26}N_4O_2Br_2$	280	61	59.84	59.72	3.81	3.75	8.21	8.40
14.	CH_3	Br	Br	$C_{35}H_{28}N_4O_2Br_2$	245	63	60.36	60.45	4.02	4.05	8.04	7.98
15.	OCH_3	Br	Br	$C_{35}H_{28}N_4O_3Br_2$	257	64	59.00	59.00	3.93	4.10	7.86	7.90
16	Cl	Br	Br	$C_{34}H_{25}N_4O_2ClBr_2$	215	67	56.95	56.90	3.49	3.50	7.81	7.76

*All the compounds were recrystallised from ethylacetate.

4.02 (t, J=4.5 Hz, 4H, $-C\underline{H}_2-N-C\underline{H}_2$), 3.66 (t, J=4.5Hz, 4H, $C\underline{H}_2-O-C\underline{H}_2$) and 2.23 (s, 3H, $-OC\underline{H}_3$).

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References

1. K.K.Tangri,T.N.Bhalla, M.B. Gupta, and K.P.Bhargava, *Intr.Symp. of Inflammation, Biochemistry and Drug Interaction Amsterdam, 308 (1968)*
2. W.E.Coyne, & J.W.Cusis, *J.Med.Chem.*, **11**, *1200 (1968)*
3. S.S.Tiwari, S.M.M.Zaidi, & R. K. Satsangi, R.K., *Die Pharmazie. 35 (H), 2 (1980)*
4. V.S.Misra, C.Singh, R.Agarwal and C.Chaudhary, *J.Chem.Soc.Pak.*, **3(4)**, *209-13 (1981)*
5. R.K.Satsangi, *Indian Drugs*, **17(3)**, *79 (1979).*
6. H.Yamamoto, C.Saito, R.Okamoto, H.Awata, T.Inukai, A.Hirohashi, and Y.Yukawa, *Arzeim-Forsch.*, **19**, *981 (1969).*
7. B.Y.Eryshev,T.P. Ershova, E. A.Berlyand, S.S.Liberman,and N.N.Suvorov, *Khim.Pharm.Zh.*, **9**, *22 (1975).*
8. C.A.Winter, E.A.Risley, and G.W.Nuss, *J.Pharmac.Exp.ther.* **141**, *369 (1963)*
9. J.M.Delgado, and E.I.Isaacson, *Medicinal Chemistry Vol.II, ed. A. Burger,(N.Y.:Wiley Intersciences),1970, pp. 390.*

10. C.S.Weil, *Biometrics* **8**, *249 (1952)*
11. C.A.Winer, E.A.Risley, and G. W.Nuss, *Proc.Soc.Exp.Biol.Med.*, **111**, *544 (1962)*.
12. A.S.K.Wheeler, and W.N.Oates, *J.Amer.Chem.Soc.*, **32**, *770 (1910)*.
13. C.J.Klemme, and J.H.Hunter, *J.Org.Chem.*, **15**, *222 (1940)*.
14. M.K.Shukla, *Synthesis of Potential Anthelmintics, Ph.D. Thesis, Lucknow Univeristy, 1978.*
15. J.A.Weisbach, E.Macko, N.J. Desanctis, M.P.Cara, and B. Dougles, *J.Med.Chem.*, **7**, *735 (1964)*.
16. G.Buchman, and D.Rossner, *J.Prakt.Chem.*, **25**, *117 (1964)*.