

CAVELIER

ABOGADOS

www.cavelier.com
cavelier@cavelier.com

EDIFICIO SISKI
CARRERA 4 No. 72 - 35
BOGOTÁ 8, COLOMBIA

Teléfono: (57-1) 347 3611
Telefax: (57-1) 211 8650
(57-1) 700 4814
Fax in U.S.A.: (1-305) 675 7743

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 08-138163- -00007-0000

Fecha: 2012-09-14 16:39:31

Tra. 11 PATENTEIYII

Act. 523 RESPUESTA

Dep. 2020 DIR.NUEVASCR
Eve: 378 FASENACIONALI
Folios: 12

Señor Director
DIRECCION DE NUEVAS CREACIONES
Superintendencia de Industria y Comercio
E. S. D.

Trámite : 011
Evento : 378
Actuación : 444

Referencia : Expediente No. **08.138.163**
Asunto : Solicitud de patente para: **INHIBIDORES DE SULFONAMIDA TRICICLICA FUSIONADA DE GAMASECRETASA**
Solicitante : ELAN PHARMACEUTICALS, INC.
Fecha solicitud : 30 de diciembre de 2008

1. Yo, Luz Clemencia DE PÁEZ, en mi condición de apoderada de la sociedad solicitante de la patente de la referencia, de conformidad con la sustitución de poder otorgada a mí por el doctor Emilio FERRERO me refiero al oficio No. **10717** notificado por fijación en lista del 20 de junio de 2012.

2. Mediante oficio No. **10717** el Examinador a cargo del estudio de patentabilidad de la presente solicitud, en virtud del artículo 46 de la Decisión 486, solicitó la presentación de los siguientes documentos:

2.1.1 INDIAN JOURNAL OF CHEMISTRY B, 19, 1980, Páginas 297-300.

2.1.2 INDIAN JOURNAL OF CHEMISTRY B, 24, 1985, Páginas 639-644.

3. Respuesta al requerimiento

Con el ánimo de dar respuesta al requerimiento formulado por el Examinador, se presenta junto con el presente memorial, copia de los dos documentos arriba mencionados.

4. Puesto que se han atendido a cabalidad las observaciones hechas por su Despacho sobre la presente solicitud de patente, atentamente solicito que se continúe su tramitación.

5. Anexos

- Documento: INDIAN JOURNAL OF CHEMISTRY B, 19, 1980, Páginas 297-300.
- Documento: INDIAN JOURNAL OF CHEMISTRY B, 24, 1985, Páginas 639-644.

Señor Director,


LUZ CLEMENCIA DE PAEZ
C.C. 35.456.344 de Usaquén
T.P.A. No. 23.555

 COLO-13170-0841-008-2
JMS\JMS\ID-225680\WPC13170
No. M-2012-225680\JMS

Studies in Antifertility Agents : Part XXVII — Synthesis of 2-Acetyl-3-aryl-5-tosyl-7/8-H (or methoxy)-3,3a,4,5- tetrahydropyrazolo[4,3-c]quinolines†

PRABHAKAR M. KELKAR, NARESH K. SANGWAN, SHRI NIVAS RASTOGI* & NITYA ANAND
Division of Medicinal Chemistry, Central Drug Research Institute, Lucknow 226 001

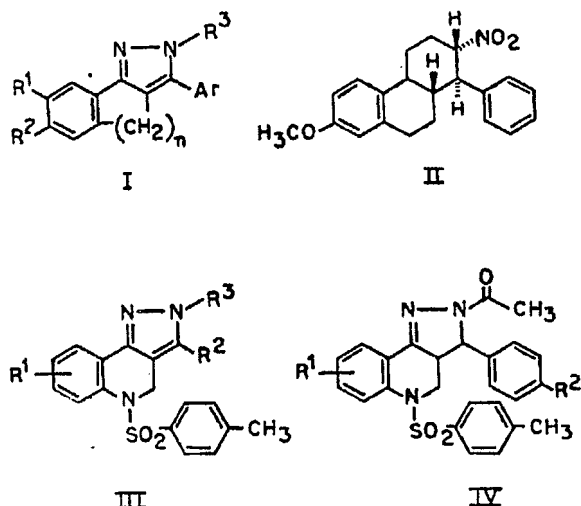
Received 25 July 1979; accepted 20 November 1979

N-Tosyl-2,3-dihydro-4-quinolones (12-14), prepared from aniline, *m*- and *p*-anisidines by reported procedures, on condensation with araldehydes in the presence of NaOMe give the corresponding 3-arylidene-4-quinolones (15-18). Refluxing of 15-18 with $\text{NH}_2\text{NH}_2\cdot\text{H}_2\text{O}$ in gl. AcOH affords the title compounds, 2-acetyl-3-aryl-5-tosyl-7/8-H (or methoxy)-3,3a,4,5-tetrahydropyrazolo[4,3-c]quinolines (19-22). The stereochemistry of the title compounds based on the assignments of $\text{C}_5\text{-H}$, $\text{C}_{3a}\text{-H}$, $\text{C}_4\text{-H}$, protons has been studied by PMR decoupling experiments. In preliminary screening, compounds 19 and 22 have been found to prevent pregnancy at 20 mg/kg dose in female albino rats, but are ineffective at lower doses. None of the compounds tested shows any significant pharmacological activity.

THE contraceptive, abortifacient and anti-hypertensive activities exhibited by pyrazolo-benzocycloalkanes (I)¹ and weak antifertility activity possessed by 1-phenyl-2-nitro-1,2,3,9,10,10a-hexahydrophenanthrene (II) (unpublished work) prompted us to investigate the antifertility activity of pyrazoloquinolines (III), in continuation² of our search for non-steroidal antiimplantation agents. In this paper, we report the synthesis and antifertility screening results of 2-acetyl-3-aryl-5-tosyl-7/8-H (or methoxy)-3,3a,4,5-tetrahydropyrazolo[4,3-c]quinolines (IV).

The starting intermediates, N-tosyl-2,3-dihydro-4-quinolones (12-14) were prepared in a similar manner as described by Johnson *et al.*³ and Speckamp *et al.*⁴ except that ethyl acrylate, instead of methyl acrylate, was reacted with aromatic amines. Thus the addition of aniline or *m*-anisidine to ethyl acrylate in the presence of AcOH, or of *p*-anisidine in the presence of SnCl_4 gave ethyl β -anilinopropionates (1-3) as oil in good yields. Treatment of 1-3 with *p*-TsCl in pyridine yielded the corresponding N-tosyl propionates (4-6) as viscous oils which could not be purified by distillation and were, therefore, hydrolysed as such with methanolic KOH to give the corresponding N-tosyl acids (7-9). In the case of acids 8-9, the hydrolysis was accompanied by retero Michael reaction as is evident by the isolation of N-tosyl-*m/p*-anisidines (10-11) from the reaction mixture. The tosyl acids (7-9) were treated with PCl_5 to give acid chlorides which were cyclized under reported^{3,4} Friedel-Crafts conditions in the presence of AlCl_3 or SnCl_4 to furnish the desired N-tosyl-2,3-dihydro-4-quinolones (12-14). In the case of *m*-anisidino compound (13), only 7-methoxyquinolone was formed.

Condensation of quinolones (12-14) with araldehydes in the presence of NaOMe in MeOH



yielded crystalline N-tosyl 3-arylidene-4-quinolones (15-18) in good yields (Table I). The PMR spectra† of these arylidenes (15-18) showed N-CH₂ protons as a doublet around 5.0 (*J* = 2 Hz) and arylideno olefinic proton as a triplet around 7.70 (*J* = 2Hz). The chemical shift of these arylideno protons⁵ and their quantitative conversion² into dihydropyrazoles with $\text{NH}_2\text{NH}_2\cdot\text{H}_2\text{O}$ suggested *trans*-configuration for arylidenes (15-18). Refluxing of 15-18 with $\text{NH}_2\text{NH}_2\cdot\text{H}_2\text{O}$ in gl. AcOH for 6-8 hr furnished the title compounds, 2-acetyl-3-aryl-5-tosyl-7/8-H (or methoxy)-3,3a,4,5-tetrahydropyrazolo[4,3-c]quinolines (19-22) in excellent yields (Table I).

In the PMR spectra of 19-22, $\text{C}_8\text{-H}$, $\text{C}_{3a}\text{-H}$, and $\text{C}_4\text{-H}$, exhibited interesting spectral features and the two protons of $\text{C}_4\text{-H}_2$ appeared at different chemical

†CDRI Communication No. 2632.

‡Chemical shift in δ (ppm) throughout the paper.

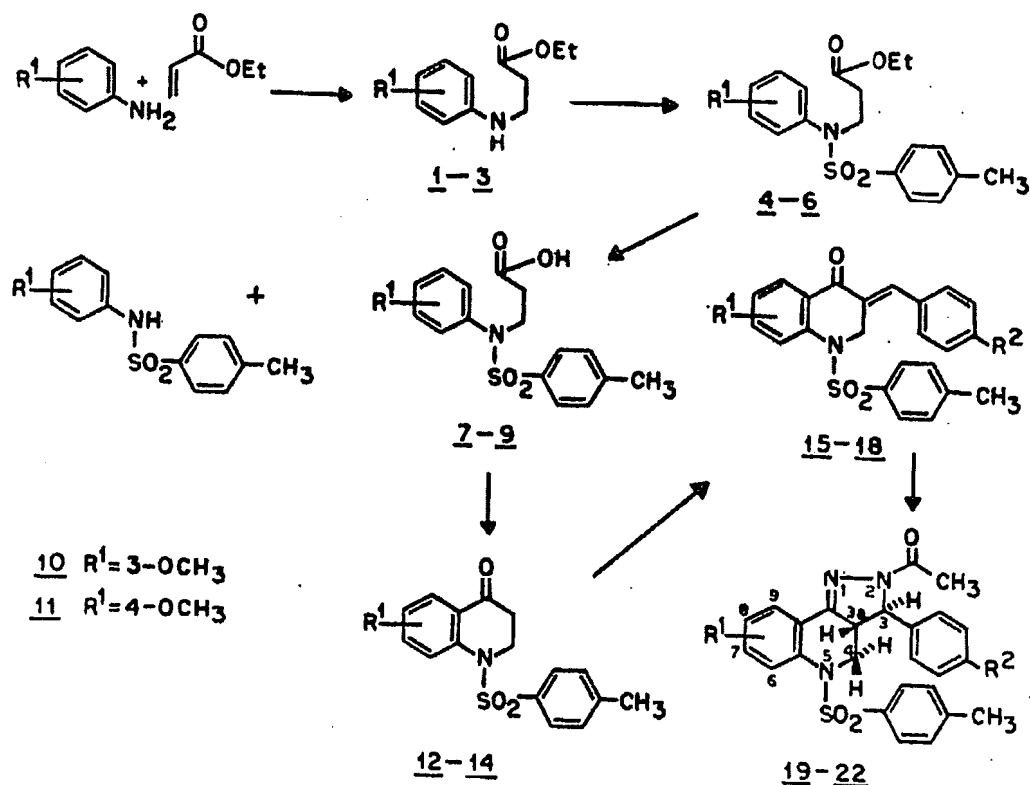
TABLE 1 — PHYSICAL AND SPECTRAL DATA OF N-TOSYL-3-ARYLIDENE-2,3-DIHYDRO-4-QUINOLONES (15-18) AND 2-ACETYL-3-ARYL-7/8-H(OR METHOXY)-3,3A,4,5-TETRAHYDROPYRAZOLO[4,3-c]QUINOLINES (19-20)

Compd*	R ¹	R ²	m.p.† °C	Yield (%)	Mol. formula	Ana- lyzed for‡	NMR (CDCl ₃)	ALD ₅₀ [§] mg/kg in mice
15	H	H	135	90	C ₂₃ H ₁₉ NO ₂ S	CHN	2.32 (s, 3, -C ₆ H ₄ -CH ₃), 5.33 (d, 2, NCH ₃ , J=1.5 Hz), 7.70 (t, 1, olefinic H, J=1.5 Hz).	800
16	7-OCH ₃	H	197	95	C ₂₄ H ₂₁ NO ₂ S	CHN	2.31 (s, 3, -C ₆ H ₄ -CH ₃), 3.92 (s, 3, OCH ₃), 5.17 (d, 2, NCH ₃ , J=1.5 Hz), 7.92 (d, 1, C ₈ -H, J=8 Hz).	
17	7-OCH ₃	OCH ₃	148	94	C ₂₅ H ₂₃ NO ₂ S	CHN	2.30 (s, 3, -C ₆ H ₄ -CH ₃), 3.82 (s, 3, OCH ₃), 3.85 (s, 3, OCH ₃), 4.98 (d, 2, NCH ₃ , J=1.5 Hz), 7.78 (d, 1, C ₈ -H, J=8.5 Hz).	
18	6-OCH ₃	H	131	91	C ₂₄ H ₂₁ NO ₂ S	CNH	2.34 (s, 3, -C ₆ H ₄ -CH ₃), 3.85 (s, 3, OCH ₃), 5.02 (d, 2, NCH ₃ , J=2 Hz), 7.53 (t, 1, olefinic H, J=2 Hz), 7.72 (d, 1, C ₈ -H, J=9 Hz).	681
19	H	H	179	91	C ₂₄ H ₂₃ N ₂ O ₃ S	CHN	2.21 (s, 3, COCH ₃), 2.24 (s, 3, -C ₆ H ₄ -CH ₃), 2.30-2.70 (m, 1, C _{3a} -H), 3.48 (t, 1, C ₄ -H, J _g =J _v =14 Hz), 4.48 (dd, 1, C ₄ -H, J _g =14 Hz, J _v =5 Hz), 4.70 (d, 1, C ₃ -H, J=10 Hz).	800
20	7-OCH ₃	H	216-17	53	C ₂₄ H ₂₃ N ₂ O ₄ S	CHN	2.23 (s, 6, COCH ₃ and -C ₆ H ₄ CH ₃), 2.34 (m, 1, C _{3a} -H, enveloped in the signal of COCH ₃ and -C ₆ H ₄ CH ₃), 3.47 (t, 1, C ₄ -H, J _g =J _v =14 Hz), 3.79 (s, 3, OCH ₃), 4.47 (dd, 1, C ₄ -H, J _g =13 Hz, J _v =5 Hz), 4.69 (d, 1, C ₃ -H, J=10 Hz), 7.70 (d, 1, C ₈ -H, J=9 Hz).	
21	7-OCH ₃	OCH ₃	224	70	C ₂₇ H ₂₇ N ₂ O ₆ S	CHN	2.19 (s, 3, COCH ₃), 2.23 (s, 3, -C ₆ H ₄ CH ₃), 2.42 (m, 1, C _{3a} -H, enveloped in the signal of COCH ₃ and -C ₆ H ₄ CH ₃), 3.43 (t, 1, C ₄ -H, J _g =J _v =13 Hz), 3.73 (s, 3, OCH ₃), 3.78 (s, 3, OCH ₃), 4.48 (dd, 1, C ₄ -H, J _g =13 Hz, J _v =5 Hz), 4.62 (d, 1, C ₃ -H, J=10 Hz), 7.70 (d, 1, C ₈ -H, J=8 Hz).	
22	8-OCH ₃	H	198	97	C ₂₆ H ₂₅ N ₂ O ₄ S	CHN	2.21 (s, 3, COCH ₃), 2.24 (s, 3, -C ₆ H ₄ CH ₃), 2.40 (m, 1, C _{3a} -H), 3.48 (t, 1, C ₄ -H, J _g =J _v =14 Hz), 3.78 (s, 3, OCH ₃), 4.42 (dd, 1, C ₄ -H, J _g =14 Hz, J _v =5 Hz), 4.67 (d, 1, C ₃ -H, J=10 Hz), 7.71 (d, 1, C ₈ -H, J=9 Hz).	681

*Compounds 2, 3, 5, 6, 8 and 9 were prepared by the reported procedures^{8,4} for their methyl analogs. Compounds 16-18 and 20-22 were prepared by the method described in experimental section for 15 and 20 respectively. †All compounds were recrystallized from MeOH. ‡All compounds were analyzed within ± 0.5%. §Compounds 16, 17, 20 and 21 are under testing for their pharmacological activity.

shifts. The assignment of these protons and their stereo-orientation was determined by decoupling experiments in the case of compounds 19 and 22. In 19, C₃-H appeared as a doublet at 4.70 (J=10 Hz) which corresponds to C₃, C_{3a} *trans*-configuration in such systems⁶. The multiplet of C_{3a}-H enveloped in the signals of COCH₃ and CH₃ was located by decoupling at 4.70 which affected the multiplicity of the signals at 2.30-2.70. By decoupling experiments, the two protons of C₄-H₂, adjacent to asymmetric carbon C_{3a}, were assigned. One of the C₄-H appeared as a triplet at 3.48 (J=14 Hz) due to geminal (J_g=14 Hz) and vicinal (J_v=14 Hz) couplings. Such a vicinal coupling constant (14 Hz) is indicative of *trans*- relationship to C_{3a}-H. The other C₄-H appeared as double doublet at 4.48

(J_g=14 Hz and J_v=5 Hz) which is suggestive of its *cis*-orientation with respect to C_{3a}-H. Similar decoupling experiments in the PMR spectrum of 22 proved to be useful in assigning C₄H₂ and its stereochemistry. In analogy to the PMR spectra of 19 and 22, it is presumed that 20 and 21 would have similar spectral features on decoupling. The PMR spectral data of all these compounds are given in Table 1 and the stereochemical structure of 19-22 is depicted in Scheme 1. The preliminary antiimplantation and pharmacological screening of these compounds were carried out by the reported procedures^{6,7}. Compounds 19 and 22 inhibited pregnancy at 20 mg/kg dose in female albino rats and were ineffective at lower doses. No improvement in this activity could be achieved by



SCHEME 1

structural modification of 19. Interestingly 7/8-unsubstituted or 8-methoxy compound showed activity while the corresponding 7-methoxy analog was inactive which indicated that unsubstituted 7-position is preferred for this activity. Substitution in 3-phenyl group destroyed the activity. Earlier, we have reported² that the corresponding B-ring seco compounds lacking N-tosyl group were ineffective as antifertility agents. Thus, the skeleton present in 19 appears to be a likely framework for the antifertility activity of such a system.

No significant pharmacological activity was exhibited by the compounds tested.

Experimental Procedure

M.ps and b.ps are uncorrected. Purity of the compounds was routinely checked on silica gel-G TLC plates using C_6H_6 or C_6H_6 -MeOH as mobile phase. IR spectra ($\nu_{\max}$ in cm^{-1}) were recorded on a Perkin-Elmer infracord 137, 157 or 177 model. PMR spectra were recorded in $CDCl_3$ on a Varian A-60D or a Perkin Elmer R-32 spectrometer using TMS as internal standard.

Ethyl β -anilinopropionate (1) — A mixture of aniline (139.5 g, 1.5 mol), ethyl acrylate (165 g, 1.65 mol) and AcOH (5 ml) was refluxed for 15 hr and the reaction mixture distilled *under vacuo* to give 1, yield 210 g (71%), b.p. 127-30°/0.4 mm Hg, $n_D^{25} = 1.5220$, PMR : 1.23 (t, 3, C- CH_3 , $J=7$ Hz) 2.58

(t, 2, C- CH_2 , $J=7$ Hz), 3.43 (t, 2, N- CH_2 , $J=7$ Hz), 3.85 (s, 1, NH, D_2O exchangeable), 4.14 (q, 2, OCH_2 , $J=7$ Hz) (Found : C, 68.00; H, 8.27; N, 7.75. $C_{11}H_{13}NO_2$ requires C, 68.37; H, 7.82; N, 7.25%).

Ethyl N-tosyl- β -anilinopropionate (4) — To a cooled and stirred solution of 1 (96.5 g, 0.5 mol) in pyridine (1 litre), *p*-TsCl (114.5 g, 0.6 mol) was added in small lots. After stirring for 15 min at this temperature, the reaction mixture was heated on a steam-bath for 30 min and then just to refluxing. The reaction mixture was poured onto ice-HCl and extracted with ether. The extract was washed successively with 3N HCl, water, 1% KOH, water and saturated NaCl solution, dried (Na_2SO_4) and solvent removed to give 4, yield 168 g (97%); PMR: 1.18 (t, 3, C- CH_3 , $J=7$ Hz), 2.41 (s, 3, $-C_6H_4-CH_3$), 2.55 (t, 2, C- CH_2 , $J=8$ Hz), 3.88 (t, 2, N- CH_2 , $J=8$ Hz), 4.05 (q, 2, OCH_2 , $J=7$ Hz), (Found : C, 59.90; H, 5.95; N, 3.64. $C_{18}H_{21}NO_4S$ requires C, 60.25; H, 6.05; N, 4.03%).

N-Tosyl- β -anillinopropionic acid (7) — To a stirred solution of ester 4 (168 g, 0.48 mol) in 80% aq. MeOH (1400 ml), 10% KOH (380 ml) was added at room temperature during 30 min. The reaction mixture was stirred at room temperature for 4 hr and allowed to stand overnight. The clear solution was diluted with water (2 lit) and poured with stirring into cold dil. HCl. The separated acid was filtered, washed with cold water, dried and recryst-

tallized from C_6H_6 to get 7, yield 143 g (92%), m.p. 145°.

N-Tosyl-2,3-dihydro-4-quinolones (12-14) — Cyclization of acids 7-9 with PCl_5 - $AlCl_3$ or $SnCl_4$ by the reported procedure^{3,4} gave 12-14 in 86, 63 and 70% yields respectively.

N-Tosyl-3-benzylidene-2,3-dihydro-4-quinolone (15) — A solution of benzaldehyde (3.18 g, 30 mmol) in MeOH (6 ml) was added to a cold (15°) solution of sodium (0.3 g, 13 mmol) in MeOH (30 ml). To this stirred solution, 12 (9.03 g, 30 mmol) was added at 15°. The reaction mixture was allowed to attain room temperature and continuously stirred for 4 hr. The product separated was filtered and washed with methanol to get 15, yield 10.95 g (94%), m. p. 135°.

Similarly 16-18 were prepared in yields given in Table 1.

2-Acetyl-3-phenyl-5-tosyl-3, 3a, 4, 5-tetrahydropyrazolo[4,3-c]quinoline (19) — A mixture of benzylidene 15 (5.46 g, 14 mmol), $NH_2-NH_2 \cdot H_2O$ (5.6 ml, excess) and gl. AcOH (50 ml) was refluxed for 6-8 hr. The reaction mixture was cooled, poured onto ice, and the precipitated product was filtered, washed with water and crystallized from MeOH to get 19, yield 5.7 g (91%), m.p. 179°.

Similarly 20-22 were obtained in yields given in Table 1.

Acknowledgement

The authors are thankful to Drs S. N. Chatterji and B. N. Dhawan for providing preliminary anti-fertility and pharmacological screening results and to Mrs K. Kapoor for PMR decoupling experiments.

References

1. COOMBS, R. V. & HOULIHAN, W. J., *US Pat.* 3, 843, 666 (1974); *Chem. Abstr.*, 82 (1975), 57684y.
2. SANGWAN, N. K. & RASTOGI, S. N., *Indian J. Chem.*, 18B (1979), 65.
3. JOHNSON, W. S., WOROCH, E. L. & BUELL, B. G., *J. Am. chem. Soc.*, 71 (1949), 1901.
4. SPECKAMP, W. N., PANDIT, U. K. & HUISMAN, H. O., *Recl. Trav. chim. Pays. Bas.*, 82 (1963), 39.
5. ANANTHANARAYANAN, C. V., ANAND, N., BINDRA, J. S., NEYYARAPALLY, A. T. & RASTOGI, S. N., *Indian J. Chem.*, 15B (1977), 154.
6. HASSNER, A. & MICHELSON, M. J., *J. org. Chem.*, 27 (1962), 3974.
7. SANGWAN, N. K., RASTOGI, S. N. & ANAND, N., *Indian J. Chem.*, (in press).

Antifertility Agents: Part XLIII—Synthesis of 3-Aryl-4,5-dihydro-2-substituted-5-tosyl-2*H*-pyrazolo[4,3-*c*]quinolines & 2,4-Dihydro-3-phenyl[1]benzopyrano[4,3-*c*]pyrazoles & Their Derivatives†

NARESH K SANGWAN‡, PRABHAKAR M KELKAR, SHRI NIVAS RASTOGI* & N ANAND

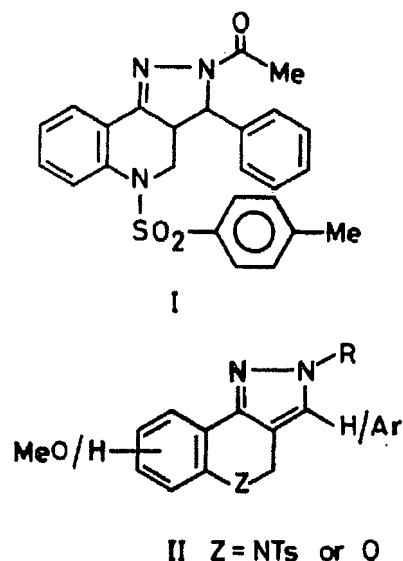
Division of Medicinal Chemistry, Central Drug Research Institute, Lucknow 226 001

Received 23 April 1984; accepted 23 August 1984

2,3-Dihydro-1-tosyl-4(1*H*)-quinolones (5-7) on formylation give the corresponding 3-hydroxymethylene derivatives (11-13) of which 12 and 13 react with piperazine to afford *N,N*-bis-substituted piperazines (15 and 16). Refluxing of 11-13 with substituted hydrazines yields the tricyclic 4,5-dihydro-2-substituted-5-tosyl-2*H*-pyrazolo[4,3-*c*]quinolines (17-22). Detosylation of 18 gives, besides the expected dihydro derivative 23, an aromatised pyrazoloquinoline (24) while the detosylation of 19 and 20 affords only the aromatised products 25 and 26. Condensation of dihydroquinolones (5-7) and chromanones (9, 10) with araldehydes produces the corresponding 3-arylidene derivatives (27-33). Surprisingly, a similar condensation of 2,3-dihydro-8-methoxy-1-tosyl-4(1*H*)-quinolone (8) with araldehydes or its formylation results in retro-elimination to give *N*-tosyl-*o*-anisidine (14). Epoxidation of 27-33 gives the 3,α-oxido derivatives (34-40) which on treatment with $\text{NH}_2\text{NH}_2\cdot\text{H}_2\text{O}$ or PhNHNH_2 form the title compounds 3-aryl-4,5-dihydro-2-substituted-5-tosyl-2*H*-pyrazolo[4,3-*c*]quinolines (41-46) and 2,4-dihydro-3-phenyl[1]benzopyrano[4,3-*c*]pyrazoles (48, 49). Acetylation of 41 gives 47. Detosylation of 41 affords the aromatised pyrazoloquinolines (50) while that of 42 furnished a mixture of the dihydro product 52 and the aromatised pyrazoloquinoline 51. However, detosylation of 42 with pyridine hydrochloride gives only 51 and no dihydro product. None of the compounds prepared exhibits any significant CNS, CVS or antifertility activity except 51 which shows weak CNS depressant and hypotensive activities.

In our earlier work on non-steroidal antifertility agents¹⁻³, it was proposed that a mixture of 3,3a-*trans/cis*-2-acetyl-3,3a, 4,5-tetrahydro-3-phenyl-5-tosyl-2*H*-pyrazolo[4,3-*c*]quinolines (I) and its derivatives possess oral antiimplantation activity^{2,3} in rats while the pure *trans*-isomer was inactive thereby indicating that the activity resides in *cis*-isomer only. To explore further this class of compounds and improve antifertility activity, it was proposed to prepare their aromatised analogues and congeners in which N-Ts has been replaced by oxygen atom and study the structure-activity relationship. In this paper we report the synthesis and biological screening results of 3-aryl-4,5-dihydro-2-substituted-5-tosyl-2*H*-pyrazolo[4,3-*c*]quinolines (II, Z=NTs) and 2,4-dihydro-3-phenyl[1]benzopyrano[4,3-*c*]pyrazoles and their derivatives (II, Z=O).

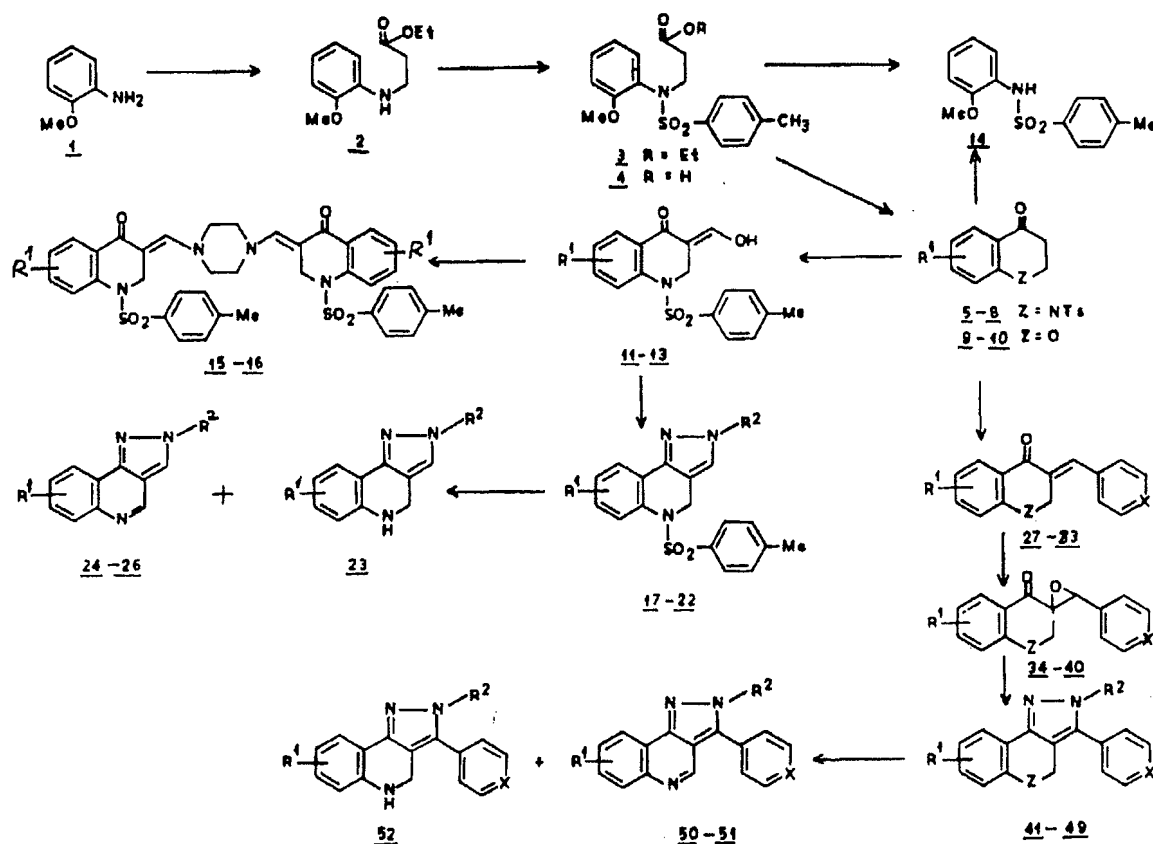
The starting materials 1-tosyl-2,3-dihydro-4(1*H*)-quinolones^{2,4} (5-7; $\text{R}^1 = \text{H}$, 6- or 7-OMe and Z=NTs) and 4-chromanones (9 and 10; $\text{R}^1 = \text{H}$ or 7-OMe and Z=O) were prepared by the methods reported earlier. The known 2,3-dihydro-8-methoxy-1-tosyl-4(1*H*)-quinolone (8; $\text{R}^1 = 8\text{-OMe}$ and Z=NTs) was prepared starting from *o*-anisidine (1) employing a route other than that reported in literature⁶.



Treatment of 1 with ethyl acrylate in the presence of acetic acid gave ethyl β(*o*-anisidino)propionate (2) which on tosylation with *p*-toluenesulphonyl chloride in pyridine followed by alkaline hydrolysis of the resulting ethyl β(*N*-tosyl-*o*-anisidino)propionate (3) furnished β(*N*-tosyl-*o*-anisidino)propionic acid (4) along with appreciable amounts of *N*-tosyl-*o*-anisidine (14). Cyclisation of the acid 4 with $\text{AlCl}_3\text{-PCl}_5$ afforded the required dihydroquinolone (8) (Scheme 1).

†CDRI Communication No. 3425.

‡Present address: Department of Chemistry, Haryana Agricultural University, Hissar-125 004.



SCHEME 1

The dihydroquinolones (5-7) on condensation with ethyl formate in the presence of NaH gave 3-hydroxymethylene derivative (11-13; Table I) in good yields while under similar reaction conditions the dihydroquinolone 8 underwent retro-elimination to yield N-tosyl-*o*-anisidine (14). A plausible reason for such fragmentation could not be put forward. Condensation of 12 and 13 with half a mole-equivalent of piperazine in benzene gave the required 1,4-bis(6-or 7-methoxy-2,3,4-tetrahydro-4(1*H*)-oxo-1-tosyl-3-quinolinylidenemethyl)piperazine (15 or 16). As 15 and 16 were insoluble, their PMR spectra could not be recorded.

Refluxing of 11-13 with various substituted hydrazines furnished the corresponding 2-substituted 4,5-dihydro-5-tosyl-2*H*-pyrazolo[4,3-*c*]quinolines (17-22; Table I). Detosylation of 4,5-dihydro-2-phenyl-5-tosylpyrazolo[4,3-*c*]quinoline (18) with conc. HCl in refluxing gl. AcOH gave the required detosylated product 23 along with detosylated aromatised product, 2-phenyl-2*H*-pyrazolo[4,3-*c*]quinoline (24). Interestingly, the detosylation of other tosylpyrazoloquinolines (19 and 20) gave only the aromatised products (25 and 26).

The dihydroquinolones (5-7) and 4-chromanones (9, 10) on condensation with araldehydes in the presence of NaOMe or HCl following the methods reported earlier^{2,3,5} gave the corresponding 3-arylidene-quinolones (27-31) and 3-arylidene-4-chromanones (32, 33) (Table I). However, the 8-methoxyquinolone (8) under similar reaction conditions did not produce the required arylidene derivative but gave a retro-eliminated product 14 as described above. Epoxidation of 27-33 with H₂O₂ - NaOH in methanol furnished the corresponding 3,α-oxido derivatives (34-40; Table I); the C-3 became assymmetric resulting C-2 methylene protons magnetically non-equivalent and thus in PMR spectra they appeared at different chemical shifts e.g. in 35 they appeared as doublets at δ 3.80 and 4.20 with a coupling constant of 16 Hz while in chroman derivative 40 the doublets due to these protons appeared at δ 3.97 and 4.27 with a coupling constant of 12 Hz.

The 3,α-oxido derivatives (34-40) on treatment with hydrazine hydrate or phenylhydrazine in abs. ethanol in the presence of a catalytic amount of gl. AcOH furnished the corresponding 2-substituted 3-aryl-4,5-dihydro-2*H*-pyrazolo[4,3-*c*]quinolines (41-46) and 3-

Table 1—Characterisation and Toxicity Data of 4,5-Dihydro-2*H*-pyrazolo[4,3-*c*]quinolines and 2,4-Dihydro[1]benzopyrano[4,3-*c*]pyrazoles and Their Intermediates

Compd*	R ¹	R ²	X	m.p. °C	Yield (%)	Mol. formula	Found (%) (Calc.)			ALD ₅₀ (mg/kg)
							C	H	N	
11	H	—	—			C ₁₇ H ₁₅ NO ₄ S				—
12	6-OMe	—	—	164	95	C ₁₈ H ₁₇ NO ₅ S	60.3 (60.1)	4.6 4.7	3.7 (3.9)	—
13	7-OMe	—	—	98	93	C ₁₈ H ₁₇ NO ₅ S	60.4 (60.1)	4.8 4.7	4.9 (3.9)	—
15	6-OMe	—	—	260	96	C ₄₀ H ₄₀ N ₄ O ₈ S ₂	62.2 (62.5)	5.3 5.2	7.1 (7.3)	—
16	7-OMe	—	—	284	95	C ₄₀ H ₄₀ N ₄ O ₈ S ₂	62.8 (62.5)	5.0 5.2	7.0 (7.3)	
17	H	H	—	150	90	C ₁₇ H ₁₅ N ₃ O ₂ S	61.4 (61.6)	4.8 4.5	12.4 (12.7)	> 800
18	H	Ph	—	171	82	C ₂₃ H ₁₉ N ₃ O ₂ S	68.9 (68.6)	4.5 4.7	10.1 (10.4)	> 800
19	H	C ₂ H ₄ OH	—	144	55	C ₁₉ H ₁₉ N ₃ O ₃ S	61.6 (61.8)	5.3 5.1	11.2 (11.4)	> 800
20	7-OMe	Ph	—	191	76	C ₂₄ H ₂₁ N ₃ O ₃ S	66.4 (66.8)	4.7 4.9	9.5 (9.7)	825
21	8-OMe	H	—	138	96	C ₁₈ H ₁₇ N ₃ O ₃ S	60.5 (60.8)	5.1 4.8	11.7 (11.8)	681
22	8-OMe	Ph	—	203	93	C ₂₄ H ₂₁ N ₃ O ₃ S	67.2 (66.8)	4.9 4.8	9.8 (9.7)	> 1000
23	H	Ph	—	142	54	C ₁₆ H ₁₃ N ₃	78.0 (77.7)	5.5 5.2	16.7 (17.0)	
24	H	Ph	—	156	27	C ₁₆ H ₁₁ N ₃	78.2 (78.3)	4.8 4.5	17.2 (17.2)	
25	H	C ₂ H ₄ OH	—	237	38	C ₁₂ H ₁₁ N ₃ O	67.8 (67.6)	5.3 5.1	19.4 (19.7)	
26	7-OMe	Ph	—	142	51	C ₁₇ H ₁₃ N ₃ O	73.9 (74.1)	4.3 4.7	15.0 (15.2)	
27-33 ^{2,3,5}										
34	H	—	CH	72-74	99	C ₂₃ H ₁₉ NO ₄ S	67.8 (68.0)	5.0 4.7	3.1 (3.4)	
35	6-OMe	—	CH	138	94	C ₂₄ H ₂₁ NO ₅ S	66.4 (66.2)	5.0 4.8	2.9 (3.2)	
36	6-OMe	—	N	165	96	C ₂₃ H ₂₀ N ₂ O ₅ S	63.2 (63.3)	4.9 4.6	6.1 (6.4)	
37	7-OMe	—	CH	102	80	C ₂₄ H ₂₁ NO ₅ S	65.8 (66.2)	4.0 3.8	3.0 (3.2)	
38	7-OMe	—	C-OMe	130	98	C ₂₃ H ₂₃ NO ₆ S	64.8 (64.5)	5.0 4.9	2.6 (2.8)	
39†	H	—	CH	128	85	C ₁₆ H ₁₂ O ₃	76.3 (76.2)	4.9 4.8		> 1000
40†	7-OMe	—	CH	132	92	C ₁₇ H ₁₄ O ₄	72.0 (72.3)	4.7 4.9		825
41†	H	H	CH	160	90	C ₂₃ H ₁₉ N ₃ O ₂ S	69.0 (68.8)	5.0 4.7	10.0 (10.4)	825
42†	H	Ph	CH	189	69	C ₂₉ H ₂₃ N ₃ O ₂ S	72.7 (73.0)	4.5 4.8	8.6 (8.8)	
43†	7-OMe	Ph	CH	176	43	C ₃₀ H ₂₅ N ₃ O ₃ S	69.7 (71.1)	4.6 4.9	7.9 (8.2)	
44†	7-OMe	H	C-OMe	150	23	C ₂₅ H ₂₃ N ₃ O ₄ S	64.8 (65.0)	5.1 5.0	8.8 (9.1)	
45†	8-OMe	H	CH	118	50	C ₂₄ H ₂₁ N ₃ O ₃ S	66.9 (66.8)	4.7 4.8	9.5 (9.7)	
46†	8-OMe	H	N	158	93	C ₂₃ H ₂₀ N ₄ O ₃ S	64.1 (63.9)	4.9 4.6	13.1 (13.0)	

(Contd.)

Table 1—Characterisation and Toxicity Data of 4,5-Dihydro-2*H*-pyrazolo[4,3-*c*]quinolines and 2,4-Dihydro[1]benzopyrano-[4,3-*c*]pyrazoles and Their Intermediates—Contd.

Compd ^a	R ¹	R ²	X	m.p. °C	Yield (%)	Mol. formula	Found (%) (Calc.)			ALD ₅₀ (mg/kg)
							C	H	N	
47†	H	COMe	CH	142	97	C ₂₃ H ₂₁ N ₃ O ₃ S	67.4 (67.7)	4.6 4.7	9.2 9.5	681
48†	H	H	CH	273	86	C ₁₆ H ₁₂ N ₂ O	74.6 (74.4)	5.0 4.8	11.4 11.3	> 1000
49†	7-OMe	H	CH	250	90	C ₁₇ H ₁₄ N ₂ O ₂	73.7 (73.7)	4.9 5.0	9.9 10.0	681
50	H	H	CH	350(d)	68	C ₁₆ H ₁₁ N ₃	68.2 (67.8)	5.7 6.0	14.5 14.8	
51	H	Ph	CH	186	39	C ₂₂ H ₁₃ N ₃	81.8 (82.2)	5.0 4.7	12.8 13.1	> 1000
52	H	Ph	CH	155-60	44	C ₂₂ H ₁₇ N ₃	81.4 (81.7)	5.0 5.2	12.9 13.0	

^aNumbers described in this column refer to those given in Scheme 1.

27² (R¹=H, Z=NTs, X=H); 28² (R¹=6-OMe, Z=NTs, X=CH); 29² (R¹=6-OMe, Z=NTs, X=N); 30² (R¹=7-OMe, Z=NTs, X=CH); 31² (R¹=7-OMe, Z=NTs, X=C-OMe); 32³ (R¹=H, Z=O, X=CH); 33³ (R¹=7-OMe, Z=O, X=CH).

†Z=O

‡Z=NTs

phenyl-2,4-dihydro[1]benzopyrano[4,3-*c*]pyrazoles (48, 49) (Table 1). Acetylation of 41 with acetyl chloride gave the corresponding 2-acetyldihydropyrazoloquinoline (47). In quinoline derivative 45 and benzopyran derivative 49, the C-4 methylene protons appeared at δ 4.90 and 5.40 respectively. Detosylation of 41 with conc. HCl in refluxing AcOH brought about aromatisation to give 3-phenyl-2*H*-pyrazolo[4,3-*c*]quinoline (50), while that of 42 gave a mixture of 2,3-diphenyl-2*H*-pyrazolo[4,3-*c*]quinoline (51) and the corresponding 4,5-dihydro derivative (52). However, with pyridine hydrochloride as the detosylating agent, 42 gave only 51. All these compounds were identified by their spectral and analytical data.

Biological activity

Acute toxicity (ALD₅₀) and gross behavioural effects were studied in mice by i.p. administration of the compounds. The effects on blood pressure and respiration and interaction with acetylcholine, histamine and adrenaline were determined in anaesthetised cats by i.v. administration. None of the compounds showed any significant CNS or CVS activity except compound 51 which showed weak CNS depressant and hypotensive activities.

The antiimplantation activity of the compounds 17-26 and 41-52 was determined in mated female albino rats by the reported procedure⁷. None of these prevented pregnancy at an oral dose of 20 mg/kg.

Experimental Procedure

Melting points were determined in capillary tubes in sulphuric acid-bath and are uncorrected.

Homogeneity of the compounds was routinely checked on silica gel-G TLC plates. IR spectra were recorded in KBr on a Perkin-Elmer 137 or 157 spectrophotometer ($\nu_{\max}$ in cm⁻¹), and PMR spectra in CDCl₃, unless otherwise stated, on a Perkin-Elmer R-32 or Varian A 60D instrument using TMS as internal reference (chemical shifts in δ , ppm).

General methods for the preparation of various compounds are described. All compounds showed expected spectral characteristics. Only those spectral data which have a direct bearing on structural assignment have been given.

Ethyl β -(*o*-anisidino)propionate (2)

A mixture of *o*-anisidine (1: 12.3 g, 100 mmol), ethyl acrylate (12.0 g, 120 mmol), AcOH (1 ml) and benzene (10 ml) was refluxed for 24 hr, cooled and worked-up as usual to give a residue which on distillation *in vacuo* furnished 2, b.p. 143-45°/4 mm, yield 21.9 g (98%); IR(neat): 3400 (NH) and 1720 (CO); PMR: 1.20 (*t*, 3H, CH₂CH₃, *J*=7 Hz), 2.38 (*t*, 2H, COCH₂, *J*=7 Hz), 3.42 (*t*, 2H, NCH₂, *J*=7 Hz), 3.75 (*s*, 3H, OCH₃), 4.12 (*q*, 2H, OCH₂, *J*=7 Hz) (Found: C, 64.5; H, 7.8; N, 6.5. C₁₂H₁₇NO₃ requires C, 64.6; H, 7.6; N, 6.3%).

Ethyl β -(*N*-tosyl-*o*-anisidino)propionate (3)

To a stirred solution of 2 (8.92 g, 40 mmol) in pyridine (33 ml) and benzene (14 ml) was added *p*-toluenesulphonyl chloride (9.5 g, 50 mmol) in small lots. After stirring for 48 hr at room temperature, the reaction mixture was diluted with water and extracted with ether. The extract was washed successively with

10% HCl, 5% KOH, water and saturated NaCl solution, dried (Na_2SO_4) and ether removed to give **3**, n_D^{20} 1.541, yield 13.3 g (88%); IR (neat): 1730 (C=O), 1345 and 1162 (Ts); PMR: 1.08 (t, 3H, CH_2CH_3 , $J=7$ Hz), 2.28 (s, 3H, $\text{C}_6\text{H}_4-\text{CH}_3$), 2.40 (t, 2H, COCH_2 , $J=7$ Hz), 3.27 (s, 3H, OCH_3), 3.70 (t, 2H, NCH_2 , $J=7$ Hz), 3.80 (q, 2H, OCH_2 , $J=7$ Hz) (Found: C, 60.6; H, 6.4; N, 4.0. $\text{C}_{19}\text{H}_{23}\text{NO}_5\text{S}$ requires C, 60.5; H, 6.1; N, 3.7%).

β -(N-Tosyl-o-anisidino)propionic acid (4)

The ester **3** (11.3 g, 30 mmol) on hydrolysis with 6N KOH (5.3 ml) in methanol (90 ml) by stirring for 48 hr at room temperature followed by usual work-up of the hydrolysate afforded **4** which recrystallised from benzene, yield 7.54 g (72%), m.p. 125–27°; IR: 1720 (C=O); PMR: 2.23 (s, 3H, $\text{C}_6\text{H}_4-\text{CH}_3$), 2.67 (t, 2H, $\text{CO}-\text{CH}_2$, $J=8$ Hz), 3.38 (s, 3H, OCH_3), 3.88 (t, 2H, NCH_2 , $J=8$ Hz), 10.1 (br s, 1H, D_2O exchangeable COOH) (Found: C, 58.2; H, 5.6; N, 4.0. $\text{C}_{17}\text{H}_{19}\text{NO}_5\text{S}$ requires C, 58.5; H, 5.4; N, 4.0%).

From the remaining benzene extract 2.1 g of N-tosyl-o-anisidine (**14**), m.p. 134°, was isolated.

2,3-Dihydro-8-methoxy-1-tosyl-4(1H)-quinolone (8)

A mixture of **4** (5.24 g, 15 mmol) and PCl_5 (4.2 g, 20 mmol) was warmed to initiate the reaction and left at room temperature for 10 hr. After adding benzene (20 ml) the reaction mixture was distilled *in vacuo* to remove the POCl_3 formed. The residual acid chloride was taken in benzene (20 ml) and added dropwise to a cold (5°) and stirred suspension of AlCl_3 (4.0 g, 30 mmol) in benzene (90 ml) and stirring continued at room temperature for 6 hr. The reaction mixture was diluted with equal volume of ether and the complex decomposed by slow addition of dil. HCl maintaining the temperature below 15°. The neutral material was isolated in the usual way to get **8**, yield 1.8 g (36%), m.p. 149–51° (lit.⁶, m.p. 150–51°).

2,3-Dihydro-3-hydroxymethylene-6-methoxy-1-tosyl-4(1H)-quinolone (12; $R^1=6\text{-Ome}$)

Ethyl formate (8.88 g, 120 mmol) was added to a stirred and cooled (10°) suspension of NaH (50% dispersion in oil, 3.6 g) in dry benzene (100 ml) and the mixture stirred for 15 min. To this stirred solution was added 2,3-dihydro-6-methoxy-1-tosyl-4(1H)-quinolone (**6**; 19.86 g, 60 mmol) in small lots and the reaction mixture stirred at 10° for 30 min. Stirring was continued for 24 hr at room temperature. Thereafter, it was diluted with three times hexane and the precipitated sodium salt of **12** filtered, dissolved in water and decolourised with animal charcoal. This aqueous solution was acidified with dil. HCl and the precipitated solid filtered, washed with water, dried

and recrystallised from benzene to give **12**, yield 20.5 g (95%), m.p. 164°, IR: 1630 (C=O), 1345 and 1165 (Ts); PMR: 2.36 (s, 3H, $\text{C}_6\text{H}_4-\text{CH}_3$), 3.88 (s, 3H, OCH_3), 4.58 (s, 2H, 2-CH_2), 7.72 (d, 1H, C_8-H , $J=9$ Hz) (Found: C, 60.3; H, 4.6; N, 4.1. $\text{C}_{18}\text{H}_{17}\text{NO}_5\text{S}$ requires C, 60.2; H, 4.7; N, 3.9%).

1,4-Bis(1,2,3,4-tetrahydro-6-methoxy-4-oxo-1-tosyl-3-quinolinylidenemethyl)piperazine (15; $R^1=6\text{-Ome}$)

A solution of **12** (1.8 g, 5 mmol) and piperazine (0.22 g, 2.5 mmol) in benzene (30 ml) was refluxed for 13 hr, cooled and the separated solid filtered, washed with benzene and dried to get **15**, yield 1.6 g (96%), m.p. 260°; IR: 1650 (C=O) (Found: C, 62.1; H, 5.4; N, 7.1. $\text{C}_{40}\text{H}_{40}\text{N}_4\text{O}_8\text{S}_2$ requires C, 62.5; H, 5.2; N, 7.3%).

4,5-Dihydro-8-methoxy-5-tosyl-pyrazolo[4,3-c]-quinoline (21; $R^1=8\text{-OMe}$, $R^2=H$)

A solution of **12** (3.59 g, 10 mmol) and hydrazine hydrate (3.6 ml) in abs. ethanol (140 ml) was refluxed in the presence of acetic acid (1 ml) for 8 hr. The solvent was removed, the residual product triturated with water, and the precipitated solid filtered, washed with water, dried and crystallized from methanol to give **21**, yield 3.4 g (96%), m.p. 138°; IR: 3320–3130 (NH), 1335 and 1150 (Ts); PMR: 2.08 (s, 3H, $-\text{C}_6\text{H}_4-\text{CH}_3$), 3.73 (s, 3H, OCH_3), 4.79 (s, 2H, 2-CH_2), 7.60 (d, 1H, C_6-H , $J=9$ Hz) (Found: C, 60.6; H, 5.1; N, 11.8. $\text{C}_{18}\text{H}_{17}\text{N}_3\text{O}_3\text{S}$ requires C, 60.8; H, 4.8; N, 11.8%).

4,5-Dihydro-2-phenyl-2H-pyrazolo[4,3-c]-quinoline (23; $R^1=H$, $R^2=Ph$) and 2-Phenyl-2H-pyrazolo[4,3-c]quinoline (24; $R^1=H$, $R^2=Ph$)

A mixture of **18** (1.6 g, 4 mmol), gl. acetic acid (8 ml) and conc. HCl (8 ml) was refluxed for 10 hr, and the reaction mixture diluted with water, neutralized with 20% KOH, extracted with benzene and the extract worked-up to give a mixture (0.8 g) of **23** and **24** in 66:34 ratio. These were separated by fractional crystallisation from hexane to give **24** (0.26 g), m.p. 155–56°; PMR: 8.28 (s, 1H, C_3-H), 9.25 (s, 1H, C_4-H) (Found: C, 78.5; H, 4.6; N, 17.3. $\text{C}_{16}\text{H}_{11}\text{N}_3$ requires C, 78.4; H, 4.5; N, 17.1%) and **23** (0.14 g), m.p. 140–42°; PMR: 3.87 (h, 1H, NH, D_2O exchangeable), 4.53 (s, 2H, 2-CH_2) (Found: C, 77.5; H, 5.4; N, 16.8. $\text{C}_{16}\text{H}_{13}\text{N}_3$ requires C, 77.7; H, 5.3; N, 17.0%).

3-Arylidene-2,3-dihydro-1-tosyl-4(1H)-quinolones (27–31; $Z=NTs$) and 3-Arylidene-4-chromanone (32, 33; $Z=O$)

These were prepared from 2,3-dihydro-4(1H)-quinolones (**5–7**) and 4-chromanones (**9**, **10**) by the method reported earlier^{2,3,5}.

3-Benzyl-2,3-dihydro-6-methoxy-3,α-oxido-N-tosyl-4(1H)-quinolone (35; $R^1 = 6\text{-OMe}$, $X = \text{CH}$, $Z = \text{NTs}$)

To a stirred suspension of 28 (4.61 g, 11 mmol) in methanol (150 ml) was added H_2O_2 (30%, 4.4 ml) at 10° with stirring. Thereafter, 6N NaOH (1 ml) was added to it and stirring continued at room temperature for 4 hr. The reaction mixture was diluted with water and the precipitated product filtered, washed with water and crystallized from methanol to give 35, yield 4.5 g (94%), m.p. 138° ; IR: 1690 (C=O), 1345 and 1160 (Ts); PMR: 2.37 (s, 3H, $-\text{C}_6\text{H}_4-\text{CH}_3$), 3.80 (d, 1H, C_2-H , $J = 16$ Hz), 3.83 (s, 3H, OCH_3), 4.20 (d, 1H, C_2-H , $J = 16$ Hz), 4.47 (s, 1H, $\text{C}_\alpha-\text{H}$), 7.71 (d, 1H, C_8-H , $J = 8$ Hz) (Found: C, 66.5; H, 5.0; N, 2.8. $\text{C}_{24}\text{H}_{21}\text{NO}_5\text{S}$ requires C, 66.2; H, 4.8; N, 3.2%).

3-Benzyl-7-methoxy-3,α-oxido-4-chromanone (40; $R^1 = 7\text{-OMe}$, $X = \text{CH}$, $Z = \text{O}$)

To a suspension of 33 (3.99 g, 15 mmol) in acetone (20 ml) was added H_2O_2 (30%, 2.6 ml) and 2N NaOH (2.1 ml) and resulting reaction mixture stirred for 24 hr. The precipitated product was filtered and washed with acetone to give 40, yield 3.9 g (92%), m.p. 132° ; IR: 1665 (C=O); PMR: 3.75 (s, 3H, OCH_3), 3.97 (d, 1H, C_2-H , $J = 12$ Hz), 4.27 (d, 1H, C_2-H , $J = 12$ Hz), 4.43 (s, 1H, $\text{C}_\alpha-\text{H}$) (Found: C, 72.0; H, 5.7. $\text{C}_{17}\text{H}_{14}\text{O}_4$ requires C, 72.3; H, 5.0%).

4,5-Dihydro-8-methoxy-3-phenyl-5-tosyl-2H-pyrazolo[4,3-c]quinoline (45; $R^1 = 8\text{-OMe}$, $R^2 = \text{H}$, $X = \text{CH}$, $Z = \text{NTs}$)

A mixture of 35 (0.44 g, 1 mmol), hydrazine hydrate (0.5 ml, excess) and AcOH (2 drops) was refluxed in abs. ethanol (10 ml) for 15 hr, the reaction mixture concentrated and diluted with water. The separated solid was filtered, washed with water and dried to give 45, yield 0.21 g (50%), m.p. 118° ; IR: 3300-3100 (NH), 1350 and 1160 (Ts); PMR: 2.14 (s, 3H, $-\text{C}_6\text{H}_4-\text{CH}_3$), 3.77 (s, 3H, OCH_3), 4.90 (s, 2H, 4-CH_2), 7.33 (br s, 5H, $-\text{C}_6\text{H}_5$) (Found: C, 66.9; H, 4.7; N, 9.5. $\text{C}_{24}\text{H}_{21}\text{N}_3\text{O}_3\text{S}$ requires C, 66.8; H, 4.9; N, 9.7%).

2-Acetyl-4,5-dihydro-3-phenyl-5-tosyl-2H-pyrazolo[4,3-c]quinoline (47; $R^1 = \text{H}$, $R^2 = \text{COCH}_3$, $X = \text{CH}$, $Z = \text{NTs}$)

A mixture of 4,5-dihydro-3-phenyl-5-tosyl-2H-pyrazolo[4,3-c]quinoline (41; 0.4 g, 1 mmol), AcCl (0.1 g, 1.25 mmol) and anhyd. K_2CO_3 (200 mg) in dry Me_2CO (20 ml) was stirred for 4 hr at room temperature, then refluxed for 2 hr and worked-up as usual. The residue on crystallization from C_6H_6 -

hexane gave 47, yield 430 mg (97%), m.p. $141\text{-}42^\circ$; IR: 1738 (C=O); PMR: 2.88 (d, 2H, NCH_2 , $J = 9$ Hz).

2,4-Dihydro-7-methoxy-3-phenyl-2H-[1]benzopyrano[4,3-c]pyrazole (49; $R^1 = 7\text{-OMe}$, $R^2 = \text{H}$, $X = \text{CH}$, $Z = \text{O}$)

It was prepared by the method described for 45 starting from 40 in 90% yield, m.p. 250° ; PMR: 3.71 (s, 3H, OCH_3), 5.42 (s, 2H, 4-CH_2), 7.58 (d, 1H, C_9-H) (Found: C, 73.7; H, 4.9; N, 9.9. $\text{C}_{17}\text{H}_{14}\text{N}_2\text{O}_2$ requires C, 73.7; H, 5.0; N, 10.1%).

2,3-Diphenyl-2H-pyrazolo[4,3-c]quinoline (51; $R^1 = \text{H}$, $R^2 = \text{Ph}$, $X = \text{CH}$) and 4,5-Dihydro-2,3-diphenyl-2H-pyrazolo[4,3-c]quinoline (52; $R^1 = \text{H}$, $R^2 = \text{Ph}$, $X = \text{H}$)

Method-A

A mixture of 42 (3.0 g, 6.3 mmol), gl. AcOH (25 ml) and conc. HCl (25 ml) was refluxed for 12 hr, cooled and diluted with water. After neutralization with 20% KOH it was extracted with benzene and the extract worked-up as usual to give a residual product which was extracted with hot hexane and the extract cooled to get 51, yield 0.8 g (39%), m.p. 186° ; PMR: 9.08 (s, 1H, C_4-H) (Found: C, 82.4; H, 4.4; N, 13.0. $\text{C}_{22}\text{H}_{15}\text{N}_3$ requires C, 82.2; H, 4.7; N, 13.1%). The residual product after extraction with hexane was crystallized from benzene to give 52, yield 0.9 g (44%), m.p. $155\text{-}60^\circ$ (Found: C, 81.5; H, 5.5; N, 13.2. $\text{C}_{22}\text{H}_{17}\text{N}_3$ requires C, 81.7; H, 5.3; N, 13.0%).

Method-B

A mixture of 42 (0.48 g, 1 mmol) and pyridine hydrochloride (10 g) was refluxed for 2 hr, and the reaction mixture worked-up as usual to get 51, yield 0.27 g (84%), m.p. 186° .

Acknowledgement

We are thankful to Drs B N Dhawan and V P Kamboj of Pharmacology and Endocrinology Divisions of Central Drug Research Institute for providing screening results of CNS/CVS and antifertility activity respectively.

References

- 1 Sangwan N K & Rastogi S N, *Indian J Chem*, **18B** (1979) 65.
- 2 Kelkar P M, Sangwan N K, Rastogi S N & Anand N, *Indian J Chem*, **19B** (1980) 297.
- 3 Sangwan N K & Rastogi S N, *Indian J Chem*, **20B** (1981) 135.
- 4 Sangwan N K, Rastogi S N & Anand N, *Indian J Chem*, **17B** (1979) 653.
- 5 Sangwan N K & Rastogi S N, *Indian J Chem*, **19B** (1980) 500.
- 6 Atwal M S, Bauer L, Dixit S N, Gearien J E & Morris R W, *J mednl Chem*, **8** (1965) 566.
- 7 Sangwan N K & Rastogi S N, *Indian J Chem*, **20B** (1981) 140.