Syntheses and Bioevaluation of Substituted Dihydropyridines for Pregnancy-Interceptive Activity in Hamsters[1]

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A number of 2,6-dimethyl-3,5-bis(methoxycarbonyl)-4-substituted-1,4-dihydropyridines were synthesized and evaluated for pregnancy-interceptive activity in mated hamsters. Out of 24 compounds, **12**, **15**, **21**, **22**, **28**, and **34** caused a marked reduction in the number of implantations when administered on days 3–8 postcoitum. In an in vitro competition assay, none of the compounds exhibited noticeable binding affinity for uterine progesterone receptors. The results reported here have helped to identify new leads for developing pregnancy-interceptive agents and the active compounds do not seem to elicit their interceptive effect through receptor-mediated inhibition of progesterone action in hamster uterus.

In the search for effective nonsteroidal pregnancy-interceptive agents, potentiality was discovered in dihydroquinoline derivatives in our laboratory.[2] These compounds were devoid of hormonal activity and did not possess any noteworthy affinity for uterine progesterone receptor either.[3] Inspite of these positive attributes, the compounds were not considered suitable for development because of their short shelf life. Nevertheless, this interesting lead prompted development of comparatively more stable 1,4-dihydropyridines.

The considerations behind the design of substituted dihydropyridines of the present study were 2-fold. The first consideration led to avoiding pharmacophores responsible for eliciting cardiac activity and the second one was directed to incorporating pharmacophores which could be expected to interact at uteroplacental complex. On the basis of these considerations, the syntheses of 2,6-dimethyl-3,5-bis(methoxycarbonyl)-4-substituted-1,4-dihydropyridines have been carried out and their details along with their pregnancy-interceptive activity are reported here.

Chemistry

Reaction of the appropriate aromatic and heterocyclic aldehydes **1–11** with methyl β-aminocrotonate furnished pentasubstituted 1,4-dihydropyridine derivatives **12–23** (Figure 1). Various aldehydes required for this reaction were synthesized with the following details.

4-(Methoxycarbonyl)benzaldehyde (**1**) was prepared by the method of Snyder and Demuth.[4] Vilsmeier reaction of 2,4-dimethoxy-4′-methylbenzophenone gave 2,4-dimethoxy-5-formyl-4′-methylbenzophenone (**2**). 4-Chloro-3-nitrobenzaldehyde (**3**) was obtained by the nitration of 4-chlorobenzaldehyde with fuming nitric acid.[5] 4-Acetamidobenzaldehyde with **4**,[6] after nitration and alkaline hydrolysis, furnished **5**. Pterphthaldehyde (**6**), for preparing bis(dihydropyridine) derivative **17**, was obtained commercially and its monoketal **7** was used for preparing

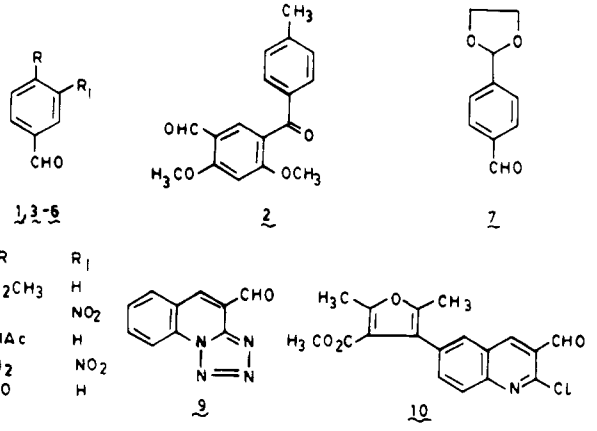
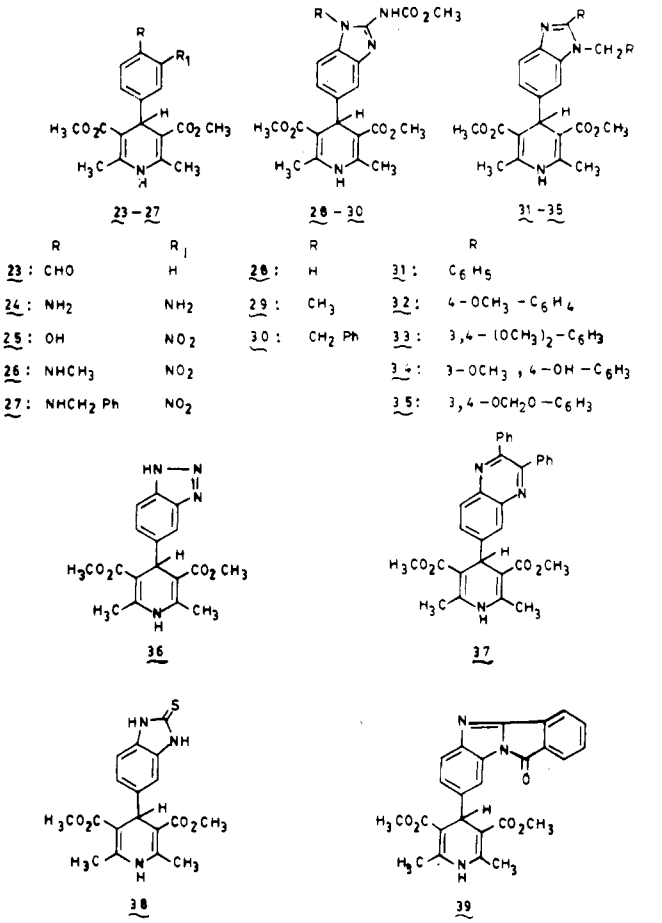


Chart I



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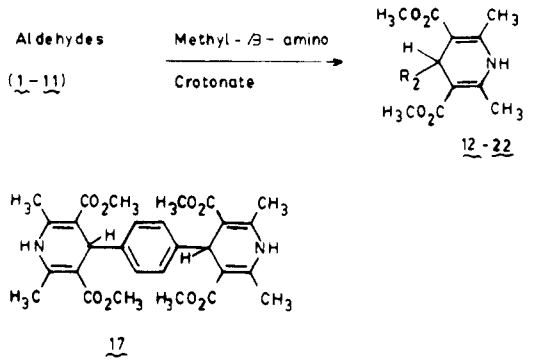

Figure 1. Various aldehydes (1–11) used for the preparation of substituted dihydropyridines (12–22). The substituent R_2 corresponds to the moiety in 1–11, except for 17.

18. Acidic hydrolysis of the 1,3-dioxolane 18 furnished 23. 2-Chloro-3-formylquinoline (8) was prepared by Vilsmeier–Haack reaction of acetanilide,[7] and its reaction with sodium azide gave 9.[8] 2-Chloro-6-[2,5-dimethyl-3-(methoxycarbonyl)furan-4-yl]-3-formylquinoline (10) was obtained by Vilsmeier–Haack reaction of 4-(4-acetamidophenyl)-2,5-dimethyl-3-(methoxycarbonyl)furan, which was obtained by the method reported earlier.[9] Commercially available *d*-mannose (11) was utilized to obtain water-soluble substituted 1,4-dihydropyridine 22.

In order to build heterocycles on the phenyl ring of the pentasubstituted 1,4-dihydropyridines, the appropriate functional groups present on the phenyl ring were elaborated to obtain the desired heterocycles (Chart I). For example, hydrogenation of 16 in the presence of Raney nickel yielded the corresponding diamine 24 and reaction of 14 with aqueous ammonia and methylamine under pressure gave 25 and 26, respectively. However, 14 reacted with benzylamine at atmospheric pressure to furnish 27. Hydrogenation of 16, 26, and 27 in the presence of Raney nickel gave the corresponding diamines, which were reacted in situ with *N,N'*-bis(methoxycarbonyl)-*S*-methylisothiourea to give the benzimidazole-2-carbamate derivatives 28–30. Reaction of 24 with substituted benzaldehyde furnished the 2-substituted benzimidazoles 31–35 while its reaction with sodium nitrate gave the triazole derivative 36. Ring closure of 24 with benzil, carbon disulfide, and phthalic anhydride yielded 37, 38, and 39, respectively. See Table I for the physical and analytical data of various dihydropyridines.

Results and Discussions

Biological Activity. Results presented in Table II revealed that two (12 and 15) out of 24 compounds caused a marked reduction in the number of implantations while four more (21, 22, 28, and 34) showed relatively less activity. The remaining compounds were virtually ineffective (activity (mM): 13, 7.83; 14, 13.15; 16, 13.85; 17, 9.54; 19, 19.43; 20, 6.36; 23, 15.20; 24, 15.11; 26, 6.66; 27, 5.54; 30, 26.88; 32, 8.82; 35, 8.40; 36, 14.62; 37, 4.95; 38, 6.70; and 39, 5.64). In the competitive-binding assay for hamster and rabbit uterine progesterone receptor, compounds 12, 15, 17, and 38 caused 40, 30, 36, and 30% inhibition in [^{3}H]progesterone binding to uterine cytosol at a 10^{-5} M concentration. Other compounds showed lesser inhibition at this concentration. However, all the compounds exhibited negligible activity at 10^{-9} M.

Table I. Physical and Analytical Data of 4-Substituted-3,5-bis(methoxycarbonyl)-2,6-dimethyl-1,4-dihydropyridines

no.	mp, °C	% yield	mol formula	anal.
2	159–60	60	$C_{17}H_{16}O_4 \cdot {}^1/_2H_2O$	C, H
10	168–9	50	$C_{18}H_{14}ClNO_4$	C, H, N
12	230–1	70	$C_{19}H_{21}NO_6 \cdot {}^1/_2H_2O$	C, H, N
13	135–6	50	$C_{27}H_{29}NO_7 \cdot {}^1/_2H_2O$	C, H, N
14	138–9	60	$C_{17}H_{17}ClN_2O_6$	C, H, N
15	264–5	62	$C_{19}H_{22}N_2O_5$	C, H, N
16	231–2	68	$C_{17}H_{19}N_3O_6$	C, H, N
17	301–2	60	$C_{28}H_{32}N_2O_8$	C, H, N
18	224 dec	63	$C_{20}H_{23}NO_6 \cdot H_2O$	C, H, N
19	220–2	35	$C_{20}H_{19}ClN_2O_4$	C, H, N
20	190–2	62	$C_{20}H_{19}N_5O_4$	C, H, N
21	220–1	65	$C_{28}H_{27}ClN_2O_7$	C, H, N
22	121–2	55	$C_{16}H_{25}NO_9$	C, H, N
23	179–80	65	$C_{18}H_{19}NO_5 \cdot {}^1/_2H_2O$	C, H, N
24	239–40	72	$C_{17}H_{21}N_3O_4$	C, H, N
25	168–9	41	$C_{17}H_{18}N_2O_7$	C, H, N
26	149–50	80	$C_{18}H_{21}N_3O_6$	C, H, N
27	206–7	63	$C_{24}H_{25}N_3O_6$	C, H, N
28	240–1	70	$C_{20}H_{22}N_4O_6$	C, H, N
29	205–6	80	$C_{21}H_{24}N_4O_6$	C, H, N
30	186–7	67	$C_{27}H_{28}N_4O_6$	C, H, N
31	195–6	58	$C_{31}H_{29}N_3O_4$	C, H, N
32	135–6	66	$C_{33}H_{33}N_3O_6$	C, H, N
33	220–1	62	$C_{35}H_{37}N_3O_8$	C, H, N
34	130	58	$C_{33}H_{33}N_3O_8$	C, H, N
35	180–1	53	$C_{33}H_{29}N_3O_8$	C, H, N
36	139–40	72	$C_{17}H_{18}N_4O_4$	C, H, N
37	172–3	65	$C_{31}H_{27}N_3O_4$	C, H, N
38	268–9	70	$C_{18}H_{19}N_3O_4S$	C, H, N
39	225–6	55	$C_{25}H_{21}N_3O_5$	C, H, N

The present study has furnished a new lead as is evident from the pregnancy-interceptive activity of six of the compounds. It also suggests that structural modification of 1,4-dihydropyridines may help the molecule to reach the uterus. These findings are significant because the search for new chemical structures for the development of a once-a-month contraceptive is highly desirable. The low binding affinity of compounds for uterine progesterone receptors suggests that their pregnancy-interceptive effect does not seem to operate through receptor-mediated inhibition of progesterone action in the uterus. It may be presumed that the active compounds possibly directly interfere at the uteroplacental junction or with the growing trophoblast. In view of the report[10] that the structurally related calcium channel blocker nifedipine neither affects the base-line sex steroid hormone levels nor the release of pituitary hormones, the site of action of the 1,4-dihydropyridines reported here appears to be local (trophoblast/uteroplacental complex). Studies on the SARs of these compounds suggest that more than one substituent on the phenyl ring of 1,4-dihydropyridines (24–27) diminish the pregnancy-interceptive activity. The structures of active compounds indicate that the environment around the 4'-position of the phenyl ring governs the ability of the compounds to evoke the desired bioresponse. The presence of carbonyl group(s) or a hydroxy group(s) in the envisaged environment around the 4'-position of the phenyl ring may lead to the contragestational effect. However, the distance of carbonyl or hydroxyl group(s) from the 4'-position of the phenyl ring appears to be critical and the optimum distance could not be ascertained since lead optimization studies in this class of compounds have not been carried out. The apparent exceptions to this

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Table II. Pregnancy-Interceptive Activity and Percent Inhibition of [^{3}H]Progesterone Binding to Uterine Cytosol Receptor

compd no.	dose, mmol/kg	pregnancy-interceptive activity: no. of implantations (mean ± SEM)[c]	n[a]	% inhibn of [^{3}H]progesterone binding[b] 10^{-5} M	10^{-6} M	10^{-7} M	10^{-8} M	10^{-9} M
normal control	-	7.32 ± 1.98	8					
12	6.96	0.72 ± 0.52	11	40 (25)	32 (15)	27 (20)	10 (0)	10 (0)
13	7.83	6.00 ± 0.49	13	18 (23)	15 (18)	15 (15)	12 (11)	8 (10)
14	13.15	2.60 ± 0.70	5	24 (18)	14 (10)	10 (5)	5 (0)	2 (0)
15	6.98	0.66 ± 0.47	6	30 (15)	25 (18)	12 (0)	0 (0)	0 (0)
16	13.85	7.00 ± 0.52	5	10 (5)	5 (1)	5 (0)	0 (0)	0 (0)
17	9.54	6.20 ± 0.51	6	34 (36)	31 (26)	15 (16)	13 (10)	9 (4)
19	19.43	3.00 ± 0.42	12	14 (17)	14 (16)	11 (10)	10 (11)	6 (8)
20	6.36	2.50 ± 0.47	6	10 (14)	9 (8)	10 (12)	8 (10)	0 (0)
21	9.31	1.80 ± 0.26	19	17 (8)	20 (10)	9 (5)	10 (0)	5 (0)
22	6.67	1.16 ± 0.50	12	25 (10)	19 (8)	20 (0)	5 (0)	0 (0)
23	15.20	5.15 ± 0.37	6	12 (15)	10 (10)	5 (8)	9 (4)	0 (3)
24	15.11	2.30 ± 0.67	4	18 (21)	14 (15)	9 (16)	0 (10)	0 (13)
26	6.66	6.80 ± 0.52	5	12 (14)	13 (10)	10 (10)	4 (8)	4 (5)
27	5.54	2.50 ± 1.02	6	10 (12)	6 (10)	4 (0)	0 (10)	0 (0)
28	12.08	1.50 ± 0.36	10	28 (20)	15 (16)	16 (16)	10 (5)	0 (5)
30	26.88	3.58 ± 1.02	12	ND[d]				
32	8.82	6.00 ± 0.47	5	24 (20)	20 (16)	15 (10)	12 (6)	10 (2)
33	7.97	4.00 ± 0.54	5	16 (8)	10 (10)	5 (8)	5 (0)	2 (0)
34	8.35	1.20 ± 0.49	6	18 (20)	18 (15)	12 (15)	5 (8)	3 (5)
35	8.40	4.40 ± 0.58	4	16 (18)	15 (12)	8 (5)	5 (0)	0 (0)
36	14.62	5.20 ± 0.52	5	26 (22)	18 (20)	16 (12)	12 (8)	9 (10)
37	4.95	4.60 ± 0.37	5	18 (16)	15 (18)	12 (10)	9 (2)	6 (2)
38	6.70	5.00 ± 0.39	5	30 (20)	26 (18)	18 (15)	10 (10)	9 (0)
39	5.64	3.80 ± 0.42	5	16 (15)	10 (15)	8 (0)	9 (0)	6 (0)

[a] n = number of animals. [b] Values given in parentheses are for rabbit uterine progesterone receptors. [c] Statistical analysis used was the Student's t test. [d] ND = not detected.

observation are compounds **13**, **17**, **23**, **29**, **30**, and **39**. It is likely that compound **23** possibly reacts on biophase to loose its carbonyl character while in compounds **13**, **17**, **29**, **30**, and **39** either the disposition of the carbonyl groups from position 4′ is not optimum or the carbonyl group does not fall in the envisaged zone around position 4′ of the phenyl ring. Incorporation of other heteroatoms alone (**36**–**38**) does not help in eliciting the desired biological response.

Experimental Section

The melting points were determined on a sulfuric acid bath or an electrically heated block and are uncorrected. IR spectra were recorded on Perkin-Elmer 157 Infracord and Beckmann Acculab-1 grating instruments and the values are expressed in cm^{-1}. ^{1}H NMR spectra were recorded on a Varian EM-360L or a Perkin-Elmer R-32 instrument using TMS as an internal reference (chemical shift in δ ppm). Mass spectra were recorded on a JEOL-D 300 instrument. Elemental analyses were determined on a Carlo Erba-MOD 1106 instrument; for all compounds the analysis agreed well within 0.3% of the calculated values.

2,4-Dimethoxy-5-formyl-4′-methylbenzophenone (2). To a precooled flask containing $POCl_3$ (4.0 mL, 0.026 mol) was added dry DMF (3.0 mL, 0.04 mol), and after 5 min 2,4-dimethoxy-4′-methylbenzophenone (3.8 g, 0.015 mol) dissolved in dry DMF (6.0 mL, 0.08 mol) was added slowly with stirring. The resulting mixture was heated at 70 °C with stirring for 4 h. Finally it was poured onto crushed ice and neutralized with an ammonia solution (1.0 mL). On cooling, a solid separated out which was filtered, washed with water, and dried. It was recrystallized from a chloroform–hexane mixture.

2-Chloro-6-[2,5-dimethyl-3-(methoxycarbonyl)furan-4-yl]-3-formylquinoline (10). To a precooled flask containing $POCl_3$ (15.4 mL, 0.1 mol) was added dry DMF (7.3 mL, 0.1 mol), slowly with stirring, and after 5 min 4-(4-acetamidophenyl)-2,5-dimethyl-3-(methoxycarbonyl)furan (2.9 g, 0.01 mol) was added. The resulting mixture was heated at 70–74 °C with stirring for 16 h. Finally it was poured onto crushed ice and then the separated solid was filtered, washed with water, and dried. It was recrystallized from a chloroform–hexane mixture.

2,6-Dimethyl-3,5-bis(methoxycarbonyl)-4-substituted-1,4-dihydropyridines (12–22). General Procedure. A mixture of the appropriate aldehyde (1–11, 0.01 mol) and methyl β-aminocrotonate (2.3 g, 0.02 mol), in methanol or ethylene glycol (for **14**–**16**, **20**, and **21**) as solvent, was heated on a water bath for 24 h. Thereafter water was added to the reaction mixture and it was stirred at room temperature (25–30 °C) for 2 h; the separated solid was filtered, washed with water, and dried. In the case of **21**, the workup was different. In this case, dry ether was added to the reaction mixture and the solid obtained after trituration was filtered and dried. All of the compounds were recrystallized from hot methanol.

2,6-Dimethyl-3,5-bis(methoxycarbonyl)-4-(4′-formylphenyl)-1,4-dihydropyridine (23). To a solution of **18** (2.2 g, 0.006 mol) in methanol (7.0 mL) was added concentrated hydrochloric acid (0.5 mL) and the mixture was stirred at room temperature (20–22 °C) for 1 h. Upon addition of ice water (10.0 mL), a solid separated out which was filtered, washed with water, and recrystallized from chloroform–hexane.

4-(3,4-Diaminophenyl)-2,6-dimethyl-3,5-bis(methoxycarbonyl)-1,4-dihydropyridine (24). To a suspension of **16** (1.0 g) in methanol (100 mL) was added Raney Ni (~0.2 g) and the mixture was hydrogenated at 2.5 kg/cm^2 for 2 h. The catalyst was filtered off, the solvent was removed under reduced pressure, and the residue was triturated with water. The solid so obtained was filtered, dried, and recrystallized from aqueous methanol.

2,6-Dimethyl-3,5-bis(methoxycarbonyl)-4-(substituted phenyl)-1,4-dihydropyridines (25 and 26). General Procedure. A mixture of **14** (3.8 g, 0.01 mol) and aqueous ammonia or methylamine (0.04 mol) in methanol (20.0 mL) was heated in a steel bomb at 150 °C for 24 h. The volume of the reaction mixture was reduced to 10 mL and to this was added water (20 mL) and the mixture was allowed to stand at room temperature for 3 h. The separated solid was filtered, washed with water, and dried. These compounds were recrystallized from aqueous methanol.

4-[4-(Benzylamino)-3-nitrophenyl]-2,6-dimethyl-3,5-bis(methoxycarbonyl)-1,4-dihydropyridine (27). A mixture of **14** (3.0 g, 0.01 mol) and benzylamine (6.3 mL, 0.06 mol) was heated at 110 °C, with stirring for 8 h. Water was then added to the reaction mixture and it was extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and concentrated to dryness. The oil so obtained on trituration with petroleum ether–benzene yielded a solid, which was recrystallized from a chloroform–petroleum ether mixture.

Hydrogenation of 26 and 27. The procedure was essentially the same as that described for **16**, and diamines so obtained were

used for the next step without purification.

Methyl 5-[2,6-Dimethyl-3,5-bis(methoxycarbonyl)-1,4-dihydropyrid-4-yl]-1-substituted-benzimidazole-2-carbamate (28–30). General Procedure. A mixture of the corresponding diamines (0.001 mol), *N,N'*-bis(methoxycarbonyl)-*S*-methylisothiourea (0.001 mol), and a catalytic amount of *p*-TSA in methanol (5 mL) was refluxed for 4 h. The reaction mixture was diluted with water. The solid so obtained was filtered, washed with water, and dried. These compounds (**28–30**) were recrystallized from aqueous methanol.

2-Aryl-6-[2,6-dimethyl-3,5-bis(methoxycarbonyl)-1,4-dihydropyrid-4-yl]-1-(substituted benzyl)benzimidazole (31–35). General Procedure. A mixture of **24** (0.33 g, 0.001 mol) and substituted benzaldehyde (0.002 mol) in glacial acetic acid (2 mL) was heated on a water bath for 4 h. Water was then added to the reaction mixture and it was extracted with ethyl acetate. Usual workup of the organic layer yielded a residual mass, which on trituration with petroleum ether furnished the solid. The compounds **31–35** were recrystallized from aqueous methanol.

5-[2,6-Dimethyl-3,5-bis(methoxycarbonyl)-1,4-dihydropyrid-4-yl]benzotriazole (36). To a solution of **24** (0.66 g, 0.002 mol) in acetic acid (2 mL) was added water (2 mL) and to this mixture was added a solution of sodium nitrate (0.41 g, 0.006 mol) in water (1 mL), with cooling (5–10 °C) and stirring. It was stirred with cooling for 15 min and then it was heated at 80–90 °C for 1.5 h. The reaction mixture was poured onto crushed ice. The separated solid was filtered, washed with water, dried, and recrystallized from aqueous methanol.

6-[2,6-Dimethyl-3,5-bis(methoxycarbonyl)-1,4-dihydropyrid-4-yl]-2,3-diphenylquinoxaline (37). A mixture of **24** (0.33 g, 0.001 mol) and benzil (0.21 g, 0.001 mol) in methanol (5 mL) was refluxed with stirring for 5 h. Water was then added to the reaction mixture and the separated solid was filtered, washed with water, dried, and recrystallized from aqueous methanol.

2,3-Dihydro-5-[2,6-dimethyl-3,5-bis(methoxycarbonyl)-1,4-dihydropyrid-4-yl]-2-thioxobenzimidazole (38). To a solution of **24** (0.33 g, 0.001 mol) in ethanol (2 mL) and water (2 mL) was added carbon disulfide (2 mL). The reaction mixture was heated with stirring at 60 °C for 6 h. Water was then added to it and the separated solid was filtered, washed with water, dried, and recrystallized from aqueous DMF.

10,10a-Dihydro-2-[2,6-dimethyl-3,5-bis(methoxycarbonyl)-1,4-dihydropyrid-4-yl]-10-oxoisoindolo[3,2-*a*]benzimidazole (39). A mixture of **24** (0.33 g, 0.001 mol) and phthalic anhydride (0.14 g, 0.001 mol) in methanol (5 mL) was refluxed for 10 h. Water was added to the reaction mixture, and the separated solid was filtered, washed with water, dried, and recrystallized from aqueous methanol.

Pregnancy-Interceptive Activity. Syrian golden hamsters of the Institute's animal colony weighing 85–120 g were used. Animals were maintained in air-conditioned quarters at 21 ± 2 °C and 70% humidity, with a regulated photoperiod (14 h light/10 h dark) and were provided pelleted diet (Hindustan Lever Ltd., India) and ad lib. tap water. Females were mated with coeval males (4:2 ratio) of proven fertility and the presence of sperm in a vaginal smear on the following morning was considered as day 1 of gestation.

Compounds were administered (subcutaneously, sc) either by initially solubilizing them in 100% ethanol and adding the desired amount of olive oil and then evaporating the ethanol on a water bath or by macerating, (compounds that did not dissolve in ethanol) then in 0.1–0.2 mL of Tween-80[2] and then by suspending the mixture in the required quantity of triple-distilled water.

Mated females were injected (sc) with compounds in respective dosage (Table II) on days 3–8 postcoitum (pc) and autopsied on day 12 pc. The number of implantations, resorbing fetuses, and/or endometrial scars were recorded. Potentiality percentage was calculated by dividing the number of animals showing resorbing fetuses, dead fetuses, or endometrial scars against the animals showing normal/live embryos. Animals with no sign of implantation or having apparently normal-looking uteri and the absence of corpora lutea were not included.

Progesterone Receptor Binding Affinity. Immature female rabbits (1000 g) and hamsters (20–25 g) were primed with estradiol-17β (sc; 100 μg/rabbit and 1 μg/hamster) for 3 days and autopsied 24 h after the last injection.

Uterine homogenate was prepared in 50 mM Tris·HCl buffer at pH 7.4 containing 1 mM EDTA, 1 mM mercaptophenol, and 10% glycerol and centrifuged at 105000*g* for 60 min at 4 °C to obtain cytosol.

Test compounds were evaluated for binding affinity to progesterone receptor through a competition assay, described earlier.[3] The compounds were incubated with [^{3}H]progesterone and cytosol receptors (preincubated with 500-fold molar excess of cortisol). Uterine cytosol (200 μL, prepared in TEMG buffer, pH 7.4) was incubated in triplicate with radiolabeled progesterone with or without test compounds for 3 h at 4 °C. Following incubation, bound and free steroids were separated by addition of dextran-coated charcoal at 4 °C. The radioactivity was assessed in the bound fraction and percent inhibition in [^{3}H]progesterone binding was calculated.

Registry No. **1**, 1571-08-0; **2**, 121497-02-7; **3**, 16588-34-4; **4**, 122-85-0; **5**, 51818-99-6; **6**, 623-27-8; **7**, 40681-88-7; **8**, 73568-25-9; **9**, 121497-03-8; **10**, 121497-04-9; **11**, 3458-28-4; **12**, 121497-05-0; **13**, 121497-06-1; **14**, 51384-20-4; **15**, 121497-07-2; **16**, 121497-08-3; **17**, 115951-97-8; **18**, 121497-09-4; **19**, 121497-60-7; **20**, 121497-11-8; **21**, 121497-12-9; **22**, 121497-13-0; **23**, 121497-14-1; **24**, 121497-15-2; **25**, 105572-51-8; **26**, 121497-16-3; **27**, 121497-17-4; **28**, 121497-18-5; **29**, 121497-19-6; **30**, 121524-32-1; **31**, 121497-20-9; **32**, 121497-21-0; **33**, 121524-33-2; **34**, 121497-22-1; **35**, 121497-23-2; **36**, 121497-24-3; **37**, 121497-25-4; **38**, 121497-26-5; **39**, 121497-27-6; PhCHO, 100-52-7; *p*-MeOC$_6$H$_4$CHO, 123-11-5; 3,4-(MeO)$_2$C$_6$H$_3$CHO, 120-14-9; 3-MeO,4-HOC$_6$H$_3$CHO, 121-33-5; 3,4-OCH$_2$OC$_6$H$_3$CHO, 120-57-0; 2,4-dimethoxy-4'-methylbenzophenone, 78589-05-6; 4-(4-acetamidophenyl)-2,5-dimethyl-3-(methoxycarbonyl)furan, 89447-05-2; methyl β-aminocrotonate, 14205-39-1; 4-[4-(methylamino)-3-aminophenyl]-2,6-dimethyl-3,5-bis(methoxycarbonyl)-1,4-dihydropyridine, 121497-28-7; 4-[4-(benzylamino)-3-aminophenyl]-2,6-dimethyl-3,5-bis(methoxycarbonyl)-1,4-dihydropyridine, 121497-29-8; *N,N'*-bis(methoxycarbonyl)-*S*-methylisothiourea, 34840-23-8; benzil, 134-81-6; phthalic anhydride, 85-44-9.