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Design, Synthesis and Pregnancy-Terminating Activity of 2-Aryl Imidazo[2,1-*a*]isoquinolines

SHANG, Zhi-Cai*[,a](商志才) HU, Gui-Xiang[a,b](胡桂香) WU, Tian-Xing[a](吴天星)
FANG, Yui-Ying[c](方瑞英) YU, Qing-Sen[a,b](俞庆森)

[a]*Department of Chemistry, Zhejiang University, Hangzhou, Zhejiang 310027, China*
[b]*Ningbo Institute of Technology, Zhejiang University, Ningbo, Zhejiang 315104, China*
[c]*Department of Pharmacology, Zhejiang University, Hangzhou, Zhejiang 310031, China*

In order to clarify the structural requirement of pregnancy-terminating drugs, the quantitative structure-activity relationship (QSAR) of 2-aryl imidazo[2,1-*a*]isoquinolines was studied on the basis of quantum mechanical calculation and multiple regression analysis. A Good correlation equation was obtained (r^2=0.925, q^2=0.871). Some new compounds were designed according to the equation. Two of them, compounds **21** and **22**, were synthesized and evaluated in NIH mice. The results showed that the difference of activity between **21** (median effective dose ED_{50}=0.943 mg/kg/day) and **22** (ED_{50}=1.099 mg/kg/day) was small and both of them were potent. It is also agreed with the computational results. Compared with L14105 which is the most potent pregnancy-terminating agent, these two compounds possess high activity. The evaluation of the anti-implanting activity showed that they were 100% effective at tested dosage 50.0, 25.0, 12.5 mg/kg/day×3 days in oral administration, which proved the both of them had anti-implanting activity and low first-pass effects.

Keywords 2-aryl imidazo[2,1-*a*]isoquinolines, quantitative structure-activity relationship (QSAR), pregnancy-terminating activity, anti-implanting, first-pass effect

Introduction

Symmetrical trizol bioisosterisms, such as 2-aryl pyrazolo[5,1-*a*]isoindoles and isoquinolines, pyrazolo-[1,5-*a*]indoles and quinolines, 2-aryl imidazo[2,1-*a*]-isoquinolines and isoindoles, 3,5-diaryl-*s*-triazoles, were shown to be active as non-hormonal post-implantation contragestational agents in various animal species after parenteral administration.[1-7] Some compounds had good oral activity.[8] Among them, **DL204-IT**[9] [2-(3-ethoxyphenyl)-5,6-dihydro-s-triazole[5,1-*a*]isoquinoline], **DL-111-IT**[10,11] [3-(2-ethylphenyl)-5-(3-methoxyphenyl)-1H-1,2,4-triazole] and **L14105**[8] [2-(1,1'-biphenyl-4-yl)-*s*-triazole[5,1-*a*]isoquinoline] show high pregnancy-terminating activity in various animal species. Their structures were shown in Figure 1. **DL204-IT**, when administered subcutaneous (s.c.) or intramuscular (i.m.) in single or multiple non-toxic doses, terminated pregnancy in all the species studied, including rat, hamster, rabbit, dog, rhesus monkey and baboon. The experiments showed that **DL111-IT** possessed little embryotoxicity and teratogenicity except retarded ossification of skull and slightly delayedness of development at dosage below terminating early pregnancy and did not induce behavioral teratogenicity of offsprings.[12-14] In particular, compound **L14105**, which had very high subcutaneous and high oral activity, appeared to be the least affected by metabolic deactivation. In order to clarify the structural requirement of non-hormonal pregnancy-terminating drugs, Our group studied the quantitative structure-activity relationship (QSAR) of 2-aryl imidazo[2,1-*a*]isoquinolines on the basis of the favorable results obtained from symmetrical trizol bioisosterisms. Some new compounds were designed. Two of them were synthesized and their pregnancy-terminating activity was tested.

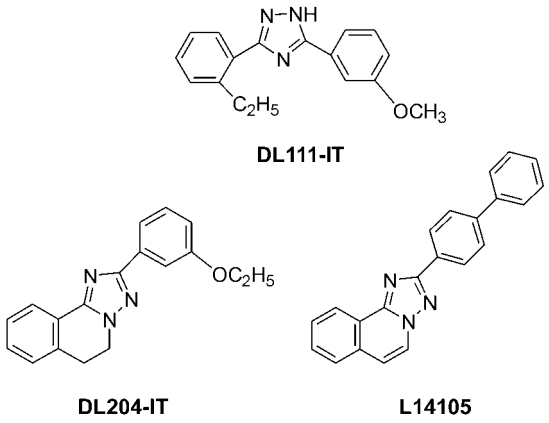

Figure 1 Structures of **DL111-IT**, **DL204-IT** and **L14105**.

* E-mail: shangzc@mail.hz.zj.cn
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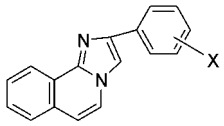
Computational methods

The entire set of 18 compounds taken from the reference[7] was calculated by Chem3D software (version 5.0). Conformational analysis was performed by AM1 quantum mechanics. In order to obtain the low energy conformation of the 2-aryl imidazo[2,1-*a*]isoquinolines, the compounds, whose substituent was not at the *p*-position of the substituted benzene ring, were considered to have two stable conformations, that is, the dihedral angles, defined by the imidazo[2,1-*a*]isoquinolines plane and the benzene ring plane, were more or less than 90°. So 27 conformations were computed and the lower one was obtained.

Parameters/descriptors of the molecules, derived from the AM1 calculated data, were: the eigenvalue of the highest occupied molecular orbital in eV units (E_{HOMO}), the eigenvalue of the lowest unoccupied molecular orbital in eV units (E_{LUMO}), the frontier electronic density (f_p) of *p*-carbon of the substituted benzene ring and the distance (*ID*) between *p*-carbon and the adjacent atom of the substituent. For compound **1**, *ID* represents the distance between *p*-carbon and the adjacent hydrogen atom. The hydrophobic parameters π of the substituent were taken from Hansch *et al.*[15] and were additive if there were more than one substituent in the molecule. *I* was the topological charge index, which was obtained from a corrected adjacency matrix. Structures of compounds and values of the parameters calculated for each compound are listed in Table 1.

Table 1 Structures, experimental, calculated and predicted values of 2-aryl imidazo[2,1-*a*]isoquinolines and the values of their descriptors



Compound	X	log(1/ED$_{50}$)		E_{HOMO}/ eV	E_{LUMO}/ eV	$\Sigma\pi^d$	f_p	*ID*	*I*
		Exp.[a]	Calcd. / pred.						
1	H	2.98998	3.11337	−8.40018	−0.57076	0.00	0.08788	1.099503	0.037
2	2-OCH_3	2.13723	2.18150	−8.20929	−0.44644	−0.02	0.07418	1.099884	0.089
3	3-OCH_3	3.11604	2.92925	−8.41788	−0.60683	−0.02	0.12476	1.098480	0.117
4	4-OCH_3	2.89419	2.78616	−8.20781	−0.54665	−0.02	0.10340	1.381470	0.127
5	3-Cl	2.26911	2.37685	−8.53716	−0.66634	0.71	0.08266	1.099884	0.117
6	4-Cl	3.84314	3.78264	−8.48334	−0.68088	0.71	0.09252	1.700485	0.095
7	4-Br	3.81049	4.06236	−8.53162	−0.71002	0.86	0.08981	1.872574	0.095
8	4-F	3.41878	2.99325	−8.46019	−0.67528	0.14	0.09342	1.354477	0.095
9	4-CH_3	2.71319	3.65719[c]	−8.30985	−0.55762	0.56	0.10585	1.480377	0.095
10	4-C_6H_5	4.20465	3.86458	−8.28958	−0.62438	1.96	0.10971	1.461182	0.138
11	4-NO_2	1.28524	1.19599	−8.91887	−1.22057	−0.28	0.05934	1.484497	0.183
12	3,4-Cl_2	2.92761	3.07280	−8.59564	−0.76656	1.42	0.08946	1.695877	0.176
13	3,4-OCH_2O	3.06192	3.12848	−8.33100	−0.63993	−0.05	0.11930	1.390976	0.127
14	3-OH	2.41547	2.46527	−8.46021	−0.63667	−0.67	0.11774	1.098282	0.117
15	3-OC_2H_5	2.76095	2.84315	−8.39543	−0.59997	0.38	0.12922	1.098480	0.148
16	3-OC_3H_7	2.78158	3.15297	−8.39849	−0.59758	1.05	0.12864	1.098495	0.148
17	3-OAllyl	3.07970	2.94400	−8.42717	−0.61413	0.79[e]	0.12474	1.098495	0.148
18	4-CN	1.95313	2.03715	−8.67878	−0.85599	−0.57	0.07805	1.420883	0.127
19	2-Cl	1.44520[b]	2.39597[c]	—	—	0.71	0.04986	1.099884	0.057
20	2,5-$(OCH_3)_2$	1.48337[b]	1.98988[c]	—	—	−0.04	0.11071	1.098877	0.169
21	4-$CH_2CH_2CH_3$	—	3.76285[c]	—	—	1.55	0.10606	1.487808	0.127
22	2,4-$(CH_3)_2$	—	3.61970[c]	—	—	1.12	0.10337	1.480484	0.116

[a] Pregnancy-terminating activity in hamster taken from the reference.[7] [b] Inactive at the dose shown (0% of pregnancy terminated, >90% of live fetuses). [c] Predicted values according to the Eq. (2). [d] The values of π were taken from the reference.[15] [e] π was got from log *P* (allyl phenyl ether) − log *P* (benzene) = 0.79.

The pregnancy-terminating activity was expressed as log ($1/ED_{50}$) (median effective dose ED_{50}: mmol/kg/day, s.c., which terminate pregnancy in 50% of the animals). The vehicle was sesame oil containing 20% of benzyl benzoate.

E_{HOMO}, E_{LUMO}, f_p, *ID*, $\sum\pi$ and *I* were chose as independent variables to do multiple regression analysis. The relationship between activity and descriptors is given by Eq. (1):

$$\log(1/ED_{50}) = 0.211(0.829) + 0.480(0.134) \times \sum\pi - 10.550(2.394) \times I + 19.560(4.511) \times f_p + 1.336(0.384) \times ID$$
$$n = 18,\ r^2 = 0.835,\ q^2 = 0.776,\ S.E. = 0.330,$$
$$F(4,13) = 16.476 > F_{0.05} = 3.18 \quad (1)$$

Where *n* is the number of compounds submitted to the regression, r^2 is the correlation coefficient, q^2 the predictive ability of the model by leave-one-out cross-validation, *S.E.* the standard error, and *F* the overall statistical significance of the equation. In the model, it is found that compound **9** is outlier. Its predictive value by Eq. (1) is larger than *S.E.* value twice. So the compound was deleted to get the better Eq. (2) between activity and descriptors.

$$\log(1/ED_{50}) = -0.029(0.587) + 0.481(0.094) \times \sum\pi - 12.079(1.732) \times I + 21.513(3.215) \times f_p + 1.545(0.276) \times ID$$
$$n = 17,\ r^2 = 0.925,\ q^2 = 0.871,\ S.E. = 0.232,$$
$$F(4,12) = 36.744 > F_{0.05} = 3.26 \quad (2)$$

The process of drugs *in vivo* is very complicated. It includes absorption, transportation, metabolism, distribution, and excretion so on.[16] So it is too difficult to obtain the good mathematics model. The correlation coefficient r^2 of our model was 0.925, and the equation had four descriptors. The correlation between activity and descriptors was not very good compared with other models whose activity data were *in vitro*. Four descriptors were too much for 17 samples. But it could explain some problems for our system *in vivo*. The activity of drugs is related closely to its lipophilicity. In our model, high $\sum\pi$ values were beneficial to the activity of the compounds. This point was pertinent to the process of drugs *in vivo*. High lipophilicity could lead to good absorption and transportation, as well as bad metabolism and excretion. All these factors were advantageous to high activity. The topological charge index, *I*, was negatively correlated with the pregnancy-terminating activity. *I* was obtained from a corrected adjacency matrix and affected by charge property and molecular size. High *I* value demonstrated that there was electron-withdrawing group (*e.g.* NO_2, CN) or large group (*e.g.* OC_3H_7, OAllyl) in the molecule. Negative correlation between activity and *I* revealed that electron-contributing group or small group was beneficial to the activity. From Table 1, it could be found that electron-contributing group on the substituted benzene ring would result in high f_p values. f_p was positive correlation with $\log(1/ED_{50})$. It is suggested that electron-contributing group on the substituted benzene ring was favorable to the activity. These two points were in agreement with each other. f_p may be related to forming charge transfer complex between compound and its target. High f_p value is beneficial to forming charge transfer complex and further leads to high biological activity. When there was substituent at *p*-carbon of benzene ring, *ID* value was high. Positive correlation of *ID* with log ($1/ED_{50}$) demonstrated that the existence of substituent at *p*-carbon of benzene ring was advantageous to the pregnancy-terminating activity. This might be due to the metabolism of compound. Hydroxylation for metabolism often happened in *p*-carbon of substituted benzene ring. The existence of substituent at *p*-carbon of benzene ring could prevent from hydroxylation.

The Eq. (2) enabled us to conclude that the pregnancy-terminating activity of the 2-aryl imidazo[2,1-*a*]-isoquinolines is related to molecular hydrophobicity, charge property, frontier electronic density of *p*-carbon of the substituted benzene ring and the distance between *p*-carbon and the adjacent atom of the substituent. Hydrophobicity and *ID* are pertinent mainly to the transfer process of compounds *in vivo*. Charge property and frontier electronic density of *p*-carbon of the substituted benzene ring have some concerns with the interaction between compound and its target. The pregnancy-terminating activity of the 2-aryl imidazo[2,1-*a*]-isoquinolines is the synthetic action of these factors. The results also lead us to conclude that the steric effect of substituent on the activity is not too great.

For the four descriptors used in the model, the cross-correlations in *r* is as follows (Table 2):

Table 2 Cross-correlations in *r*

	I	f_p	*ID*
$\Sigma\pi$	0.244	0.194	0.318
I		0.140	0.137
f_p			0.392

The cross-correlation of descriptors was very low and the largest cross-correlation in *r* was only 0.392 between *ID* and f_p.

Compounds **19** and **20** were not regarded as regression samples for without established data. The activity of them was predicted with the Eq. (2). $\text{Log}(1/ED_{50})$ of compounds **19** and **20** was 2.39597, 1.98988 respectively. Although the deviation between experimental and predicted values was great, the low predicted value was coincident with the low experimental activity, which proved the Eq. (2) had some predictable functions. The calculated and predicted values of compounds are listed in Table 1.

Some new compounds were designed according to the Eq. (2). The computational method was the same as described 18 compounds. Two of them, **21** and **22** were

chose to synthesize on the basis of highly prediction values (3.76285, 3.61970, respectively) and cheap reactants as well as easy synthesis methods.

Chemistry

2-Aryl imidazo[2,1-*a*]isoquinolines **21** and **22** were prepared from isoquinoline and substituted phenacyl bromides as reported method[7] (Figure 2). By running the reaction of the quaternary salts with ammonium acetate in the presence of oxidant such as ferric chloride or cupric acetate in acetic acid at 150 ℃ for 6 h, good yields of 2-aryl imidazo[2,1-*a*]isoquinolines were obtained without any detectable formation of isomers. A possible explanation is that the unstable kinetic intermediate arising from the addition at the most electrophilic site (1-position of the isoquinolinium salt) is rapidly converted to the expected compound by the oxidising agent, thus avoiding the slower competing reaction at the 3-position of the isoquinolinium salt. In the synthesis of 4'-propylphenyl derivatives, 2-bromo-4'-propylacetophenone (**21b**) could not be extracted by reduced pressure distillation as it would melt at *ca.* 10 ℃. But it could be extracted by recrystallization from petroleum ether. 2-Bromo-2',4'-dimethylacetophenone (**22b**) precipitated after some of methanol and water was evaporated by reduced pressure distillation. Then white crystal was obtained by cooling the residual.

Pharmacology

The females were mated with males of proven fertility and the presence of spermatozoa in the vaginal smear was considered presumptive evidence of pregnancy (day 1 of gestation). The tested compounds were administered dissolved in refined tea oil. The animals received a daily intramuscular dosage on an mg/kg basis for 3 consecutive days, during the most effective time of pregnancy, that is, from day 4 to day 6 in NIH mice. The volume of vehicle employed for the intramuscular injection was 10 mg/kg/day. Groups of 8 animals were used for each dose level. The effects on gestation were examined on day 14. At autopsy the number of implantation sites and live fetuses were counted. The pregnancy was assumed to have been interrupted when no live fetuses were present in the uterus but on implantation sites (resorbing conceptuses or placental scars), indicating that the animals had been pregnant. The ED_{50}, the dose at which pregnancy is terminated in 50% of animals, was determined graphically.

Results and discussion

The pregnancy-terminating activity was evaluated in NIH mice after multiple intramuscular treatments. ED_{50} and 95% confidence intervals of **21** and **22** were obtained by Bliss method for different dosages and the results are reported in Table 3.

The difference of pregnancy-terminating activity between compound **21** (ED_{50}=0.943 mg/kg/day) and **22** (ED_{50}=1.099 mg/kg/day) was small, which was coincident with the computational results. In order to explain their activity, the two compounds were compared with L14105. L14105 was so far as the most potent symmetrical trizol bioisosterisms in hamster. Its pregnancy-terminating activity was evaluated in NIH mice after simple s.c. treatment on day 6 gestation, and its ED_{50} value was 3.297 mg/kg, 95% confidence intervals was 2.455—4.362.[17] The total ED_{50} of **21** and **22** were both about 3 mg/kg. The activity was not very different between intramuscular treatment and subcutaneous treatment.[9] It is reasonable to regard that **21** and **22** have very high pregnancy-terminating activity, since ED_{50} between tested compounds and L14105 was the same.

The anti-implanting activity of **21** and **22** were also evaluated. The animals received a daily oral dosage for 3 consecutive days from day 1 to day 3 gestation and were killed on day 12. At autopsy the number of implantation sites and live fetuses were counted. The results showed that two compounds were 100% effective at the tested dosage 50.0, 25.0, 12.5 mg/kg/day×3 days, indicating that the two tested compounds had high anti-implanting activity and low first-pass effects.[18]

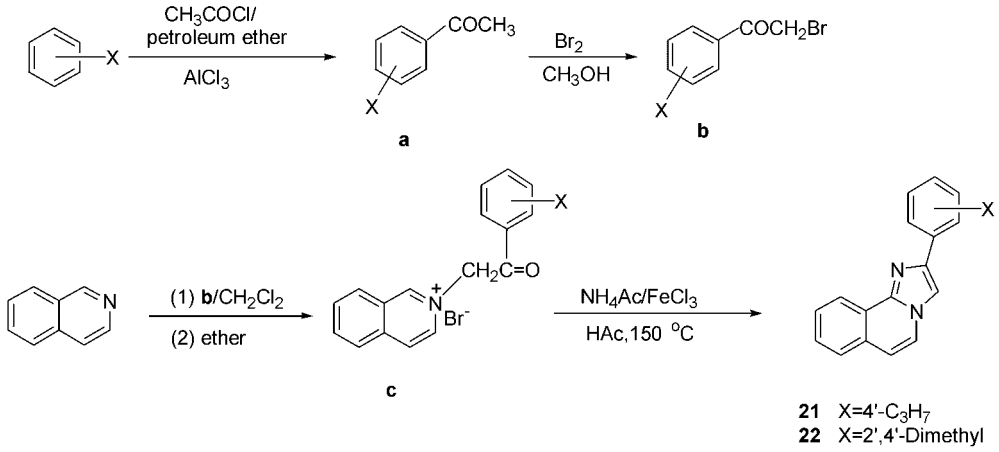


Figure 2 Synthetic procedure to compounds **21** and **22**.

Table 2 Pregnancy-terminating activity of compound **21** and **22** in NIH mice

Dose/ (mg/kg/day)	Treatment days of pregnancy	No. of NIH mice	Pregnancy termination (No. of animals)		ED_{50} & (95%confidence intervals)/ (mg/kg/day)	
			21	**22**	**21**	**22**
0.5	4—6	8	1	0		
0.7	4—6	8	2	2	0.943	1.099
1.0	4—6	8	4	4	(0.728—1.201)	(0.855—1.469)
1.4	4—6	8	6	5		
2.0	4—6	8	8	7		

Progesterone is necessary to regulate a normal cycle, promote embryo implantation, and maintain normal pregnancy in female.[19] It can stimulate endometrium luteinization and mitotic activity to establish an applicable surroundings for normal growth and the development of fertilized eggs. More or less progesterone will lead to pregnancy termination. During the implantation session of the blastula, it can not be implanted if progesterone is less or disappears. It has been proposed that serum progesterone concentration is relative to two enzymes:[20] 3β-hydroxysteroid dehydrogenase (3β-HSD) which is responsible for the conversion of pregnenolone to progesterone, and 20α-hydroxysteroid dehydrogenase (20α-HSD) which converts progesterone into 20α-dihydroprogesterone. The anti-implanting activity of **21** and **22** is probably performed by inhibiting the activity of 3β-HSD and then lowering the concentration of progesterone, which lead to blastula not being implanted.

Conclusion

Our mathematics model of 2-aryl imidazo[2,1-*a*]-isoquinolines possesses some predictable functions. Compared with **L14105**, the synthesized two compounds had good activity. The evaluation of anti-implanting activity proved the two tested compounds had high anti-implanting activity and low first-pass effects. The anti-implanting activity of the two tested compounds is probably performed by inhibiting the activity of 3β-HSD and then reducing the concentration of progesterone, which results in blastula not being implanted.

Experimental

Melting points were determined with a WRR apparatus and were not corrected. Infrared spectra were measured with a NICOLET DX spectrophotometer. NMR spectra were recorded on a Varian Em-360A spectrophotometer using CCl_4 as a solvent. Chemical shifts are expressed in δ units, downfield from tetramethylsilane as an internal standard. Elements analysis was determined with a CARLO-ERBA 1106 apparatus and analytical results were within $\pm$0.3% of the theoretical values. GC-MS data was obtained on HP5971MSD apparatus.

We take **21** as example to elaborate the synthesis of 2-aryl imidazo[2,1-*a*]isoquinolines.

4'-Propylacetophenone (21a)

To a solution of 4'-propylphenone (116 g, 0.965 mol) in 60—90 ℃ petroleum ether (100 mL) was added aluminium trichloride (145 g, 1.087 mol). The mixture was stirred and then acetyl chloride (90 g, 1.146 mol) was added dropwise within 1 h. At the same time the temperature was kept less than 20 ℃. After the reaction proceeded for 1 h, water (200 mL) was added dropwise at the temperature less than 50 ℃. The water layer was separated to remove the inorganic salts. Evaporation of petroleum ether under reduced pressure yielded 140 g (87.7%) **21a**.

2'-Bromo-4'-propylacetophenone (21b)

To a solution of **21a** (21 g, 0.129 mol) in methanol (140 mL) was added dropwise the solution of bromine (19.8 g, 0.124 mol) dissolved in methanol (80 mL) at the temperature less than 30 ℃ within 1 h. After the reaction was completed, water (75 mL) was added. The mixture was cooled to yield compound **21b**. The resulting precipitate was collected by filtration and recrystallized from petroleum ether, giving compound **21b** (29 g, 93.3%).

4'-Propylpheacyl isoquinolinium bromide (21c)

A solution of isoquinoline (14.5 g, 0.112 mol) and **21b** (18 g, 0.075 mol) in methylene chloride (75 mL) was refluxed for 3 h. Ether (30 mL) was added, followed by cooling to give 25.8 g (93.1%) of **21c**. Its melting point is 131.2—141.4 ℃.

2-(4'-Propylphenyl)imidazo[2,1-*a*]isoquinoline (21)

A mixture of **21c** (6.2 g, 0.017 mol), acetic acid (50.5 g, 0.841 mol), ammonium acetate (13 g, 0.169 mol) and iron trichloride (10 g, 0.062 mol) was stirred for 6 h at 150 ℃ (internal pressure: 3×10^5—4×10^5 Pa). After cooled to room temperature, the precipitated solid was filtered, washed with acetic acid, water, then taken up with methylene chloride and aqueous ammonia. The organic layer was condensed and 10% hydrochloric acid was added to the residue, precipitating the muriate of **21**. After filtration and extraction of the muriate with ether and aqueous ammonia, the ether layer was cooled to precipitate **21** which was dried to afford 2.5 g (52.2%)

21, m.p. 112.7—113.7 ℃. ^{1}H NMR (CCl_4, 60 MHz) δ: 0.96 (t, J=7.0 Hz, 3H, CH_3), 1.36—2.02 (m, 2H, CH_2), 2.58 (t, J=7.2 Hz, 2H, Ar-CH_2), 6.75 (d, J=6.4 Hz, 1H, CH-6), 7.02—7.60 (m, 7H, ArH), 7.70— 7.84 (m, 2H, overlapping peaks of CH-3 and CH-5), 8.56—8.73 (m, 1H, CH-10); IR (KBr) v: 3140, 3050, 3020, 2960, 2920, 2880, 1645, 1610—1450, 790 cm^{-1}; MS (*m/z*) (%): 286 (M^+, 56), 257 (100), 128 (31), 101 (5). Anal. calcd for $C_{20}H_{18}N_2$: C 83.88, H 6.34, N 9.78; found C 83.91, H 6.31, N 9.81.

22 m.p. 101.8—102.9 ℃; ^{1}H NMR (CCl_4, 60 MHz) δ: 2.32 (s, 3H, CH_3), 2.51 (s, 3H, CH_3), 6.80—7.50 (m, 7H, overlapping peaks of CH-6 and Ar-H), 7.73—7.85 (m, 2H, overlapping peaks of CH-3 and CH-5), 8.56—8.73 (m, 1H, CH-10); IR (KBr) v: 3120, 3010, 2920, 2860, 1645, 1610, 1520—1450, 1380, 790, 750, 700 cm^{-1}; MS (*m/z*) (%): 272 (M^+, 90), 271 (100), 128 (61), 101 (8). Anal. calcd for $C_{19}H_{16}N_2$: C 83.79, H 5.92, N 10.29; found C 83.77, H 5.81, N 10.15.

References

1 Neelima; Mehrotra, P. K.; Bhaduri, A. P.; Kamboj, V. P. *Indian J. Med. Res.* **1987**, *86*, 256.

2 Mehrotra, P. K.; Neelima; Bhaduri, A. P.; Kamboj, V. P. *Indian J. Med. Res.* **1986**, *83*, 614.

3 Lerner, L. J.; Galliani, G.; Carminati, P.; Mosca, M. C. *Nature* **1975**, *256*, 130.

4 Toja, E.; Omodei-Sale, A.; Cattaneo, C.; Galliani, G. *Eur. J. Med. Chem.* **1982**, *17*, 223.

5 Winters, G.; Odasso, G.; Conti, M.; Tarzia, G.; Galliani, G. *Eur. J. Med. Chem.* **1984**, *19*, 215.

6 Galliani, G.; Assandri, A.; Gallico, L.; Luzzani, F.; Oldani, C.; Omodei-Sale, A.; Soffientini, A.; Lancini, G. *Contraception* **1981**, *23*, 163.

7 Toja, E.; Omodei-Sale, A.; Favara, D.; Cattaneo, C.; Gallico, L.; Galliani, G. *Arzneim.-Forsch./Drug Res.* **1983**, *33*, 1222.

8 Galliani, G.; Cristina, T.; Guzzi, U.; Omodei-Sale, A.; Assandri, A. *J. Pharm. Dyn.* **1982**, *5*, 55.

9 Galliani, G.; Gallico, L.; Cattaneo, C.; Assandri, A. *Arzneim.-Forsch./Drug Res.* **1980**, *30*, 972.

10 Omodei-Sale, A.; Consonni, P.; Galliani, G. *J. Med. Chem.* **1983**, *26*, 1187.

11 Galliani, G.; Assandri, A.; Lerner, L. J.; Omodei-Sale, A.; Lancini, G.; Nock, P. E.; Grant, A. M. *Contraception* **1982**, *26*, 165.

12 Zhou, H.; Fang, R.; Yang, B.; Zhang, Y. *Contraception* **1991**, *43*, 287.

13 Ying, Y.; Fang, R. *Carcinogene, Teratogene, Mutagene* **1995**, *7*, 355 (in Chinese).

14 Ying, Y.; Fang, R.; Fan, Y.; Wang, Z. *Carcinogene. Teratogene. Mutagene.* **1996**, *8*, 25 (in Chinese).

15 Hansch, C.; Leo, A.; Unger, S. H.; Kim, K. H.; Nikaitani, D.; Lien, E. J. *J. Med. Chem.* **1973**, *16*, 1207.

16 Smith, D. A.; Jones, B. C.; Walker, D. K. *Med. Res. Rev.* **1996**, *16*, 243.

17 Ye, J.; Fang, R.; He, Q.; Wang, J. *Chin. J. Family Planning* **1998**, *3*, 104 (in Chinese).

18 Assandri, A.; Omodei-Sale, A.; Galliani, G. *Rev. Drug Metab. Drug Interact.* **1982**, *4*, 237.

19 Wynn, R. M. *Biology of the Uterus*, Translated by Zhou, S. People's Medical Publishing House, Beijing, **1982**.

20 Kuhn, B. N. T.; Briley, M. S. *Biochemistry* **1970**, *117*, 193.

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