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Synthesis and Pregnancy Terminating Activity of 2-Aryl imidazo [2,1-a] isoquinolines

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Abstract: Two 2-aryl imidazo [2,1-a] isoquinolines were synthesized and tested for pregnancy terminating activities. Both of them are new compounds and their structures were confirmed by IR, ^{1}HNMR, MS and elemental analysis. They both showed high activities in NIH mice.

Keywords: 2-Aryl imidazo [2,1-a] isoquinolines, synthesis, pregnancy terminating activity.

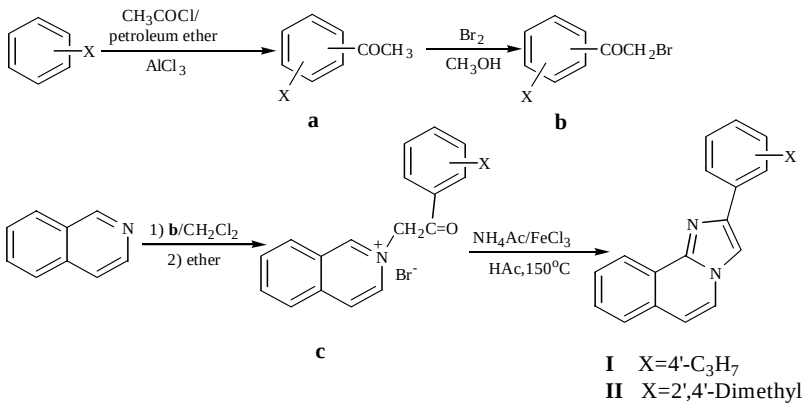
Several kinds of potential pregnancy terminating agents have been identified such as 2-aryl pyrazolo [5,1-a] isoindoles and isoquinolines[1], pyrazolo[1,5-a] indoles and quinolines[2], 3,5-diaryl-s-triazoles[3], 2-phenyl triazole, pyrozole, imidazole isoindoles and homologues[4] *etc*. In order to investigate their structure-activity relationship, the quantitative structure-activity relationship (QSAR) of 2-aryl imidazo [2,1-a] isoquinolines[5] has been studied with multiple regression and BP Artificial Neural Network[6]. We designed forty compounds based on the computational results and synthesized two of them: 2-(4'-propylphenyl)imidazo[2,1-a] isoquinoline **I** and 2-(2',4'-dimethylphenyl)imidazo[2,1-a]isoquinoline **II**. Their structures were confirmed by IR, ^{1}HNMR, MS and elemental analysis.

The title compounds were prepared by the method in **scheme 1**.

General procedures for the preparation of compounds **I** and **II** were as follows: To a solution of substituted benzene in petroleum ether was added equimolar of aluminium trichloride. The mixture was stirred and then equimolar of acetyl chloride was added dropwise. After the reaction proceeded for 1 h, water was added and the water layer was separated to remove the inorganic salts. Evaporation of petroleum ether under reduced pressure yielded compound **a**. Equimolar quantity of bromine was added dropwise to the solution of **a** in methanol for 1 h. After the reaction was completed, water was added, and the mixture was cooled to yield compound **b**. Equimolar quantity of isoquinoline and **b** were heated to reflux for 3 h in CH_2Cl_2. Then ether was added, followed by cooling to give compound **c**. A mixture of **c**, acetic acid, ammonium acetate and iron trichloride (the molar ratio = 1:50:10:4) was stirred for 6 h at 150°C, then cooled to RT and filtered. The resulting filtrate was extracted with CH_2Cl_2 and aqueous ammonia. The organic layer was condensed and 10% hydrochloric acid was added to the residue, precipitating the hydrochloride of **I** or **II**. After filtration and

extraction of the hydrochloride with ether and aqueous ammonia, the ether layer was cooled to precipitate **I** or **II**.

Scheme 1



I X=4'-C_3H_7
II X=2',4'-Dimethyl

Both I and **II** showed excellent pregnancy terminating activities in NIH mice, ED_{50} **I** = 0.943 mg/kg/day; ED_{50} **II** = 1.099 mg/kg/day.

References and note

1. E. Toja, A. Omodei-Sale, C. Cattaneo, G. Galliani, *Eur. J. Med. Chem.*, **1982**, *17* (3), 223.
2. G. Winters, G. Odasso, M. Conti, G. Tarzia, G. Galliani, *Eur. J. Med. Chem.*, **1984**, *19* (3), 215.
3. A. Omodei-Sale, P. Consonni, G. Galliani, *J. Med. Chem.*, **1983**, *26* (8), 1187.
4. A. Assandri, A. Omodei-Sale, G. Galliani, *Rev. Drug Metab. Drug Interact.*, **1982**, *4*, 237.
5. E. Toja, A. Omodei-Sale, D. Favara, C. Cattaneo, L. Gallico, G. Galliani, *Arzneim.-Forsch./Drug Res.*, **1983**, *33* (9), 1222.
6. Z. C. Shang, *The Dissertation of Ph. D.*, Zhejiang University, **1998**, p41.
7. The data of compound Ⅰ and Ⅱ have deposited in the editorial office of CCL.
   Compound **I**: mp: 112.7~113.7℃; IR (KBr cm^{-1}): 3140, 3050, 3020, 2960, 2920, 2880, 1645, 1610 ~ 1450, 790; ^{1}HNMR (60MHz, CCl_4 ppm) δ : 0.96 (t, J = 7.0Hz, 3H, C**H**$_3$), 1.66 (m, 2H, C**H**$_2$), 2.58 (t, J = 7.2Hz, 2H, Ar-C**H**$_2$), 6.75 (d, J = 6.4Hz, 1H, C**H**-6), 7.02~7.60 (m, 7H, Ar**H**), 7.70~7.84 (m, 2H, overlapping peaks of C**H**-3 and C**H**-5), 8.65 (m, 1H, C**H**-10); 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%.
   Compound **II**: mp: 101.8 ~ 102.9℃; IR (KBr cm^{-1}): 3120, 3010, 2920, 2860, 1645, 1610, 1520 ~ 1450, 1380, 790, 750, 700; ^{1}HNMR (60MHz, CCl_4 ppm) δ : 2.32 (s, 3H, C**H**$_3$), 2.51 (s, 3H, C**H**$_3$), 6.80 ~ 7.50 (m, 7H, overlapping peaks of C**H**-6 and Ar-**H**), 7.73 ~ 7.85 (m, 2H, overlapping peaks of C**H**-3 and C**H**-5), 8.65 (m, 1H, C**H**-10); 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%.

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