# 2-芳基-3-吲哚取代乙酰胺类衍生物的合成及抗焦虑活性

周　勇*, 杨洪菊, 殷明昭, 姚霞君, 恽榴红

(军事医学科学院毒物药物研究所, 北京 100850)

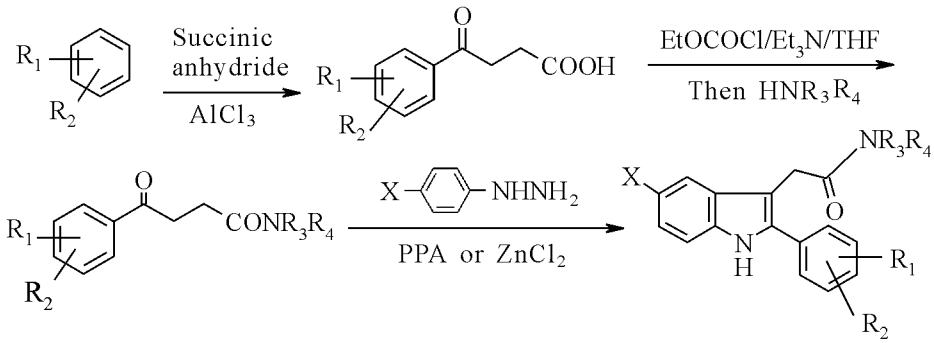
摘要: 目的　合成 2-芳基-3-吲哚取代乙酰胺类化合物,从中筛选有抗焦虑作用而无镇静、肌松等副作用的活性化合物。方法　由取代苯和琥珀酸酐经傅-克反应得到取代苯甲酰基丙酸,取代苯甲酰基丙酸和氯甲酸乙脂生成混合酸酐,再和相应的胺反应得到取代酰胺,取代酰胺和取代苯肼经费歇尔反应得到目标化合物。结果　得到新化合物 20 个。结论　初步受体结果表明,多数化合物均与外周苯二氮䓬受体有较强结合,在小鼠高架十字迷宫试验中发现一些化合物有明显的抗焦虑作用,且不能拮抗印防己毒素(PTX)诱发的惊厥作用,显示无镇静作用。

关键词: 吲哚衍生物; 抗焦虑; 外周苯二氮䓬受体

中图分类号: R916.41; R916.62; R962.2　　文献标识码: A　　文章编号: 0513-4870(2001)12-0902-04

焦虑和抑郁严重影响人们的日常生活,长期患病会引发其他相关疾病;在军事上,应激性心理异常会削弱部队的战斗力。传统的安定类抗焦虑剂在抗焦虑的同时会产生镇静、肌松等副作用,限制了他们的使用。受体和分子生物学研究发现,在神经中枢中,苯并二氮䓬除了在 $GABA_A$ 受体上存在结合位点外,还与另外一类受体结合,这类受体位于线粒体的外膜上,和一种内源性多肽有着高度的亲和性,被称之为外周苯二氮䓬受体。目前,对这种受体的结构及与配体的结合位点等正在深入研究中[1]。外周苯二氮䓬受体与适当的配体结合后,能刺激线粒体分泌类固醇,调节生物的行为,表现出明显的抗焦虑作用,且无镇静、肌松等副作用。

在基于外周苯二氮䓬受体药物的研究中,吲哚类化合物有重要作用,本研究组合成了一系列 2-芳基-3-吲哚取代乙酰胺类化合物,探索取代胺、吲哚上取代基和 2 位苯环上取代基对化合物活性的影响。对这些化合物进行了外周苯二氮䓬受体竞争性抑制试验,发现多数化合物对外周苯二氮䓬受体有较高的结合率,在小鼠高架十字迷宫试验中发现一些化合物有明显的抗焦虑作用,且不能拮抗印防己毒素(PTX)诱发的惊厥作用。化合物的合成路线见图 1,各化合物的结构、物理常数及元素分析结果见表 1,均为新化合物,并经 IR, $^1$HNMR, MS 和元素分析确证(表 2)。




Scheme 1　Route of synthesis of compounds **1 - 20**

X: Br, $NO_2$; $R_1$, $R_2$: F, Cl, $CH_3$; $R_3$, $R_4$: See table 1

收稿日期: 2001-04-20.

基金项目: 全军医药卫生科研基金资助项目(9960626).

作者简介: 周　勇(1972 - ),男,博士研究生;

恽榴红(1944 - ),男,研究员,博士生导师.

* Tel: (010) 66931643, Fax: (010) 68211656, E-mail: hbzhouyong@bj163.com

**Table 1 Physical constants and elemental analysis of compounds 1 - 20**

| No. | $NR_3R_4$ | X | $R_1$ $R_2$ | Formula | MP/ ℃ | Found (calcd) / % | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | C | H | N |
| 1 | N(n-$C_3H_7$)$_2$ | H | 2′,4′-diF | $C_{22}H_{24}F_2N_2O$ | 142 - 143 | 71.18(71.35) | 6.43(6.53) | 7.47(7.56) |
| 2 | N(n-$C_6H_{13}$)$_2$ | H | 2′,4′-diF | $C_{28}H_{36}F_2N_2O$ | 132 - 134 | 74.11(74.01) | 7.95(7.93) | 6.22(6.17) |
| 3 | Piperidino | H | 2′,4′-diF | $C_{21}H_{20}F_2N_2O$ | 221.5 - 223 | 70.85(71.19) | 5.68(5.65) | 7.94(7.91) |
| 4 | Morpholino | H | 2′,4′-diF | $C_{20}H_{18}F_2N_2O_2$ | 183 - 184.5 | 67.49(67.41) | 5.00(5.06) | 7.79(7.87) |
| 5 | N(n-$C_6H_{13}$)$_2$ | H | 2′-Cl,4′-$CH_3$ | $C_{29}H_{39}ClN_2O$ | 112 - 114 | 74.86(74.57) | 8.58(8.42) | 5.89(6.00) |
| 6 | N(n-$C_6H_{13}$)$_2$ | H | 2′-$CH_3$,4′-Cl | $C_{29}H_{39}ClN_2O$ | 124 - 125 | 74.71(74.57) | 8.67(8.42) | 5.70(6.00) |
| 7 | N(n-$C_3H_7$)$_2$ | H | 2′-Cl,4′-$CH_3$ | $C_{23}H_{27}ClN_2O$ | 171 - 172 | 72.04(72.14) | 7.08(7.11) | 7.23(7.32) |
| 8 | N(n-$C_3H_7$)$_2$ | H | 2′-$CH_3$,4′-Cl | $C_{23}H_{27}ClN_2O$ | 174 | 72.10(72.14) | 7.18(7.11) | 7.35(7.32) |
| 9 | N[$CH(CH_3)_2$]$_2$ | H | 2′-Cl,4′-$CH_3$ | $C_{23}H_{27}ClN_2O$ | 237 - 238 | 72.05(72.14) | 7.16(7.11) | 7.38(7.32) |
| 10 | N[$CH(CH_3)_2$]$_2$ | H | 2′-$CH_3$,4′-Cl | $C_{23}H_{27}ClN_2O$ | 265 - 266 | 72.09(72.14) | 7.13(7.11) | 7.27(7.32) |
| 11 | Piperidino | H | 2′-Cl,4′-$CH_3$ | $C_{22}H_{23}ClN_2O$ | 169 - 170 | 72.20(72.02) | 6.28(6.32) | 7.34(7.64) |
| 12 | Piperidino | H | 2′-$CH_3$,4′-Cl | $C_{22}H_{23}ClN_2O$ | 162 | 72.51(72.02) | 6.35(6.32) | 7.65(7.64) |
| 13 | Morpholino | H | 2′-Cl,4′-$CH_3$ | $C_{21}H_{21}ClN_2O_2$ | 181 | 68.42(68.38) | 5.57(5.74) | 7.46(7.59) |
| 14 | Morpholino | H | 2′-$CH_3$,4′-Cl | $C_{21}H_{21}ClN_2O_2$ | 154 - 156 | 68.51(68.38) | 5.73(5.74) | 7.63(7.59) |
| 15 | Pyrrolidino | H | 2′-Cl,4′-$CH_3$ | $C_{21}H_{21}ClN_2O$ | 214 - 215 | 71.41(71.48) | 6.01(6.00) | 7.82(7.94) |
| 16 | N(n-$C_3H_7$)$_2$ | H | 3′,4′-diCl | $C_{22}H_{24}Cl_2N_2O$ | 185 - 186 | 65.59(65.68) | 5.75(5.76) | 6.86(6.96) |
| 17 | Piperidino | H | 3′,4′-diCl | $C_{21}H_{20}Cl_2N_2O$ | 264 - 265 | 65.01(65.12) | 5.26(5.20) | 7.31(7.23) |
| 18 | N(n-$C_3H_7$)$_2$ | 5-Br | 3′,4′-diCl | $C_{22}H_{23}BrCl_2N_2O$ | 115 - 116 | 65.59(65.68) | 5.75(5.76) | 6.86(6.96) |
| 19 | N(n-$C_3H_7$)$_2$ | 5-Br | 2′,4′-diF | $C_{22}H_{23}BrF_2N_2O$ | 132 - 133 | 59.20(58.81) | 5.15(5.16) | 5.98((6.23) |
| 20 | N(n-$C_6H_{13}$)$_2$ | 5-$NO_2$ | 2′,4′-diF | $C_{28}H_{35}F_3N_2O$ | 175 - 176 | 63.43(63.61) | 5.26(5.54) | 10.02(10.12) |

**Table 2 MS, $^1$HNMR and IR spectral data of compounds 1 - 20**

| No. | HNMR($CDCl_3$)/δ | IR(KBr)/$cm^{-1}$ | FAB-MS(m/z) |
|---|---|---|---|
| 1 | 8.28(s,1H),7.67(d,1H),7.61(q,1H),7.36(d,1H),7.28(t,1H),7.15(t,1H),6.97(m,2H),3.84(s,2H),3.26,3.13(tt,4H),1.65(b,4H),0.819,0.713(t,6H) | 3220,2966,1626,1260 | 471($M^+$) |
| 2 | 8.34(s,1H),7.66(d,1H),7.57(q,1H),7.32(d,1H),7.19(t,1H),7.11(t,1H),6.95(m,2H),3.8(s,2H),3.27,3.13(tt,4H),1.43 - 0.83(m,22H) | 3250,2940,1620 | 455($M^+$) |
| 3 | 8.27(s,1H),7.69(d,1H),7.56(q,1H),7.36(d,1H),7.22(t,1H),7.13(t,1H),6.09(m,2H),3.83(s,2H),3.33,1.5,1.26(10H) | 3500,2980,1630,1160 | 355($M^+$) |
| 4 | 8.31(s,1H),7.67(d,1H),7.52(m,1H),7.37(d,1H),7.25(t,1H),7.15(m,1H),7.00(m,2H),3.84(s,2H),3.53(b,4H),3.35(b,4H) | 3390,2950,1620,1200 | 357($M^+$) |
| 5 | 7.95(s,1H),7.76(d,1H),7.35 - 7.12(m,6H),3.65(s,2H),3.23(s,2H),3.01(s,2H),2.26(s,3H),1.39 - 0.84(m,24H) | 3210,2927,1619 | 467($M^+$) |
| 6 | 8.15(s,1H),7.76(d,1H),7.35 - 7.12(m,6H),3.65(s,2H),3.23(s,2H),3.01(s,2H),2.26(s,3H),1.39 - 0.84(m,24H) | 3209,2927,1618,1456 | 467($M^+$) |
| 7 | 8.12(s,1H),7.54(d,1H),7.33 - 7.12(m,6H),3.63(s,2H),3.23(t,2H),3.02(t,2H),2.25(s,3H),1.41(m,4H),0.82(t,3H),0.67(t,3H) | 3205,2960,1614,1456 | 383($M^+$) |
| 8 | 8.23(s,1H),7.79(d,1H),7.42 - 7.11(m,6H),3.76(s,2H),3.24(t,2H),3.05(t,2H),2.41(s,3H),1.44(q,2H),1.40(q,2H),0.82(t,3H),0.67(t,3H) | 3236,2967,1616,1456 | 383($M^+$) |
| 9 | 7.92(s,1H),7.78(d,1H),7.34 - 7.10(m,6H),3.65(s,2H),3.77(m,1H),3.25(m,1H),2.25(s,3H),1.33(d,3H),0.83(s,3H) | 3237,2929,1616,1448 | 383($M^+$) |
| 10 | 8.21(s,1H),7.77(d,1H),7.38 - 7.10(m,6H),3.96(s,2H),3.83(m,1H),3.28(m,1H),2.40(s,3H),1.33(d,3H),0.82(s,3H) | 3224,2966,1615,1456 | 383($M^+$) |
| 11 | 8.50(s,1H),7.75(d,1H),7.31 - 7.13(m,6H),3.63(s,2H),3.43(s,2H),3.11(S,2H),2.22(s,3H),1.46 - 1.38(m,6H) | 3290,2970,1626,1448 | 367($M^+$) |
| 12 | 8.33(s,1H),7.79(d,1H),7.35 - 7.11(m,6H),3.77(s,2H),3.46(s,2H),3.13(S,2H),2.41(s,3H),1.44 - 1.35(m,6H) | 3290,2970,1626,1448 | 367($M^+$) |
| 13 | 8.02(s,1H),7.72(d,1H),7.37 - 7.16(m,6H),3.66(s,2H),3.53(s,4H),3.32(s,2H),3.18(s,2H),2.25(s,3H) | 3253,2910,1623,1456 | 369($M^+$) |
| 14 | 8.32(s,1H),7.85(d,1H),7.45 - 7.20(m,6H),3.86(s,2H),3.58(s,4H),3.30(s,2H),3.24(s,2H),2.48(s,3H) | 3253,2916,1614,1456 | 369($M^+$) |
| 15 | 8.00(s,1H),7.73(d,1H),7.35 - 7.14(m,6H),3.62(s,2H),3.38(s,2H),3.17(s,2H),2.24(s,3H),1.78(s,4H) | 3268,2977,1618,1448 | 353($M^+$) |
| 16 | 8.67(s,1H),7.50(s,1H),7.49 - 7.01(m,6H),3.83(s,2H),3.36(t,2H),3.26(t,2H),1.60(m,4H),0.88(m,6H) | 3268,2962,1625,1457 | 403($M^+$) |
| 17 | 8.40(s,1H),8.13(s,1H),7.63 - 7.09(m,6H),3.85(s,2H),3.53(s,2H),3.32(s,2H),2.02(s,3H),1.66 - 1.34(m,6H) | 3237,2929,1616,1448 | 387($M^+$) |
| 18 | 9.43(s,1H),7.45(s,1H),7.23 - 6.67(m,6H),3.72(s,2H),3.46(t,2H),3.35(t,2H),1.72(m,4H),0.96(m,6H) | 3268,2929,1625,1457 | 483($M^+$) |
| 19 | 9.43(s,1H),7.45(s,1H),7.23 - 6.67(m,6H),3.72(s,2H),3.46(t,2H),3.35(t,2H),1.72(m,4H),0.96(m,6H) | 3253,2964,1625,1450 | 449($M^+$) |
| 20 | 9.34(s,1H),8.42(d,1H),7.7(q,1H),7.24(m,1H),7.07(d,1H),6.85(m,2H),3.77(s,2H),3.6(tt,4H),1.627(m,4H),0.92(t,6H) | 3250,2950,1630,1260 | 415($M^+$) |

对合成的 20 个化合物进行了体外受体竞争性抑制试验[2] ,结果( 表 3) 表明,在化合物吲哚 5 位上引入吸电子基如溴原子或硝基,能显著提高化合物与受体的结合能力,如 **18** ,**19** 和 **20** 。在受体实验的基础上,对部分活性相对较高的化合物进行小鼠高架迷宫实验[3] ,化合物 **1** ,**2** 和 **18** 在实验中表现出较明显的抗焦虑活性( 表 4) 。对化合物 **1** ,**2** 和 **18** 进行抗印防己毒素( PTX) 诱发的惊厥的实验,结果( 表 5) 表明他们不能拮抗印防己毒素( PTX) 诱发的惊厥( Dunnett's test) ,显示无镇静作用 。

**Table 3 Displacement of [$^3$H] PK 11195 binding from peripheral benzodiazepine receptor by compounds 1 - 20**

| Compd. | Concentration/ mol·L$^{-1}$ | Inhibition/ % | Compd. | Concentration/ mol·L$^{-1}$ | Inhibition/ % |
|---|---|---|---|---|---|
| 1 | $10^{-5}$ | 100 | 11 | $10^{-6}$ | 88 |
| 2 | $10^{-6}$ | 82 | 12 | $10^{-6}$ | 91 |
| 3 | $10^{-6}$ | 91 | 13 | $10^{-7}$ | 25 |
| 4 | $10^{-6}$ | 53 | 14 | $10^{-7}$ | 21 |
| 5 | $10^{-6}$ | 84 | 15 | $10^{-7}$ | 70 |
| 6 | $10^{-6}$ | 91 | 16 | $10^{-7}$ | 97 |
| 7 | $10^{-6}$ | 96 | 17 | $10^{-7}$ | 41 |
| 8 | $10^{-6}$ | 95 | 18 | $10^{-7}$ | 97 |
| 9 | $10^{-6}$ | 51 | 19 | $10^{-7}$ | 94 |
| 10 | $10^{-6}$ | 38 | 20 | $10^{-7}$ | 100 |

**Table 4 Antianxiey effects of compounds measured in the elevated-plus maze**

| Compd. | *n* | % of number in the open arms | % of time in the open arms |
|---|---|---|---|
| 1 | 10 | 41 ±22* | 29 ±29* |
| 2 | 9 | 38 ±23* | 44 ±75* |
| 3 | 6 | 25 ±13 | 9 ±6 |
| 16 | 7 | 26 ±20 | 22 ±22 |
| 18 | 10 | 43 ±19* | 47 ±42* |
| CMC | 10 | 18 ±17 | 21 ±42 |
| Diazepine | 10 | 51 ±20* | 47 ±42* |

* $P < 0.05$ compared with CMC ( Dunnett's test) ; Dose: 1 mg·kg$^{-1}$ ; CMC: 0.5 % Carboxymethyl cellulose sodium

**Table 5 Effect of compounds on picrotoxin-induced convulsions in mice ( *n* = 8)**

| Compd. | Dose/ mg·kg$^{-1}$ | Incubation period/s | Onset time of convulsions/s |
|---|---|---|---|
| 1 | 10 | 781 ±351 | 20 ±7 |
| 1 | 20 | 561 ±103 | 28 ±8 |
| 2 | 10 | 547 ±73 | 21 ±12 |
| 18 | 1 | 792 ±190 | 21 ±14 |
| 18 | 10 | 900 ±300 | 18 ±10 |
| 18 | 20 | 760 ±292 | 12 ±10 |
| CMC | | 710 ±218 | 23 ±9 |

## 实 验 部 分

熔点用天津分析仪器厂的 RY-1 型熔点测定仪测定,温度未校正。核磁共振仪为 JNM-GX 400 , Bruker ARX 400 或 INOVA-600 型仪器,TMS 为内标。质谱仪为 Zabspec 型仪器。红外分析仪为 Nicolet magna-IR$^{TM}$ spectromet 550 型。元素分析仪为 Carlo ERBA-1106 型。所用试剂均为市售分析纯和化学纯。薄层色谱硅胶( $GF_{254}$ ) 和层析硅胶( $H_{60}$ ) 为青岛海洋化工厂产品。

**1 2-(2 ,4-二氟苯基)-3-吲哚乙二正丙酰胺(1)的制备**

二氟苯( 228.2 g) 、丁二酸酐( 100 g) 、三氯化铝( 293.3 g) 和二硫化碳 500 mL 加热回流并搅拌 ,36 h 后停止反应,倒去二硫化碳,加水得糊状物,糊状物用饱和碳酸钠加热溶解,滤除固体,收集滤液,用 1 % HCl 水溶液中和得白色沉淀,滤集固体得 3-(2 ,4-二氟苯酰基) 丙酸 140 g 。取 3-(2 ,4-二氟苯酰基) 丙酸( 0.01 mol) 和三乙胺( 0.03 mol) 溶在四氢呋喃 25 mL 中,冷却到 - 40 ℃ 。搅拌溶液并逐滴加入氯甲酸乙酯( 0.01 mol) ,溶液在 - 20 ℃下继续反应 0.5 h ,然后加入二正丙胺( 0.01 mol) ,搅拌,在室温下继续反应 1 h 。所得悬浊液用硅胶柱进行色谱分离( 乙酸乙酯-石油醚 = 1∶2) ,收集洗脱液,蒸干得到酰胺。酰胺中加入苯肼( 0.02 mol) 、多聚磷酸 5 g 混合并用温度计搅拌,在外温 120 ℃油浴中慢慢加温,反应发生时内温突然上升,并有气体产生,在热浴中搅拌至反应平息[4] 。冷却后加入水 50 mL ,滤集固体,用乙酸乙酯重结晶或用硅胶柱进行色谱分离( 乙酸乙酯-石油醚 = 1∶5) ,得白色固体产物。同样方法得到化合物 **1 - 20** 。

致谢: 核磁氢谱 、质谱和元素分析由本院仪器中心测定。

**REFERENCES**:

[1] Zhou Y, Yun LH, Yao XJ. New antianxiety drugs acting at peripheral benzodiazepine receptor [J]. *Foreign Med Sci* (in Chinese) , 2001 ,**28**(2) :69 - 73 .

[2] Kozikowski AP, Ma D, Brewer J, *et al*. Chemistry ,binding affinities and behavioral properties of new class of antineophobic mitochondrial DBI receptor complex ligands [J]. *J Med Chem*, 1993 ,**36**(20) :2908 - 2920 .

[3] Pellow S, Chopin P, Sandra E, *et al*. Validation of open closed arm entries in an elevated plus-maze as a measure of anxiety in the rat [J]. *J Neurosci Methods*, 1985 ,**14**(3) :149 - 167 .

[4] Hughes DL. Progress in the Fischer indole reaction [J]. *Org Prep Proced*, 1993 ,**25**(6) :607 - 632.

# SYNTHESIS AND ANTIANXIETY ACTIVITY OF 2-ARYL-3-INDOLACETAMIDE DERIVATIVES

ZHOU Yong, YANG Hong-ju, YIN Ming-zhao, YAO Xia-jun, YUN Liu-hong

(*Academy of Military Medical Science, Institute of Pharmacology and Toxicology, Beijing 100850, China*)

**ABSTRACT**: **AIM** To search for antianxiety drugs with fewer side effects and improved activities. **METHODS** Reaction of aryl compounds with succinic anhydride to give benzoylpropionic acid. Then, the benzoylpropionic acid was converted to its mixed anhydride with ethyl chloroformate, and the intermediate reacted with the amine of choice to afford the corresponding amide. The amide was reacted with the appropriate phenylhydrazine and anhydrous zinc chloride. A series of 2-aryl-3-indolacetamides derivatives with different substituted groups in their phenyl rings and indole groups were synthesized. **RESULTS** Twenty new compounds have been synthesized. Their structures were confirmed by IR, $^1$HNMR, MS and elemental analysis. The antianxiety activities were screened. The structure-activity ralationship has been studied. **CONCLUSION** Most of the compounds was shown to bind to peripheral benzodiazepine receptor with high affinity. Several compounds exihbited marked antianxiety effects in animal experiments without seizure effects.

**KEY WORDS**: indole; antianxiety; peripheral benzodiazepine receptor