



A Facial Synthesis and Antimicrobial Activity of Some Pyrazole Derivatives Carrying Indole

K. NARASIMHA SARMA*, M.C.S.SUBHA and K.CHOWDOJI RAO

Department of Chemistry,
Sri Krishnadevaraya University, Anantapur-515003, A.P., India.

organic_sarma@rediffmail.com

Received 31 August 2009; Accepted 20 October 2009

Abstract: The title compounds (**7a-h**) were prepared by esterification of indole-5-carboxylic acid (**1**) and subsequent treatment with hydrazine hydrate in methanol *via* the hydrazide (**3**). Finally hydrazide (**3**) condensed with different substituted aldol (**6**) in acetic acid / PTSA catalytic media produced (3,5-substituted-4,5-dihydropyrazol-1-yl)(1*H*-indol-5-yl)methanone (**7a-h**) in good yields. All the newly synthesized compounds are by elemental analysis and spectral studies and evaluated for antimicrobial activities.

Keywords: Acid hydrazide, Chalkones, Pyrazole derivatives of indole, Schiff bases.

Introduction

The synthesis of condensed pyrazole heterocycles has been explored to a maximum extent owing to their association with wide spectrum of pharmacological activities such as antifungal^{1-2,5-7}, cytotoxicity³, anti-inflammatory⁴, antidepressant⁸⁻⁹ and antibacterial activity¹⁰⁻¹³. Encouraged by these facts and in continuation of our research program, synthesis of pharmacologically interesting pyrazole derivatives have been carried out. We report in this paper annulation of (3,5-substituted-4,5-dihydropyrazol-1-yl)(1*H*-indol-5-yl)methanone (**7a-h**) moiety and screening the compounds for antimicrobial activities.

Experimental

The melting points were determined in open capillaries. The purity of the compound was checked by the thin layer chromatography (TLC) on a silica-coated aluminum sheet (silica gel 60F₂₅₄) using dichloromethane and methanol (8:2, v/v). The IR spectra were recorded on a Nicolet Avatar 330-FTIR spectrometer. The ¹H- and ¹³C NMR (**5a**) spectra was recorded on a Varian 300 MHz NMR spectrometer using TMS as the internal standard the chemical shift (δ) are reported in ppm and the signals are described as singlet (*s*), doublet (*d*), triplet (*t*), quartet (*q*), broad (*br*) and multiplet (*m*). The FAB mass spectra were recorded on Jeol

SX 102/DA-6000 spectrophotometer/data system using argon/xenon (6 KV, 10 mA) FAB gas, at 70 eV. Elemental analysis was carried out a flash EA 1112 Series, CHNSO analyzer (Thermo). The solvent and reagents were purchased from commercial vendors in the appropriate grade and were used without purification.

Procedure for the preparation of methyl or ethyl 1H-indole-5-carboxylate (2)

To a solution of indole-5-carboxylic acid (**1**) (0.0015 mol), dry DMF and ethyl (or) methyl iodide (0.0015 mol) was added drop wise in 500 mL round bottom flask. Flask provided with a mechanical stirrer. The reaction mixture was stirred for 2-3 h at 20-25 °C, reaction monitored by TLC technique up to completion. After the reaction completed, ice water was added and stirred for 30 min. The crude indole ester isolated by filtration technique was purified by silica column chromatography technique with methanol and dichloromethane with good yield (96%). The ¹H NMR (300 MHz) spectra of methyl ester (**2**) recorded in DMSO-d₆ shows 1.33 ppm (t, 3H, -CH₃), 4.3 ppm (q, 2H, -CH₂).

Procedure for the preparation of 1H-indole-5-carbohydrazide (3)

To a solution of methyl or ethyl 1H-indole-5-carboxylate **2** (0.001 mol) in a dry methanol in 500 mL round bottom flask, hydrazine hydrate (0.0015 mole) was added. Flask provided with a mechanical stirrer. The reaction mixture was stirred for 3-4 h at 55-60 °C temperature, reaction monitored by TLC technique up to completion. After the reaction completed, methanol was removed by vacuum into that ice cold water was charged, solids collected by filtration technique, purified by silica column chromatography technique with methanol and dichloromethane with good yield (96%). The ¹H NMR (300 MHz) spectra of 1H-Indole-5-carbohydrazide (**3**) recorded in DMSO-d₆ shows disappearance of ester peaks and appearance of 4.4 ppm (2H, -NH₂), 9.5 ppm (1H, -CO-NH).

General procedure for the preparation of arylideneacetophenones (Chalkones) (6a-k)

To solution of 3 g of sodium hydroxide in 30 mL of water and 18 mL of ethyl alcohol in 500 mL round bottom flask. Flask provided with a mechanical stirrer, 7 mL of acetophenone was added. The reaction mixture cooled to 0-5 °C, into that 6 mL of pure aryl aldehyde was added. Stirred the reaction mixture for 3 h at 20-25 °C temperature, reaction was monitored by TLC technique up to completion. After the reaction completed, pH 6-7 was adjusted by using diluted hydrochloric acid. The reaction mixture washed with ether, ether layer was separated. The organic layer was dried by anhydrous Na₂SO₄ and stiff of the solvent using vacuum. The isolated crude chalkone was purified by silica column chromatography technique with methanol and dichloromethane with good yield (96%). The same procedure was followed for the preparation of all chalkones (**6a-h**).

General procedure for the preparation of (3,5-diphenyl-4,5-dihydropyrazol-1-yl)(1H-indol-5-yl)methanone (7a-h)

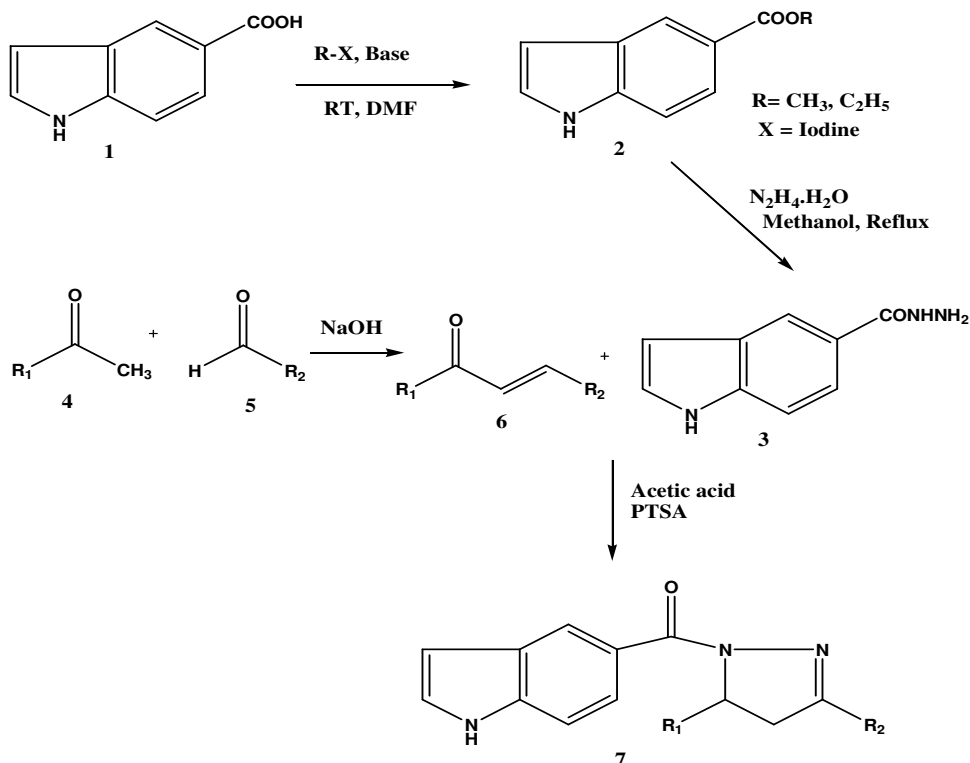
A mixture of compound (**3**) (0.01 mole) and benzylideneacetophenone (**6a**) (0.01 mole) taken in 500 mL round bottom flask. Flask provided with a mechanical stirrer, into that acetic acid (30 mL) and catalytically amount of *p*-toluenesulphonic acid (PTSA) was added. The reaction mixture was stirred for 6-8 h at 105-108 °C temperature, reaction monitored by TLC technique up to completion. After the completion of reaction, the mass cooled to room temperature and poured into ice cold water. The precipitate was collected by filtration technique, wet cake washed with water and recrystallized from ethanol to afford **7a**. The same procedure was followed for the preparation of all pyrazol derivatives of indoles (**7b-h**). The structure of **7a** was conformed by the analytical data given below.

(3,5-Diphenyl-4,5-dihydropyrazol-1-yl)(1H-indol-5-yl)methanone (7a)

Compound was obtained as a off-white crystalline solid; yield 79%, $^1\text{H NMR}$ (DMSO- d_6 , δ / ppm): 11.5(s, 1H, NH), 8.02 (s, 1H, Aromatic proton at 4th position) 7.3-7.73(m, 13H, -Ar-H), 6.55(s, 1H, 3rd position of five member ring) 3.02-3.15(m, 2H, -CH₂), 4.4(m, 1H, -CH), $^{13}\text{C-NMR}$ (DMSO- d_6): 29.89 (-CH of pyrazole ring), 43.12(CH₂ of pyrazole ring), 102.55(C3 of indole five member ring), 111.8 (C₆,C₇ of indole six member ring), 121.23 (C₄ of indole six member ring), 124.12 (C₂ of indole six member ring), 124.3 (C₅ of indole six member ring), 127-128.15 (Substituted benzene -CH), 128.31(C₉), 137.98 (C₈), 142.6 (-C of substituted benzene), 195.3(C=O), IR (KBr, cm⁻¹) 1705.93 (C=O), 1622.3 (C=N), LC-MS (m/z): 365.91 (M, 100%), M.p. 226-228 °C (Found: C, 78.99; H, 5.45; N, 11.69%. Calc. for C₂₄H₁₉N₃O; C, 78.88; H, 5.24; N, 11.50).

Results and Discussion

The reaction sequences employed for the synthesis of title compound is shown in Scheme 1. The key intermediates 1-(1H-indole-5-yl) propan-1-one (2), 1H-indole-5-carbohydrazide (3), Chalkones (6), required for the preparation of the target compounds was obtained by the indole-5-carboxylic acid (1) treated with alkyl halides in presence of base in polar solvents afforded ester (2) in a very good yields (96%). The ester compound (2) treated with the hydrazine hydrate in presence of alcohol (methanol, ethanol, etc.) gave acid hydrazide compound (3) in good yields (86%). The Compound (3) was reacted with chalkones (6) in presence of acetic acid / PTSA at reflux temperature to give target compound (7a-h) in good yields (79%).



Scheme 1.

The structural elucidation of new compounds were based on their elemental analysis and spectral (IR, ^1H NMR, mass) data. The characterization data of all the new compounds and their spectral data are given below.

(3,5-Diphenyl-4,5-dihydropyrazol-1-yl)(1H-indol-5-yl)methanone (7a)

The compound was obtained as a off-white crystalline solid; Yield 79%, ^1H NMR (DMSO-*d*₆, δ / ppm): 11.5(s, 1H, NH), 8.02 (s, 1H, Aromatic proton at 4th position) 7.3-7.73(m, 13H, -Ar-H), 6.55(s, 1H, 3rd position of five member ring) 3.02-3.15(m, 2H, -CH₂), 3.9-4.1(m, 1H, -CH), ^{13}C -NMR(DMSO-*d*₆): 29.89 (-CH of pyrazole ring), 43.12(CH₂ of pyrazole ring), 102.55(C3 of indole five member ring), 111.8 (C₆, C₇ of indole six member ring), 121.23 (C₄ of indole six member ring), 124.12 (C₂ of indole six member ring), 124.3 (C₅ of indole six member ring), 127-128.15 (Substituted benzene -CH), 128.31(C₉), 137.98 (C₈), 142.6 (-C of substituted benzene), 195.3(C=O), IR (KBr, cm⁻¹) 1705.93 (C=O), 1622.3 (C=N), LC-MS (*m/z*): 365.91 (M, 100%), M.p. 226-228 °C (Found: C, 78.99; H, 5.45; N, 11.69%. Calc. for C₂₄H₁₉N₃O; C, 78.88; H, 5.24; N, 11.50).

(1H-indol-5-yl)(5-phenyl-3-p-tolyl-4,5-dihydropyrazol-1-yl)methanone (7b)

The compound was obtained as a off-white crystalline powder; Yield 76%, ^1H NMR (DMSO-*d*₆, δ / ppm): 11.45(s, 1H, NH), 8.04 (s, 1H, Aromatic proton at 4th position) 7.13-7.75(m, 12H, -Ar-H), 6.65(s, 1H, 3rd position of five member ring), 3.02-3.15(m, 2H, -CH₂), 3.9-4.1(m, 1H, -CH), 2.36(s, 3H, -CH₃), IR (KBr, cm⁻¹) 1706 (C=O), 1624 (C=N), LC-MS (*m/z*): 380.21 (M, 100%) M.p. 231-232 °C, (Found: C, 79.01; H, 5.35; N, 11.35. Calc. for C₂₅H₂₁N₃O; C, 79.13, H, 5.58, N 11.07).

(1H-indol-5-yl)(3-(4-methoxyphenyl)-5-phenyl-4,5-dihydropyrazol-1-yl)methanone (7c)

The compound was obtained as a semi-solid; Yield 78%, ^1H NMR (DMSO-*d*₆, δ / ppm): 11.5(s, 1H, NH), 8.02 (s, 1H, Aromatic proton at 4th position) 7.03-7.75(m, 12H, -Ar-H), 6.55(s, 1H, 3rd position of five member ring) 3.02-3.15(m, 2H, -CH₂), 3.9-4.1(m, 1H, -CH), 3.86(s, 3H, -CH₃), IR (KBr, cm⁻¹) 1705 (C=O), 1622 (C=N), LC-MS (*m/z*): 396.12 (M, 100%) M.p. 238-239 °C, (Found: C, 76.01; H, 5.43; N, 10.49 .Calc. for C₂₅H₂₁N₃O₂; C, 75.93; H, 5.35; N, 10.63).

(1H-indol-5-yl)(3-(4-chlorophenyl)-5-phenyl-4,5-dihydropyrazol-1-yl)methanone (7d)

The compound was obtained as a off-white crystalline powder; Yield 77%, ^1H NMR (DMSO-*d*₆, δ / ppm): 11.49(s, 1H, NH), 8.03 (s, 1H, Aromatic proton at 4th position) 7.13-7.75(m, 12H, -Ar-H), 6.55(s, 1H, 3rd position of five member ring), 3.02-3.15(m, 2H, -CH₂), 3.9-4.1(m, 1H, -CH) IR (KBr, cm⁻¹) 1705 (C=O), 1622 (C=N), LC-MS (*m/z*): 400.11 (M, 100%), M.p. 242-243 °C, (Found: C, 72.41; H, 4.64; N, 10.41 .Calc. for C₂₄H₁₈ClN₃O; C, 72.09; H, 4.54; N, 10.51).

(1H-indol-5-yl)(3-phenyl-5-p-tolyl-4,5-dihydropyrazol-1-yl)methanone (7e)

The compound was obtained as a light-yellow white crystal solid; Yield 76%, ^1H NMR (DMSO-*d*₆, δ / ppm): 11.49(s, 1H, NH), 8.05 (s, 1H, Aromatic proton at 4th position) 7.03-7.95(m, 12H, -Ar-H), 6.6(s, 1H, 3rd position of five member ring), 3.02-3.15(m, 2H, -CH₂), 3.9-4.1(m, 1H, -CH), 2.36(s, 3H, -CH₃), IR (KBr, cm⁻¹) 1706.27 (C=O), 1624 (C=N), LC-MS (*m/z*): 380.21 (M, 100%), M.p. 231-232 °C, (Found: C, 79.01; H, 5.35; N, 11.35. Calc. for C₂₅H₂₁N₃O; C, 79.13; H, 5.58; N, 11.07).

(1H-indol-5-yl)(3,5-dip-tolyl-4,5-dihydropyrazol-1-yl)methanone (7f)

The compound was obtained as a off-white solid; Yield 78%, ^1H NMR (DMSO-*d*₆, δ /ppm): 11.49(s, 1H, NH), 8.03 (s, 1H, Aromatic proton at 4th position) 7.03-7.75 (m, 11H, -Ar-H),

6.55 (s, 1H, 3rd position of five member ring), 3.02-3.15(m, 2H, -CH₂), 3.9-4.1(m, 1H, -CH), 2.36(s, 3H, -CH₃), 2.31(s, 3H, -CH₃), IR (KBr, cm⁻¹) 1710 (C=O), 1622 (C=N), LC-MS (*m/z*): 394.50 (M, 100%), M.p. 239-241 °C, (Found: C, 79.22; H, 5.88; N, 10.53. Calc. for C₂₆H₂₃N₃O; C, 79.36; H, 5.89; N, 10.68).

(1H-indol-5-yl)(3-(4-methoxyphenyl)-5-p-tolyl-4,5-dihydropyrazol-1-yl)methanone (7g)

The compound was obtained as a off-white solid; ¹H NMR (DMSO-*d*₆, δ / ppm): 11.49(s, 1H, NH), 8.04 (s, 1H, Aromatic proton at 4th position) 7.13-7.75(m, 11H, -Ar-H), 6.55(s, 1H, 3rd position of five member ring), 3.02-3.15(m, 2H, -CH₂), 3.9-4.1(m, 1H, -CH), 3.86(s, 3H, -CH₃), 2.31(s, 3H, -CH₃), IR (KBr, cm⁻¹) 1704 (C=O), 1624 (C=N), LC-MS (*m/z*): 409.98 (M, 100%), M.p. 236-238 °C, (Found: C, 76.55; H, 5.45; N, 10.12 .Calc. for C₂₆H₂₃N₃O₂; C, 76.26; H, 5.66 ; N, 10.26)

(1H-indol-5-yl)(3-(4-chlorophenyl)-5-p-tolyl-4,5-dihydropyrazol-1-yl)methanone (7h)

The compound was obtained as a white solid; Yield 78%, ¹H NMR (DMSO-*d*₆, δ / ppm): 11.49(s, 1H, NH), 8.05 (s, 1H, Aromatic proton at 4th position) 7.13-7.75(m, 11H, -Ar-H), 6.55(s, 1H, 3rd position of five member ring), 3.02-3.15(m, 2H, -CH₂), 3.9-4.1(m, 1H, -CH), 2.31(s, 3H, -CH₃), IR (KBr, cm⁻¹) 1702.27 (C=O), 1625 (C=N), LC-MS (*m/z*): 414.13 (M, 100%), M.p. 241-242 °C, (Found: C, 72.65; H, 4.98; N, 10.32 .Calc. for C₂₅H₂₀ClN₃O; C, 72.55; H, 4.87 N, 10.15)

Biological screening

The *in vitro* antimicrobial activity was carried out against 24 h old cultures of three bacteria and three fungi by cup-plate method. Compounds (**7a-h**) has been tested for their antimicrobial activity against *E. coli*, *P. aeruginosa* and *S. aureus* and antifungal activity against *A. niger*, *A. flavus* and *A. terreus* at a concentration of 1000 µg/mL in distilled DMSO using cup plate diffusion method. Nutrient agar and potato dextrose agars were used to culture the bacteria and fungus respectively. The solution of getamycine 1000 µg/mL and fluconazole 1000 µg/mL were prepared in sterilized water and used for standards for comparison of antibacterial and antifungal activities respectively the results were discussed in Table 1.

Table 1. Antimicrobial activity of the title compounds (**7a-h**).

Compd.	Zone of inhibition in mm					
	Antibacterial activity			Antifungal activity		
	<i>E. coli</i>	<i>P. aeruginosa</i>	<i>S. aureus</i>	<i>A. niger</i>	<i>A. flavus</i>	<i>A. terreus</i>
7a	18	16	15	20	23	15
7b	15	18	19	16	27	13
7c	16	22	15	14	22	15
7d	19	20	17	15	20	17
7e	17	16	20	17	21	12
7f	15	21	16	21	19	14
7g	14	18	15	18	18	17
7h	16	15	19	16	28	12
Getamycine	20	24	22	-	-	-
Fluconazole	-	-	-	22	30	18

The Compounds **7a** and **7d** exhibiting good activity against *E. coli* and compounds **7c** and **7f** show good activity of against *P. aeruginosa*, and compounds **7b**, **7e** and **7h** showing good activity against *S. aureus*. All remaining compounds exhibited moderate activity

against all the organisms used for screening. In anti-fungal activity the compounds **7a** and **7f** exhibited excellent activity against *A. niger* and compounds **7b** and **7h** exhibiting good activity against *A. flavus* and compounds **7d** and **7g** showed a good activity *A. terreus* and all remaining compounds exhibiting moderate activity against all the three organisms used for screening.

Conclusion

The successful synthesis of series of heterocyclic compounds and evaluation of the antimicrobial activity of pyrazole derivatives of indole were reported. From the results of the antimicrobial activity is due to the presence of pyrazole systems in the structure.

Acknowledgment

The author are grateful to the NMR Research Center II Sc., Bangalore for providing the NMR & Mass spectral data and Central Library center II Sc., Bangalore for providing for the Literature survey.

References

1. Damljanović I, Vukićević M, Radulović N, Palić R, Ellmerer E, Ratković Z and Joksović M D and Vukićević R D, *Bioorg Med Chem Lett.*, 2009, **19(4)**, 1093-1096.
2. Zainaba Dardari, Meryem Lemrani, Abdelfatah Sebban, Abdelmejid Bahloul, Mohammed Hassar, Said Kitane, Mohammed Berrada, Mohammed Boudouma, *Archiv der Pharmazie*, 2006, **339(6)**, 291-298.
3. Nusrat Bintra Ahasan and Rabiul Islam M D, *Bangladesh J Pharmacol.*, 2007, **2**, 81-87.
4. Sahu S K, Banerjee M, Samantray A, Behera C and Azam M A, *Tropical J Pharma Res.*, 2008, **7(2)**, 961-968.
5. Kidwai M, Kumar P, Goel Y and Kumar K, *Indian J Chem.*, 1997, **36B**, 175.
6. Kidwai M, Goel Y and Kumar R, *Indian J Chem.*, 1998, **37B**, 174.
7. Mogilaiah K, Chowdary D S and Rao R B, *Indian J Chem.*, 2001, **40B**, 43.
8. Havaladar F H and Mishra K J, *Indian J Heterocycl Chem.*, 2003, **13**, 165.
9. Ramamurthy V and Venkatesan K, *Chem Rev.*, 1987, **87**, 433.
10. Desiraju G R and Goud B S, *Reactivity of Solids Past, Present and Future*, edited by Boldyrev V V (Blackwell Science, London), 1994, p. 233.
11. Toda F, *Syn Lett.*, 1993, 303.
12. Toda F, *Acc Chem Res.*, 1995, **28**, 480.
13. Tanaka K and Toda F, *Chem Rev.*, 2000, **100**, 1025.