

# SYNTHESIS OF 1-ARYL-5-METHYL-4-[4-ARYL-6-(3-OXO-1,4-BENZOTHAZIN-6-YL)PYRID-2-YL]PYRAZOLES AND 1-ARYL-5-METHYL-4-[2-AMINO-4-ARYL-PYRIMIDIN-6-YL]PYRAZOLES AS ANTIBACTERIAL AGENTS

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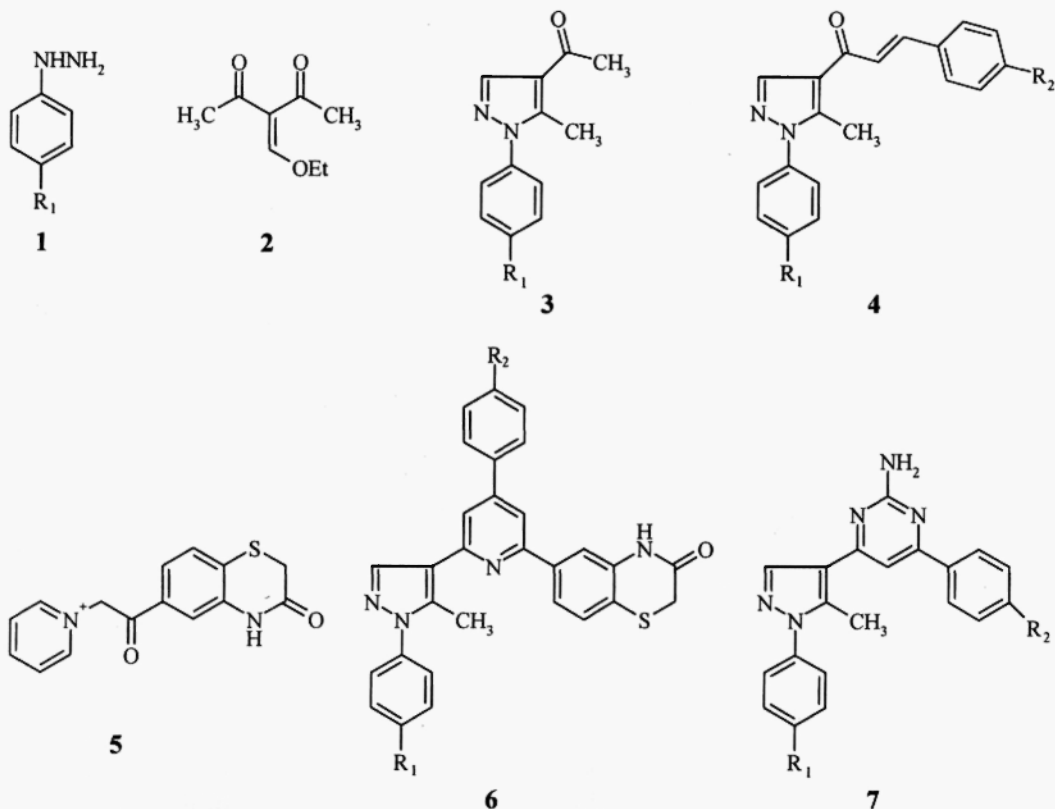
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**Abstract :** A series of 1-Aryl-5-methyl-4-[4-aryl-6-3-oxo-1,4-benzothiazin-6-yl]pyrid-2-yl]pyrazoles (6a-g) and 1-Aryl-5-methyl-4-[2-amino-4-arylpyrimidin-6-yl]pyrazoles (7a-d) have been synthesized and tested for their antibacterial activity.

## Introduction

A number of pyrazole derivatives have been reported as antibacterial<sup>1</sup>, anticoagulant<sup>2</sup> and anticancer<sup>3</sup> agents. Pyrazole ring forms part of several pyrazolo pyridines and pyrazolo pyrimidines with biological activities<sup>4</sup>. The findings of COX-2 inhibition activity by drugs like *celecoxib* and *etoricoxib*<sup>5</sup> exemplifies the importance of di- and triaryl templates of pyrazole and pyridine rings. Pyridine ring forms a major pharmacophore in a variety of natural products and drugs<sup>6</sup>. Furthermore 1,4-benzothiazine derivatives are known to exhibit interesting biological activities like Ca<sup>+2</sup> antagonist, blood platelet aggregation inhibitory and coagulant<sup>7</sup> activities. Our previous publications have reported the synthesis of several benzothiazine substituted pyridines<sup>8</sup> and benzopyranopyridines<sup>9</sup>. In view of the above findings and in continuation of our work, we now report the synthesis of some new pyrazoles substituted with benzothiazinyl pyridines and pyrazolo pyrimidines.

The desired pyrazole ring (3) was synthesized by the reaction of arylhydrazines (1) with ethoxymethyleneacetylacetone 2 in refluxing ethanol<sup>10</sup>. 1-Aryl-5-methyl-4-acetyl pyrazoles 3 were reacted with various araldehydes in presence of sodium methoxide to get the chalcones 4 in good yields. Pyrazolo benzothiazinyl pyridines 6 were synthesized using Kröhnke's method<sup>11</sup>. Thus reaction of chalcones 4 with 3-oxo-2H-[1,4]-benzothiazine-3,4-dihydro-6-acetylpyridinium salt 5 in refluxing acetic acid in presence of ammonium acetate gave the title compounds 6 in good yields. Reaction of chalcones 4 with guanidine hydrochloride in presence of sodium ethoxide gave the corresponding 6-pyrazolyl-2-aminopyrimidines 7 in good yields. Keeping in view of advantages of microwave irradiation<sup>12</sup> in its simplicity, reduction in reaction times, the condensation reactions were also carried out under microwave irradiation conditions and the reaction times and yields were compared with conventional heating. The reactions were completed in 7-8 minutes under Microwave conditions when compared to 3-4 hrs under conventional heating.

**4 & 6**

- $R_1 = R_2 = H$
- $R_1 = SO_2CH_3, R_2 = H$
- $R_1 = SO_2CH_3, R_2 = Cl$
- $R_1 = Cl, R_2 = H$
- $R_1 = Cl, R_2 = CH_3$
- $R_1 = F, R_2 = Cl$
- $R_1 = F, R_2 = CH_3$

**7**

- $R_1 = H, R_2 = Cl$
- $R_1 = Cl, R_2 = H$
- $R_1 = Cl, R_2 = CH_3$
- $R_1 = R_2 = Cl$

**Scheme-1**

The structures of the reaction products **6** & **7** were established based on their IR,  $^1H$ -NMR, mass spectra and correct elemental analyses. The IR spectra of **6** exhibited the absorption at  $1700\text{ cm}^{-1}$ .  $^1H$ -NMR spectra of **6** exhibited characteristic signals for pyrazole methyl,  $-SCH_2$  of benzothiazine ring and lactam NH around  $\delta$  2.7, 3.5 and 10.7 apart from aromatic and pyridine protons.  $^1H$ -NMR spectra of **7** are characterized by the pyrazole methyl, amino group of pyrimidine and pyrimidine protons around  $\delta$  2.68, 5.07 and 8.10 apart from aromatic and pyrazole protons.

## Biological Activity

Antimicrobial activity of the compounds **6a-g** was determined against *staphylococcus aureus* (gram +ve) and *Escherichia coli* (gram -ve). Inhibitory activities were assayed by taking *S. aureus* in 5 ml of growth medium and *E. Coli* in 2 ml of growth medium and adding varying amounts of sterilized test compounds dissolved in 0.5 ml of a 1:1 mixture of water and DMSO. Growth at 37°C after 24 hrs of incubation was measured by turbidimetry at 650 nm. Inhibitory activity values have been expressed on the basis of concentrations of the sample (in µg/ml) necessary to obtain a 50% inhibition of growth. Compounds **6b**, **6c**, & **6f** were found to exhibit a relatively narrow range of antibacterial activity against gram positive bacteria by inhibiting the growth of *S. aureus* at 25, 30 & 28 µg/ml. None of the compounds exhibited any activity against gram negative bacteria *E-Coli*.

## Experimental Section

Melting points were determined in open capillaries and are uncorrected. The purity of all the compounds was routinely checked by TLC on silica gel coated plates. IR spectra were recorded on KBr pellets on a Perkin-Elmer system 2000 FT IR spectrometer. <sup>1</sup>H-NMR spectra on a Varian 200 MHz instrument with TMS as internal standard and chemical shifts expressed in δ ppm. Mass spectra were recorded on Hewlett Packard mass spectrometer operating at 70 eV.

### 4-Acetyl-5-methyl-1-arylpyrazoles (**3**) General procedure:

A mixture of arylhydrazine (**1**, 0.01 mole) and ethoxy methylene acetyl acetone<sup>10</sup> (**2**, 0.01 mole) in ethanol (5.0 ml) was refluxed for 1 hr. The reaction mixture was cooled and filtered to give **3** as crystalline powder.

### 1-(1-Aryl-5-methylpyrazol-4-yl)-3-aryl-2-propen-1-ones **4**: General procedure

To a mixture of 4-acetyl-5-methyl-1-arylpyrazole (**3**, 0.01 mole) and a substituted aromatic aldehyde (0.01 mole) in methanol (50 ml) was added sodium (0.02 mole). The reaction mixture was stirred at room temperature until the disappearance of starting materials as monitored by TLC. The separated solid was filtered and washed with methanol to give pure **4** as crystalline solids.

The melting points and yields of different **4** prepared are given below.

**4a** 102°C, 67%; **4b** 211°C, 62%; **4c** 228°C, 65%; **4d** 157°C, 71%; **4e** 145°C, 72%; **4f** 176°C, 68%; **4g** 150°C, 67%.

### 1-Aryl-5-methyl-4-[4-aryl-6-(3-oxo-1,4-benzothiazin-6-yl)pyrid-2-yl]pyrazole **6**:

#### General procedure under conventional heating

A mixture of **4** (0.01 mole), 3-oxo-2H-[1,4]-benzothiazine-3,4-dihydro-6-acetylpyridinium salt (**5**, 0.01 mole) ammonium acetate (0.06 mole) and acetic acid (50 ml) was refluxed for 3-4 hrs. The reaction mixture was monitored by TLC. At the end of the reaction, it was cooled, filtered and the solid was washed with cold water, dried and recrystallized from DMF methanol to give pure **6** as crystalline compounds. Characterization data of all the compounds **6a-g** thus prepared are listed in **Table -1**.

**General procedure for the synthesis of 6 under microwave irradiation conditions.**

A mixture of **4** (0.01 mole), **5** (0.01 mole) ammonium acetate (0.06 mole) and acetic acid (10 ml) taken in an Erlenmeyer flask was irradiated for 7 minutes in 7 x 1 with 1 minute intervals using domestic microwave oven and worked up as described above.

**1-Aryl-5-methyl-4-(2-amino-4-arylpyrimidin-2-yl)pyrazoles 7: General procedure**

A mixture of **4** (0.01 mole) guanidine hydrochloride (0.01 mole) and sodium ethoxide (0.04 mole) in absolute ethanol (100 ml) was heated under reflux for 4 hrs, the solvent was removed and to the residue water (100 ml) was added. It was acidified with acetic acid, the separated solid was filtered, washed with water, dried and recrystallized from methanol to give **7** as pure crystalline solids. Characterization data of **7** are listed in Table-1.

**Table-1:** Characterisation data of compounds **6** & **7**

Compd*	Yield %	m.p °C	Mol. formula	<sup>1</sup> H NMR (DMSO- <i>d</i> <sub>6</sub> ) δ ppm
<b>6a</b>	61	277	C <sub>29</sub> H <sub>22</sub> N <sub>4</sub> OS	2.77(s, 3H), 3.52(s, 2H), 7.43-7.59(m, 10H), 7.85-7.98(m, 5H), 8.43(s, 1H), 10.76(bs, 1H)
<b>6b</b>	64	291	C <sub>30</sub> H <sub>24</sub> N <sub>4</sub> O <sub>3</sub> S <sub>2</sub>	2.84(s, 3H), 3.31(s, 3H), 3.52(s, 2H), 7.44-7.61(m, 10H), 7.86-7.96(m, 4H), 8.52(s, 1H), 10.76(bs, 1H)
<b>6c</b>	67	>300	C <sub>30</sub> H <sub>23</sub> N <sub>4</sub> O <sub>3</sub> S <sub>2</sub> Cl	2.85(s, 3H), 3.32(s, 3H), 3.53(s, 2H), 7.46(d, 1H), 7.63(d, 2H), 7.85(m, 4H), 8.03(m, 4H), 8.12(d, 2H), 8.53(s, 1H), 10.77(bs, 1H)
<b>6d</b>	69	280	C <sub>29</sub> H <sub>21</sub> ClN <sub>4</sub> OS	2.70(s, 3H), 3.41(s, 2H), 7.46-7.64(m, 4H), 7.86-8.02(m, 8H), 8.16(d, 2H), 8.42(s, 1H), 10.76(bs, 1H)
<b>6e</b>	71	284	C <sub>30</sub> H <sub>23</sub> ClN <sub>4</sub> OS	2.43(s, 3H), 2.78(s, 3H), 3.41(s, 2H), 7.36-7.91(m, 13H), 8.18(s, 1H), 10.64(bs, 1H)
<b>6f</b>	65	261	C <sub>29</sub> H <sub>20</sub> FCIN <sub>4</sub> OS	2.76(s, 3H), 3.47(s, 2H), 7.38-7.96(m, 13H), 8.42(s, 1H), 10.76(bs, 1H)
<b>6g</b>	66	251	C <sub>30</sub> H <sub>23</sub> FN <sub>4</sub> OS	2.46(s, 3H), 2.79(s, 3H), 3.48(s, 2H), 7.37-7.98(m, 13H), 8.42(s, 1H), 10.77(bs, 1H)
<b>7a</b>	74	159	C <sub>20</sub> H <sub>16</sub> ClN <sub>5</sub>	2.69(s, 3H), 5.08(bs, 2H), 7.21(s, 1H), 7.43-7.96(m, 9H), 8.12(s, 1H)
<b>7b</b>	76	176	C <sub>20</sub> H <sub>16</sub> ClN <sub>5</sub>	2.71(s, 3H), 5.12(bs, 2H), 7.23(s, 1H), 7.46-7.98(m, 9H), 8.14(s, 1H)
<b>7c</b>	72	158	C <sub>21</sub> H <sub>18</sub> ClN <sub>5</sub>	2.43(s, 3H), 2.72(s, 3H), 5.07(bs, 2H), 7.19(s, 1H), 7.43-7.97(m, 8H), 8.12(s, 1H)
<b>7d</b>	75	212	C <sub>20</sub> H <sub>15</sub> Cl <sub>2</sub> N <sub>5</sub>	2.68(s, 3H), 5.07(bs, 2H), 7.21(s, 1H), 7.41-7.50(m, 6H), 7.98(d, 2H), 8.11(s, 1H)

\* Satisfactory C, H and N analyses have been obtained for all the compounds

## References

1. G. Daidone, B. Maggio, S. Prescia, D. Rafia, C. Musiu, C. Milia and G. Perra, Marongiu, *Eur. J. Med. Chem.*, **33**, 375, (1998).
2. J. R. Prutt, D. J. P. Pinto, R. A. Galemno, R. S. Alexander, K. A. Rossi, B. L. Wells, S. Drummond, L. L. Bostron, D. Burdik, R. Bruckmer, H. Chen, A. Smallwood, P. C. Wang, M. R. Wright, S. Bai, J. M. Lhettegen, R. M. Knabb, P. Y. S. Lam and R. R. Wexler, *J. Med. Chem.*, **46**, 5298, (2003).
3. N. Pommery, T. Taverne, A. Teuiez, L. Goosons, C. Charuier, J. Pommery, J. F. Goosens, R. Houssin, F. Durant and J. Hemichent. *J. Med. Chem.*, **47**, 6195, (2004).
4. N. Meary and J. Castaner, *Drugs of the future*, **21** (1), 37, (1996).
5. S. M. Sakya and B. Rast, *Tetrahedron Lett.*, **44**, 7629, (2003).
6. M. Balasubrahmanyam and J. G. Keek, *Comprehensive Heterocyclic Chemistry*, Edited by A. R. Katritzky, Pergamon press (Oxford), **5**, 245, (1996).
7. a) M. Fujita, S. Ito, A. Ota, N. Kato, K. Yamato, Y. Kawashime, H. Yamachi and J. Iwa, *J. Med. Chem.*, **33**, 1898, (1990).  
b) P. W. Combs, M. S. Rampulla, J. P. Demers, R. Falotico and J. B. Moora, *J. Med. Chem.*, **35**, 172, (1992).  
c) J. A. Willardsen, D. A. Dudley, W. L. Cody, L. Chi, T. B. Meelanahan, T. E. Mertz, R. E. Potoczak, L. S. Narasimhan, D. R. Holland, S. T. Rapundalo and J. J. Edmunds, *J. Med. Chem.*, **47**, 4069, (2004).
8. D. Ashok, K. Pallavi, G. Jagath Reddy and K. Srinivasa Rao, *Heterocyclic Communications*, **12** (3 & 4), 197, (2006).
9. D. Ashok, K. Pallavi, G. Jagath Reddy and K. Srinivasa Rao, *Indian J. Het. Chem.*, (2006) Communicated.
10. H. Naito, S. Ohsuki, R. Atsuni, M. Minami, M. Mochizaki, K. Hirotani, E. Kumazawa and A. Ejima, *Chem. Pharm. Bull.*, **53** (2), 153, (2005).
11. F. Kröhnke, *Synthesis*, **1**, (1976).
12. V. K. Ahluwalia and M. Kidwai, *New Trends in Green Chemistry*, Anamaya, New Delhi 59, (2004) and references cited therein.

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