Synthesis and Characterization of 2-Pyrazoline Derivatives

S. Rathina Manivannan[*1] , B. Ashok Kumar[2]

[*1]Research Scholar, Department of Chemistry, PRIST University

[2]Assistant Professor, Department of Chemistry, PRIST University

ABSTRACT

Cancer still remains a mean threat to human health, representing the second leading cause of death worldwide. Its estimate that 13.1 million people will die from cancer in 2030. Recently, many efforts have been made to develop safe and effective ways of treating this disease and to search for novel chemotherapeutic agents with minimal side effects. The identification of the central role of protein kinases in cell signalling and their implication in malignant pathologies has led to extensive efforts to develop specific protein kinases inhibitors as treatment for wide range of cancers. Aminopyrazoles emerged as a powerful pharamacophore scaffold and they have been extensively used to design various kinase inhibitors. The major challenge is the development of more effective and safe drugs for the treatment of cancer. Pyrazole is a versatile lead compound to design potent bioactive molecules for drug discovery and development, particularly in cancer therapy. The aim of this review is to present the most recent deeds in the field of synthetic route made for functionalized pyrazole derivatives active against cell proliferation disease. The review article covers the synthesis of pyrazolopyrazoles, and synthesis of pyrazoles fused with a naturally occurring moiety. Some of these reported compounds have passed the preclinical or initial-phase clinical trials for their anticancer activity. The aim of the current research work is mainly focused to synthesized substituted 2-pyrazoline derivatives from biphenyl chalcone derivatives. The chemical structure of the synthesized compounds were confirmed using FT-IR, 1H NMR and, 13 C NMR Spectral data. The molecular docking studies were carried out for synthesized 2-pyrazoline derivatives using bacterial protein (1UAG) and breast cancer protein (1OQA). From the result of molecular docking studies using breast cancer protein, the high binding affinity score compound was subjected to in-vitro anticancer activity (MCF-7) by MTT assay. Furthermore, synthesized compounds were screened for antibacterial activity by agar disk diffusion method.

1. INTRODUCTION

The chemistry of chalcone has generated intensive scientific studies throughout the world. Especially the main focus is to synthesis the biodynamic activities of chalcone. The name “Chalcone” was given by Kostanecki and Tambor [1]. These type of compounds also known as benzalacetophenone or benzylidene acetophenone. In the structure of chalcones have two phenyl rings are directly linked by an aliphatic carbon chain. Chalcone bears a very good synthon so that of novel heterocycles with good pharmaceutical profile can be designed. Chalcones having keto-ethylene -CO-CH=CH-. These type of compounds are coloured because the chromophore -CO-CH=CH- are present, which depends in the presence of other auxochromes. Many number of methods are available for the preparation of chalcones [2]. The most convenient methods is the Claisen-Schmidt condensation of equimolar quantities of

arylmethylketone with aryl aldehyde in the presence of alcoholic alkali [3]. Many number of heterocyclic ring systems like Cyanopyridines, Pyrazolines, isoxazole and pyrimidines were synthesized using chalcones [4].

2. SYNTHETIC METHODS OF PREPARING CHALCONES

2.1. CLASIEN-SCHMIDT REACTION

A lot of methods are available in the synthesis of chalcone derivatives. Especially, Claisen-Schmidt condensation method was mainly used in the synthesis of chalcone derivatives using equal mol of acetophenone with equal mol of aldehydes in the presence of aqueous alcoholic alkali [5]. In the Claisen-Schmidt reaction the concentration of alkali used, usually ranges between 10 and 60% [6-8]. This reaction was carried out for 12-15 hours at 50 oC or kept in room temperature for one week. Under these condition, the Cannizsaro reaction [9] also takes place and thereby decreases the yield of the desired product. To avoid the disproportionation of aldehyde in the above reaction, the use of benzylidene-diacetate in place of aldehyde has been recommended [10].

3. VARIOUS CONDENSING AGENTS USED IN SYNTHESIS OF CHALCONES

3.1. ALKALI

Alkali medium is mainly used in the synthesis of chalcones. The various concentration of aqueous solution are used viz. 30%, 40%, 50% and 70%.

3.2. HYDROCHLORIC ACID

Dry hydrochloric gas in a suitable solvent like ethyl acetate at 0℃ was used as acondensing agent in a few synthesis of chalcones from aromatic ketones. Methanolic solution of dry hydrochloric acid gas at 0℃ was used by Lyle, Paradis [11] and Marathey [12].

3.3. OTHER CONDENSING AGENTS

Raval and Shah [13] used phosphorous oxychloride as a condensing agent to synthesize of chalcones. Szell and Sips [14] condensed 2-hydroxy-5-nitro-acetophenone with benzaldehyde using anhydrous AlCl3. Kuroda, Matsukuma and, Nakasmura has been synthesized chalcone using acetophenone and methoxyaldehyde in the presence of anhydrous aluminium [15]. Besides the above, other condensing agents used in synthesize of chalcones have been,

(1) Amino acid [16]

(2) Aqueous solution of borax [17]

(3) Perchloric acid [18]

(4) Piperidine [19]

(5) Boron trifloride [20]

(6)Alkali metal alkoxide [21]

(7) Magnesium tert-butoxide [22]

(8) Organocadmium compound [23]

4. AIM AND OBJECTIVES

- To synthesize new series of substituted phenyl pyrazole-1-yl butan-1-one derivatives (5a-5e) from biphenyl chalcone with n-butyric propionic acid by cyclization method.

5. EXPERIMENTAL METHODS

5.1. Materials and methods:

The n-butyric acid (500 mL) was purchased from sigma Aldrich. The melting points of the compounds were determined through open capillary method and values were uncorrected. The FT-IR spectrum (cm-1) was recorded through KBr in a Fourier Transform IR spectrometer (model shimadzu 8400s) in the range of 400-4000 cm-1. The 1H, 13C NMR spectra and 1H-1H Cosy were recorded by Brucker 400 MHz spectrometer and chemical shifts are recorded in δ value (ppm) with Tetra Methyl Silane (TMS) as internal standard, as well as CDCl3 used as a solvent.

5.2. General procedure for the preparation of TLC plates:

Analytical TLC was performed on precoated silica gel (Merck, Germany). Silica gel G. 10g was dispersed in 15 ml of distilled water. The resulted homogenous solution was applied on glass plates using an applicator. The plates were allowed to dry in Owen for 30 minutes and activated in an Owen for one hour before use.

5.3. Percentage of the product:

All the synthesized compounds were purified by recrystallization procedures. The purity of the compound was checked by TLC method. The percentage of yield of the compounds was calculated as shown below.

$$\% \text{ Yield} = \frac{\text{Weight of the product obtained}}{\text{Theoretical weight}} \times 100$$

5.4. General procedure for the synthesis of (e)-3-(phenyl)-1-(biphenyl-2-yl) 3- arylprop-2-en-1-one derivatives: (3a-3e)

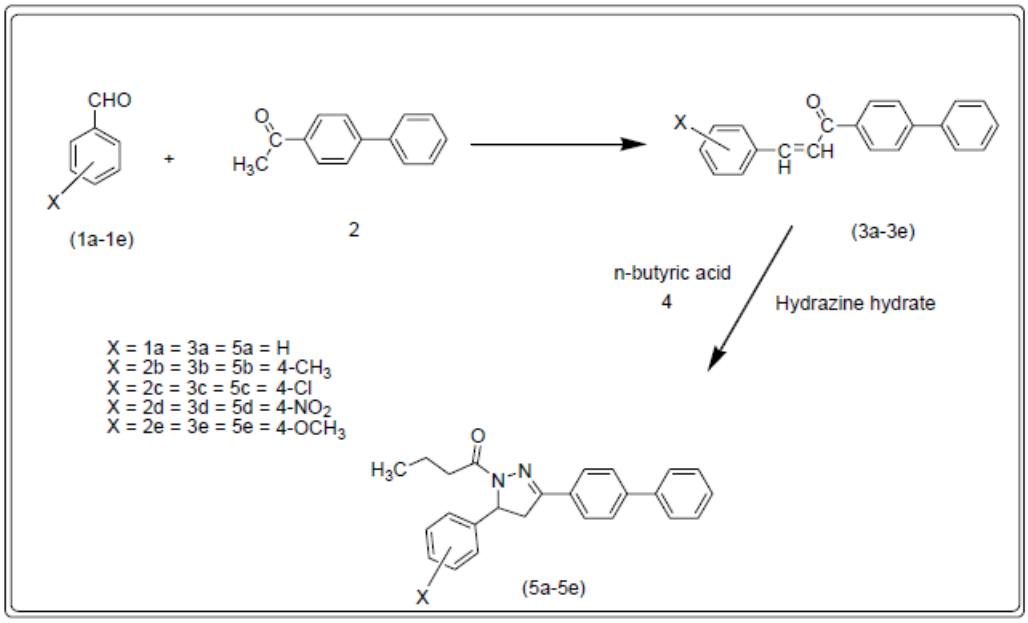
One mol of 4-acetyl biphenyl and one mole of various substituted aromatic aldehydes were taken in a beaker and to this approximately added 30 ml of ethanol containing 2g of NaOH pellets. Then the mixture was stirred well for 30 minutes in an ice cold bath, after it was poured into the crushed ice containing 500 ml beaker and this reaction mixture was kept into overnight at room temperature. The chalcone were precipitated out as solid. After that the solid product was filtered and dried. Then that solid product was recrystallized using ethanol. The purity of the compound was checked by TLC by using CHCl3 as a solvent [93].

5.5. General procedure for the synthesis of 1-(4, 5-dihydro-3-diphenyl-5-substituted pyrazol-1-yl) butan-1-one derivatives: (5a-5e)

Chalcone (1 mol) and hydrazine hydrate (1 mol) were taken in a 250 ml round bottom flask and approximately added 30 ml of n-butyric acid. Then the mixture was refluxed for 14-

16 hours. The completion of the reaction was monitored by TLC using 100% CHCl3. After this reaction mixture was poured into the crushed ice containing 500 ml beaker and this reaction mixture was kept into overnight at room temperature. The product were precipitated out as solid. After that the solid product was filtered and dried. Then the solid product was recrystallized using ethanol. The purity of the compound was checked by TLC using 9:1 ratio (P.E+ E.A).

SCHEME

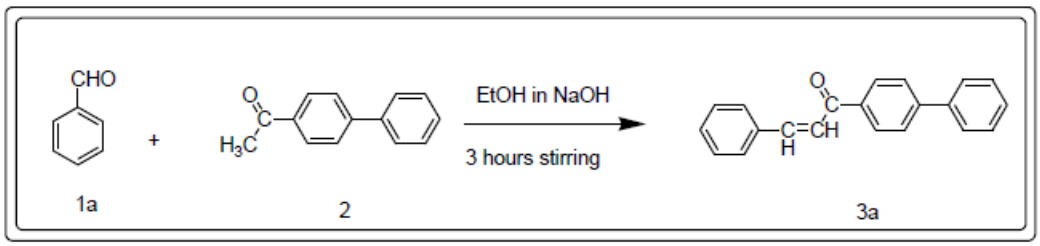


6. RESULT AND DISCUSSION

The synthesized chalcones are deeply studies throughout the world. Especially interest has been focused on the synthesis and biodynamic activity of chalcones. In chalcones, two aromatic rings are linked by an aliphatic three carbon chain. Chalcones bears a very good python so that variety of novel heterocyclic with good pharmaceutical profile can be designed. Biphenyl chalcone were prepared from various substituted aromatic aldehydes reacted with 4-acetyl biphenyl in the presence of strong base. The biphenyl chalcone were then cyclization with hydrazine hydrate and n-butyric acid to give 2-pyrazoline derivatives.

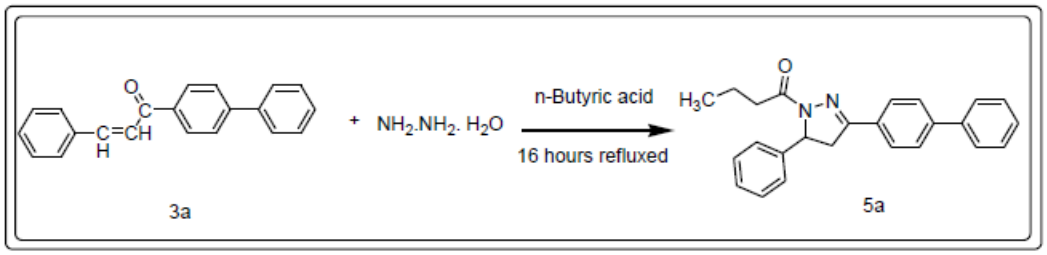
General procedure for the synthesis of (e)-3-(phenyl)-1-(biphenyl-2-yl) 3-arylprop-2-en-1-one derivative: 3a

One mol of 4-acetyl biphenyl (2) and one mol of Benzaldehyde (1a) were taken in a beaker and to this approximately added 30 ml of ethanol containing 2g of NaOH pellets. Then the mixture was stirred well for 30 minutes in an ice cold bath, after it was poured into the crushed ice containing 500 ml beaker and this reaction mixture was kept into overnight at room temperature. The chalcone were precipitated out as solid. After that solid was filtered and dried. Then that solid was recrystallized using ethanol. The purity of the compound was checked by TLC by using CHCl3 as a solvent.



General procedure for the synthesis of 1-(4, 5-dihydro-3-diphenyl-5-phenyl pyrazol-1-yl) butan-1-one derivative: 5a

Chalcone (1 mol) and hydrazine hydrate (1 mol) were taken in a 250 ml round bottom flask and approximately added 30 ml of n-butyric acid. Then the mixture was refluxed for 14-16 hours. The completion of the reaction was monitored by TLC using 100% CHCl3. After this reaction mixture was poured into the crushed ice containing 500 ml beaker and this reaction mixture was kept into overnight at room temperature. The product were precipitated out as solid. After that the solid was filtered and dried. Then that solid product was recrystallized using ethanol. The purity of the compound was checked by TLC using 9:1 ratio (P.E+ E.A).



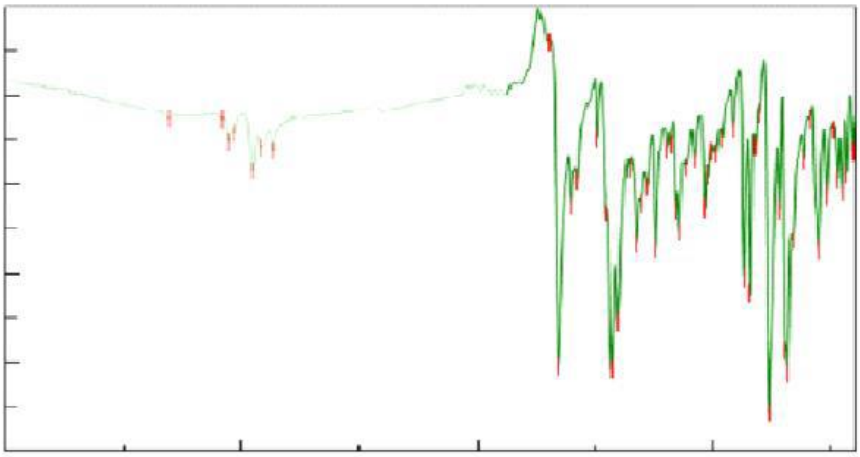


Fig 1. The FT-IR spectrum for synthesized compound 5a

The FT-IR spectrum of the compound shows that the characteristic absorption frequency at 1405.85 cm-1 is due to C=N stretching frequency of pyrazole moiety. The absorption band at 1661.37 cm-1 is due to C=O stretching frequency. The absorption band at 1156.52 cm-1 is due to C-N stretching frequency. The absorption band around at 3085.55 cm-1 is assigned to aromatic CH stretching vibration. The bands at 839.847 cm-1, 762.709 cm-1, 696.177 cm-1and 686.534 cm-1 are aromatic ring stretching vibrations.

7. CONCLUSION

Substituted aromatic benzaldehyde reacted with 4-Acetyl biphenyl in the presence of strong base, finally it was gives chalcone derivatives (3a-3e).

- Synthesis of (E)-3-(phenyl)-1-(biphenyl-2-yl) 3-arylprop-2-en-1-one derivative(3a)

The chalcone derivatives (3a-3e) react with hydrazine hydrate and n-butyric acid by cyclization method, to give 2-pyrazoline compounds (5a-5e).

- Synthesis of 1-(4, 5-dihydro-3-diphenyl-5-Phenyl pyrazol-1-yl) butan- 1-one derivative(5a)

REFERENCES

[1]. (a) A. R. Katritzky and A. F. Pozharskii, Handbook of Heterocyclic Chemistry: 2000, 2nd ed.; Pergamon Press: New York, (2000) (b) E. J. Noga, G. T. Barthalmus and M. K. Mitchell, Cell Biology Int. Rep., 10, 239 (1986) (c) P. N. Craig, In Comprehensive Medicinal Chemistry; Drayton, C. J., Ed.; Pergamon Press: New York, vol.8 (1991) (d) T. Kodama, M. Tamura, T. Oda, Y. Yamazaki, M. Nishikawa, S. Takemura, T. Doi, Y. Yoshinori and M. Ohkuchi, U. S. Patent., 983928 (2003) (e) A. Padwa and S. Bur, Chem. Rev., 104, 2401 (2004).

[2]. (a) A. Mori, A. Sekiguchi, K. Masui, M. Horie, T. Ikeda and T.Shimoda, J. Am. Chem. Soc., 125, 1700 (2003) (b) K. Masui, H. Ikegami and A. Mori, J. Am. Chem. Soc., 1265074 (2004).

[3]. A. Nagaraj and C. Sanjeeva Reddy, J. Iran. Chem.Soc., 5 (2), 262-267 (2008).

[4]. K. M. Mahadevan, G. K. Prakash, D. B. Anunakumar, M. N. Kumaraswamy, B. P. Nandeshwarappa and B. S. Sherigara, Indian J. Chem., 45 B, 1699-1703 (2006).

[5]. M. Amir and S. A. Javed, Acta Pharma, 58, 467-477(2008).

[6]. (a) K. S. Atwal, G. C. Rovnyak, S. D. Kimball and S. Moreland, J. Med. Chem., 33, 2629 (1990) (b) K. S. Atwal, B. N. Swanson, S. Moreland, D. M. Floyd and S. E. Unger, J. Med. Chem., 34, 806 (1991) (c) K. S. Atwal, G. C. Rovnyak and M. F. Malley, J. Med. Chem., 35, 3254 (1992) (d) G. C. Rovnyak, S. D. Kimball, B. Beyer, S. Moreland, M. Molley, A. Hedberg and R. Zhang, J. Med. Chem., 38, 119 (1995).

[7]. K. S. Nimavat, K. H. Popat, S. L. Vasoya and H. S. Joshi, Indian J. Heterocyclic Chem., 12, 217 (2003).

[8]. (a) K. Vashi and H. B. Naik, Asian J. Chem., 17, 240 (2005) (b) R. Vyas, P. C. Choudhary, H. Sharma and B. L. Verma, Indian J. Heterocyclic Chem., 17, 237 (2008) (c) P. B. Bharucha and H. B. Naik, Asian J. Chem., 11, 1553 (1999).

[9]. D. J. Bhatt, G. C. Kamdar and A. R. Parikh, J. Inst. Chemists (India), 56, 233 (1984).

[10]. R. R. Lakhani and A. R. Parikh, J. Inst. Chemists (India), 59, 230 (1987).

[11]. H. S. Joshi and A. R. Parikh, J. Inst. Chemists (India), 62, 22, 251 (1990).

[12]. S. A. Shah, Ph. D. Thesis, V. N. South Gujarat Uni., Surat (2002).

[13]. A. V. Naik, Ph. D. Thesis, V. N. South Gujarat Uni., Surat (2005).

[14]. K. K. Vaidya, Ph. D. Thesis, V. N. South Gujarat Uni., Surat (2006).

[15]. P. K. Desai, P. Desai, C.M. Desai, D.M. Machhi and Dinesh Patel, Ind. J. Chem., 35 (B), 971 (1996).

[16]. P. K. Desai, P. Desai and C.M. Desai, Ind. J. Microbial, 36, 71 (1996).

[17]. B. D. Naik, C.M. Desai, P. Desai and Dinesh Patel, Asian J. Chem, 10, 623 (1998).

[18]. C. Mehwala, D. Patel, C.M. Desai, P. Desai and A. G. Mehta, J. Inst. Chemists (India), 72, 117 (2000).

[19]. R. C. Khunt, N. J. Datta and A.R. Parikh, J. Inst. Chemists (India), 74 (1), 18 (2002).

[20]. J. Machhi; R. Shetty, C. M. Desai, D. Patel and H. D. Joshi, J. Inst. Chemists (India), 74 (2), 68-70 (2002).

[21]. J. Machhi, D. Patel, C. M. Desai, P. Desai and H. D.Joshi, J. Inst. Chemists (India), 74 (3), 110-112 (2002).

[22]. N. Rao, A. Narendra Babu, C. Gopinath and B. Raman, J. Inst. Chemists (India), 76 (1), 10 (2004).

[23]. C. M. Desai, D. Patel, D.Desai and H. D. Joshi, J. Inst. Chemists (India), 76 (3), 94 (2004).