Synthesis and Antibacterial Evaluation of some New Pyrazole Derivatives

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Abstract

Ten new chalcones were prepared in three steps, firstly phthalic anhydride reacted with 4- amino acetophenone to produce 2-(4-acetyl phenyl carbamoyl) benzoic acid (A_1), secondly [2-(4-acetyl phenyl carbamoyl) benzoic acid (A_1)] suffers from the loss of a water molecule via reaction with (anhydrous sodium acetate and acetic anhydride) to produce 2-(4-acetyl phenyl) isoindoline-1,3-dione (A_2), thirdly this compound condensed with various substituted benzaldehydes affording chalcones (A_3- A_{12}) were reacted with hydrazine hydrate to produce pyrazole compounds (A_{13}- A_{22}).

The prepared compounds were characterized by determination of melting point, FT-IR and some of the prepared compounds have been characterized by (^{1}H-NMR and ^{13}C-NMR) techniques.

Keywords*: Claisen 1,2-addition, chalcones, pyrazol, phenylcarbamoyl, isoindoline.*

Introduction

Heterocyclic compounds are very widespread in the natural and in non-natural molecules, from this they are used as an essential compounds in the life, many compounds such as vitamins, essential amino acids, hormones and the synthetic drugs includes heterocyclic ring system.

Isoindoline-1,3-dione are very important compounds in the pharmacological and synthetic fields because they contain two amid bonds –CO-N-CO- which produce an imide ring [1- 2- 3] they are hydrophobic and neutral therefore cross biological membranes in vivo. These compounds possess considerable biological effects like anti-cancer [4] , antimicrobial [5] , anti-virals [6] , anxiolytics [7] , anti-inflammatory [8] and anticonvulsant [9] .

Chalcones and substituted chalcones are aromatic derivatives of α, β- unsaturated ketones with one unsaturated position [10] . the properties of chalcones depend on suitable substituted groups on the ring and the presence of α, β- unsaturated group [11] . Chalcones showed a biological activity such as anticancer [12] . antioxidative [13] , antimalarial [14] ,antiangiogenic [15] , antibacterial [16] , immunosuppress [17] , antiparasitic, antileishma [18] , antidiabetic [19] , anal-gesic [20] and anti-inflammatory [21] .

Pyrazole heterocyclic compound has a five-membered ring containing two nitrogen atoms and because they have two nitrogen atoms they are prepared by many methods, one of these methods is the condensation of hydrazine or substituted hydrazine with α, β- unsaturated carbonyl compounds [22] , pyrazole used as intermediates for the many syntheses of new compounds which have biological activity. They possess medicinal properties, like anti-inflammatory, antibacterial [23-24] antioxidant [25] , anti-diabetic [26] , antimicrobial [27] , antiviral [28] and antimalarial [29] .

Experimental

Materials and Method

4–Aminoacetophenone, phthalic anhydride, hydrazine hydrate, acetone, glacial acetic acid, ethanol and all aromatic aldehydes are providing from Fluka, BDH and Aldrich, they used without further purification.

Melting points of the compounds were determined by using an electro-thermal digital device and were not corrected. FT-IR spectrum was recorded on Shimadzu FTIR-8400 spectrophotometer as KBr disc Tikrit University in Iraq. ^{1}HNMR and ^{13}CNMR spectra were registered on Bruker spectroscopic ultra-shield magnets 300 MHz instruments using tetramethylsilane (TMS) as an standard and Dimethyl Sulfoxide -d6 as a solvent.

Preparation Methods

Preparation of compound (A_1). [30]

(0.01 mol) 1.4g of isobenzofuran-1,3-dione was dissolved in (20 mL) of acetone in a round-bottom flask fitted with dropping funnel. The funnel continued supplied with (0.01 mol) 1.35 g of p-amino acetophenone dissolved in (10 mL) of acetone, the solution of amino acetophenone and acetone was added to the mixture of (isobenzofuran-1,3-dione and acetone) dropwise with stirring for (2) hours. The produced precipitate was purified by filtered and recrystallized from ethanol, some of the physical properties are given in table (1).

Preparation of compound (A_2). [32]

Compound (A_1) (0.02 mol, 5.66 g) in (50 mL) of acetic anhydride was mixed with (0.25 g) of anhydrous sodium acetate and refluxed for 6 hours with stirring. The reaction mixture was refrigerated and poured into crushed snow together with stirring; the precipitate was filtered, dehydrated and recrystallized from acetone. The physical properties are showing in table (1)

Preparation of chalcones (A_3-A_{12}). [32]

A mixture of compound A_2 (0.008 mol, 2.12g) and substituted benzaldehydes (0.008 mol) was dissolved in (30 mL) of ethanol, a solution of aqueous potassium hydroxide (15 ml, 40%) was added. The mixture was stirred for (6-8) hours at room temperature. The resulting mix kept in a good conditions until the morning of the next day at room temperature, poured into crushed snow and HCl has been added to equivalent the base. The produced precipitate was purified by filtered and recrystallized from ethanol, some of the physical properties are given in table (2).

Comp. No	R	Molecular Formula	M.wt (g/mol)	M.p oC	Yield %	Color
A3	H	C23H15NO3	352.997	86-88	87	Yellow
A4	4- Br	C23H14NO3Br	431.901	206-208	88	Light Yellow
A5	4- Cl	C23H14NO3Cl	387.45	196-198	81	Light Yellow
A6	4-OH	C23H15NO4	368.99	214-216	71	Light Yellow
A7	4- OCH3	C24H17NO4	382.996	165-167	91	Yellow
A8	2,4- DiCl	C23H13NO3Cl2	421.903	202-204	86	Light Yellow
A9	4- NO2	C23H14 N2O5	397.95	159-161	73	Dark Brown
A10	4- N(CH3)2	C25H20N2O3	395.97	108-110	89	Reddish Orang
A11	2- Br	C23H14NO3Br	431.901	112-124	84	Yellow
A12	3,4- DiOCH3	C25H19NO5	413	148-150	92	Yellow

Preparation of pyrazole compounds (A_{13}-A_{22}) (33)

(0.004 mol) of hydrazine hydrate and (0.004 mol) of chalcones dissolved in 30 mL glacial acetic acid, the mix was refluxed for 8 h, then cooled and pour on 50 mL of ice water. The produced precipitate was purified by filtered and recrystallized from ethanol, some of the physical properties are given in table (3).

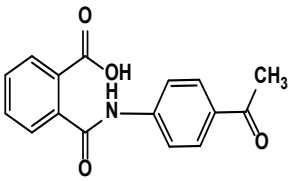
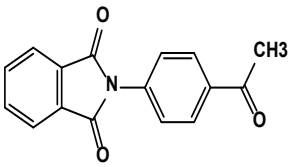
Results and Discussion

The first step includes the synthesis of 2-(4-acetyl phenyl carbamoyl) benzoic acid from the reaction between phthalic anhydride and 4-aminoacetophenone. The second step includes the synthesis of 2-(4-acetyl phenyl) isoindoline-1,3-dione via reaction a mixture of 2-(4-acetyl phenyl carbamoyl) benzoic acid with (anhydrous sodium acetate and acetic anhydride). The third step includes the synthesis of chalcones **(A_3-A_{12})** via reaction of 2-(4-acetyl phenyl) isoindoline-1,3-dione with various substituted benzaldehydes, finally production of pyrazole compounds **(A_{13}-A_{22})** via condensation of chalcones **(A_3-A_{12})** with hydrazine hydrate. Structures of all compounds that prepared were diagnosed by FTIR, ^{1}HNMR and ^{13}CNMR techniques.

Identification of compounds (A_1), (A_2)

Compound (A_1) given a bands in FTIR spectrum at (3403)$^{cm-1}$ and (3233)$^{cm-1}$ denote to stretching vibration of (NH) group and stretching vibration of υ(OH) of amide group, other absorptions appeared at (1647)$^{cm-1}$ and (1708)$^{cm-1}$ denote to υ(C=O) of amide group and υ(C=O) of carboxylic group. Note table (4). Compound (A_2) exhibit bands at (1708, 1663)$^{cm-1}$ denote to υ(C=O) bond of imide and at (1326)$^{cm-1}$ for υ(C-N) bond , Note and table (4).

Table (4): Shows the IR data of compound (A_1 , A_2)

Co.No	Compound Structure	IR (KBr) cm^{-1}					
		υ(O-H) Carboxylic	υ(N-H) Amide	υ(C=O) carboxylic	υ(C=O) imide	υ(C=O) amide	υ(C-N) imide
A_1		3233	3403	1708	-	1647	-
A_2		-	-	-	1708 1662	-	1326

^{1}H-NMR spectrum for compound (A_1), (in Dimethyl Sulfoxide -d6 as a solvent) exhibit a singlet signal at δ(2.43) ppm denotes to CH_3 group, also noted a multiple signals at δ(7.56-7.98)ppm indicate to the protons of aromatic ring and singlet signal at δ(10.69) ppm denotes to N-H group, another singlet signal at δ(13.09) ppm for O-H carboxylic group, the singlet signal at δ(2.5) ppm indicate to two CH_3 groups in a solvent DMSO, , while compound (A_2) (in Dimethyl Sulfoxide -d6 as a solvent) exhibit a singlet signal at δ(2.75) ppm denotes to CH_3 group, also noted a multiple signals at δ(7.34 -8.18) ppm indicate to the protons of aromatic ring, the singlet signal at δ(2.5) ppm indicate to the two CH_3 groups in a solvent DMSO.

^{13}CNMR spectrum of compound (A_1), (in Dimethyl Sulfoxide -d_6 as a solvent) exhibit a signals at δ(26.91) ppm denotes to CH_3 group, at δ(168.36) ppm denotes to amide carbonyl group (N-C=O), at δ(167.73) ppm denotes to (C=O) carboxyl group, another signal at δ(198.02) ppm denotes to (C=O) ketone group and multiples signals at (119.15-144.32)ppm denotes the carbons of aromatic ring, while ^{13}C-NMR spectrum of compound (A_2) exhibit an signal at δ(27.29) ppm denotes to CH_3 group, an signal at δ(167.09) ppm denotes to imide carbonyl group (C=O), an signal at δ(197) ppm denotes to carbonyl group (C=O) of ketone and multiple signals at δ(124-136.27) ppm denotes to the carbons of aromatic ring.

Identification of Chalcones (A_3-A_{12}).

Chalcones (A_3-A_{12}) were prepared via reaction of aromatic benzaldehydes with 4-(isoindolin-2-yl-1,3-dione) acetophenone in absolute ethanol in presence 40 % KOH. The reaction follows the following mechanism(34)

The Chalcones (A_3-A_{12}) were identification by melting point, FT-IR spectra, ^{1}HNMR and ^{13}CNMR. IR spectrum of compound (A_6) exhibited bands at (1681) $^{cm-1}$, ,(1655)$^{cm-1}$,(1583,1525)$^{cm-1}$, (1326)$^{cm-1}$ denotes to stretching vibration of υ(C=O) of ketone, υ(C=C) of aliphatic, υ(C=C) of aromatic, and υ(C-N) of imid group respectively.

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Conflict of Interest: None to declare.

Ethical Clearance: All experimental protocols were approved under the Ministry of Education, Iraq and all experiments were carried out in accordance with approved guidelines.

References

1. Hussain M, Hussam Z, Naji. Synthesis, Characterization and Study of Biological Activity of Some New Schiff Bases, 1, 3-Oxazepine and Tetrazole Derived from 2, 2 di thiophenyl Acetic Acid." Ibn AL-Haitham Journal For Pure and Applied Science. 2018; 189-202.
2. Sharma S. "A review: synthesis and biological activity of imides." The Global Journal of Pharmaceutical Research. 2012; 411-421.
3. Arif R. "Investigation of DNA binding and molecular docking propensity of phthalimide derivatives: in vitro antibacterial and antioxidant assay." Journal of Analytical Science and Technology.2019; 19.
4. Santos L. Synthesis and in vitro anti Mycobacterium tuberculosis activity of a series of phthalimide derivatives." Bioorganic & medicinal chemistry. 2009; 3795-3799.
5. Amin M. Synthesis, characterization and anti-microbial activity of some novel isoindole-1, 3-dione derivatives." Der Pharm. Chem 5. 2013; 97-108.
6. Selvam P C, Pannecouque, and E. De Clercq. "Synthesis, Anti HIV activity and Cytotoxicity of N-Substituted Phthalimide derivatives." Int. J. of Pharmacy and Anal. Res. 2013; 12-14.
7. Hassanzadeh F. "Synthesis and evaluation of the anxiolytic activity of some phthalimide derivatives in mice model of anxiety." Iranian journal of pharmaceutical research: IJPR 11.1. 2012; 109.
8. Pophale R A, Deodhar M N. Synthesis and evaluation of novel phthalimide derivatives as analgesic and anti-inflammatory agents. Der Pharm. Chem. 2010; 2: 185–193.
9. Bhat, Mashooq A., and Mohammed A. Al-Omar. "Synthesis, characterization and in vivo anticonvulsant and neurotoxicity screening of Schiff bases of phthalimide." Acta poloniae pharmaceutica 68.3. 2011; 375-380.
10. Majeed, Nadia Sadik, and Moustafa Abd Al-Kadoum. "Synthesis and identification of some new thiazin and oxazin compounds and new derived from chalcones." Iraqi National Journal of Chemistry 46. 2012; 260-269.
11. Ghali, Thaer Saleh, and Jumbad Hermiz Tomma. "Synthesis and Characterization of Indazol-3-one and Thioxo Pyrimidines Derivatives from Mono and Twin Chalcones." Iraqi Journal of Science 58.4c. 2017; 2265-2277.
12. Castaño, Lina Fernanda, et al. "New chalcone-sulfonamide hybrids exhibiting anticancer and antituberculosis activity." European journal of medicinal chemistry 176. 2019; 50-60.
13. Chen, Xiangrong, et al. "Antioxidative and anticancer properties of Licochalcone A from

licorice." Journal of ethnopharmacology 198. 2017; 331-337.

14. Singh, Parvesh, Amit Anand, and Vipan Kumar. "Recent developments in biological activities of chalcones: A mini review." European journal of medicinal chemistry 85. 2014; 758-777.
15. Nuti, Elisa, et al. "Synthesis and antiangiogenic activity study of new hop chalcone Xanthohumol analogues." European journal of medicinal chemistry 138. 2017; 890-899.
16. Al-Badrany, Khalid A, Amar S, Mohammed, and Yuosra K. Alasadi. "Synthesis of some new 1, 3, 4-oxadiazole compounds derived from 1H-imidazole and study their biological activity." Eurasian Journal of Biosciences 13.1. 2019; 501-507.
17. Hayat, Faisal, et al. "Antiprotozoal activity of chloroquinoline based chalcones." European journal of medicinal chemistry 46.5. 2011; 1897-1905.
18. Ortalli, Margherita, et al. "Identification of chalcone-based antileishmanial agents targeting trypanothione reductase." European journal of medicinal chemistry 152. 2018; 527-541.
19. Srinivas S, V. Aparna. "Design, Synthesis, Biological Evaluation and Molecular Docking Studies of Novel Quinazoline Derivatives as GSK-3β Inhibitors." World Journal of Pharmacy and Pharmaceutical Sciences 2.6. 2013; 5842-5851.
20. Zhang, Xue-Wu, et al. "Synthesis and evaluation of antiinflammatory activity of substituted chalcone derivatives." Medicinal Chemistry Research 19.4. 2010; 403-412.
21. Shenvi, S. "Synthesis, anticancer and antioxidant activities of 2, 4, 5-trimethoxy chalcones and analogues from asaronaldehyde: Structure–activity relationship." European journal of medicinal chemistry 62. 2013; 435-442.
22. Ghali T, Jumbad H. Synthesis and Characterization of Indazol-3-one and Thioxo Pyrimidines Derivatives from Mono and Twin Chalcones." Iraqi Journal of Science 58.4c. 2017; 2265-2277.
23. Sondhi, M. Synthesis of acridinyl-thiazolino derivatives and their evaluation for anti-inflammatory, analgesic and kinase inhibition activities." Bioorganic & medicinal chemistry 13.13. 2005; 4291-4299.
24. Faria, J. "Recently reported biological activities of pyrazole compounds." Bioorganic & medicinal chemistry 25.21. 2017; 5891-5903.
25. Babu V. "Synthesis and biological evaluation of some novel pyrazolines." Indian Journal of Pharmaceutical Sciences 69.3. 2007; 470.
26. M Gomha, Sobhi, Sayed M Riyadh, and Mohamed M Abdalla. "Solvent-drop grinding method: efficient synthesis, DPPH radical scavenging and anti-diabetic activities of chalcones, bis-chalcones, azolines, and bis-azolines." Current Organic Synthesis 12.2. 2015; 220-228.
27. Gomha, S "Microwave-assisted synthesis of some novel azoles and azolopyrimidines as antimicrobial agents." Molecules 22.3. 2017;346.
28. Gomha, Sobhi, et al. "Ecofriendly one-pot synthesis and antiviral evaluation of novel pyrazolyl pyrazolines of medicinal interest." Turkish Journal of Chemistry 40.3. 2016; 484-498.
29. Bekhit, Adnan A. "Synthesis, in silico experiments and biological evaluation of 1, 3, 4-trisubstituted pyrazole derivatives as antimalarial agents." European journal of medicinal chemistry 163. 2019; 353-366.
30. Ali R. "Synthesis of New Schiff's Bases Derived from 4-Phthalimidyl Acetophenone." Al-Nahrain Journal of Science 14.3. 2011; 1-8.
31. Al-Azzawi A, M S Abd Al-Razzak. "Synthesis, characterization and antibacterial screening of new Schiff bases linked to phthalimide." International Journal of Research in Pharmacy and Chemistry 3.3. 2013; 682-690.
32. Boopathy M, Kathavarayan S. "Preparation of polycyclic pendant chalcone moiety based antimicrobial polyacrylamides." Advances in Polymer Technology 36.3. 2017; 284-294.
33. Samshuddin S. "Synthesis, characterization and biological evaluation of functionalized derivatives of versatile synthon 4, 4'-difluoro chalcone." Der Pharma Chemica 4.4 2012; 1445-1457
34. D Cantillo, B Gutman, C O Kappe, J A m. Chem .Soc. 2011;133: 4465-4475 .