Heterocyclic Letters
Vol. 10| No.1|153-169|Nov–Jan|2020
ISSN : (print) 2231–3087 / (online) 2230-9632
CODEN: HLEEAI
http://heteroletters.org

SYNTHESIS, REACTIONS, AND PROPERTIES OF CHALCONES

Amira A. ghoneim

[a] *Chemistry Department, College of Science, Jouf University, P. O. Box 2014, Sakaka, Aljouf, Kingdom of Saudi Arabia. Tel.: 00966541609390.*
[b]*Chemistry Department, Faculty of Science, Zagazig University, Zagazig, Egypt*
Email: aa_amiraatef@yahoo.com

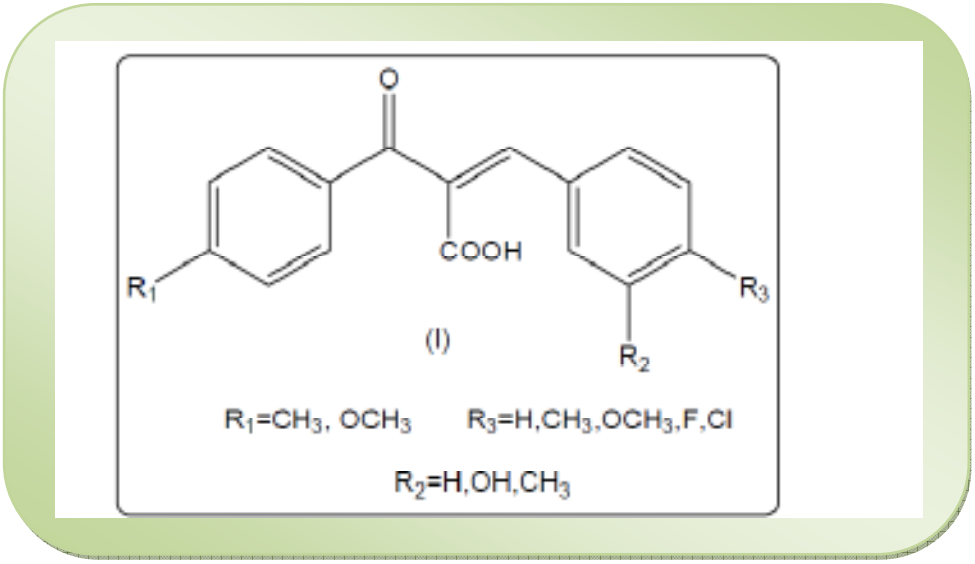
Abstract:
Chalcones, *α, β*-unsaturated ketones attached to two aromatic rings (ring A and B) (Figure 1), plentiful to fit for human consumption plants. Chalcones have several biological activities including antiviral, antibacterial, anti-inflammatory, antifungal, anticancer, antioxidant, analgesic, antiulcer, antimalarial and anthelmintic, and thus comp and consequently incorporate rise a class with critical therapeutic potential. The Michael addition is a completely vital reaction in natural chemistry formation of C-C, C-N, C-S, C-O and C-P bonds. The conjugate because it allows at addition of thiols to α, β-unsaturated carbonyl compounds is known thia-Michael addition, which is a key reaction for the synthesis of *β*-mercapto carbonyl compounds.

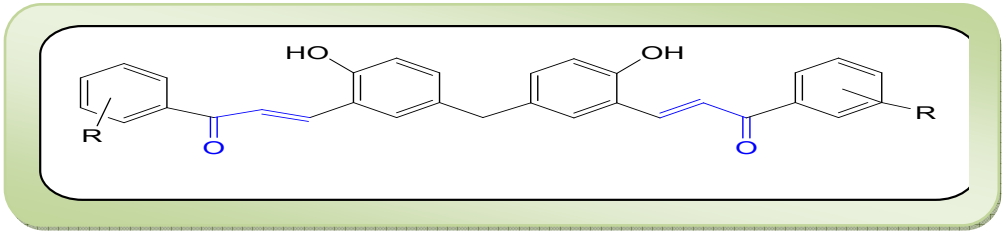
Keywords: Chalcones, Synthesis, reactions, *α, β*-unsaturated ketones and aromatic rings

Introduction:

The time period "chalcone" is a generic term used to explain compounds with the 1,3-diphenylprop-2-en-1-one framework(Figure1). Chalcones are clearly occurring compounds located in numerous plant species like *Angelica, Glycyrrhiza, Humulus*and *Scutellaria*, whichare extensively used as traditional people remedies. Chalcones are intermediates inside the biosynthesis of flavonoids, which are substances widespread in plants and with an array of biological activities[I]. These are abundant in edible plants and are considered to be precursors of flavonoids and is flavonoids. Chalcones are also intermediates in the Auwers synthesis of flavones. Chalcone (and related compounds "chalconoids") [[II]is an aromatic ketone that forms the central core for a variety of important biological compounds, which are known collectively as chalcones. They show antibacterial[III], antimicrobial[IV], antifungal[VI], antitumor and anti-inflammatory properties[VI]. Methyl hydroxychalcone found in cinnamon, was thought to be insulin mimetic, improving insulin response of diabetics. It has since been determined that a

flavonoid is responsible for the insulin-like biological activity[VII]. Malaria is considered a global health problem. In year 2012, there were an estimated 207 million malaria cases and the disease was responsible for 627,000 deaths [VIII]. Even though several anti- malarial capsules were used, their applications are constrained because of toxicity and resistance [IX]. Excessive rates of resistance of Plasmodium falciparum to sulfadoxine-pyrimethamin (SP) and chloroquine were recognized in several endemic regions in Indonesia [X]. Mutations in the pfdhfr. Resistance to Artemisinin-based totally aggregate treatment plans (ACTs) has also already pronounced in 4 nations of the extra Mekong sub region Cambodia, Myanmar, Thailand, and Vietnam [XI]. Primarily based on the cited scenario, the need for brand new anti-malarial agents has inspired the research to find artificial molecules which are capable of answer the problem Plasmodium falciparum possesses a non-photosynthetic plastid organelle known as apicoplast which may be very crucial for the parasite's survival. This respiratory organelle is Plasmodium falciparum-unique and it isn't always present in humans [XII]. For the duration of the respiratory method, electron switch to ferredoxin (PfFd catalyzed through ferredoxin NADP+ reeducates (PfFNR) takes place within the apicoplast[XIII]. The interaction of PfFNR-PfFd proceeds thru an intermolecular electrostatic interaction between acidic amino acid residues of PfFd with simple amino acid residues of PfFNR. There are two acidic regions of PfFd that dominantly make contributions to the electrostatic interplay with PfFNR, the ones are Asp26, Glu29, Glu34, and the others consist of Asp65 and Glu66 [XIV]. Therefore concentrated on inhibition of the interplay of those proteins should open new possibilities to locate new and selective anti-malarial compounds[XV].Chalcones are natural merchandise that can also be obtained synthetically using a exceptionally simple synthesis procedure. The general method implemented to synthesize chalcones is the Claisen-Schmidt response, whilst a present day alternative to synthesize chalcones uses the palladium-catalyst move coupling reactions of styryltrifluoroborates with benzoyl chlorides [XVI]. Chalcone derivatives are widely known for his or her huge spectrum of pharmacological sports, including radical scavenger [XVII], anti-hepatotoxic [XVIII] anticancer [XIX], and anti-malarial houses [XX]. Alkoxylatedchalcone derivatives exhibited better anti-malarial hobby compared to hydroxylatedchalcones[XXI] The synthesis and bioactivity of the prepared compounds have been already pronounced. The interplay of compounds 1–three with bovine serum albumin (BSA)—a protein particularly responsible for the transportation of a number compounds in a dwelling gadget has been studied, and it turned into determined that compound 1 became the most reactive [XXII]. Chalcones are broadly unfold in nature (fruits, greens, spices tea and soy primarily based nutrition) and their 2'-hydroxy derivatives play a vital role inside the flavonoid synthesis and biosynthesis as both precursors and merchandise [XXIII]. Chalcones are the situation of continuous experimental and theoretical investigations. These bendy molecules appear in numerous conformations, and their houses rely upon a appropriate ring substitution as well as at the presence of the *α,β*-unsaturated ketone moiety The CH=CH double bond can exist either in the shape 1, 2 in (*E*)- or (Zconfiguration (Fig. 1), being the (E)-shape the thermodynamically maximum stable and consequently, the general public of the chalcones is isolated as the (*E*)-isomer [XXIV].





(2)

Figure 1

Synthetic methods of preparing chalcones

1- Claisen-Schmidt reaction.

The methods are available for the prepration of chalcones, the important convenient method is the one that involves the Claisen-Schmidt condensation of equimolar quantities of a substituted acetophenone**2** derivatives with substituted aldehydes **3** in the presence of aqueous alcoholic alkali. [XXV]. In the Claisen-Schmidt reaction, used alkali concentration between 10 and 60 % [XXVI-XXVIII]. The reaction is heated out at about 50 ^{o}C for 12-15 hours or at room temperature for one week. Under these conditions, the Cannizaro reaction [XXIX] also takes place and thereby decreases the yield of the desired product. To avoid the disproportionate of aldehyde in the above reaction, the use of benzylidene-diacetate**4** in place of aldehyde has been recommended [XXX] figure (2).

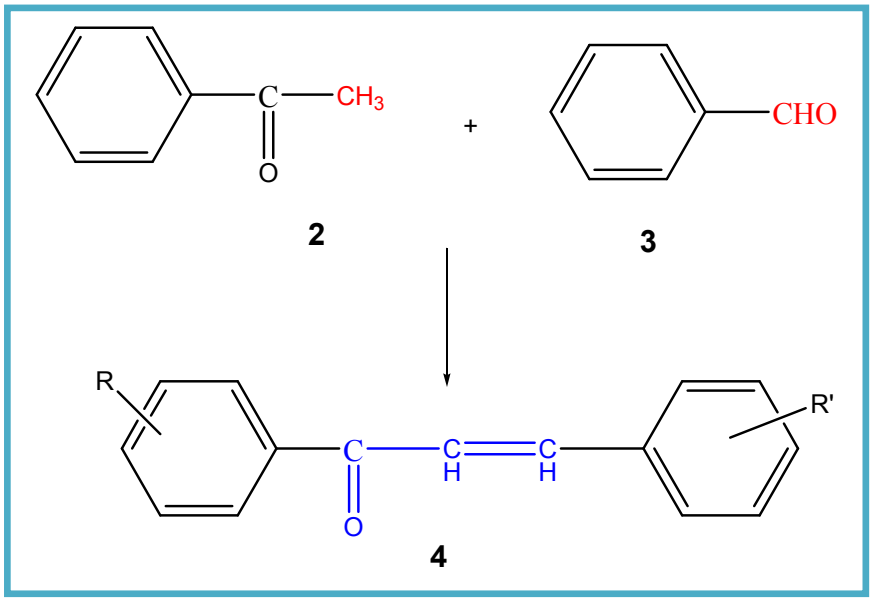


Figure 2. Chalcones by Claisen-Schmidt condensation

Chalcones are generally located in plants, vegetables, and fruits. They have uses in preventing coronary heart ailment, and they also have anti-microbial uses. Chalcones are used as intermediates on the way to make extra complex molecules. Even though the yield of the synthesis above changed into low, the yield changed into pure. Via implementing a few exceptional strategies, the yield may be stepped forward to provide a very useful reaction[XXXI].

Chalcones have many makes use of, some of which might be preventative of microbial illnesses and coronary heart sickness, however chalcones can also be used as intermediates in the synthesis of extra complicated compounds. by using adding sodium borohydride, methanol, and THF to 4-methoxy chalcone**6**, the carbonyl can be reduced to an alcohol, whilst further treatment with NBS and methyl cyanide results in 2, 4-diphenyloxetane[XXXII].This three-step artificial direction acquired excessive yields, and the process changed into finished in a single day. The new mechanism of obtaining 2,4-diphenyloxetane may also allow for more superior studies of this molecule and allow for new scientific breakthroughs relating to this molecule [XXXIII]in figure 3.

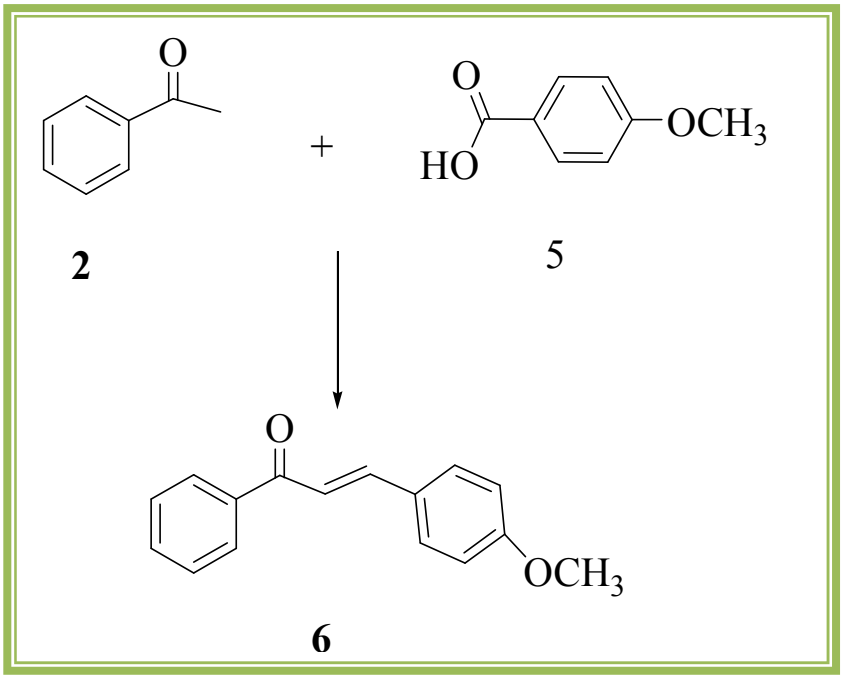


Figure3.Preparation of 4-methoxychalcones

2. Heckr reaction

Chalcones**9** and different flavonoids can be organized via coupling an aryl vinyl ketone **7**with an aryl iodide **8** below Heck reaction situations figure (4) [XXXVI].

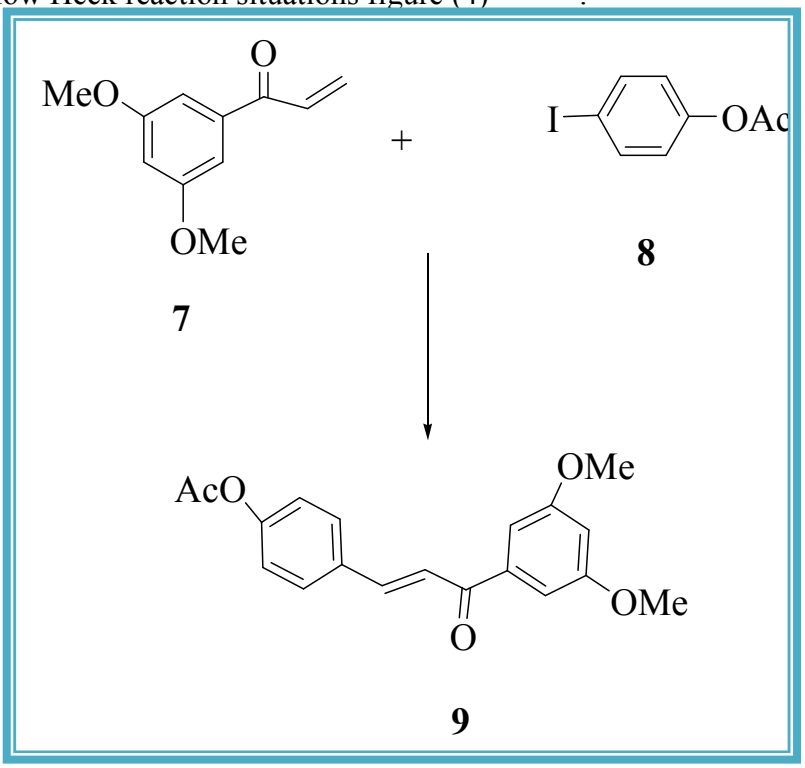


Figure 4. Chalcones by Heck coupling.

General Methods of Synthesis of Chalcones

Chalcones can be synthesis by the acid or base catalyzed aldol condensation of acetophenonederivatives with aromatic aldehydes derivatives [XXXV-XXXVII] such as 2-hydroxyacetophenone **10** react with benaldehyde 3in the presence of 0.1M NaOH to afford chalcone**11**[XXXVIII]figure(5).

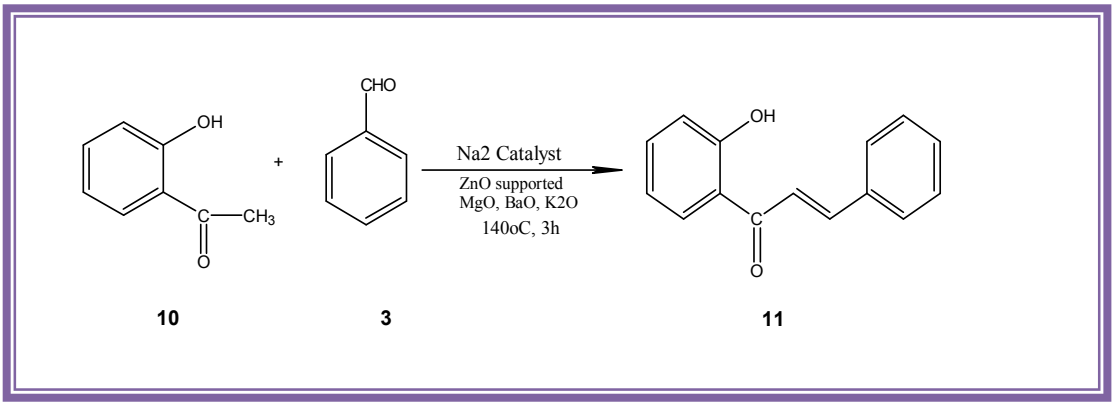


Figure 5.

Another way 2`-hydroxyacetophenone **10**and benzaldehyde**3**was carried out over a zinc oxide used as metal oxide catalyst under solvent free conditions to give 2-hydroxychalcone **11**figure(6).[XXXIX].

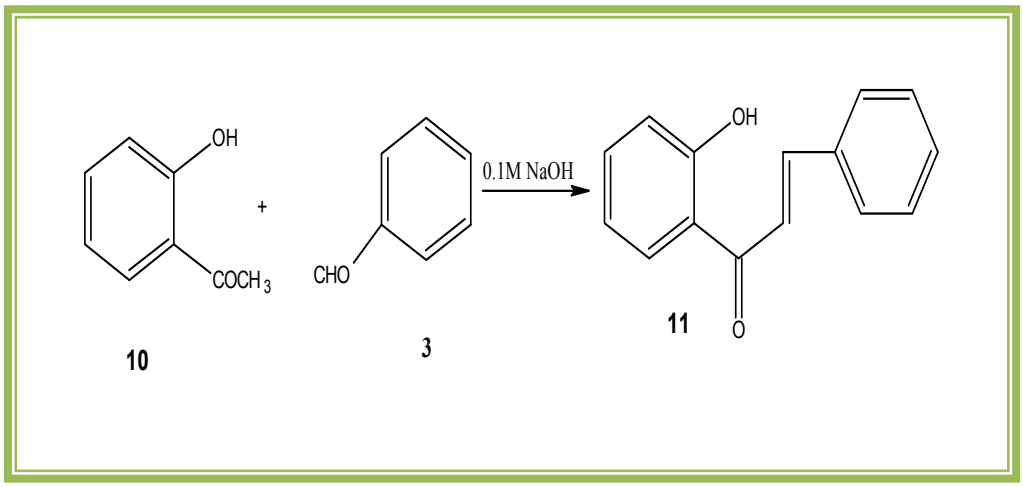


Figure 6.

2,4,5-trimethoxyacetophenone**12**reacted with equimolar proportions of aromatic aldehydes**3** supported by of 30 % alcoholic alkali at room temperature to give chalcones**13**figure(7).[XL].

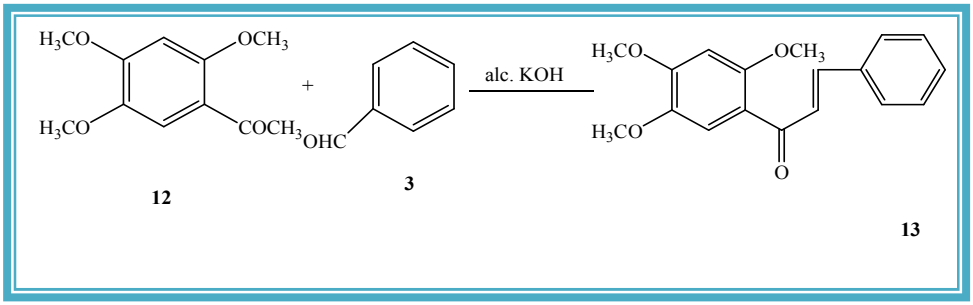


Figure 7.

Another methods when 4-acetyl-3-aryl-syndones **14**subjected to grinding with many aryl aldehydes **3**in the presence of base as a catalyst under solvent free conditions to give sydnonechalcones**15**[XLI]. Figure(8).

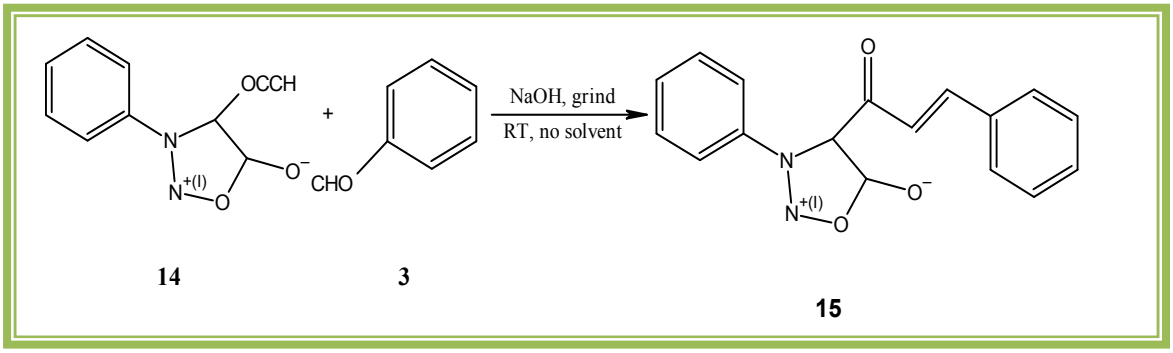


Figure 8.

2-Naphthylmethyl ketones **16**condensed with aryl aldehydes derivatives**3** in the presence of NaOH under methanol as solvent yielded chalcones**17**figure(9).[XLII].

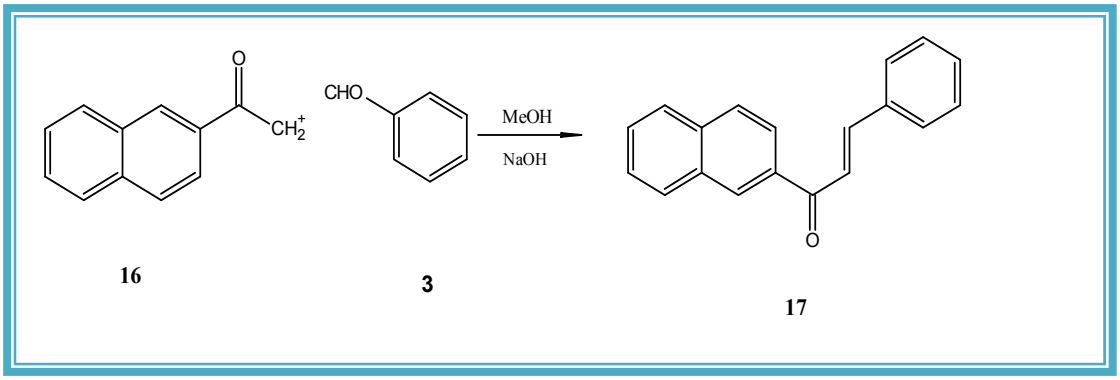


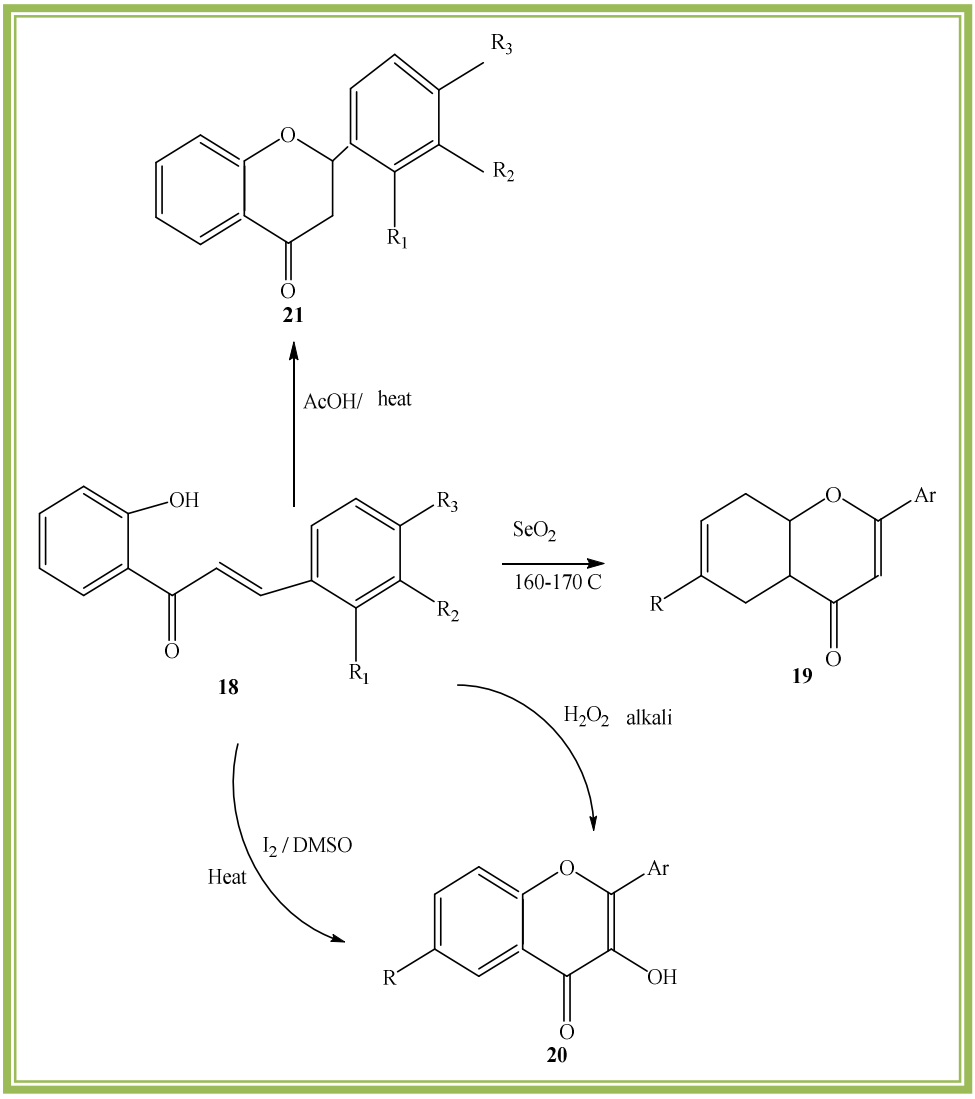
Figure9.

Chemical reactions ofchalcones

1. Oxidation ofchalcones: a-Algar-Fly oxidation of chalcones

Whilst the reaction of acetaminochalcones**18**with selenium dioxide gives 6- acetamino flavones **19**, the response of acetaminochalcones with alkaline hydrogen peroxide deliver 6-acetaminoflavonols **20** as the result of Algar-Flynn oxidation [XLIII]. Moreover I_2/ DMSO can be used as oxidation reagent to synthesize flavones **12**[XLIV, XLV]figure (10). Flavanone

derivatives **21** are composed via refluxing 2`-hydroxy chalcones with glacial acetic acid [XLVI]figure(***10***and 11).



.Ar: C_6H_5, p-$C_6H_4OCH_3$, 3,4-C_6H_3 (CH_2O_2), m-C_6H_4OH; R:CH_3CONH, H

Figure.10. Oxidation of chalcones

b-Epoxidation of chalcones

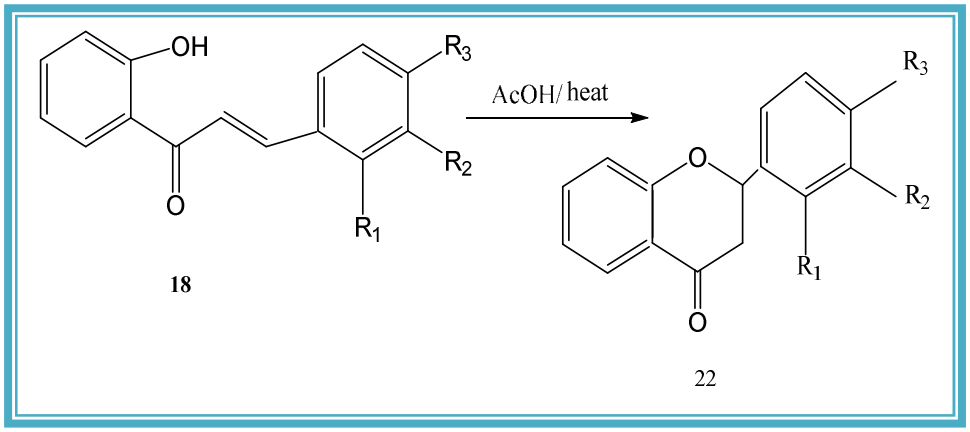


Figure.11. Oxidation of chalcones

The epoxidation of ethylenic corporations of herbal compounds including chromone, chalcone and isoflavone with hydrogen peroxide happens very fastly and with excessive yield in 1-butyl-three-methyl imidazoliumtetrafluoroborate ([bmim] BF_4) **23**[XLVII]figure 12.

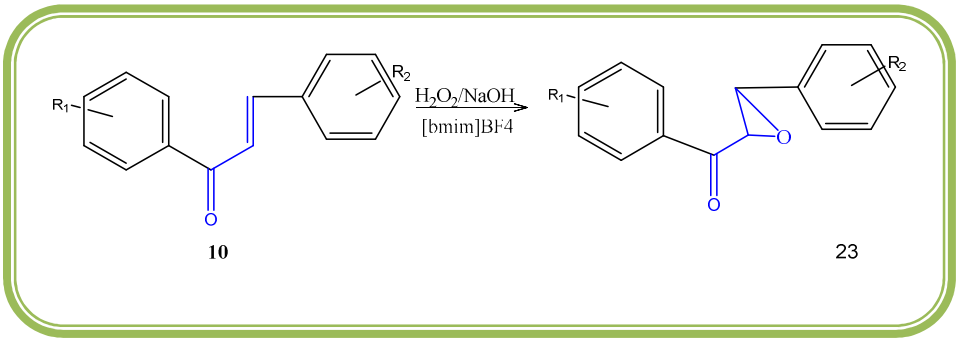
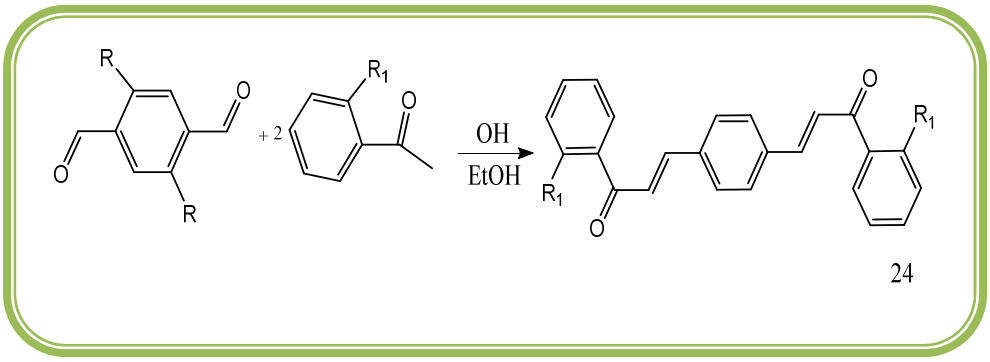


Figure12. Oxidation reactions of chalcones

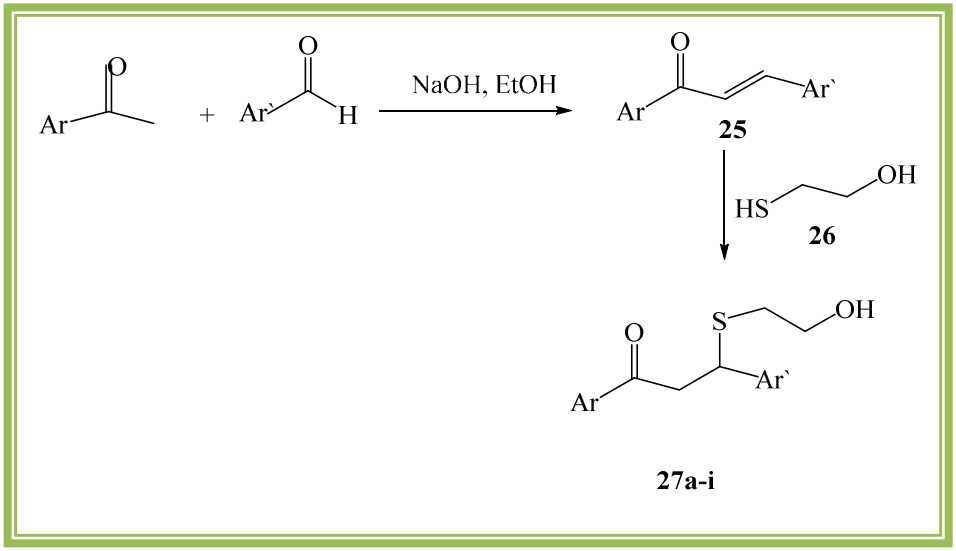
We record two collections of bis-chalcone derivatives**24** (figure13) in which the emission efficiency also confirmed dramatic development after addition of the methoxy (OMe) moiety at the significant phenyl ring. This research offers another way to improve the emission efficiency of chalcone associated compounds apart from the usage of the complexation approach as mentioned by way of D'Al´eo et al. [XLVIII]figure(13).



Comp.	R	R1
24a	H	H
24b	H	OH
24c	OCH_3	H
24d	OCH_3	OH

Figure13.**Synthesis of bis-chalcones**

A series of novel *β*-mercapto carbonyl derivatives (3-(2-hydroxyethylthio)-1,3- diarylpropan-1-one) (**27a-i**) had been prepared via the addition of 2-mercaptoethanol (**26**) to chalcones (**25a-i**) within the presence of a catalytic amount of iodine (10 mol %) in CH_2Cl_2[XLIX]figure(14).



	Ar	Ar'
a •	Ph	3-Cl-C_6H_4
b •	Ph	4-Cl-C_6H_4
c •	Ph	4-CH_3O-C_6H_4
d •	4-Br-C_6H_4	Ph
e •	4-Cl-C_6H_4	4-Cl-C_6H_4
f •	4-CH_3-C_6H_4	4-CH_3-C_6H_4
g •	4-CH_3O-C_6H_4	4-CH_3O-C_6H_4
j •	2-OH-C_6H_4	2-thienyl
i •	2-thienyl	2-thienyl

Figure 14. Synthesis of 3-(2-hydroxyethylthio)-1,3-diarylpropan-1-one (**27a-i**)

Narwal et al. [L] synthesized a few pyrimidine derivatives via the respons of chalcones with exceptional reagents to provide distinctive derivatives of pyrimidine**29.**, and synthesis of pyrazolone derivatives**30**fused with cyclohexenone and thioxo pyrimidine **31**mono and twin via chalcones as an intermediates [LI]figure(15).

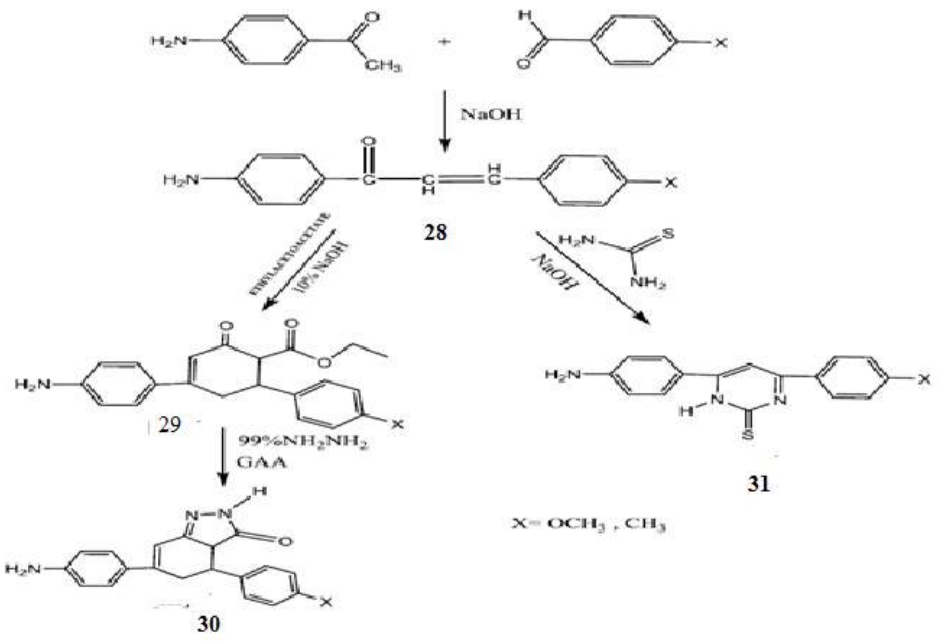


Figure (15).

4,4′-Difluoro chalcone**32**was synthesized by using the base-catalyzed Claisen– Schmidt condensation of 4- fluoroacetophenone and 4-fluorobenzaldehyde (figure **16**)[LII].

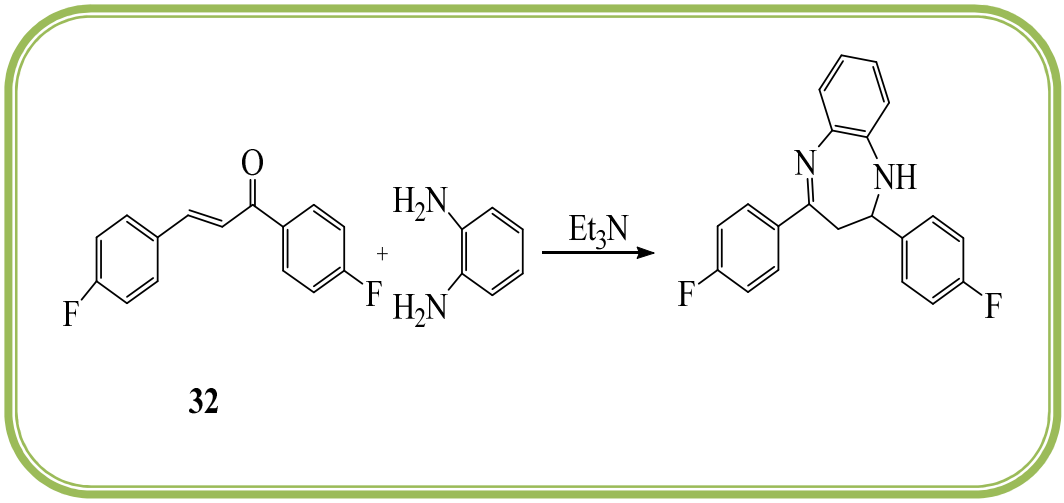


Figure (16).

Some functionalized derivatives of 4,4'-difluoro chalcone**32** have been prepared by condensing it with hydrazine derivatives, orthophenylenediamine, ammonium acetate/acetic acid, ethyl cyanoacetate, malononitrile, acetylacetone, esters of acetoacetic acid, acetoacetanilde, aminoguanidine hydrochloride, urea and thiourea[LIII]figure(17).

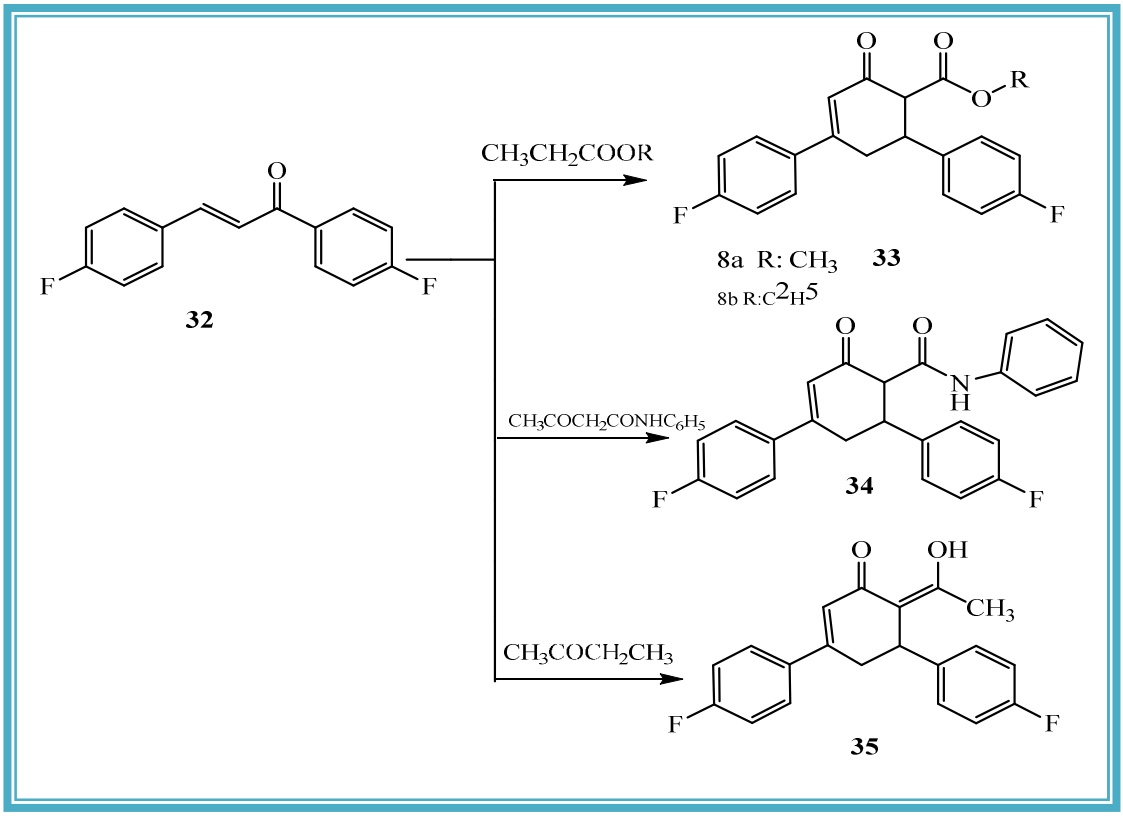
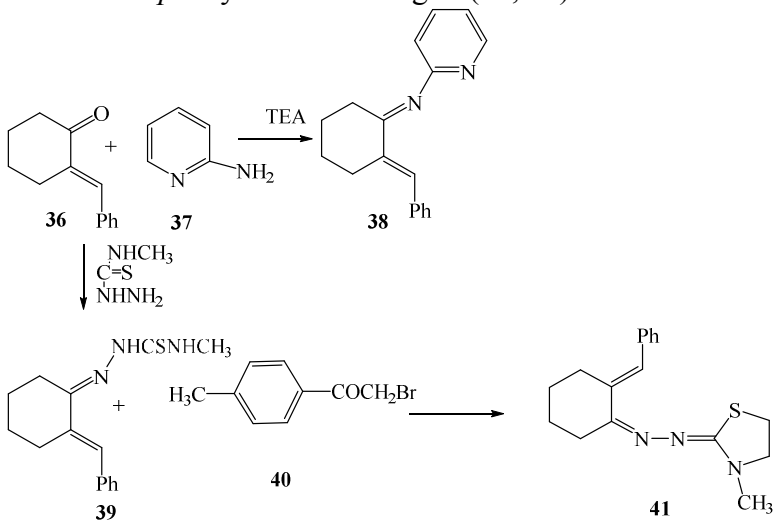
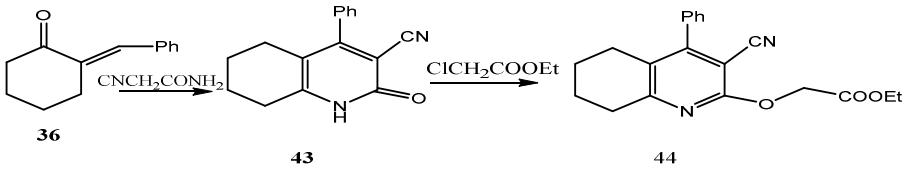


Figure17. Synthesis of cyclohexsenone derivatives

We synthesized several heterocyclic compounds from (*E*)-2-benzylidenecyclohexanone**36**. That was reacted with pyridine-2-amino 37,and also reacted with 4- ethylthiosemicarbazide followed by cyclizationwith 2-bromo-1-*p*-tolyehanone[LIV]figure(18, 19).



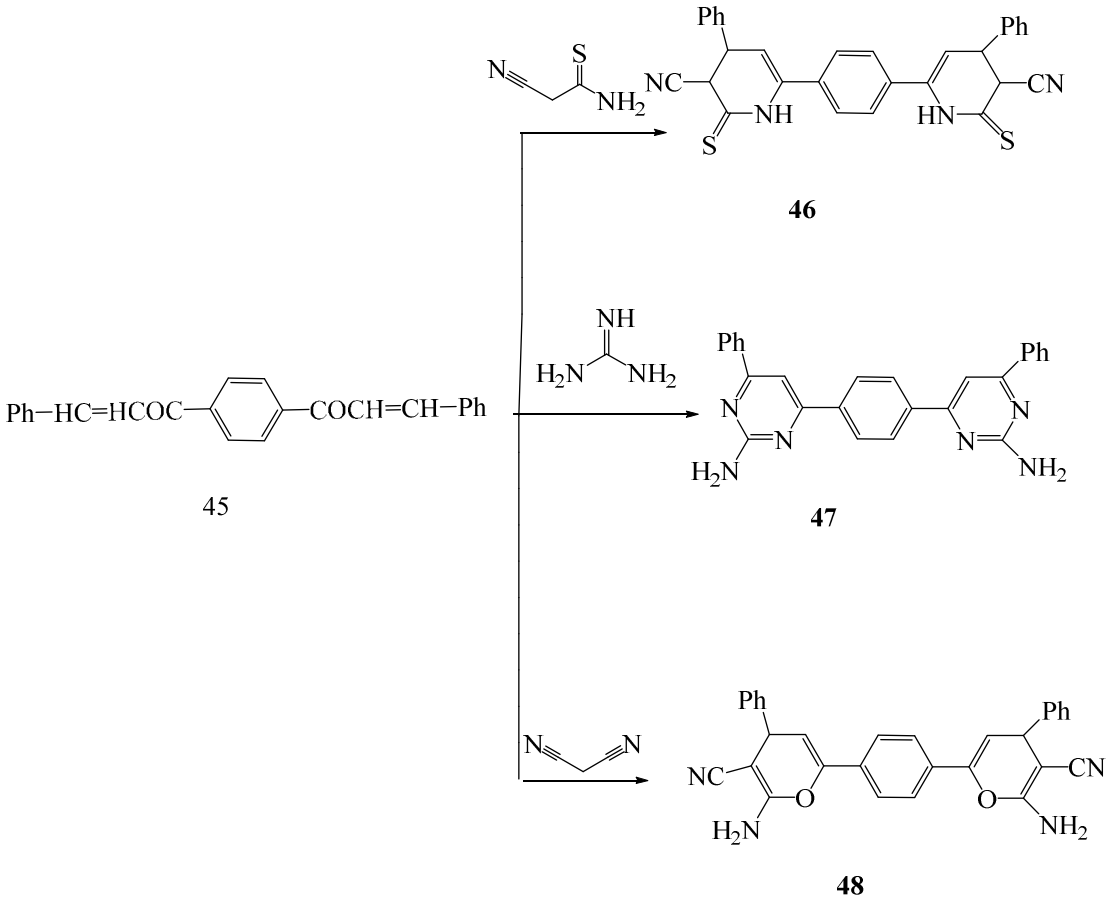
Figure(18).



36 43 44

Figure (19).

A chalcone**45**was prepared by the reaction of 1,4-diacetylbenzene with benzaldehyde. Reaction of this chalcone withcynanothioacetamide/guanidine hydrochloride and malnonitrile in presence of piperdene afforded the corresponding pyridine, pyrimidine,and pyrans derivatives in good yields respectively. Further, bis-chalcone**45** was cyclized to pyrazole analogs by using thiosemicarbazide,semicarbazide and tertiarybutylcarbazate[LV]figure(20).

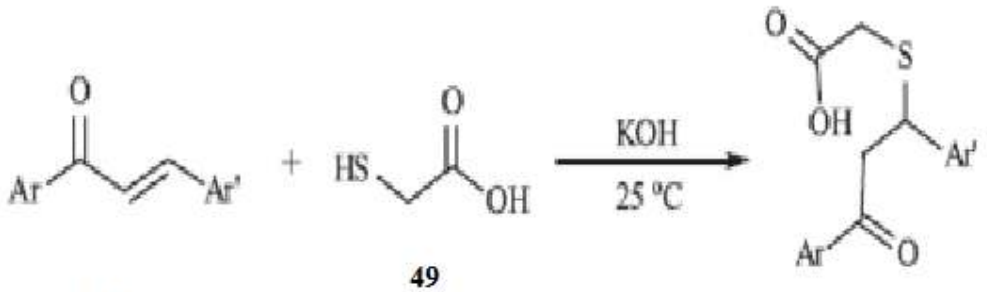


45 46 47 48

Figure (20).

A sequence of 2-(3-oxo-1,3-diarylpropylthio) acetic acid derivatives (**50a-l**) have been organized in excellent yields by the response of chalcone derivatives (**25**) with thioglycolic acid (**49**) and KOH at 25^{o}C. In vitro antibacterial sports of 3anl had been decided towards cultures of micro organism and the biological conduct of those compounds become as compared with popular

antibiotics. Syntheses of chalcone derivatives (1anl) had been performed through Claisenn-Schmidt condensation [LVII]



25 **49** **50a-i**

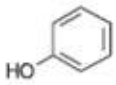
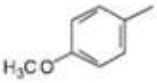
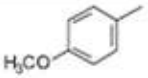
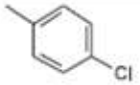
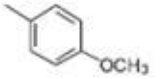
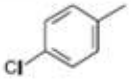
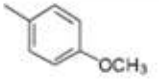
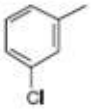
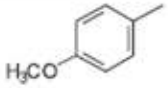
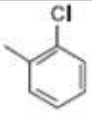
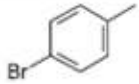
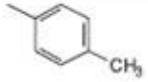
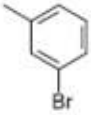
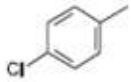
	Ar	Ar'		Ar	Ar'
a			g		
b			h		
c			i		
d			j		
e			k		
f			l		

Figure (21).Synthesis of 2-(3-oxo-1,3-diarylpropylthio)acetic acid derivatives.

References

I. XIA Y, Yang ZY, Xia P, Bastow KF, Nakanishi Y, Lee KH. *Bioorg Med Chem Lett* 10: 699-701, 2000.
II. Nielsen SF, Kharazmi A, Christensen SB.*Bioorg Med Chem*6: 937-945, 1998.
III. Şafak OC, Şahin MF, Yeğen O, İstanbullu İ, Bilgin AA. Şalkonlar-II. *FABAD J Pharm Sci*8: 80-88, 1983
IV. Opletalova V, Hartl J, PalatKJr, Patel A. *FABAD J. Pharm. Sci., 36, 223-242, 2011.*
V. Mathıesen L, Malterud KE, Sund RB. *Biol Med* 22 (1/2): 307-311, 1997.
VI. Ducki S, Forrest R, Hadfield JA, Kendall A, Lawrence NJ, Mcgown AT, *Bioorg Med Chem Lett* 8: 1051-1056, 1998.
VII. Boumendjel A, Pietro AD, Dumontet C, Barron D. *Med Res Rev* 22 (5): 512-529,2002.
VIII. Rosenthal, P.J.; Miller, L.H. Rosenthal, P.J., Ed.; Humana Press: Totowa, NJ, USA, 2001; pp. 3–13.
IX. Tjitra, E.; Marwoto, H.A.; Ompusunggu, R.M.; Tuti, S.; Indonesia 1991, 19, 15–22.
X. Basuki, S.; Fitriah, F.; Riyanto, S.; Budiono; Dachlan, Y.P.; Uemura, H. Indonesia. Malaria J. 2014, 13, 135.
XI. Milani, M.; Balconi, E.; Aliverti, A.; Mastrangelo, E.; Seeber, F.; Bolognesi, M.; Zanetti, G.; J. Mol. Biol. 2007, 367, 501–513.
XII. Kimata-Ariga, Y.; Kurisu, G.; Kusunoki, M.; Aoki, S.; Sato, D.; Kobayashi, T.; Kita, K.; Horii, T.; Hase, T. J. Biochem. 2007, 141, 421–428.
XIII. Kimata-Ariga, Y.; Sitoh, T.; Ikegami, T.; Horii, T.; Hase, T. J. Biochem. 2007, 142, 715–720.
XIV. Al-Masum, M.; Eunice, Ng.Wai, M.C.; Tetrahedron Lett. 2011, 52, 1008–1010.
XV. Kim, B.T.; Chun, J.C.; Hwang, K.J. Bull. Korean Chem. Soc. 2008, 29, 1125–1130.
XVI. Khan, S.A.; Ahmed, B.; Alam, T. Pak. J. Pharm. Sci. 2006, 19, 290–294.
XVII. Yoon, G.; Kang, B.Y.; Cheon, S.H. Arch. Pharm. Res. 2007, 30, 313–316.
XVIII. Awasthi, S.K.; Mishra, N.; Kumar, B.; Sharma, M.; battacharya, A.; Mishra, L.C.; Bhasin, V.K.. Med. Chem. Res. 2009, 18, 407–420.
XIX. Liu, M.; Wilariat, P.; Go, M.L. Med. Chem. 2001, 44, 4443–4452.
XX. Garg, S.; Singh, M.; Raghav, N. IJPSR 2014, 5, 2657–2661.
XXI. Pophale, RA.; Deodhar, M.N. Der Pharma Chemica 2010, 2, 185–193.
XXII. Rueping, M.; Bootwicha, T.; Baars, H.; Sugiono, E. Beilstein J. Org. Chem. 2011, 7, 1680–1687.
XXIII. Syam, S.; Abdelwahab, S.I.; Al-Mamary, M.A.; Mohan, S. Molecules 2012, 17, 6179–6195.
XXIV. Bandgar, B.D.; Gawande, S.S.; Bodade, R.G.; Totre, J.V.; Khobragade, C.N. Bioorg. Med. Chem. 2010, 18, 1364–1370.
XXV. E. P. Kohler and H. M. Chandwell, Org. Synth. Coll., 1922, 2, 1,
XXVI. .Falcao de Fonseca L and BolFac Farm, Univ. Coimbra, Ed. Cient, 28, 49, 1968, C. A., 1970, 72, 121124p.
XXVII. N. Dhar and J. B. Lal, J. Org. Chem., 1958, 23, 1159.
XXVIII. W. Davey and J. R. Gwilt, J. Chem. Soc., 1957, 1008,
XXIX. R. E. Lyle and L. P. Paradis, J. Am. Chem. Soc., 1955,77, 6667
XXX. . M. G. Marathey, J. Uni. Poona, 1952, 1-19.
XXXI. . Yadav, K.; Sharma, J.; Srivastava, J. N. IJGHC. 2012, 1, 264-270.

XXXII. Santos, L.; Pedrosa, R. C.; Correa, R.; Filho, V. C.; Nunes, R. J.; Yunes, R. A. Arch. Pharm. Chem. Life. Sci, 2006, 339, 541-546.
XXXIII. Chang, M-Y.; Tsai, C-Y.; Wu, M-H. Tetrahedron, 2013, 69, 6364-6370.
XXXIV. Bianco A, Cavarischia C, Farina AGuiso M and Marra CA. new synthesis of flavonoids via Heck reaction. Tetrahedron Let, 2003; 44(51): 9107-9109.
XXXV. Claisen, L. and Claparede, A., Ber., 14, 2463 (1881).
XXXVI. Datta, S.C., Murthi, V.V.S. and Seshadri, T.R., Ind. J. Chem., 9, 614 (1971).
XXXVII. Makrandi, J.K. and Kumar, S., Asian J. Chem., 16, 1189 (2004).
XXXVIII. Reichel, L. and Muller, K., Ber., 74,1741 (1941).
XXXIX. Saravanamurugan, S., Palanichamy, M. and Banumathi, A., Catalysis Comm., 6, 399 (2005).
XL. .Anjaneyulu, A.S.R., Sudha Rani, G., Mallavadhani, U.V. and Murthy, Y.L.N., Ind. J. Het. Chem., 4, 9, (1994)
XLI. Bala Krishna, K. and Ganesha Rani., Ind. J. Chem., 42B, 2556 (2003).
XLII. Deshpande, A.M., Narshinha, P.A., Arvind, A.N. and Joseph, E., Bioorg. Med. Chem., 7, 1237 (1999).
XLIII. Raval AA, Shah NM. J Org Chem 22 (3): 304-306, 1957.
XLIV. Huang WH, Chien PY, Yang CH, Lee AR. Chem Pharm Bull 51 (3): 339-340, 2003.
XLV. Cabrera M, Simoens M, Falchi G, Lavaggi ML, Piro OE, Castellano EE, Vidal A, Azqueta A, Monge A, Lo´pez de Cera´in A, Sagrera G, Seoane G, Cerecetto H, Gonza´lez M. Bioorg Med Chem 15: 3356-3367, 2007.
XLVI. G.Cabrera M, Simoens M, Falchi G, Lavaggi ML, Tetrahedron 60: 967- 971, 2004.
XLVII. Meng Guan Tay,1 MeeHing Tiong,1 Ying Ying Chia, Suzie Hui Chin Kuan,1 and Zhi-Qiang Liu, Hindawi Publishing Corporation Journal of Chemistry, Volume 2016, Article ID 3608137, 8 pages http://dx.doi.org/10.1155/2016/3608137
XLVIII. GürkanYerli, HayreddinGezegen and Mustafa Ceylan *Org. Commun*. 5:2 (2012) 70-76.
XLIX. Thaer Saleh Ghali, JumbadHermizTomma *Iraqi Journal of Science, 2017, Vol. 58, No.4C, pp: 2265-2277*
L. Al-Bogami, A.S. 2016**.** *Research on Chemical Intermediates*, **42**: 5457-5477.
LI. Narwal, S., Kumar, S. and Verma, P.K. **2017**.*Chemistry Central Journal*, **11**(52): 2-9.
LII. Al-Sabawi, A.H. **2015**. *International Journal of Enhanced Research in Science*, **4**: 89-94.
LIII. EranthimataSamshuddina, BadiadkaNarayanaa,, BalladkaKunhannaSarojinib,
LIV. Hemmige S. Yathirajanc and RamappaRaghavendradDer Pharma Chemica, 2012, 4(4):1445-1457
LV. Amira AtefGhoneim OCAIJ, 8(8), 2012 [286-292]
LVI. Ghoneim AA, El-Farargy AF (2016) OrganicChemCurr Res 5: 159. doi:10.4172/2161-0401.1000159
LVII. Blatt A.H., Ed., Organic Synthesis, J. Wiley and Sons, New York 1950.hayreddin gezegen1*, _sa karaman2*, mustafa ceylan1 and mervedilmaActaPoloniaePharmaceutica n Drug Research, Vol. 69 No. 5 pp. 893n900, 2012.

Received on December16, 2019.