Synthesis and Characterization of New Pyrazoline and Isoxazoline Derivatives Based on Fluorene

Rafid Saad Dawood , Khetam Tareq Ahmed
Department of Chemistry, College of Science, University of Baghdad , Baghdad , Iraq
E-mail: rafid_saad99@yahoo.com

Abstract:
The aim of the present work is a synthesis of new fluorene derivatives containing heterocyclic moieties. These compounds were synthesized in four groups, each group containing five compounds. The first group was made up of 2-(3-aryl-2-propenoyl) fluorene derivatives **(1a-e)** synthesized from the reaction of 2-acetyl fluorene with appropriate aromatic aldehyde in the presence of sodium hydroxide. The other three groups involved compounds produced from the reaction of **(1a-e)** with hydrazine hydrate (99%) in presence of acetic acid (96%) to give 1-acetyl-5-aryl-3-(fluoren-2-yl) pyrazoline derivatives **(2a-e)**, and with phenyl hydrazine in presence of piperidine to produce 1-phenyl-5-aryl-3-(fluoren-2-yl) pyrazoline derivatives **(3a-e)**, and with hydroxylamine hydrochloride in presence of pyridine to obtain the 5-aryl-3-(fluoren-2-yl) oxazoline derivatives **(4a-e)**. All the compounds of the above three groups were substituted at position **(5)** in pyrazoline and isoxazoline ring with different aryl groups according to aromatic aldehyde used in the preparation of the first group series compounds. The synthesized compounds were identified by spectroscopic methods: FT-IR and ^{1}H-NMR.

Keywords: Fluorene, Pyrazoline, Isoxazoline.

Introduction:
Fluorene-based aromatic ketones are of increasing interest as building blocks for production of drugs and pharmaceuticals and as fine chemicals of industrial relevance [1,2] including applications in the production of thermosetting plastics and lubricating materials. In addition, fluorene-based polymers and copolymers are of interest owing to their unusual optical and electrical properties and are for that reason commonly used in organic light-emitting diodes, flat panel displays and in solar cells [3]. Chalcones have been a subject of great interest for chemists and biochemists all over due to several reasons; their ease to synthesis, vast and interesting pharmacological activities. Synthetic and natural chalcones possess and their potential to be used as important synthetic intermediate for their reaction with different types of reagents have provided altogether diverse areas of interest. Chalcones are well known intermediates for synthesizing various heterocyclic compounds. The compounds with the backbone of chalcones have been reported to possess various biological activities [4-7]. Pyrazolines are well known, and are important nitrogen-containing five-membered heterocyclic compounds. Various methods have been worked out for their synthesis [8-11]. Numerous pyrazoline derivatives have been found to possess considerable biological activities including antimicrobial [12,13], antimycobacterial [14], analgesic [15], antidepressant [16], antifungal [17], anti-diabetic [18], immunosuppressive [19], anti-tubercular agents [20], anti-inflammatory [21], anticancer [22] and antioxidant [23]. On the other hand, isoxazolines have been reported to possess a variety of significant and diverse pharmacological properties [24-27]. Moreover, isoxazoline derivatives have play role as intermediates in the organic synthesis of number of heterocyclic pharmacological active compounds [28].

Experimental:
All reactions were monitored by thin-layer chromatography (TLC) using 0.25 mm pre-coated silica-gel F254 plates. The spots were detected with iodine vapour. The IR spectra were recorded on (SHIMDZU) FT-IR 8400 spectrophotometer. The solid samples were run in KBr discs, and the liquid samples were run as smears (Ethanol). UV spectra were recorded with UV-Visible spectrophotometer (CARY) UV-100 Conc. Melting points were determined on a Gallenkamp melting point apparatus and were uncorrected. ^{1}H-NMR spectra were recorded in (Al-Albyt University, Jordan) on ultra-shield 300 MHz NMR spectrophotometer as acetone-d_6 solutions and with tetramethylsilane (TMS) as an internal standard.

Preparation of 2-(3-aryl-2-propenoyl) fluorene (1a-e)

To a mixture of 2-acetyl fluorene (0.01 mol) and a suitable substituted benzaldehyde (0.01 mol) in absolute ethanol (10 ml), an aqueous NaOH solution (10 ml, 40%) was added dropwise with stirring. The reaction mixture was stirred at room temperature for (5 hrs). The reaction mixture was kept overnight at room temperature then poured into crushed ice and neutralized with hydrochloric acid (50%). The separated solid was filtered off, washed well with cold water, dried in the air and recrystallized from an appropriate solvent to give chalcone derivatives (**1a-e**).

Preparation of 1-acetyl-5-aryl-3-(fluoren-2-yl) pyrazoline (2a-e) and 1-phenyl-5-aryl-3-(fluoren-2-yl) pyrazoline (3a-e)

A mixture of chalcone derivatives (**1a-e**) (0.02 mol) and hydrazine hydrate (99%) (0.02 mol) and acetic acid (96%, 1 ml) [phenyl hydrazine (0.02 mol) and few drops of piperidine] in absolute ethanol was refluxed for (5 hrs). After the completion of the reaction, the contents were kept overnight at room

temperature then poured into a cold water. The solid product was filtered off, washed with cold water. The crude product was crystallized from a suitable solvent to give the corresponding products **(2a-e)** and **(3a-e)** respectively.

Preparation of 5-aryl-3-(fluoren-2-yl) oxazoline (4a-e)

A mixture of chalcone derivative (**1a-e**) (0.02 mol), hydroxylamine hydrochloride (0.02 mol) and pyridine (25 ml) was refluxed for (6 hrs). The mixture was poured onto an ice water. The precipitated product was filtered off, washed with water and recrystallized from an appropriate solvent to afford compounds **(4a-e)**.

Results and Discussion:

The reaction sequence for the synthesis of title compounds are shown in the Scheme. The syntheses of the starting chalcones (1a-e) were accomplished according to the Claisen-Schmidt condensation of 2-acetyl flourene with appropriate aromatic aldehydes in the presence of ethanolic sodium hydroxide solution. The FT-IR spectra of (**1a-e**) showed absorption bands at (1622-1627) cm^{-1} due to (C=C) olefinic stretching and (1688-1711) cm^{-1} attributed to the (C=O) ketone stretching. These chalcones (**1a-e**) are used as suitable precursors for the synthesis of pyrazolines and isoxazolines derivatives. The intermediates (**1a-e**), when treated with hydrazine hydrate/ phenyl hydrazine in absolute ethanol afforded 1-acetyl-5-aryl-3- (fluoren-2-yl) pyrazoline **(2a-e)** and 1-phenyl-5-aryl-3-(fluoren-2-yl) pyrazoline **(3a-e)** respectively. The compounds structure of (**2a-e**) was established by the presence of the imine (C=N) and (C-N) bond stretching bands in their FT-IR spectra between (1657-1672) cm^{-1} and (1257-1276) cm^{-1} respectively, (1679-1710) cm^{-1} assigned to the (C=O) ketone stretching. The ^{1}H-NMR spectrum of compound (**2e**) showed a strong singlet signal at 2.5 ppm attributed to the three protons of the acetyl group (CH_3), a signal at 3.9 ppm assigned to the two protons for (CH_2) of flourene, signal at (9.0) ppm due to (OH) proton, doublet signal at 1.8 ppm and triplet at 3.0 ppm assigned to aliphatic two protons (H4) and (H5) of the pyrazoline ring respectively. Finally a multiplet signals between (7.2-8.2) ppm assigned to the aromatic protons. The FT-IR spectra of (**3a-e**) showed absorption bands between (1667-1670) cm^{-1} and (1258-1279) cm^{-1} due to (C=N) and (C-N) stretching respectively, its ^{1}H-NMR spectrum for compound (**3d**) showed a signal at 2.7 ppm assigned to the three protons of the methoxy group (OCH_3), a signal at 3.9 ppm due to the two protons for (CH_2) of flourene, signals at 2.0 ppm and 3.1 ppm assigned to aliphatic two protons (H4) and (H5) of the pyrazoline ring respectively and a multiplet signals at (7.1-8.3) ppm belong to the aromatic protons.

On the other hand, the compounds (**1a-e**) were treated with hydroxylamine hydrochloride in pyridine under reflux condition to yielded 5-aryl-3-(fluoren-2-yl) oxazoline **(4a-e)**. The structure of these compounds was confirmed by its IR spectra which the following absorption bands at (1666-1672) cm^{-1} and (1264-1277) cm^{-1} attributed to (C=N) and (C-O) stretching respectively. The ^{1}H-NMR spectrum of compound (**4c**) showed a strong singlet signal at 2.5 ppm attributed to the three protons of the methyl group (CH_3), a signal at 3.8 ppm due to the two protons for (CH_2) of flourene, signals at 1.9 ppm and 2.9 ppm belong to aliphatic two protons (H4) and (H5) of the isoxazolin ring respectively and a multiplet signals at (7.2-7.9) ppm attributed to the aromatic protons. Table (1) represents the physical data of compounds (**1a-4e**). Characteristic absorption bands of FT-IR and U.V spectra of compounds (**1a-4e**) are listed in Table (2).

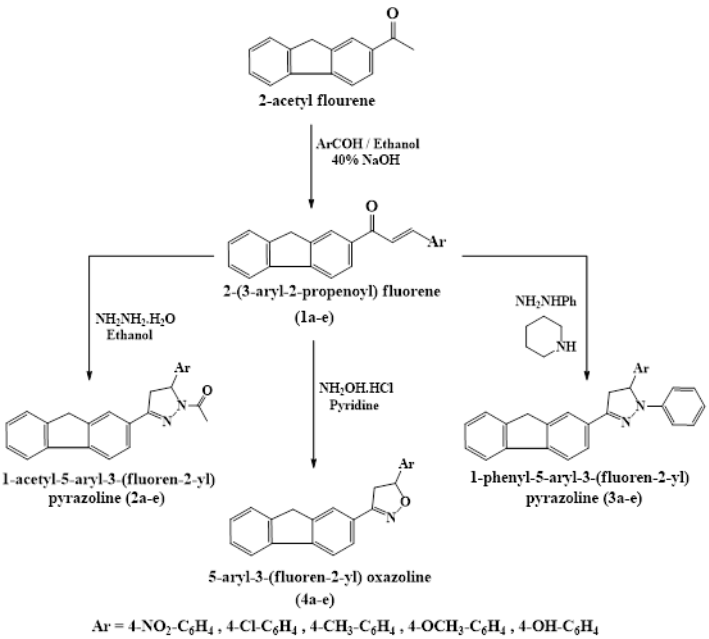


Table (1): Represent the physical data of compounds (1a-4e)

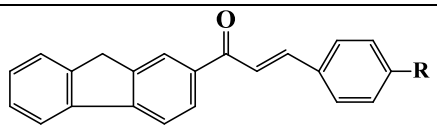
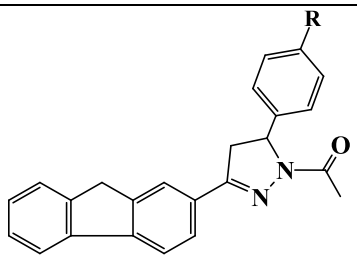
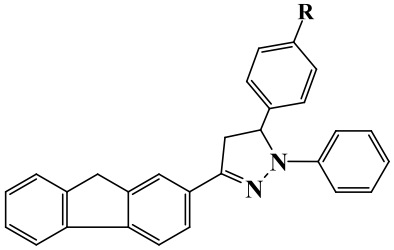
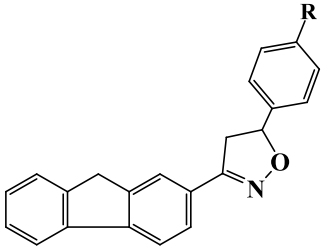
Compound structure	Comp. No.	R	Color of crystal	m.p. °C	Yield %	Solvent of Rec.
	**1a**	NO_2	Yellow	164–166	65	Benzene
	1b	Cl	Yellow	130-132	67	Benzene
	1c	CH_3	Pale-yellow	75-77	70	Chloroform
	1d	OCH_3	Brown	168-170 Dec.	72	Toluene
	1e	OH	Light yellow	129-131	70	Benzene
	**2a**	NO_2	Deep yellow	133-135	62	Chloroform
	2b	Cl	Dark-yellow	175-177	66	Benzene
	2c	CH_3	Yellow-reddish	100-102 Dec.	70	Benzene
	2d	OCH_3	Yellow	150-152 Dec.	71	Toluene
	2e	OH	Dark-yellow	60-62	70	Toluene
	**3a**	NO_2	Yellow-brown	180-182 Dec.	60	Chloroform
	3b	Cl	Pale-yellow	123–125	60	Benzene
	3c	CH_3	Brown	97–99	69	Benzene
	3d	OCH_3	Yellow	107-109	71	Benzene
	3e	OH	Light yellow	147–149	70	Chloroform
	**4a**	NO_2	Brown	123-125	61	Ethanol
	4b	Cl	Light yellow	176-178	62	Ethanol
	4c	CH_3	Yellow	119-121	69	Benzene
	4d	OCH_3	Deep yellow	126-128	75	Benzene
	4e	OH	Yellow-reddish	80-82 Dec.	72	Methanol

Table (2): Characteristic absorption bands of FT-IR and U.V spectra of compounds (1a-4e)

Comp. No.	FTIR spectral data (cm^{-1})							U.V. (λ_{max}) nm
	υ(C=O) Ketone	υ(C-H) Aromatic	υ(C=C) Aromatic	υ(C-H) Aliphatic	υ(C=N) Imine	υ(C-N) or υ(C-O)	Others (υ)	
1a	1711	3061 3053	1591 1566	2939 2843	-	-	2960 (C-H) olefinic 1626 (C=C) olefinic 1535, 1346 (NO_2)	347
1b	1709	3060 3047	1589 1568	2950 2845	-	-	2955 (C-H) olefinic 1627 (C=C) olefinic 1089 (C-Cl)	351
1c	1710	3077 3051	1581 1566	2948 2853	-	-	2959 (C-H) olefinic 1622 (C=C) olefinic	350
1d	1702	3069 3052	1588 1567	2947 2841	-	-	2952 (C-H) olefinic 1626 (C=C) olefinic 1226, 1109 (C-O-C)	358
1e	1688	3066 3039	1580 1563	2949 2858	1672	1262	2963 (C-H) olefinic 1625 (C=C) olefinic 3449 (O-H)	356
2a	1710	3078 3008	1597 1562	2962 2839	1671	1276	1539, 1338 (NO_2)	344
2b	1679	3077 3054	1588 1566	2945 2854	1671	1261	1090 (C-Cl)	367
2c	1709	3073 3055	1580 1567	2953 2843	1672	1260	-	357
2d	1694	3076 3047	1586 1565	2941 2851	1669	1257	1225, 1114 (C-O-C)	356
2e	1696	3080 3057	1585 1564	2946 2853	1657	1262	3447 (O-H)	368
3a	-	3071 3051	1590 1565	2951 2844	1667	1279	1538, 1346 (NO_2)	352
3b	-	3072 3008	1569 1539	2977 2879	1668	1258	1092 (C-Cl)	364
3c	-	3067 3052	1582 1565	2952 2849	1667	1261	-	349
3d	-	3076 3046	1589 1566	2949 2851	1670	1258	1226, 1115 (C-O-C)	371
3e	-	3080 3059	1584 1561	2948 2852	1669	1264	3450 (O-H)	360
4a	-	3079 3066	1593 1568	2951 2849	1666	1277	1541, 1349 (NO_2)	355
4b	-	3076 3053	1586 1559	2946 2854	1667	1264	1078 (C-Cl)	343
4c	-	3071 3058	1584 1563	2949 2846	1669	1268	-	367
4d	-	3097 3016	1583 1521	2968 2835	1672	1266	1228, 1100 (C-O-C)	372
4e	-	3086 3038	1581 1562	2947 2855	1671	1264	3446 (O-H)	352

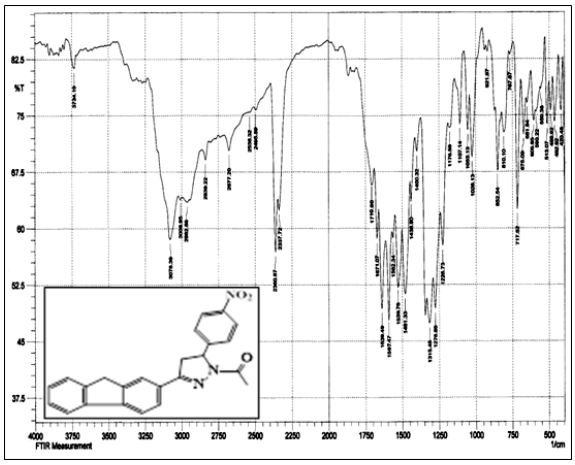


Fig.(1): FT-IR spectrum for compound (2a)

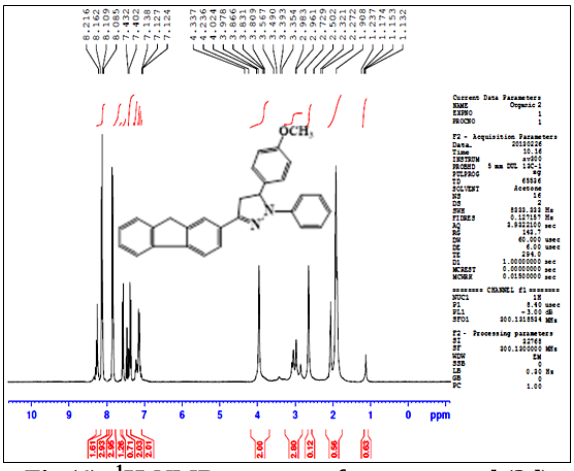


Fig.(4): ^{1}H-NMR spectrum for compound (3d)

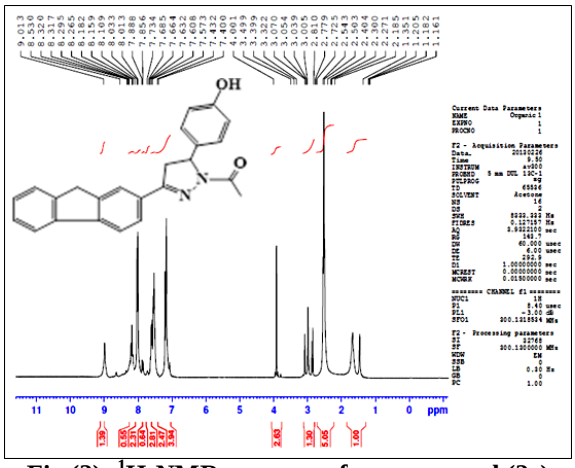


Fig.(2): ^{1}H-NMR spectrum for compound (2e)

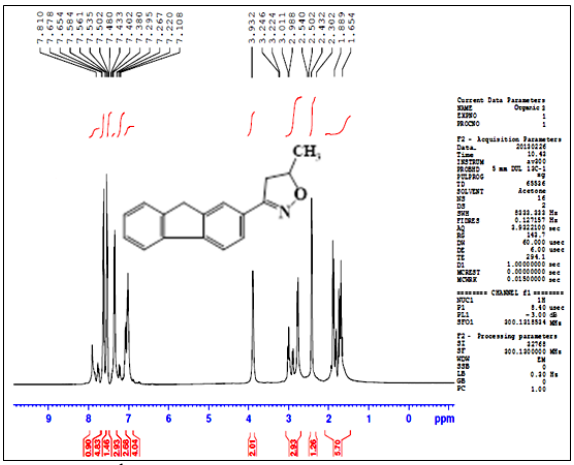


Fig.(5): ^{1}H-NMR spectrum for compound (4c)

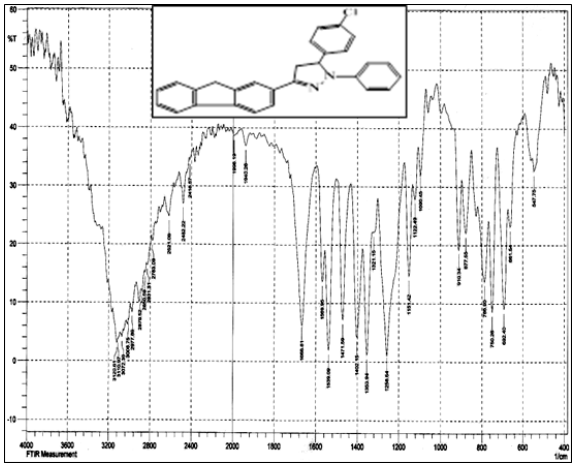


Fig.(3): FT-IR spectrum for compound (3b)

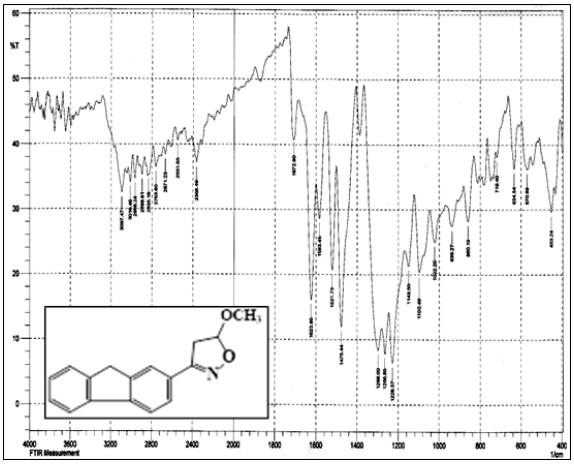


Fig.(6): FT-IR spectrum for compound (4d)

References:

1. M. Bernius, M. Inbasekaran, E. Woo, W. Wu and L. Wujkowski. "Fluorene-based polymers-preparation and applications". J. Mater. Sci. Mater. Electronics". 11(2) (2000) 111-116.
2. E. P. Woo, M. T. Bernius, M. Inbasekaran and W. Wu. "Fluorene-containing polymers and compounds useful in the preparation thereof". U.S. Pat. 6,169, 163 B1 (2001).
3. J. Jo, C. Chi, S. Hoeger and G. Wegner. "Synthesis and Characterization of Monodisperse Oligofluorenes". Chem. Eur. J. 10(11) (2004) 2681-2688.
4. M. L. Go, X. Wu and X. L. Liu. "Chalcones: An update on cytotoxic and chemoprotective properties". Curr. Med. Chem. 12(4) (2005) 483-499.
5. Z. Nowakowska. "A review of anti-infective and anti-inflammatory chalcones". Eur. J. Med. Chem. 42(2) (2007) 125-137.
6. D. Kumar, N. M. Kumar, K. Akamatsu, E. Kusaka, H. Harada and T. Ito. "Synthesis and biological evaluation of indolyl chalcones as antitumor agents". Bioorg. Med. Chem. Lett. 20(13) (2010) 3916-3919.
7. P. M. Sivakumar, S. Ganesan, P. Veluchamy and M. Doble. "Novel chalcones and 1,3,5-triphenyl-2-pyrazoline derivatives as antibacterial agents". Chem. Biol. Drug. Des. 76(5) (2010) 407-411.
8. R. H. Wiley and A. Weissberger. "Pyrazoles, Pyrazolines, Pyrazolidines, Indazoles and Condensed Rings; In The Chemistry of Heterocyclic Compounds". Ed. Inter science Publishers: New York. Vol.22 (1967) p.180.
9. J. Elguero, A. R. Katritzky, C. W. Rees and E. F. Scriven. "In Comprehensive Heterocyclic Chemistry II". Ed. Pergamon Press: Oxford. Vol.3 (1996) p.1.
10. A. Lévai. "Synthesis of 2-pyrazolines by the reactions of α,β-unsaturated aldehydes, ketones, and esters with diazoalkanes, nitrile imines, and hydrazines". J. Heterocycl. Chem. 39(1) (2002) 1-13.
11. B. S. Dawane, Y. B. Vibhute, S. G. Konda and M. R. Mali. "Synthesis of Some New 3-(Substituted phenyl) - 5 - (9-anthryl) - 2 - pyrazolines, 1-Phenyl-3-(substituted phenyl)-5-(9-anthryl)-2-pyrazolines and 2- (9 - Anthryl) – 4 - (substituted phenyl) - 1,5 - benzothiazepines as Antibacterial Agents". Asian J. Chem. 20(6) (2008) 4199-4204.
12. T. Zitouni, A. Ozdemir and K. Guven. "Synthesis of Some 1-[(N,N-Disubstituted thiocar bamoylthio) acetyl]-3-(2-thienyl)-5-aryl-2-pyrazoline Derivatives and Investigation of Their Antibacterial and Antifungal Activities". Arch. Pharm. 338(2-3) (2005) 96-104.
13. A. Ozdemir, T. Zitouni, Z. Kaplancýklý, G. Revial. and K. Guven. "Synthesis and antimicrobial activity of 1-(4-aryl-2-thiazolyl)-3-(2-thienyl)-5-aryl-2-pyrazoline derivatives". Eur. J. Med. Chem. 42(3) (2007) 403-409.
14. M. Shaharyar, A. Siddiqui, M. Ali, D. Sriram and P. Yogeeswari. "Synthesis and in vitro antimycobacterial activity of N^1-nicotinoyl-3-(4′-hydroxy -3 ′- methyl phenyl) – 5 - [(sub) phenyl] – 2 - pyrazolines". Bioorg. Med. Chem. Lett. 16(15) (2006) 3947-3949.
15. M. Amir, H. Kumar and S. A. Khan. "Synthesis and Pharmacological Evaluation of Pyrazoline Derivatives as New Anti inflammatory and Analgesic Agents". Bioorg. Med. Chem. Lett. 18(3) (2008) 918-922.
16. Y. P. Rajendra, A. R. Lakshmana, L. Prasoona, K. Murali and K. P. Ravi. "Synthesis and antidepressant activity of some 1,3,5-triphenyl-2-pyrazolines and 3-(2//-hydroxy naphthalene-1//-yl) - 1,5 – diphenyl – 2 - pyrazolines". Bioorg. Med. Chem. Lett. 15(22) (2005) 5030-5034.
17. M. G. Mamolo, D. Zampieri, V. Falagiani, L. Vio and E. Banfi. "Synthesis and antifungal activity of (±)-1-(5-aryl-3-pyridin-2-yl-4,5-dihydro-pyrazol-1-yl) – 2 - imidazol – 1 – yl - ethanone derivatives". IL Farmaco. 58(4) (2003) 315-322.
18. J. H. Ahn and Co-workers. "Synthesis and DP-IV inhibition of cyano-pyrazoline derivatives as potent anti-diabetic agents". Bioorg. Med. Chem. Lett. 14(17) (2004) 4461-4465.
19. J. G. Lombardino and I. G. Otterness. "Novel immunosuppressive agents. Potent immunological activity of some benzothiopyrano[4,3-c]pyrazol-3-ones". J. Med. Chem. 24(7) (1981) 830-834.
20. M. A. Ali, M. Shaharyar and A. A. Siddiqui. "Synthesis, structural activity relationship and anti-tubercular activity of novel pyrazoline derivatives". Eur. J. Med. Chem. 42(2) (2007) 268-275.
21. M. E. Shoman, M. A. Aziz, O. M. Alya, H. H. Farag and M. A. Morsy. "Synthesis and investigation of anti-inflammatory activity and gastric ulcerogenicity of novel nitric oxide-donating pyrazoline derivatives". Eur. J. of Med. Chem. 44(7) (2009) 3068-3076.
22. R. Bashir and Co-workers. "Synthesis of some new 1,3,5-trisubstituted pyrazolines bearing benzene sulfonamide as anticancer and anti-inflammatory agents". Bioorg. Med. Chem. Lett. 21(14) (2011) 4301-4305.
23. T. S. Jeong, J. K. Kim, K. Cho and S. Lee. "Novel 3,5-diaryl pyrazolines and pyrazole as low-density lipoprotein (LDL) oxidation inhibitor". Bioorg. Med. Chem. Lett. 14(11) (2004) 2719-2723.
24. P. Z. Zhang, X. L. Li, H. Chen, Y. N. Li and R. Wang. "The Synthesis and Biological Activity of Novel Spiro-Isoxazoline C-Disaccharides Based on 1,3-Dipolar Cycloaddition of Exo-Glycals and Sugar Nitrile Oxides". Tetrahedron Letters. 48 (44) (2007) 7813-7816.
25. S. P. Gurubasavaraja and Y. S. Agasimundin. "Synthesis and Antimicrobial Screening of Certain Substituted Chalcones and Isoxazolines Bearing Hydroxy Benzofuran". Rasayan J. Chem. 1(2) (2008) 421-428.

26. M. Imran, S. A. Khan and N. Siddiqui. "Therapeutic Potential of 2-Isoxazolines". Ind. J. Pharm. Sc. 66(4) (2004) 377-381.
27. H. S. Youn and E. J. Lee. "Synthesis and Biological Evaluation of Isoxazoline and Isoxazole Derivatives as 5-HT2A and 5-HT2C Receptor Ligands". Bull. Korean Chem. Soc. 30(8) (2009) 1873-1876.
28. D. H. Tambekar and S. B. Dahikar. "Antibacterial activity of some Indian ayurvedic preparations against enteric bacterial pathogens". J. Adv. Pharm. Tech. Res, 2(1) (2011) 24-29.

تشييد وتشخيص مشتقات جديدة للبايرازولين والايزواوكسازولين مستند على الفلورين

رافد سعد داود ، ختام طارق احمد

قسم الكيمياء ، كلية العلوم ، جامعة بغداد ، بغداد ، العراق

الملخص

يهدف هذا العمل هو تشييد مشتقات جديدة للفلورين تحتوي على حلقات غير متجانسة. هذه المركبات حضرت في اربعة مجاميع، كل مجموعة تحتوي على خمس مركبات. حضرت مركبات المجموعة الاولى وهي مشتقات 2-(3-اريل-2-بروبينويل) فلورين **(1a-e)** من تفاعل 2-أسيتيل فلورين مع الديهايدات اروماتية ملائمة وبوجود هيدروكسيد الصوديوم. أما المجاميع الثلاثة الاخرى فقد حضرت من تفاعل المركبات **(1a-e)** مع الهيدرازين المائي (99%) بوجود حامض الخليك (96%) لتكوين مشتقات 1- أسيتيل-5-اريل-3-(فلورين-2-يل) بايرازولين **(2a-2e)**, ومع الفنيل هيدرازين بوجود البابيريدين لتكوين مشتقات 1- فنيل-5-اريل-3-(فلورين-2-يل) بايرازولين **(3a-3e)**، ومع هيدروكلوريد الهيدروكسيل أمين بوجود البريدين للحصول على مشتقات 5-اريل-3-(فلورين-2-يل) آيزواوكسازولين **(4a-4e)**. إن جميع مركبات المجاميع الثلاثة أعلاه يكون التعويض فيها عند الموقع **(5)** في حلقة البايرازولين والايزواوكسازولين بمجاميع أريل وحسب المركبات الاروماتية الالدهايدية المستخدمة في تحضير مركبات المجموعة الاولى. تم تشخيص المركبات المحضرة بمطيافية FT-IR و ^{1}H-NMR.

الكلمات المفتاحية: فلورين، بايرازولين، آيزواوكسازولين.