Synthesis and Study of Some 4-Chlorophenoxy Methyl Substituted amido1,3,4-Oxadiazoles, 1,3,4-Thiadiazoles and 1,2,4-Triazoles from 4-Chloro phenoxy acetic acid

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الخلاصة:

حُضِّرَ في هذا البحث عدد من معوضات 4,3,1–أوكسادايازول و 4,3,1–ثايادايازول و4,2,1–ترايازول ذات الفعالية البيولوجية المتوقعة من خلال تفاعل كلوريد 4–كلوروفينوكسي الخليك (C_1) مع ألانينات المثيل في رباعي هيدروفيوران ليعطي (C_4) والذي اعطى عند تفاعله مع الهيدرازين المائي هيدرازيد الحامض (C_5). ثم مفاعلة الهيدرازيد الناتج (C_5) مع ثنائي كبريتيد الكربون في محلول هيدروكسيد البوتاسيوم الكحولي ليعطي 4,3,1–أوكسادايازول معوض (C_6) بينما اعطى تفاعل الهيدرازيد (C_5) مع كل من آيزوثايوسيانات الأليل والآيزوثايوسيانات الفنيل معوضي الثايوسميكاربازيد (C_7 و C_{13}).

تم تحويل معوضي الثايوسميكاربازيد (C_7 و C_{13}) الى مركبي ثايادايازول (C_8 و C_{14}) ومركبي ترايازول (C_9 و C_{15}) من خلال تفاعلهما مع حامض الكبريتيك المركز ومحلول هيدروكسيد الصوديوم المائي على التوالي. وأعطى تفاعل هيدرازيد الحامض (C_5) مع ثايوسيانات الامونيوم ثايوسميكاربازيد معوض (C_{10}) و حُضِّرَ منه ثايادايازول (C_{11}) وترايازول (C_{12}) من خلال تفاعله مع حامض الكبريتيك المركز ومحلول هيدروكسيد الصوديوم المائي على التوالي. شُخِّصَتْ المركبات المحضرة باستخدام طيف U.V و I.R والطرق الفيزياوية.

Abstract:

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In this paper the synthesis of some substituted 1,3,4-oxadiazole, 1,3,4-thiadiazoles and 1,2,4-triazoles is reported. 4-Chlorophenol was treated with chloroacetic acid to give 4-chlorophenoxy acetic acid (C_1) which was reacted with thionyl chloride followed by methyl alaninate (C_3) to give the methyl ester (C_4). The ester (C_4) was converted to corresponding hydrazide (C_5) by it's reaction with hydrazine hydrate in ethanol. Hydrazide (C_5) was treated with carbon disulfide in alcoholic potassium hydroxide to give substituted 1,3,4-oxadiazole (C_6), while the reaction of hydrazide (C_5) with ally isothiocyanate and with phenyl isothiocyanate gave substituted thiosemicarbazides (C_7) and (C_{13}) respectively.

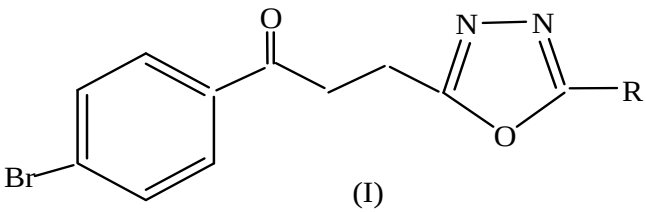
Thiosemicarbazides (C_7 and C_{13}) were converted to substituted 1,3,4-thiadiazoles (C_8 and C_{14}) and 1,2,4-triazoles (C_9 and C_{15}) by their reactions with concentrated sulfuric acid and with aqueous sodium hydroxide solution respectively. The reaction of acid hydrazide (C_5) with ammonium thiocyanate gave thiosemicarbazide (C_{10}) from which substituted 1,3,4-thiadiazole (C_{11}) and 1,2,4-triazole (C_{12}) were synthesized by it's reaction with concentrated sulfuric acid and with aqueous sodium hydroxide solution respectively.

The structures of the synthesized compounds were established on the bases of U.V and I.R spectrum analysis and physical measures.

Keywords: Thiosemicarbazide, 1,3,4-oxadiazole, 1,3,4-thiadiazole, 1,2,4-triazole.

Introduction:

Five member heterocyclic compounds showed various type of biological activities such as 2,5-disubstituted 1,3,4-oxadiazoles (I) which are associated with diverse antimicrobial biological activities[(1)].

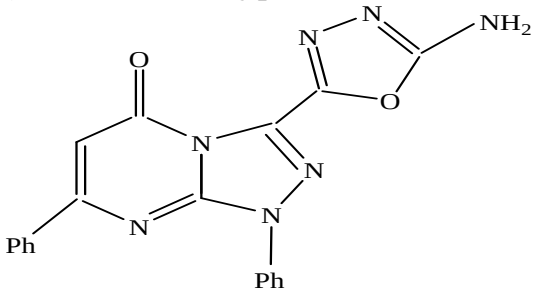


(I)

3, 5- Diaryl- 1,2,4-oxadiazole derivatives showed significant reduction of tumor cell count as well as tumor weight, where as life span of the treated mice also increased, this derivatives was prepared of 2-chlorobenzamidoxime with substituted benzoyl chloride in pyridine[(2)].

A series of novel 1,2,4-oxadiazole and 1,3,4-oxadiazole derivatives were synthesized and evaluated for *in-vitro* antibacterial and antifungal activity[(3,4)]. 1,2,4-oxadiazoles possess analgesic properties[(5)]. In another research 1,2,4-oxadiazole compounds were prepared from reaction of

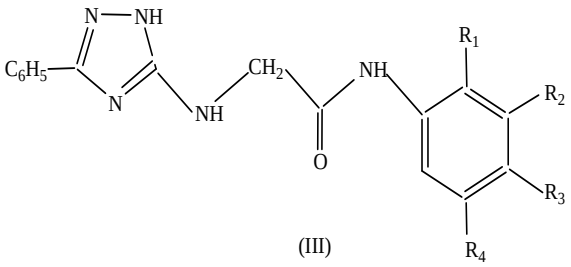
hydroxylamine with chloroform in pyridine[6]. The thiosemicarbazide and 1,3,4-oxadiazole (II). Possess antihypertensive and diuretic activities[7].



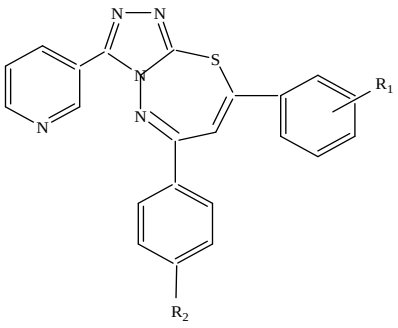
(II)

In another search 1,3,4-oxadiazole was prepared by G.V. Suresh Kumar[8].

In recent years 1,2,4-triazoles and its derivatives have received considerable attention owing to their synthetic and effective biological importance. The heterocycles bearing a symmetrical triazoles moiety were reported from cyclization of Benzamidoguanidine with a solution of sodium in absolute alcohol[9], treated of thiosemicarbazides with concentrated sodium hydroxide solution[10] or reaction of thiocarbohydrazide with carboxylic acid in pyridine[11]. The compounds (III) and (IV) shows antiviral[12] and antileishmanial activities[13] respectively.

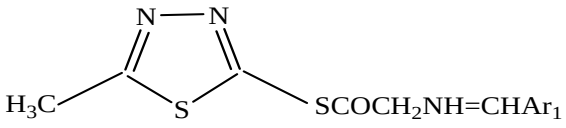


(III)

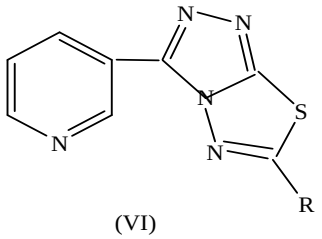


(IV)

Substituted 1,3,4-thiadiazole showed various biological activity like antibacterial[14] as (V) and Anti-microbial[15] as (VI).



(V)



(VI)

Experimental:

a. Measurements:

Melting points were determined in open capillary tubes in a Thomas Hoover melting point apparatus and are uncorrected. U.V-

Visible/Shimadzu-1601 and Infrared spectrum were recorded on FT-IR , Shimadzu/157.

b. Preparations:

4-Chlorophenoxy acetic acid(C_1)[16]:

A solution of sodium hydroxide (4.5 g/25 ml) was added slowly to mixture of 4-chlorophenol (6.63 g, 0.049 mole) and chloroacetic acid (4.7 g, 0.049 mole). The mixture was heated with stirring for (30 minutes) to evaporate most of the solvent, then water (150 ml) was added and the solution acidified with concentrated hydrochloric acid. The resultant precipitate was filtered and recrystallized from ethanol / water. m.p. 154-155ºC (Lit.[16] 154-155 ºC).

Methyl alaninate hydrochloride(C_2)[17]:

In a dry round bottom flask (250 ml) in ice bath, alanine (8.9 g, 0.1 mole) in absolute methanol (100 ml) was added, thionyl chloride (8 ml, 0.11 mole) was added slowly with stirring for (30 minutes), the mixture was refluxed for (15 minutes) the solution become clear, the solvent was evaporated under reduced pressure, The solid product was recrystallized from ethanol,m.p. 112 ºC (Lit.[17] 105-107 ºC).

Methyl alaninate(C_3)[18]:

A mixture of methyl alaninate hydrochloride (12.5 g, 0.1 mole) in methylene dichloride (100 ml) in dry conical flask (250 ml), dry ammonia gas was bubbled through the mixture with stirring (ammonia gas generated by a concentrated ammonium hydroxide in round bottom flask through anhydrous calcium chloride trap) by glass dropper in to the mixture, the precipitate of ammonium chloride, was separated by filtration, the filtrate was taken in a beaker, the solvent was evaporated to give oily methyl alaninate with characteristic amine odor. Tables (1,2).

Methyl-N-(4-chlorophenoxy acetyl) alaninate(C_4)[19]:

A mixture of 4-chlorophenoxy acetic acid (C_1) (2.47g, 0.024 mole) and thionyl chloride (2 ml, 0.027 mole) was heated until the formation of a clear solution. The solution then cooled in an ice-bath, followed by the addition of dry tetrahydrofuran (10 ml). Methyl alaninate (C_3) (2.47 g, 0.024 mole) was added slowly to the acid chloride solution and the mixture then refluxed for (15 minute). The colorless oil was formed upon the addition of water (25 ml) and 20% sodium bicarbonate solution. The residue oily ester was separated. Tables (1,2).

4-chlorophenoxy acyl alanine hydrazide(C_5)[20]:

A mixture of methyl ester (C_4) (2.81g, 0.01 mole) and hydrazine hydrate (95%, 2.5 ml, 0.05 mole) in (50 ml) absolute ethanol was

refluxed for (2 hours). The mixture was cooled to room temperature then the solvent evaporate under reduced pressure. The precipitate was filtered and recrystallized from ethanol. Tables (1,2).

5-(Phenoxy methyl substituted amido)-1,3,4-oxadiazole-2-thiol(C_6) [21]***:***

4-Chlorophenoxy acyl alanine hydrazide (C_5) (2.81g, 0.01 mole) was dissolved in solution (0.56 g, 0.01 mole of potassium hydroxide in 150 ml of ethanol 96%). Carbon disulphide (6 ml, 0.1 mole) was added as pushes, the mixture was heated under reflux for (3 hours) until the evolution of hydrogen sulphide was stopped. The solvent was evaporated under reduced pressure, the product cooled and poured on ice-water (50 ml). Acidified with dilute HCl to (pH=5-6), solid product (C_6) was obtained by filtration and purified by recrystallization from ethanol. Tables (1,2).

1-(4-Chlorophenoxy acyl alanoyl)-4-substituted thiosemicarbazides (C_7,C_{13}) [10]***:***

The hydrazide (C_5) (0.55g, 0.002 mole) was mixed with (0.002 mole) from (phenyl isothiocyanate or allyl isothiocyanate) in absolute ethanol (25 ml). The mixture was refluxed for (6 hours), the solvent was evaporated under reduced pressure. The precipitates were filtered and recrystallized from ethanol. Tables (1,2).

1-(4-Chlorophenoxy methyl substituted amido) thiosemicarbazide (C_{10}) [19]***:***

A mixture of hydrazide (C_5) (2.81g, 0.01 mole), ammonium thiocyanate (0.76 g, 0.05 mole) in ethanol (50 ml) was refluxed for (3 hours). The solvent was evaporated and the precipitate filtered, recrystallized from ethanol. Tables (1,2).

2-Amino-5-(4-Chlorophenoxy methyl substituted amido)-1,3,4-thiadiazole (C_8 C_{11},C_{14}) [18]***:***

The thiosemicarbazides (C_7,C_{10} or C_{13}) (0.005 mole) was dissolved in concentrated sulfuric acid (5 ml) with cooling. The reaction mixtures were stirred well, kept at room temperature for (2 hours), then poured onto crushed ice, concentrated ammonium hydroxide was added, the precipitated solids filtered, washed with water and recrystallized from ethanol to give (C_8,C_{11},C_{14}). Tables (1,2).

3-(4-Chlorophenoxy methyl substituted amido) -4-substituted-1,2,4-triazole-5-thiol (C_9,C_{12},C_{15}) [22]***:***

The thiosemicarbazide (C_7,C_{10} or C_{13}) (0.005 mole) was refluxed in 10% sodium hydroxide (50 ml) for (3 hours), the mixture was cooled, poured into water and filtered. The filtrates was acidified with dilute

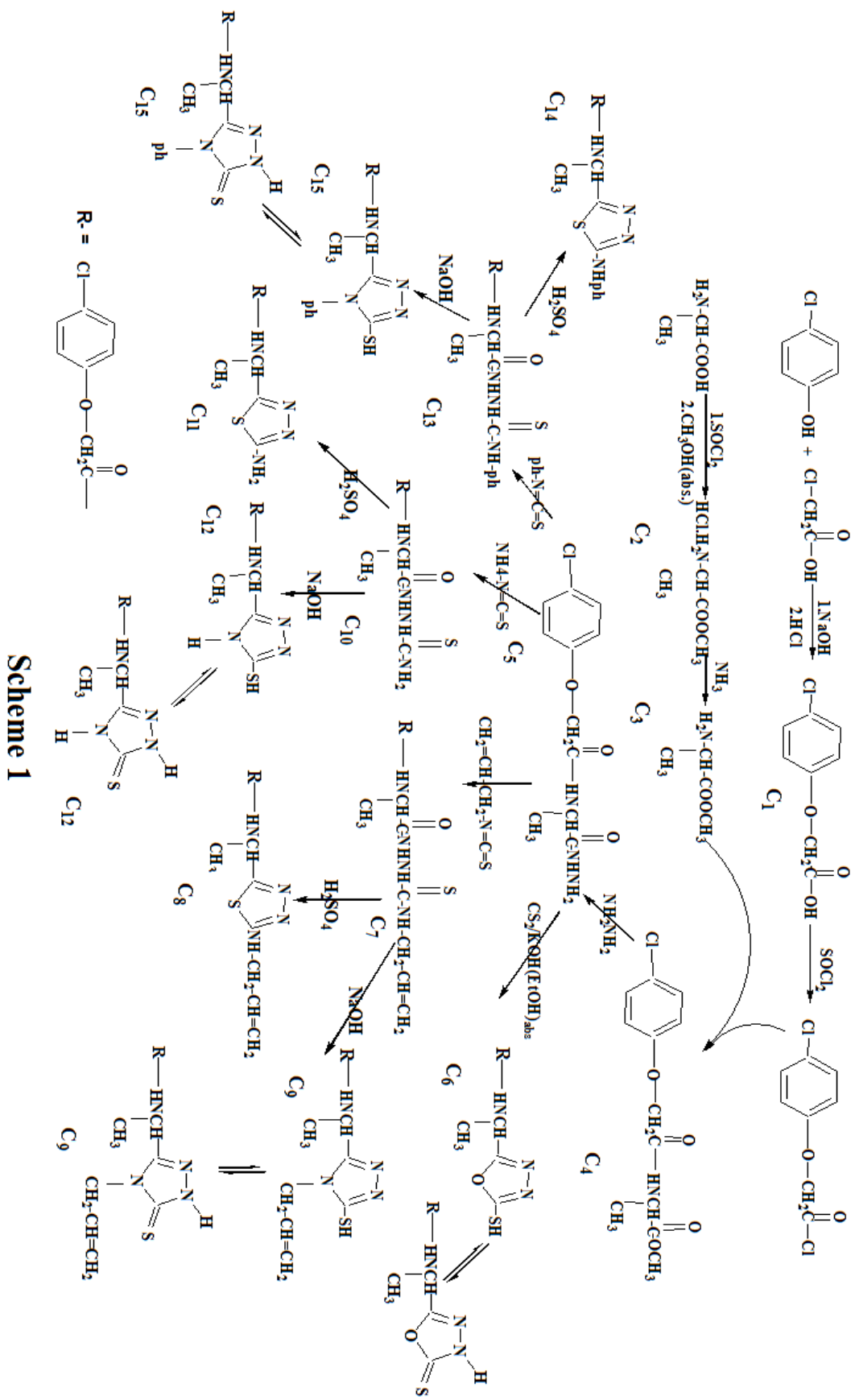
hydrochloric acid to give the crude products (C_9,C_{12} and C_{15}) which were filtered, washed with water and recrystallized from ethanol. Tables (1,2).

Table 1: physical data of compounds (C_1-C_{15})

Comp. No.	m.p. ºC	Yield %	Color	Molecular Formula
C_1	154-155	65	white	$C_8H_7ClO_3$
C_2	112	92	white	$C_4H_{10}ClNO_2$
C_3	Oily	47	colorless	$C_4H_9NO_2$
C_4	Oily	64	brown	$C_{12}H_{14}ClNO_4$
C_5	158	71	white	$C_{11}H_{14}ClN_3O_3$
C_6	130-131	16	brown	$C_{12}H_{12}ClN_3O_3S$
C_7	129-130	96	white	$C_{15}H_{19}ClN_4O_3S$
C_8	140-142	52	grey	$C_{15}H_{17}ClN_4O_2S$
C_9	136-137	47	brown	$C_{15}H_{17}ClN_4O_2S$
C_{10}	85-87	33	brown	$C_{12}H_{15}ClN_4O_3S$
C_{11}	128-130	52	pale brown	$C_{12}H_{13}ClN_4O_2S$
C_{12}	150-151	32	brown	$C_{12}H_{13}ClN_4O_2S$
C_{13}	162-164	77	white	$C_{18}H_{19}ClN_4O_3S$
C_{14}	267 dec.	15	white	$C_{18}H_{17}ClN_4O_2S$
C_{15}	202-204	59	grey	$C_{18}H_{17}ClN_4O_2S$

Table 2: spectral data of compounds (C_1-C_{15})

Comp. No.	U.V λ *max.*	*v* cm^{-1}				
		N-H	O ‖ C—— N	O ‖ C—— O	C=N	C=S
C_1	236	---	---	1706	---	---
C_2	256	3423	---	1745	---	---
C_3	290	3423	1541	1683	---	---
C_4	292	3422	1595	1735	---	---
C_5	234	3208	1667	---	---	---
C_6	227	3447	1636	---	1596	1238
C_7	226	3504	1668	---	---	1217
C_8	274	2430	1596	---	1490	---
C_9	257	3089	1646	---	1454	1231
C_{10}	345	3425	1601	---	---	1208
C_{11}	255	3311	1635	---	1492	---
C_{12}	273	3443	1595	---	1490	1235
C_{13}	227	3244	1681	---	---	1252
C_{14}	206	3454	1603	---	1552	---
C_{15}	227	3449	1635	---	1490	1239



Scheme 1

Results and Discussion:

In this paper the synthesis of substituted 1,3,4-oxadiazole, 1,3,4-thiadiazoles and 1,2,4-triazoles is reported (Scheme 1). 4-Chlorophenoxy acetic acid (C_1) was treated with thionyl chloride to give the corresponding acid chloride, which reacted with methyl alaninate (C_3) [obtained from esterification of alanine by absolute methanol/thionyl chloride then neutralized with ammonia] to produce methyl N-(4-Chlorophenoxy acetyl) alanine (C_4).

The I.R spectrum of compound (C_1) show absorption at 1706 cm^{-1} due to (C=O acid) while the (C=O) absorption for ester (C_4) appeared at 1735 cm^{-1}. UV-Visible spectrum of (C_4) showed bands at (292 nm). The ester (C_4) was converted to acid hydrazide (C_5) by it's reaction with hydrazine hydrate, the I.R spectrum for hydrazide show absorptions at 3208 cm^{-1} (N-H) and 1667 cm^{-1} for (C=O). UV-Visible spectrum of (C_5) showed bands at (234 nm). The acid hydrazide (C_5) was treated with was treated with carbon disulfide ethanolic potassium hydroxide to give substituted 1,3,4-oxadiazole (C_6) and with isothiocyanate compounds to give substituted thiosemicarbazides (C_7,C_{10} and C_{13}). The I.R spectrum of substituted 1,3,4-oxadiazole (C_6) showed absorptions at 1636 cm^{-1} (C=O), 1596 cm^{-1} (C=N) and 1238 cm^{-1} due to (C=S). UV-Visible spectrum of (C_6) showed bands at (227 nm). The I.R spectrum of thiosemicarbazides (C_7,C_{10} and C_{13}) showed absorptions at 1668-1681 cm^{-1} for (C=O) and 1217-1252 cm^{-1} for (C=S). UV-Visible spectrum of (C_7,C_{10} and C_{13}) showed bands at (226-345 nm).

The substituted thiosemicarbazides (C_7,C_{10} and C_{13}) were treated with concentrated sulfuric acid and with aqueous sodium hydroxide solution to give substituted 1,3,4-thiadiazoles (C_8,C_{11} and C_{14}) and substituted 1,2,4-triazoles (C_9,C_{12} and C_{15}) respectively. The I.R spectrum of substituted 1,3,4-thiadiazoles (C_8,C_{11} and C_{14}) showed absorption at 1490-1552 cm^{-1} (C=N) . UV-Visible spectrum of (C_8,C_{11} and C_{14}) showed bands at (206-274 nm). The I.R spectra of substituted 1,2,4-triazoles (C_9,C_{12} and C_{15}) showed absorptions at 1454-1490 cm^{-1} (C=N) and 1231-1239 cm^{-1} for (C=S). UV-Visible spectrum of (C_9,C_{12} and C_{15}) showed bands at (227-273 nm). Table (2).

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