June 2008 *Volume 4 Issue 4*

Trade Science Inc.

Organic CHEMISTRY

An Indian Journal

Full Paper

OCAIJ, 4(4), 2008 [259-265]

Synthesis and molluscicide activity of some new pyrazole heterocycles

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Received: 19th March, 2008 ; Accepted: 24th March, 2008

ABSTRACT

Some new pyrazolopyrimidines, pyrazoloimidazolopyrimidines, pyraz- olopyrimidopyrimidines, pyrazolyltetrazole, pyrazolyloxadiazole, and N,N-di-heterocyclylamidine have been synthesis starting from 5-amino-4-cyano-1-phenylpyrazole **(1)**. Some of the newly synthesized pyrazole heterocycles have been tested as Mollucicidal agents.

INTRODUCTION

Pyrazoles represent one of the most active classes of heterocyclic compounds possessing a wide range of biological activites[1-4]. These interesting biological importance of pyrazoles attracted our attention to incorporate the other biologically active heterocyclic moieties such as pyrimidine, triazole, imidazoline, tetrazole and oxadiazole with pyrazole nucleus, using 5-amino-4-cyano-1-phenylpyrazole **(1)** as a precursor for

their preparation. Generally, such incorporation may enhance the biological activity of the newly isolated pyrazole heterocycles. Therefore, some of the newly synthesized compounds have been tested as Mollucicidal agents *Biomphlaria alexandrina* snails the intermediate host Schistosoma monsoni, which help in causing intestinal Bilharzias,the national problem in Egypt.

RESULTS AND DISCUSSION

As a part of our program directed on the synthesis of bioactive pyrimidine derivatives[5] and azoles[6,7] It was found, when compound I was subjected to condensation reaction using triethyl ortoformate under fusion conditions, 4-cyano-5-ethoxymethylideneamino-1-phenylpyrazole **(2)** was obtained, which has been cyclized on refluxing with benzhydrazide in absolute ethanol to afford 5-benzamido-4-imimo-1-phenylpyrazolo[3,4-d] pyrimidine **(3)**. In a trial to cyclized the latter to 2,7-diphenylpyrazolo[4,3-e][1,2,4] triazolo [1,5-c]pyrimidine **(4)** when it boiled in diphenylether was failled[SCHEME 1]. Structures of compounds**(2-4)**were fully supported by their analytical and spectroscopic data as IR of **(2)** didn't exhibit any band attributed to NH_2 and IR of **(3)** confirm the nucleophilic attack on CN which led to disappearance of absorption band characteristic to CN group group near 2200cm^{-1}. Also, IR of **(4)** didn't show any band for carbonyl group.

On the other hand, Hydrazinolysis of **(2)** with hydrazine hydrate afforded 5-amino-4-imino-1-phenyl pyrazolo[3,4-d]pyrimidine**(1)**,which was condensed with 4-chlorobenzaldehyde togive 2-(4-chlorophenyl)-7-phenyl-3H-pyrazolo[4,3-e](1,2,4)triazolo[1,5-c]pyrimidine **(7)** through the initially formed arylideneamino **(6)** as intermediate (SCHEME 1). The MS(70 eV) of **(7)** exhibited a molecular ion peak at m/z (Ir/%) = 348, which supported its structure.

Furthermore,5-formamido-4-imino-1-phenyl pyrazolo[3,4-d]pyrimidine **(9)** and 5-acetamido-4-imino-1-phenylpyrazolo[3,4-d] pyrimidine **(11)** were

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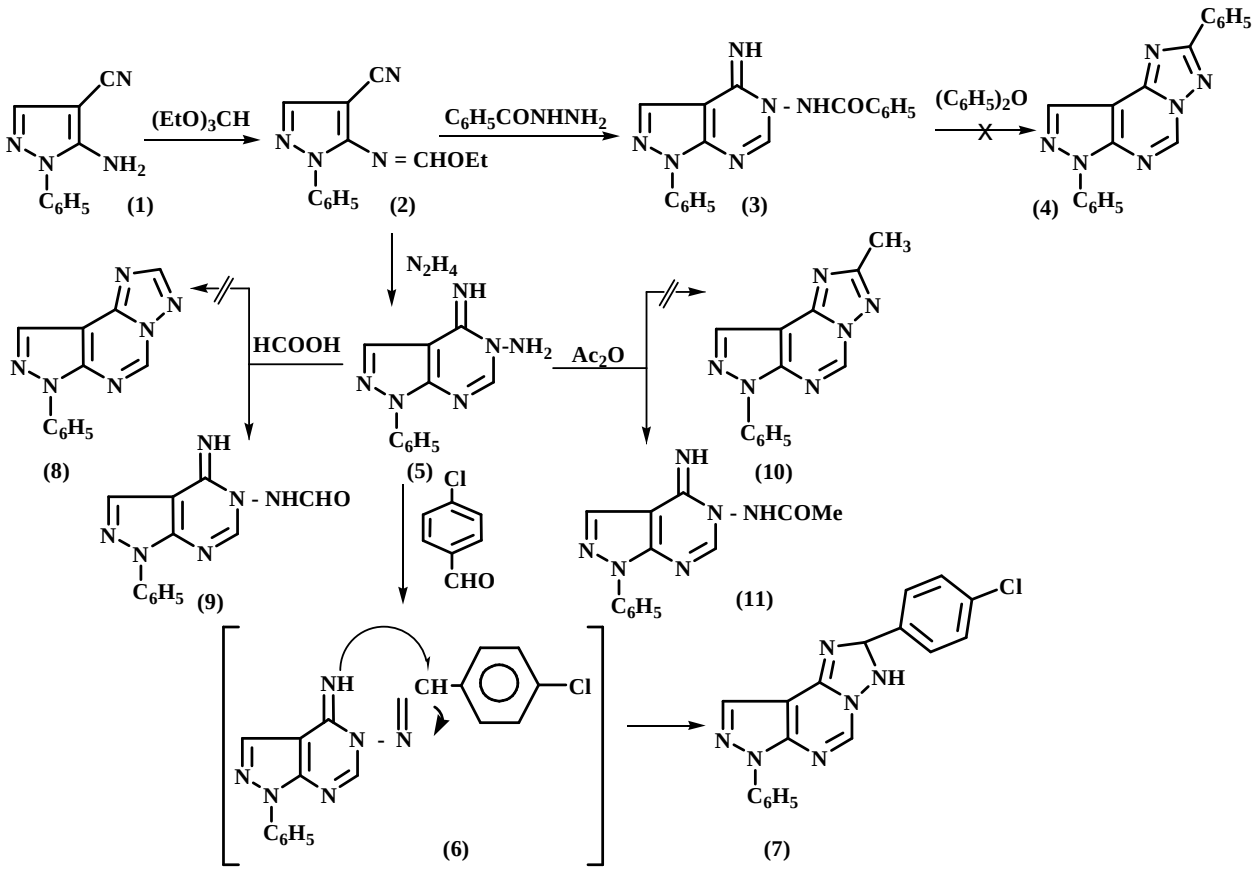
synthesized by formylation of **(5)** with formic acid or by acetylation with acetic anhydride, with unsuccessful synthesis of the desired new condensed triazoles, 7-phenyl pyrazolo[4,3-e][1,2,4] triazolo[1,5-c]pyrimidine **(8)** and 2-methyl-7-phenylpyrazolo[4,3-e][1,2,4] triazolo [1,5-c]pyrimidine **(10)**, respectively (SCHEME 1).

Moreover, cyclization of compound **(1)** with formamide was carried our in the manner described by Dave and Shukla[8] yielded 4-amino-1-phenylpyrazolo [3,4-d]pyrimidine **(12)**. Which also was utilized for the synthesis of some additional related condensed pyrazoles by cyclocondensation of **(12)** with some reagents such as 1,2-dibromoethane, ethyl cyanoacetate, malononitrile and acrylonitrile. Consequently, treatment of **(12)** with 1,2-dibromoethane in pyridine-water mixture affored 7-phenyl-2,3-dihydro-imidazolino[1,2-c]pyrazolo[4,3-e]pyrimidine **(13)** (SCHEME 2) .

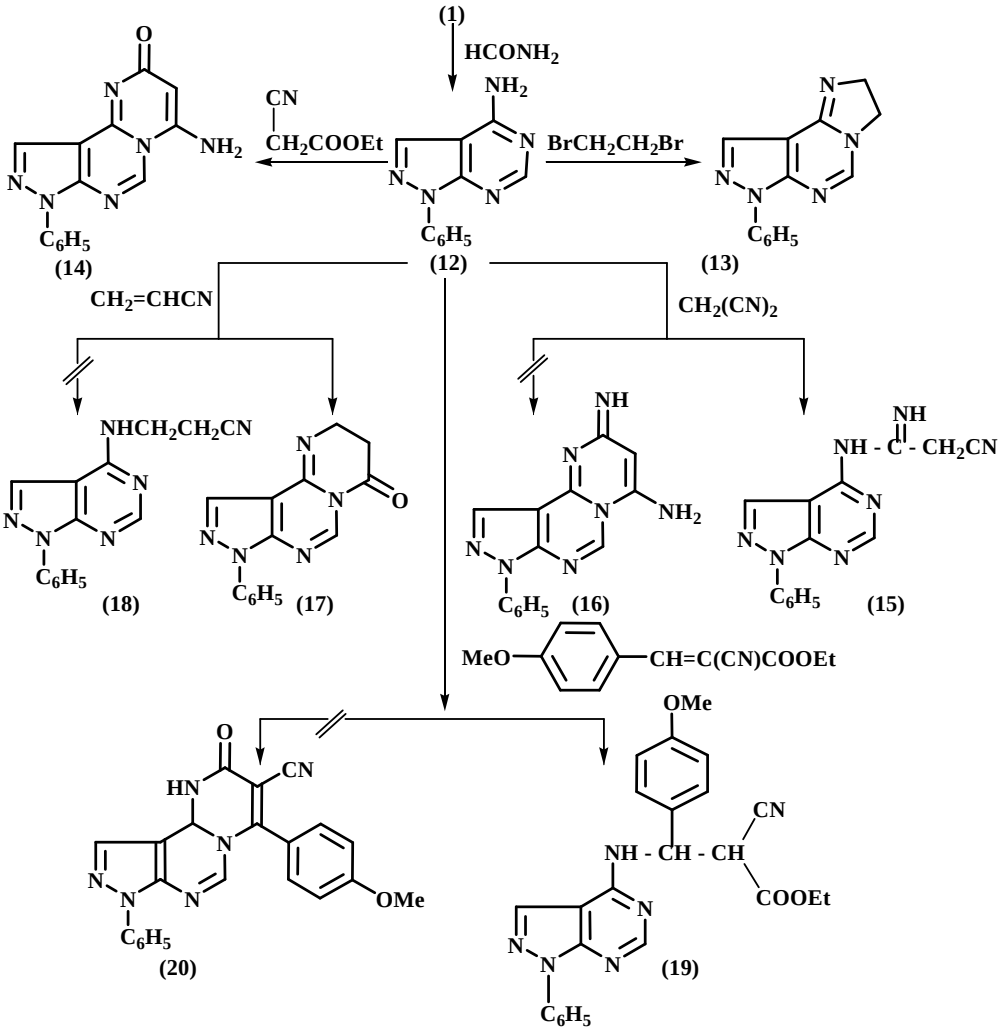
Further,compound **(12)** has been cyclized with ethyl cyanoacetate to yield 4-amino-8-phenylpyrazolo[4,3-e]pyrimido[1,2-c]pyrimidin-2-one **(14)**, while its reaction with malononitrile did not give the expected target compound 4-amino-2-imino-8-phenylpyrazolo[4,3-e] pyrimido[1,2-c] Pyrimidine **(16)**, but yielded only the Michael addition product 4-(β-cyano-α-imino-ethlamino)-1-phenylpyrazolo[3,4-d] pyrimidine **(15)** as IR spectrum of which showed CN band near 2200 cm^{-1} (SCHEME 2).

On the other hand, when compound **(12)** was treated with acrylonitrile in pyridine-water mixture, cyanoethylation and ring closure took place to form 8-phenyl-2,3-dihydro-pyrazolo[4,3-e]pyrimido[1,2-c] pyrimidin-4-one **(17)**, as the cyanoethylated product **(18)** was not formed as its didn·t displayed any band near 2200 cm^{-1} which characteristic to C=N function (SCHEME 2).

Furthermore, reaction of compound **(12)** with ethyl 2-cyano-3(4-methoxyphenyl) propionate in ethanol did not give 3-cyano-4-(4-methoxyphenyl)-8-phenyl-1H-pyrazolo[4,3-e]pyrimido [1,2-c]pyrimidin-2-one **(20)**, but afforded 4-[β-carbethoxy-β-cyano-α-(4-methoxyphenyl]-1-phenylpyra-zolo[3,4-d]pyrimidine **(19)**, as its ^1H NMR (DMSO-d_6) exhibited signals at δ



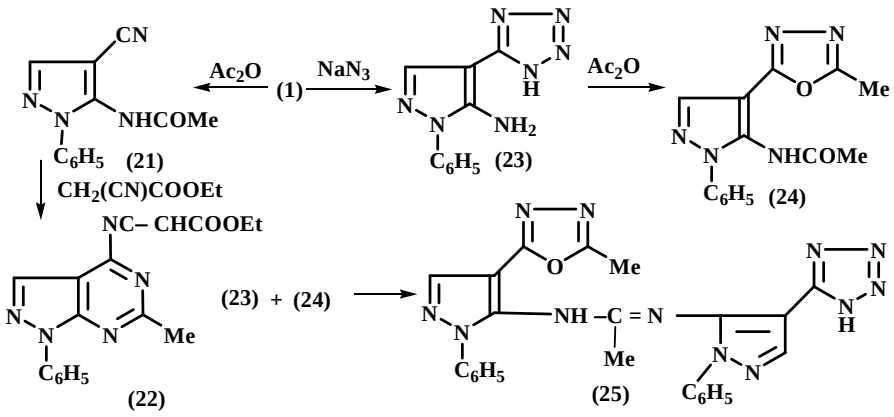
SCHEME 1



SCHEME 2

1.34(t) and 4.26(q) which attributed to OCH_2CH_3 group (SCHEME 2).

Acetylation of compound 1 with acetic anhydride gave 5- acetamido-4-cyano-1-phenyl-pyrazole **(21)**, which underwent ring closure on treatment with ethyl cyanoacetate in sodium ethoxide to give ethyl (6-methyl-1-phenylpyrazolo[3,4-d]pyrimidin-4-yl)cyano-acetate**(22)**. (SCHEME 3)



SCHEME 3

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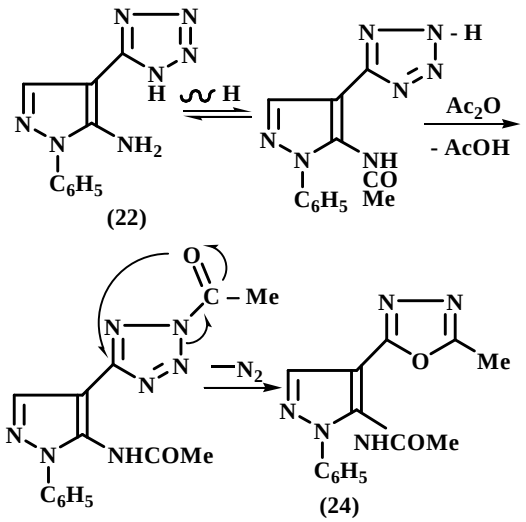
The wide range of biological as well as medicinal application of oxadiazoles and tetrazoles induced the us to synthesize pyrazolyltetrazole and pyrazolyl-1,3,4-oxadi-azole. Thus, 5-(5-amino-1-phenylpyrazol-4-yl)-1H-tetrazole **(22)** was synthesized by 1,3-dipolar cycloaddition reaction of compound **(1)** with sodium azide . Further, treatment of tetrazole **(23)** with acetic anhydride in the presence of pyridine afforded 2-methyl-5 (5-acetamido-1- phenylpyrazol-4-yl)-1,3,4-oxadiazole **(24)** (SCHEME 3).

The formation of **(24)** from **(23)** involves aclyation of the amino group and ring transformation. A probable mechanism for the transformation of tetrazole **(23)** into1,3,4-oxadiazole **(24)** could be explained according to the following SCHEME :



Finally, interaction of compound **(23)** with **(24)** in pyridine afforded N-[4-(2-methyl-1,3,4-oxadiazol-5-yl)-1-phenylpyrazol-5-yl]-N-[4-(1H-tetrazol-5-yl)-1-phenyl-pyrazol-5-yl] acetamidine **(25)** (SCHEME 3) . The structure of compound **(25)** was fully supported by elemental analysis and spectroscopic data. The IR spectrum of compound **(25)** displyed absorption bands at its characteristic wave number 3417,3307 (2NH),3046 (aromatic-CH), 2921(aliphatic-CH),1626,1569 (C=N and C=C) and 1047cm^{-1} (C-O-C). The ^{1}H NMR spectrum of which exhibited signals at δ 4.63 (s,3H,CH_3 of amidine),4.86(s,3H,CH_3 of oxadiazole),5.86 (s,1H, exocyclic NH),7.91–8.52 (m,10H,Ar – H), 9.04 (s,1H, C_3–H of pyrazole), 9.16 (s, 1H, C_3–H of pyrazole), and 11.78 ppm (s, 1H, NH of tetrazole). The structure of **(25)** was also supported by mass fragmentation which exhibited molecular ion peak at m/z (I_r/%) = 494 (M+2, 13.81%) with a base peak at m/z = 77 (100%) attributed to phenyl moiety.

EXPERIMENTAL

All reported melting points were uncorrected . The IR spectra were recorded on a Perkin-Elmer 598 spectrophotometer using KBr wafer technique. ^{1}H NMR spectra were ineasured on Bruker AC 200-NMR spectrophotometer 200 MHz using TMS (δ ppm) as an internal standard. Mass spectra were obtained using GCMS qp 1000 ex Scheimadzu instrument (70eV).

4-Cyano-5-ethoxymethylideneamino-1-phenyl pyrazole (2)

A mixture of I (0.02 mole) in triethyl orthoformate (60 ml) was heated under reflux for 24 h. Excess triethyl orthoformate was removed in vacuo and the resulting nearly pure solid **(2)** was used without further purification..

5-Benzamido-4-imino-1-phenylpyrazolo[3,4-d]pyrimidine (3)

A suspension of **(2)** (0.012 mole) and benza hydrazide (0.014 mole) in ethanol (30 ml) was refluxed for 4 h. The solid obtained was filtered off and recrystallized.

5-Amino-4-imino-1-phenylpyrazolo[3,4-d]pyrimidine (5)

A mixture of **(2)** (0.01 mole) and hydrazine hydrate (0.02 mole) in ethanol (30 ml) was filtered off and recrystallized.

2-(4′Chlorophenyl)-7-phenyl-3H-pyrazolo[4,3-e][1,2,4]-triazolo[1,5 c]pyrimidine (7)

A mixture of **(5)** (0.01 mole) and p-chlorobenzal dehyde (0.01mole) in pyridine (10 ml) was heated under reflux for 10 h. The reaction mixture was cooled, poured gradually onto crushed ice and triturated with dil HCl. The solid obtained was filtered off and recrystallized.

4-Imino-5-formamido-1-phenylpyrazolo[3,4-d] pyrimidine (9)

A solution of **(5)** (0.01 mole) in formic acid (5 ml)

was refluxed for 3 h. After cooling, the solid obtained was filtered off and recrystallized.

5-Acetamido-4-imino-1-phenylpyrazolo[3,4-d] pyrimidine (11)

A mixture of **(5)** (0.01 mole), acetic anhydride (5 ml) and glacial acetic acid (5 ml) was refluxed for 3 h. After cooling, the solid obtained was filtered off and recrystallized.

7-Phenyl-2,3-dihydro-imidazolino[1,2-c]pyrazolo [4,3-e]pyrimidine (13)

A mixture of **(12)** (0.01 mole) and dibromoethane (0.01 mole) in pyridine (20 ml) and water (10 ml) was refluxed for 4 h. The reaction mixture was cooled, triturated with dil HCl, the solid so formed filtered off and recrystallized.

4-Amino-8-phenylpyrazolo[4,3-e]pyrimido[1,2-c] pyrimidine(14)

A mixture of **(12)** (0.01 mole) and ethyl cyano acetate (0.012 mole) was fused at 220-230 ^{5}C for 1/2 h. The reaction mixture was cooled and triturated with methanol. The solid obtained was filtered off and recrystallized.

4-(β-Cyano-α-imino-ethylamino)-1-phenyl pyrazolo[3,4d]pyrimidine (15)

A mixture of **(12)** (0.01 mole) and malononitrile (0.01 mole) was fused at 220^{5}C for 1/2 h. The reaction mixture was cooled and triturated with methanol. The solid obtained was filtered off and recrystallized.

8-Phenyl-2,3-dihydropyrazolo[4,3-e]pyrimido [1,2-c]pyrimidin-4one(17)

A mixture of **(12)** (0.01 mole) and acrylonitrile (0.01 mole) in pyridine (20 ml) and water (10 ml) was refluxed for 3 h. The reaction mixture was cooled and triturated with dil HCl, filtered off and recrystallized.

4-[β-Carbethoxy-β-cyano-α-(4′-methoxyphenyl)-1-phenylpyrazolo[3,4-d] pyrimidine (14)

A mixture of **(12)** (0.01 mole) and ethyl 2-cyano-3-(p-methoxyphenyl) propenoate (0.01 mole) in ethanol (30 ml) was refluxed for 5 h. After cooling, the solid obtained was filtered off and recrystallized.

5-Acetamido-4-cyano-1-phenylpyrazole (21)

A mixture of I (0.01 mole) in acetic anhydride (10 ml) was heated under reflux for 2 h. After cooling, the reaction mixture was poured onto crushed ice and the solid obtained was filtered off and recrystallized.

Ethyl 2-(6-methyl-1-phenylpyrazolo[3,4-d]pyrimidin-4-yl) cyanoacetate (22)

To a solution of sodium ethoxide (0.02 mole) in 50 ml ethanol ethyl cyanoacetate (0.01 mole) was added followed by **(21)** (0.01 mole). The reaction mixture was refluxed for 4h.The solid obtained upon dilution with dil HCl was filtered off and recrystallized.

5-(5′-Amino-1′-phenylpyrazol-4′-yl)-1H-tetrazole (23)

A mixture of 1 (0.06 mole), sodium azide (0.03 mole), ammonium chloride (0.04 mole) and DMF (7.5 ml) was heated under reflux for 24 h. The reaction mixture was cooled and diluted with cold water then acidified with dil HCl. The solid obtained was filtered off and recrystallized.

2-Methyl-5-(5′-acetylamino-1′-phenylpyrazol-4′-yl)-1,3,4-oxadiazole (24)

A mixture of **(23)** (0.001 mole) and acetic anhydride (0.012 mole) in pyridine (5 ml) was refluxed for 20 h. The solid obtained upon dilution with dil HCl was filtered off and recrystallized.

N-[4-(2′-methyl-1′,3′,4′-oxadiazol-5′-yl)-1-phenyl pyrazol-5-yl]-N′-[4-(1′H-tetrazol-5-yl)-1-phenyl pyrazol-5-yl]acetamidine (25)

A mixture of **(23)**(0.001 mole) and **(26)**(0.001 mole) in pyridine (6 ml) was heated under reflux for 10 h. The reaction mixture was cooled and diluted with cold water and then triturated with dil HCl. The solid obtained was filtered off and recrystallized.

Mollusicide activity

In view of the significant biological activitied of pyrazole derivatives, it is interst to study the molluscicide activities of some new synthesized pyrazole against Biomphalaria alexandrina snails. For this purpose Biomphalaria alexandrina snails (shell diameter 8-11 mm), the intermediate host Schistosoma mansoni, which help in casing intestinal Bilharzias, the national problem in Egypt, were collected from canals in Abu - Rawash, Giza, Egypt, and they maintained in aquaria filled with

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TABEL 1 : Analytical data of the new compounds

Comp. no.	Formula M_t	W_I (calc.)% / W_I (found)% C	H	N	Yield %	M.p. °C	Solvent
2	$C_{13}H_{12}N_4O$ 240	65.00 / 65.00	5.00 / 5.00	23.33 / 23.31	90	49-50	EtOH
3	$C_{18}H_{14}N_6O$ 330	65.45 / 65.10	4.42 / 4.20	25.45 / 25.39	80	184	DMF
5	$C_{11}H_{10}N_6$ 226	58.40 / 58.10	4.42 / 4.50	37.16 / 37.22	60	224	EtOH
7	$C_{18}H_{13}N_6Cl$ 348.5	61.97 / 62.00	3.73 / 3.70	24.10 / 24.17	76	<270	DMF/H_2O
9	$C_{12}H_{10}N_6O$ 254	56.69 / 56.70	3.94 / 4.10	33.07 / 33.16	80	210	H_2O
11	$C_{13}H_{12}N_6O$ 268	58.20 / 58.10	4.47 / 4.50	31.34 / 31.39	62	250	DMF
13	$C_{13}H_{11}N_5$ 237	65.82 / 65.80	4.64 / 4.60	29.53 / 29.48	80	<270	DMF/H_2O
14	$C_{14}H_{10}N_6O$ 278	60.43 / 60.30	3.59 / 3.60	30.21 / 30.14	74	<270	DMF/H_2O
15	$C_{14}H_{11}N_7$ 277	60.64 / 66.40	3.97 / 4.20	35.37 / 35.43	78	>270	DMF/H_2O
17	$C_{14}H_{11}N_5O$ 265	63.39 / 63.36	4.15 / 4.20	26.41 / 26.38	82	170	EtOH
19	$C_{24}H_{22}N_6O_3$ 442	65.16 / 65.20	4.98 / 5.00	19.00 / 18.91	82	>270	EtOH
21	$C_{12}H_{10}N_4O$ 226	63.70 / 63.00	4.42 / 4.40	24.77 / 24.72	75	128	DMF/H_2O
22	$C_{17}H_{15}N_5O_2$ 321	63.55 / 63.40	4.67 / 4.70	21.80 / 21.85	70	160	H_2O
23	$C_{10}H_9N_7$ 227	52.86 / 52.20	3.96 / 4.00	43.17 / 43.13	69	216	MeOH/H_2O
24	$C_{14}H_{13}N_5O_2$ 283	59.36 / 59.40	4.59 / 4.60	24.73 / 24.68	79	140	EtOH/H_2O
25	$C_{24}H_{20}N_{12}O$ 492	58.53 / 58.80	4.06 / 4.10	34.14 / 34.19	80	254	DMF/H_2O

dechlorinated water under laboratory conditions (Temp. 25±5°C and pH 7-7.7) for three weeks before used in experimental tests. Dried lettuce leaves were added daily as food and water was changed weekly.

Preparation of mollusicidal agents

Stock solution of 1000 ppm was freshly prepared tested compounds on the bases of weight / volume in dechlorinated tap water pH (7.5-7.7). Series of concentrations expressed in terms of part per million (ppm)[100, 50, 25 and 10] were prepared. Stander procedures were followed through this study 155[9] Statistical analysis of the obtained data was carried out according to Litchfield and Wilcoxan method[10]. The mollusicidal activities of some new synthesized pyrazoles against Biomphalaria alexandrina snails after 24 hours exposure lime. The obtained results were put in the following TABLE :

The results obtained in the above TABLE indicated that the strongest effect of the tested compounds against

Comp. no.	Concentration (ppm) 100	50	25	10
1	0	0	0	0
3	100	100	50	40
4	0	0	0	0
7	0	0	0	0
11	0	0	0	0
8	100	100	0	0
14	0	0	0	0
17	0	0	0	0
19	80	40	0	0

0 = No mortality of snails; 100 = 100 % mortality of snails

TABLE 2: Spectral data of the new compounds

Comp. no.	IR (ν/ cm^{-1})	^1H NMR, δ
(2)	1151 ν(C–O–C), 1636-1657 ν(C=N, C=C), ν(CH_{aliph}), 2218 ν(C≡N), 3067 ν (CH_{arom}), 2291 ν(CH_{aliph})	
(3)	1588 ν(C=N), 1678 νC= $O_{benzamido}$),3053 υ (CH_{arom}), 3371,3129 υ (2N-H)	7.38-8.16(m, 10H, H_{arom}), 8.57(s, 1H,C-3-$H_{pyrazole}$), 8.64(s, 1H, C-6-$H_{pyrimidine}$), 8.86(s, 1H, CH=NH), 9.78(s, 1H,CO-NH)
(5)	1591 υ (C=N), 3062 ν(CH_{arom}), 3448, 3197 ν (NH_2, NH)	
(7)	1608 - 1591 ν (C=N, C=C), 3062 ν(CH_{arom}), 3204 ν(N--H)	
(9)	1625 - 1594 ν (C=N, C=C), 2922 νCH $_{aliph}$), 3062 ν (CH_{arom}), 3323,3105 ν(2N-H)	
(11)	1588ν(C=N), 1735 ν(C=O), 2922 ν(CH_{aliph}), 3012 ν(CH_{arom}), 3448, 3123 1593 ν (2N-H)	7.38-8.16 (m, 5H, H_{arom}), 8.77(s, 1H, C-3-$H_{pyrazole}$), 9.73(s, 1H, C-6-$H_{pyrimidine}$), 13.9(s, 1H, CO-NH)
(13)	1588ν (C=N), 3050ν(CH_{arom})	
(14)	1651 - 1589 ν(C=N, C=C), 1735 ν(C=O), 3200, 3116 ν(NH_2,CH_{arom}).	5.20 (s,2H, NH2), 7.28-8.08 (m, 5H, H_{arom}), 8.08 (s,1H, C-10-$H_{pyrazole}$), 8.46 (s, 1H, C-6-$H_{pyrimidine}$), 9.33(s, 1H, C-3-$H_{pyrimidine}$)
(15)	1600 - 1596 ν(C=N, C=C), 2206 ν(C≡N), 2923 νCH $_{aliph}$), 3030 ν(CH_{arom}), 3332,3201 ν(2N-H)	
(17)	1581 υ (C=N), 1697(C=O), 2962 ν(CH $_{aliph}$), 3024 ν(CH_{arom}), with absence CN band at 2200	3.06(t, 2H, CH_2N), 4.32(t, 2H, CH_2-CO), 7.59-8.06 (m, 5H, H_{arom}), 8.43(s,1H, C-10-$H_{pyrazole}$), 8.59(s, 1H, C-6-$H_{pyrimidine}$)
(19)	1659 ν (C=N), 1731 ν(C=O), 2214(C≡N), 2885 ν(CH_{aliph}), 3044 ν(CH_{arom}), 3164 ν(NH)	1.34(t, 3H, OCH_2CH_3), 3.34(s, 1H, Cα-H), 3,88 (s,3H,OCH_3), 4.26-4.36 (q, 2H, OCH_2CH_3), 7.13-8.11 (m, 9H,H_{arom}+ 1H, Cβ-H), 8.21(s,1H,C-10-H-$_{pyrazole}$), 8.34(s,1H,C-6-$H_{pyrimidine}$), 12.45(s,1H,NH)

Countinue table 2 on next page

Comp. no.	IR (ν/ cm^{-1})	^1H NMR, δ
21	1625 ν (C=N), 1686 υ (C=O), 2203(C≡N), 2995 ν(CH_{aliph}), 3035 ν(CH_{arom}), 3130 ν(NH)	
22	1600 - 1596 ν(C=N, C=C), 2241 ν(C≡N), 2947 ν(CH_{aliph}), 3012 ν(CH_{arom}), 3413 ν(NH)	
23	1631 - 1598 ν(C=N, C=C), 3060 ν(CH_{arom}), 3285,3202,3110 ν(NH_2, NH)	
24	1600 - 1585 ν(C=N, C=C), 1679 ν(C=O), 2970 ν(CH_{aliph}), 3080 ν(CH_{arom}), 3287 ν(NH)	2.49(s, 1H, CO-CH_3), 3.30 (s, 3H, CH_3 of $_{oxaiazole}$), 7.46-8.19 (m, 5H, H_{arom}), 8.57(s,1H, C-3-$H_{pyrazole}$),8.77(s, 1H, NH)
25	1615 - 1595 ν(C=N, C=C), 2985 ν(CH_{aliph}), 3036 ν(CH_{arom}), 3105 ν(NH)	4.63(s, 3H, CH_3 of $_{amidine}$), 4.86(s, 3H, CH_3 of $_{oxadiazole}$), 5.86(s,1H, exocyclic NH), 9.16(s, 1H, C-3-$H_{pyrazole}$), 11.78(s, 1H, NH of $_{tetrazole}$)

snails, pyrazolopyrimidine **(3)** and **(19)** but imidazolo pyrimidine **(13)** exhibited moderate activity in two different concentration and no activity in the others . These results exhibited that compounds **(3)** may be used as a good molluscicidal agent for mortality of snails.

In the most cases, the total electron barrier of molecular structure of the evaluated compounds led to inhibition enzymatic effect on living processes for the tested snail, via the contribution between apoenzyme and coenzyme, which may be loose that it and can be broken by a simple process of snails.

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