



The Scientific Temper

VOL-X, NO.1&2; JANUARY-JULY, 2019

ISSN 0976 8653, E ISSN 2231 6396

A Web of Science Journal

e-mail: letmepublish@rediffmail.com

Doc ID : <https://connectjournals.com/03960.2019.10.61>

SYNTHESIS AND MOLLUSCICIDAL ACTIVITY OF 6-AMINO-1-ARYLOXYACETO-4-ARYL-5-CYANO-3-METHYL-1, 4, 5, 7-TETRAHYDRO PYRAZOLO[4,5-e]PYRIDINES.

A. SINGH*, A. SINGH** & P. SINGH

*Corresponding author address: Department of Chemistry,
K.S. Saket PG College, Ayodhya -224001

Email & phone: akhileshchem@gmail.com, 9473992256

**Department of Chemistry, U. P. Autonomous College, Varanasi-221002

ABSTRACT

Several 6-Amino-1-aryloxyaceto-4-aryl-5-cyano-3-methyl-1,4,5,7-tetrahydro pyrazolo[4,5-e]pyridines (**III**) have been synthesized from synthon 1-aryloxyaceto-4-arylidine-3-methyl-pyrazol-5-ones (**II**). The molluscicidal activity of few titled compounds has been evaluated against the snail *Lymnaea acuminata*. The LC_{50} slope, t-ratio heterogeneity and g-values have been determined and discussed.

Key words- Pyridines, pyrazolo, molluscicidal activity, *Lymnaea acuminata*.

INTRODUCTION

Pyrazoles are known to exhibit broad spectrum of activities^{1,6,13}. The pyridine ring is associated with diverse biological activities^{7,10} probably by virtue of incorporating polar groups – CN, C=O, -NH and -CH₂ the importance of which has been well stressed in many pesticidal properties.^{16,17} In continuation of our work on fused heterocycles of pesticidal interest and guided by observation that the fusion of two or more heterocyclic nuclei often enhances the biological profile many fold than its parent nuclei^{12,15}; we have

undertaken the synthesis and bioassay of titled compounds. The investigation further appeared interesting because compactness and planarity of such a ring system may be an additional factor for enhancing biological profile.

The required synthon 1-aryloxyaceto-3-methylpyrazol-5-one (**I**) were prepared according to the literature method. The synthon (I) fused with 4-substituted bezaldehyde in presence of sodium acetate and acetic acid yielded 1-aryloxyaceto-4-arylidine-3-methyl-pyrazol-5-one (**II**) which on treatment with malenonitrile and ammonium acetate

in dioxane gave the desired compounds (**III**).

EXPERIMENTAL

Procedure for one typical case for each step has been described. All melting points were determined in open glass capillaries and are uncorrected. IR spectra were recorded in KBr on a Perkin-Elmer-157 spectrophotometer (cm^{-1}), ^1H NMR spectra in DMSO-d_6 on a Varian EM-360 (200 MHz) spectrometer using TMS as internal reference (chemical shift in δ ppm).

1-(4-Methylphenoxy)aceto-4-(4-hydroxyphenylidene)-3-methyl-pyrazol-5-one (**IIIk**)

Requisite, 1-(4-Methylphenoxy)aceto-3-methyl-pyrazol-5-one (2.46g, .01M), 4-hydroxybenzaldehyde (1.22g, .01M) and fused sodium acetate (1.64g, 0.02M) was refluxed in glacial acetic acid for three hours. The reaction mixture was cooled, poured into water. The precipitated mass was filtered, washed with water, dried and recrystallised from aq. ethanol. m. p. 175°C , yield (67%). IR (KBr): 3490

(-OH), 1705($\text{C}=\text{O}$), 1660 (-COC=CH-), 1630($\text{C}=\text{N}$), 1530 (aromatic ring); ^1H NMR (DMSO-d_6): δ 2.05(s, 3H, - CH_3), 2.25(s, 3H, - CH_3), 2.81(s, 1H, CH), 4.58(s, 2H, - OCH_2), 6.52-7.55(m, 8H, Ar-H), 9.3(s, 1H, -OH).

The spectral data of few more such compounds are as under.

IIa: IR (KBr): 1705($\text{C}=\text{O}$), 1665 (-COC=CH-), 1635($\text{C}=\text{N}$), 1205($\text{C}-\text{O}$) 1537 (aromatic ring); ^1H NMR (DMSO-d_6): δ 2.07(s, 3H, - CH_3), 2.25(s, 3H, - CH_3), 2.81(s, 1H, CH), 4.55(s, 2H, - OCH_2), 7.03-8.00(m, 8H, Ar-H), 3.8(s, 3H, - OCH_3).

IIg: IR (KBr): 3490 (-OH), 1705($\text{C}=\text{O}$), 1665 (-COC=CH-), 1635($\text{C}=\text{N}$), 1205($\text{C}-\text{O}$) 1537 (aromatic ring); ^1H NMR (DMSO-d_6): 2.25(s, 3H, - CH_3), 2.81(s, 1H, CH), 4.55(s, 2H, - OCH_2), 7.03-7.58(m, 8H, Ar-H), 9.5(s, 1H, -OH).

Other compounds of the type **II** were prepared similarly and are recorded in Table-1

2-Amino-1-(4-Methylphenoxy)aceto-4-(4-hydroxyphenyl)-5-cyano-3-methyl-1, 4, 5, 7-tetrahydropyrazolo[4, 5-e]pyridine(**IIIk**)

Requisite 1-(4-Methylphenoxy)aceto-4-(4-hydroxyphenylidene)-3-methyl-pyrazol-5-one (4.05g, 0.01M), malenonitrile (dicanomethane) (0.72g, 0.01M) and ammonium acetate (6.16g, 0.08M) was refluxed in dioxane for six hours. The reaction mixture was cooled, poured into water. The precipitated mass was filtered, washed with water, dried and recrystallised from aq. ethanol. m. p. 222°C , yield

(65%). IR (KBr): 3400(-OH), 3240(N-H), 2160(- $\text{C}\equiv\text{N}$), 1740($\text{C}=\text{O}$), 1630($\text{C}=\text{N}$), 1500(aromatic ring); ^1H NMR (DMSO-d_6): δ 2.07(s, 3H, - CH_3), 2.27(s, 3H, - CH_3), 4.58(s, 2H, - OCH_2), 8.1(s, 1H, -NH), 6.88-7.70(m, 8H, Ar-H), 9.3(s, 1H, -OH).

IIIa: IR (KBr): 3240(N-H), 2163(- $\text{C}\equiv\text{N}$), 1740($\text{C}=\text{O}$), 1630($\text{C}=\text{N}$), 1500(aromatic ring); 1210($\text{C}-\text{O}$); ^1H NMR (DMSO-d_6): 2.24(s, 3H, - CH_3), 4.60(s, 2H, - OCH_2), 7.9(s, 1H, -NH), 7.53-7.79(m, 9H, Ar-H), 4.0(s, 3H, - OCH_3).

IIIg: IR (KBr): 3405(-OH), 3235(N-H), 2166(- $\text{C}\equiv\text{N}$), 1745($\text{C}=\text{O}$), 1630($\text{C}=\text{N}$), 1505(aromatic ring); 1212($\text{C}-\text{O}$); ^1H NMR (DMSO-d_6): 2.22(s, 3H, - CH_3), 4.59(s, 2H, - OCH_2), 8.3(s, 1H, -NH), 7.50-7.75(m, 9H, Ar-H), 9.6(s, 1H, -OH). Other compounds of the type **III** were prepared similarly and are recorded in Table-1. All compounds gave satisfactory elemental analysis.

BIOLOGICAL ACTIVITY

The molluscicidal activity of the compounds was evaluated against the snail *Lymnaea acuminata* which is a vector of the giant liver flukes *Fasciola gigantica* and *Fasciola hepatica*. It causes endemic fasciolosis in cattle population of eastern Uttar Pradesh.

Being herbivorous, these snails cause damage to submerged paddy crops especially in Terai region of U.P. In this region the water reservoirs and submerged paddy fields have become foci for such snail pests.

Adult *L. acuminata* were collected from ponds, lakes and low lying submerged fields and were used as test animals. The snails were acclimatized for 72 hr in laboratory condition. Six

Table-1
Physical data of the compounds prepared

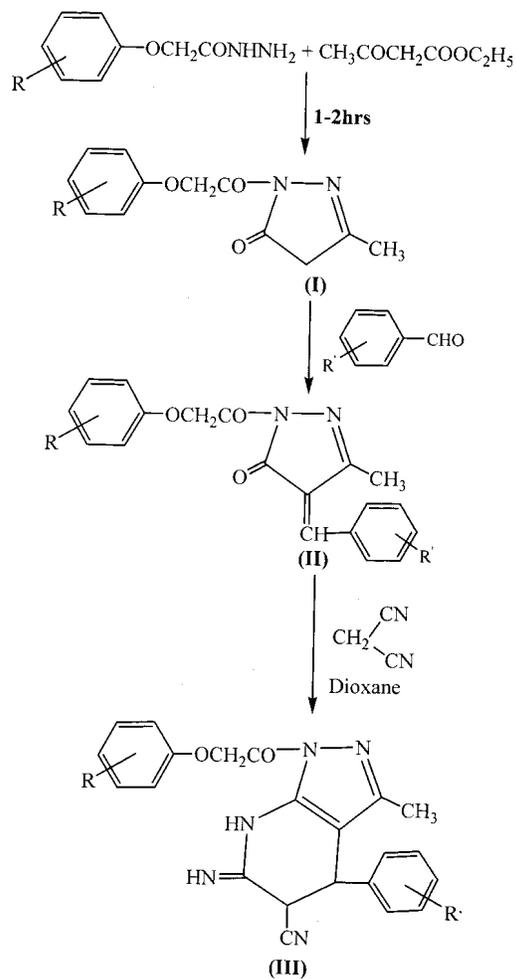
S. No.	R (°C)	R' (%)	M.P Formula	Yield	Mol.	Analysis found (Calc%) of		
						C	H	N
IIa.	H	2-OCH ₃	120	50	C ₂₀ H ₁₈ N ₂ O ₄	68.43 (68.57)	5.27 5.14	8.09 8.00)
IIb.	2-Cl	4-OCH ₃	124	52	C ₂₀ H ₁₇ N ₂ O ₄ Cl	62.54 (62.42)	4.30 4.42	7.37 7.28)
IIc.	4-Cl	4-OCH ₃	103	49	C ₂₀ H ₁₇ N ₂ O ₄ Cl	62.53 (62.42)	4.31 4.42	7.38 7.28)
IIId.	2,4-Cl ₂	4-OCH ₃	135	70	C ₂₀ H ₁₆ N ₂ O ₄ Cl ₂	57.32 (58.28)	3.90 3.82	6.53 6.68)
IIe.	2-CH ₃	4-OCH ₃	113	55	C ₂₁ H ₂₀ N ₂ O ₄	69.34 (69.23)	5.42 5.43	7.71 7.69)
IIIf.	4-CH ₃	4-OCH ₃	95	82	C ₂₁ H ₂₀ N ₂ O ₄	69.33 69.23	5.43 5.49	7.72 7.69)
IIg.	H	4-OH	159	51	C ₁₉ H ₁₈ N ₂ O ₄	67.89 (67.86)	4.85 4.76	8.21 8.33)
IIh.	2-Cl	4-OH	170	59	C ₁₉ H ₁₅ N ₂ O ₄ Cl	61.62 (61.54)	4.01 4.05	7.65 7.57)
IIi.	4-Cl	4-OH	165	49	C ₁₉ H ₁₅ N ₂ O ₄ Cl	61.62 (61.54)	4.01 4.05	7.65 7.57)
IIj.	2,4-Cl ₂	4-OH	170	51	C ₁₉ H ₁₄ N ₂ O ₄ Cl ₂	56.43 (56.30)	3.54 3.46	6.83 6.91)
IIk.	4-CH ₃	4-OH	175	67	C ₂₀ H ₁₈ N ₂ O ₄	68.43 (68.57)	5.25 5.14	8.20 8.00)
IIIa.	H	2-OCH ₃	171	40	C ₂₃ H ₂₁ N ₅ O ₃	66.34 (66.51)	5.26 5.06	16.61 16.86)
IIIb.	2-Cl	4-OCH ₃	175	67	C ₂₃ H ₂₀ N ₅ O ₃ Cl	61.25 (61.40)	4.25 4.45	15.53 15.57)
IIIc.	4-Cl	4-OCH ₃	155	56	C ₂₃ H ₂₀ N ₅ O ₃ Cl ₂	61.20 (61.40)	4.35 4.45	15.57 15.53)
IIId.	2,4-Cl ₂	4-OCH ₃	140	55	C ₂₃ H ₁₉ N ₅ O ₃ Cl ₂	56.83 (57.02)	4.04 3.93	14.56 14.46)
IIIe.	2-CH ₃	4-OCH ₃	170	47	C ₂₄ H ₂₃ N ₅ O ₃	67.03 (67.13)	5.20 5.36	16.43 16.31)
IIIIf.	4-CH ₃	4-OCH ₃	160	87	C ₂₄ H ₂₃ N ₅ O ₃	67.00 67.13	5.16 5.36	16.43 16.31)
IIIg.	H	4-OH	190	58	C ₂₂ H ₁₉ N ₅ O ₃	65.73 (65.83)	4.95 4.74	17.44 17.46)
IIIh.	2-Cl	4-OH	240	88	C ₂₂ H ₁₈ N ₅ O ₃ Cl	60.67 (60.61)	4.18 4.13	16.25 16.07)
IIIi.	4-Cl	4-OH	120	85	C ₂₂ H ₁₈ N ₅ O ₃ Cl	60.97 (60.61)	4.28 4.13	16.25 16.07)
IIIj.	2-CH ₃	4-OH	160	81	C ₂₃ H ₂₁ N ₅ O ₃	66.32 (66.51)	5.23 5.06	16.60 16.87)
IIIk.	4-CH ₃	4-OH	221	65	C ₂₃ H ₂₁ N ₅ O ₃	66.33 (66.51)	5.03 5.06	17.03 16.87)

sets of glass aquarium were used for each concentration of experiment. Ten adult snails were kept in each glass aquaria containing 3l dechlorinated tap water. Toxicity of different compounds was determined by the method of Rao & Singh¹¹. The snails were treated with different concentrations of compounds. Mortality was recorded at 24 hr intervals up to 96 hr exposure periods. Control animals were kept in a similar manner without treatment. Dead snails were removed from the aquarium to avoid contamination of water. No response to the needle probe confirmed the death of the snail.

For one compound **IIa** (arbitrarily chosen) lethal concentration (LC_{50}) values, lower and upper confidence limits (LCL and UCL), g-values, t-ratio values, slope values and heterogeneity values were calculated according to the method of POLO computer program of Rusell et al¹⁴ (Table-2).

RESULT AND DISCUSSION

The molluscicidal data indicates that all tested compounds showed strong to moderate activities. The molluscicidal activity of the tested compounds is dose and time dependent. Nature of substituents is critical to molluscicidal activity. The electron donating substituents such as methyl, methoxy enhanced the molluscicidal activity. On the other hand the electron withdrawing groups such as chloro decreased the molluscicidal activity. The slope values were steep and separate estimation of LC_{50} based on each of the six replicates was found to be within the 95% confidence limits of LC_{50} . The steep slope values indicated that even small increase in the concentration causes mortality in the snails. The 't' ratio is greater than 1.96, which indicates that



Scheme 1

Table-2
Toxicity of compound **IIa** against *L.acuminata*[#]

Period(hrs)	LC_{50}^* (LCL-UCL) mg/l	Slope	t-ratio	Heterogeneity	g
24	2.05(1.60-4.04)	3.33±0.85	3.92	0.38	0.25
48	1.78(1.42-3.49)	2.74±0.74	3.66	0.20	0.28
72	9.01(0.90-1.16)	3.27±0.71	4.58	0.20	0.18
96	0.76(0.66-0.84)	4.64±0.82	5.60	0.28	0.12

[#] Six batches of 10 snails were exposed to different concentrations of the treatment. Mortality was determined every 24hr. Concentrations given are the final concentration in the aquarium water.* The LC_{50} values of remaining compounds can be obtained from the authors on request.

regression is significant. Values of heterogeneity factor less than 1 denote that in the replicate of random sample the concentration response line would fall within 95%, confidence limit and thus the model fits the data adequately. The index of significance of potency estimation g-value indicates that the value of the mean is within limits at all probability (90, 95, and 99) as it is less than 0.5.

ACKNOWLEDGEMENT

The authors are thankful to RSIC (CDRI), Lucknow for recording spectra and carrying out elemental analysis. Authors are also thankful to Dr. D. K. Singh, Professor (Rtd), Department of Zoology, DDU Gorakhpur University Gorakhpur for help in evaluating molluscicidal activities.

REFERENCE

1. A. Ansari, A. Ali, M. Asif, Shamsuzzaman, [New J. Chem.](#), 2017, **41**, 16-41
2. B. C.Kim., Y.R.Lee, et al, *Eur. J.Med.Chem.*, 38, 2003, 525-532.
3. B. S. Holla, M. Mahaligna, M.S. Karthikenya et al., *Boorg. Med. Chem.*, 14, 2006, 2040-2047
4. B.Zacharie. et al., *J. Med. Chem.*, 38, 2003, 2883-2894.
5. C.R.Petrie 3rd, H.B. Cottam et al., *J. Med.Chem.*, 28, 1985, 1010-1016.
6. [E. N. Ovchenkova, M. E. Klyueva, T. N. Lomova Rus. J. Inorg. Chem.](#) 2017, 62, 1483-1487.
7. E. Stephanie, W. Chang, F. SaraciPhuc, H. Le Charles, J. Wals, [J. Inorg. Biochem.](#) 2017, **167**, 89-99.
8. F. Carraro, A.Naldeni, A.Pucci et al., *J. Med. Chem.*, 49, 2006, 1549-1561.
9. F.D.Da Settimo, G. Primotiore et al., *J.Med. Chem.*, 48, 2005, 5162-5174.
10. G.A.Bhat, J.L. Montero, R.P. Panzica et al., *J.Med. Chem.*, 24, 1981, 1165-1172.
11. I.G.Rao and D.K.Singh, *Chemosphere*, 44 (2001), 1691.
12. K. Kantminene, G. Mikulskene, O. Khormin, and Z. I. Krivenko, *Khim. Geterotsikl. Soedin.* 2002,487.
13. M. M. Ghorab, Z.S.Imail, S.M.Abd-Gawad, A. A. Aziem, *Hetero Atom. Chem.*, 15, 2004, 57-62.
14. R.M. Rusell, J.L. Robertson and M.E. Savin, *Bull. Entomol. Soc., Am.* **23** (1977), 209.
15. S. Chiba, Y.Furukawa, K. Saegusa, Y.Ogiwara, M.Takeda, *Japanese Heart Journal*, 1987, 28, 253-260.
16. S. M. Abdel-Gawad, A. Abdel-Azim, M. M. Ghorab et al., *Alla. Heteroatom Chem.*, 14, 2003, 530-534.
17. Z. H. Ismail, S. M. Abdel-Gawad, A. Abdel-Azim, M. M .Ghorab, *Phosphrous Sulphur Silicon*,178, 2003, 1795-1805.

www.scientifictemper.com

