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Synthesis and biological evaluation of some new aryl pyrazol-3-one derivatives as potential hypoglycemic agents

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Several new aryl substituted pyrazol-3-one **3** derivatives were prepared by the reaction of substituted phenyl hydrazine **1** with diethylethoxymethylene malonate (DEEM) **2**. The compounds were synthesized by Michael addition reaction, which is a nucleophilic addition of enolate anions to the carbon–carbon double bond of α,β-unsaturated carboxylic acid derivatives. All the compounds were characterized by UV, IR and NMR spectroscopy and tested for hypoglycemic activity on alloxan induced diabetic rats. Among the tested compounds ethyl-2-*para* nitrophenyl-2,3-dihydro-1*H*-pyrazol-3-one-4-carboxylate **3c** and ethyl-2-*meta* nitrophenyl-2,3-dihydro-1*H*-pyrazol-3-one-4-carboxylate **3d** are identified as potent hypoglycemic agents and their activities are comparable with the standard drug metformin.

Keywords: Pyrazol-3-one derivatives, diethylethoxymethylene malonate (DEEM), substituted arylhydrazines, Michael addition reaction, hypoglycemic activity

Pyrazole and pyrazolone ring systems represent an important class of compounds not only for their theoretical interest but also for their anti-inflammatory, postmenopausal osteophorosis, angiotensin antagonists, antibacterial, sedative and anticoagulant activities[1-3]. Recently some aryl pyrazole are reported to have non-nucleoside HIV-1 reverse transcriptase inhibitory activities[4].

Diabetes mellitus is a major growing public health care problem throughout the world. Research on new substances possessing hypoglycemic activity has been going on since long back. The pharmacophoric moiety 3,5 dimethylpyrazole was reported by Gerritsen *et al*. Based on this pharmacophore numerous compounds were synthesized *e.g.* 1-(2, 4-dinitrophenyl)-3,5-dimethyl-4-arylazopyrazole and evaluated for antidiabetic activity. Later, a series of 4-arylhydrazono-*N*'-guanylnitrate-3-methyl-2-pyrazolin-5-ones were synthesized and evaluated for hypoglycemic activity[5]. Similarly other series having the 5-methylpyrazole-3-carboxylic acid nucleus was also found to be 116 times more potent orally than tolbutamide in glucose-injected, fasted, intact rats[6]. Recently Bertrand Cottineau *et al.* have searched on novel structural classes of drugs which include substituted pyrazole-4-carboxylic acid and reported the pharmacophore 3-methoxy-1*H*-pyrazole-4-carboxylic acid ethyl ester[7] as a good hypoglycemic agent.

In the light of above, a new series of aryl substituted pyrazol-3-one derivatives were synthesized and evaluated for their possible hypoglycemic activity. Substituted phenylhydrazines were prepared from anilines by diazotization. Pyrazol-3-one-4-carboxylate derivatives were then generated by reacting diethylethoxymethylene malonate (DEEM) with substituted phenyl hydrazine through base catalyzed cyclisation reaction. The synthesized compounds were tested for hypoglycemic activity. The phenyl ring substituted on both N_1 and N_2 of pyrazol-3-one as in ethyl-1,2-diphenyl 2,3 dihydro-1*H*-pyrazol-3-one-4-carboxylate **3b** significantly showed increase in the antidiabetic activity but monosubstitution of phenyl ring showed a lower activity profile *e.g.* ethyl-2-phenyl 2,3dihydro-1*H*-pyrazol-3-one-4-carboxylate **3a**. The pyrazole substituted by arylhydrazines having electronegative radicals, such as nitro groups carrying at least one substituent at either *para* or *meta* position such as ethyl-2-*para* nitrophenyl 2,3dihydro-1*H*-pyrazol-3-one-4-carboxylate **3c** and ethyl-2-*meta* nitrophenyl 2,3dihydro-1*H*-pyrazol-3-one-4-carboxylate **3d** respectively were significantly active and their activities were comparable with standard drug metformin. The chloro substituted pyrazole derivative, ethyl 2,4 dichlorophenyl 2,3 dihydro-1*H*-pyrazol-3-one-4-carboxylate **3e** was not significantly active and

perhaps the nitro derivatives emerge as active compounds which can be related to their larger size and more powerful electron withdrawing characteristics. The pivotal step for the successful synthesis of the pyrazole derivatives solely depends on the maintenance of temperature at 70°C for exactly 40 min that is optimum condition for cyclisation of substituted phenyl hydrazine with diethyethoxymethylene malonate (DEEM) and immediate filtration of compounds. The physicochemical characterization like elemental analysis, melting point and yield were determined for all the synthesized compounds and characterized by UV, IR and NMR spectroscopy. All the synthesized compounds were screened for their hypoglycemic activity **Table I**, **Figure 1**.

Experimental Section

Preparation of substituted phenyl hydrazine from substituted aniline

Substituted phenylhydrazines were prepared by reducing diazonium salts of commercially available anilines with excess warm sodium sulphite solution, followed by acidification with hydrochloric acid[8].

Preparation of aryl substituted pyrazole derivatives

Substituted phenyl hydrazine (0.02 mole) was dissolved in minimum amount of cold water then ethanolic KOH was added. The solution was then refluxed for 40 min at 70°C in presence of diethylethoxymethylene malonate (0.02 mole) (DEEM). The precipitate obtained was filtered, washed with water and dried. The product (**Scheme I**) so obtained was recrystallized from ethanol and was dried for 24 hr at room temperature and kept in a vacuum dessicator.

Ethyl 2-phenyl-1*H*-pyrazol-3-one-4-carboxylate 3a

Yield: 56.65%; m.p.158°C; UV-Vis: 269 nm; IR (KBr): 3205 (NH str.), 2854 (Ar–CH str.), 1718 (-C=O), 1521 (Ar -C-C- Str.), 1492 (-CO str of ester), 761 cm^{-1} (Ar nucleus); ^1H NMR ($CDCl_3$): δ 1.3 (s,3H, $-CH_3$), 4.3 (s, 2H, $-CH_2$), 7.8 (s, 1H heterocyclic ring proton), 2.4 (s, 1H, NH D_2O exchangeable), 7.2-7.8 (m, 5H, Ar-H); Anal. Found: C, 62.32; H, 5.90; N, 11.12. $C_{12}H_{12}N_2O_3$ requires C, 63.15; H, 6.11; N, 11.33%.

Ethyl 1,2-diphenyl-2,3-dihydro-1*H*-pyrazol-3-one-4-carboxylate 3b

Yield:70.32%, m.p. 207°C; UV-Vis: 225, 317 nm; IR (KBr): 1624 (-C=O), 1070 (-C-O str. of ester), 2987 (Ar -CH), 775 cm^{-1} (Ar out of plane bending); ^1H NMR ($CDCl_3$): δ 1.5 (s, 3H, $-CH_3$), 4.3 (s, 2H, $-CH_2$), 8.0 (s, 1H heterocyclic ring proton), 6.1-7.0 (m, 5H, CH-Ar), 6.8-7.4 (m, 5H, Ar-H); Anal. Found: C, 70.24; H, 5.10; N, 8.15. $C_{18}H_{16}N_2O_3$ requires C, 70.57; H, 5.92 ; N, 8.66%.

Ethyl-2-*para* nitrophenyl-2,3-dihydro-1*H* pyrazol-3-one-4-carboxylate, 3c

Yield: 65.43%, m.p. 163°C; UV-Vis: 224,369 nm; IR (KBr): 3362 (NH str.), 1629 (-C=O), 1444 (-NO), 1587 (Ar -C-C str.), 754 (Ar-CH), 1114 cm^{-1} (-C-O str. of ester); ^1H NMR ($CDCl_3$): δ 1.5 (s, 3H, CH_3), 4.3 (s, 2H, CH_2), 7.3-8.0 (m, 5H, Ar-H), 7.5 (s, 1H heterocyclic ring proton), 2.5 (s, 1H, NH D_2O exchangeable); Anal. Found: C, 50.21; H, 3.86; N, 14.54. $C_{12}H_{11}N_3O_5$ requires C, 51.99; H, 4.00; N, 15.16%.

Ethyl-2-*meta* nitrophenyl-2,3-dihydro-1*H* pyrazol-3-one-4-carboxylate 3d

Yield: 59.96%, m.p. 151°C; UV-Vis: 209,316 nm; IR (KBr): 3338 (NH str.), 1697 (-C=O) 1406 (-NO), 1554 (Ar -C-C- str.), 1143 (-C-O str. of ester), 765 cm^{-1} (Ar -CH); ^1H NMR ($CDCl_3$): δ 1.3 (s ,3H, $-CH_3$), 4.3 (s,2H, $-CH_2$),7.5-7.8 (m, 4H, Ar-H), 7.4

Table I — Biological evaluation of compounds on wistar rats

Compd	Dose					
	Average±SD	40mg/kg %Decrease (Mean±SD)	P Value	Average±SD	20mg/kg %Decrease (Mean±SD)	P Value
Standard	151.2±11.37	73.78±1.50		171±22.7	61.81±10.244	
3a	191.4±14.66	70.54±1.693	>0.05	244.6±21.08	47.28±2.868	>0.05
3b	207.4±11.52	65.80±1.378	<0.01	258±8.17	56.20±1.608	>0.05
3c	198.8±8.07	68.42±1.678	<0.01	257±7.71	58.00±2.854	<0.05
3d	282.8±21.83	53.42±2.934	<0.001	221.8±19.15	70.16±5.35	<0.001
3e	168.4±20.86	71.62±1.787	>0.05	311.4±25.76	59.94±5.238	>0.05

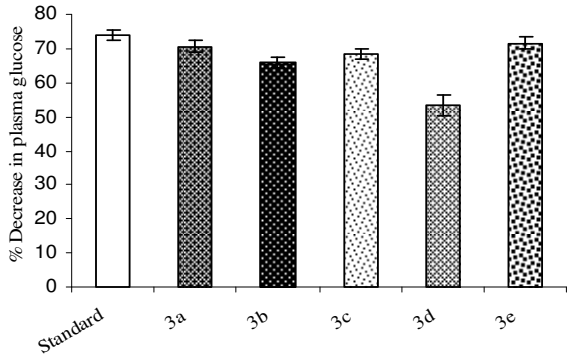
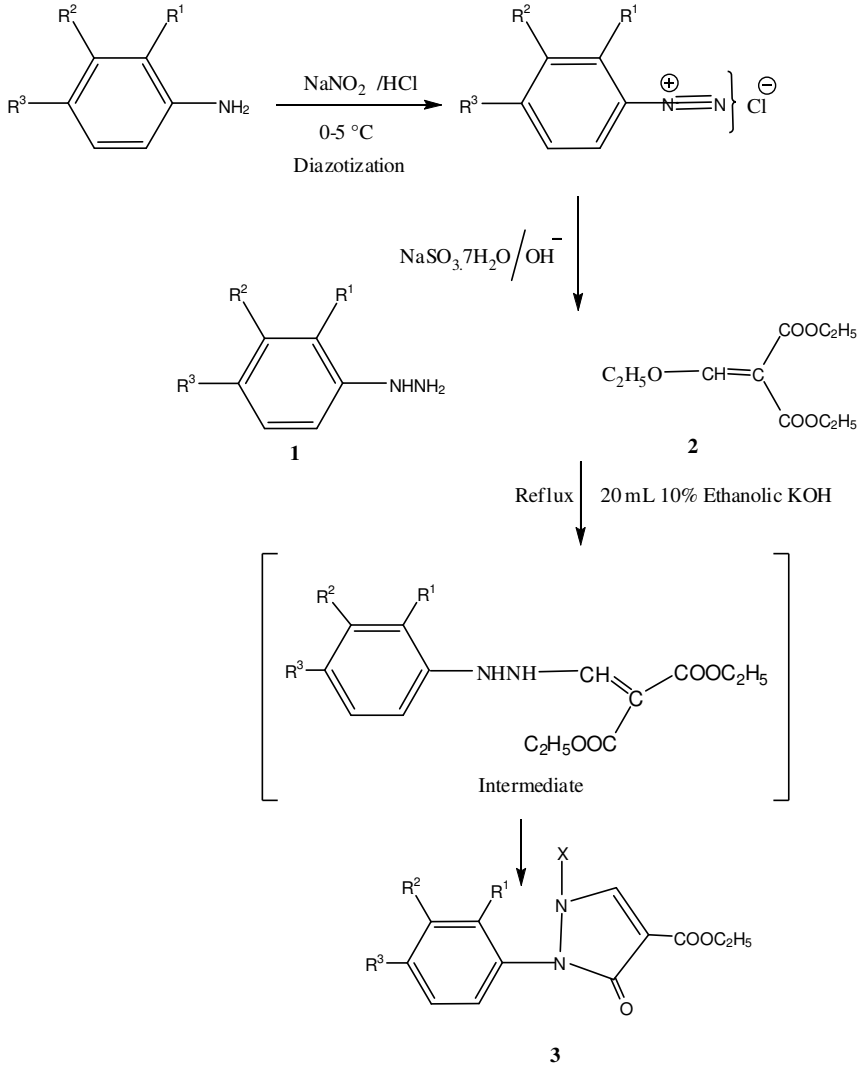


Figure 1 — Comparison of activity of the compounds along with the standard at 40 mg/kg.

(s,1H heterocyclic ring proton), 2.2 (1H, NH D_2O exchangeable); Anal. Found: C, 50.10; H, 3.59; N, 14.63. $C_{12}H_{11}N_3O_5$ requires C, 51.99; H, 4.00; N, 15.16%.

Ethyl-2,4 dichlorophenyl-2,3-dihydro-1*H* pyrazol-3-one-4-carboxylate 3e

Yield: 74.23%, m.p. 147°C; UV-Vis: 254.5 nm; IR (KBr): 3358 (NH str.), 1697(-C=O), 3043 (Ar), 1545 (Ar-C-C-str.), 1114 (-C-O str. of ester) 721 cm^{-1} (Ar - CH);^{1}H NMR ($CDCl_3$): δ 1.3 (s, 3H, $-CH_3$), 3.5 (s, 2H, $-CH_2$), 2.4 (1H, NH D_2O exchangeable), 6.1 (s,1H,Ar-H) 6.6 (s ,1H, Ar-H), 7.8 (s,1H, Ar-H), 8.5 (s,1H, heterocyclic ring proton); Anal. Found: C,



3a, $R^1 = R^2 = R^3 = X = H$
3b, $R^1 = R^2 = R^3 = H$, $X = C_6H_5$
3c, $R^1 = R^2 = X = H$, $R^3 = NO_2$
3d, $R^1 = R^3 = X = H$, $R^2 = NO_2$
3e, $R^1 = R^3 = Cl$, $R^2 = X = H$

Scheme I

47.23; H, 3.43; N, 22.92. $C_{12}H_{10}N_3C_{l2}O_3$ requires C, 47.86; H, 3.35; Cl, 23.55; N, 9.30%.

Biological evaluation

The synthesized compounds were subjected for assessment of hypoglycemic activity. The rats of both sexes of Wistar strain weighing between 150-200 g were taken for *in vivo* activity. The compounds that were synthesized for their possible antidiabetic activity based on the model generated by Bertrand Cottineau *et al.* 3-methoxy-1*H*-pyrazole-4-carboxylic acid were found to have potency. Ten animals were used for screening the activity of each compound, the animals were divided into 2 groups as above 40 mg/kg, and 20 mg/kg dose were given for three consecutive days using metformin as standard drug and alloxan was used to induce glycemia.

Conclusion

The nature of the substituent at the phenyl ring of the 2nd position of pyrazole-4-carboxylate could be correlated to an important electronic variation. In conclusion it is found that pyrazole compounds may emerge as potential and promising antidiabetic agents by preparing more derivatives and analogs and screening their toxicity. Further derivatives may be prepared so as to establish a SAR (Structure Activity Relationship) based on rational studies.

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