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ARTICLE

Microwave Assisted Synthesis and QSAR Study of 1-Substituted-3-aryl-1*H*-pyrazole-4-carbaldehydes Derivatives

Valmik S. Kapase✉

ABSTRACT

Several 1-substituted-3-aryl-1*H*-pyrazole-4-carbaldehyde (**3a-g**) derivatives were synthesized by substituted acetophenone (**1a-d**), substituted hydrazine (**2a-b**) and DMF in $POCl_3$ and reaction mixture was irradiated with microwave at 20% power to furnish 1-substituted-3-aryl-1*H*-pyrazole-4-carbaldehydes derivatives (**3a-g**).

KEYWORDS

Phosphorus trichloride, Pyrazole, Substituted hydrazine, Microwave synthesis, QSAR studies.

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INTRODUCTION

Pyrazoles are important class of heterocyclic compounds, which find a widespread use in various applications [1,2]. The pyrazole ring is a constituent of a variety of natural and synthetic products. Examples of a variety of pyrazole ring containing natural products are (*S*)-3-pyrazolylalanine [3], pyrazomycine [4] and 4,5-dihydro-3-phenyl-6*H*-pyrrole[1,2-*b*]pyrazole [5], while lonazolac [6], fezolamine [7], difenamizole [8] and mepirizole [9] are examples of biologically active synthetic pyrazole derivatives. Lonazolac is a new nonsteroidal anti-inflammatory drug [10]. Nitropyrazole derivatives, including 1-methyl-4-nitropyrazole, 4-nitro-pyrazole and 4,4-dinitro-1,1-methylene dipyrazole, are antiparasitic agents [11]. 3,4-*bis*(2,4-Dinitrobenzoyl-hydoxymethyl)pyrazole exhibits excellent antimicrobial activities. This compound is more efficient than levomycetin, penicillin and polymyxin [12]. A new non-benzodiazepine anxiolytic, lesopitron, which is currently in phase II trials, has no side effects [13].

The derivatives of pyrazole are widely applied in agrochemistry as herbicides, insecticides and fungicides [14]. For example, an efficient fungicide, containing 4-chloro-3-(3, 5-dichlorophenyl)-1*H*-pyrazole, is patented for protecting plants from phytopathogenic fungi [15]. Pyrazole-containing compounds are associated with anti-pyretic, antimicrobial, anti-inflammatory, bactericidal and hepato protective activities [16-20]. The derivatives of pyrazole are mainly utilized in medicines and present considerable potential as pharmaceutical agents because of their biological activities including anti-inflamatory, endocrinological and antihyperglycic activities [21-24]. Different

pyrazoline derivatives exhibit crucial pharmaceutical and biological activities, which led to studies on these activities in nitrogen containing heterocyclic compounds. The most significant effects of these derivatives are central nervous system [26], antimicrobial [25] and immunosuppressive activities [27]. The syntheses of these derivatives are limitedly reviewed [28-30].

Pyrazoles are prepared through 1,3-dipolar cycloaddition of olefins or acetylenes to diazoalkenes or nitrile imines or through condensation between 1,3-dicarbonyl and a hydrazine derivative. Although these basic synthesis methods are efficient and simple, the utilization of precursors which are unsymmetrically substituted results in a mixture of regioisomeric derivatives of pyrazole. 3-(Dimethylamino)propenoates are the masked 1,3-dicarbonyl complexes and can be changed into substituted pyrazole after a treatment with hydrazine derivatives [31]. Various pyrazoles have been prepared from hydrazine derivatives, whereas successful synthetic attempts have been reported for 1-[(2-acetoxyethoxy) methyl]-3,5-dimethyl-1*H*-pyrazole [32], 5-1mino-1-[(1,3-benzothiazol-2-ylthio)acetyl]-3-(methylthio)-1*H*-pyrazole-4-carbonitrile [33], 3-methyl-(2′,4′-dibromophenyl)-2-pyrazoline-4-thiosemicarbohydrazone-5-one [34], 5-hydroxyl-3-(3-nitrophenyl)-4-phenylazopyrazole [35], 1-(5-hydroxypentyl)-3,5-dimethyl-1*H*-pyrazole [36], 4-fluoro-3,5-dimethyl-1*H*-pyrazole [37], *etc*. recently.

EXPERIMENTAL

Thorough open capillary tubes, melting points were estimated and are uncorrected. The ^{1}H NMR and IR spectra were recorded in $CDCl_3$ with TMS as the internal standard on the Bruker spectrometer at 400 MHz and in KBr pellets on a Nicolet 400D spectrometer, respectively. The LC-MS of the selected samples of the compounds obtained on LC-MSD-Trap-SL 01046 purity were analyzed using TLC on silica G plates.

Synthesis of 1-substituted-3-aryl-1*H*-pyrazole-4-carbaldehydes: In 100 mL round bottom flask, 0.02 mol substituted acetophenone (**1a-d**), 0.02 mol substituted hydrazine (**2a-d**) and 10 mL DMF were mixed in ethanol (30 mL) followed by the addition of $POCl_3$ solution (1 mL). The reaction mixture was irradiated with microwaves at 20% microwave power (140 W) for 4-5 min. Reaction completion was confirmed through TLC (ethyl acetate:hexane = 1:9). The reaction mixture was cooled at room temperature, and then, was poured onto crushed ice. The separated solid was filtered, washed with a small quantity of ethanol and purified through recrystallization with ethanol to acquire pure products. The products thus obtained (**3a-g**) (**Scheme-I**). Details of the synthesized substituted pyrazoles under microwave irradiation are summarized in Table-1.

3-Phenyl-1*H*-pyrazole-4-carbaldehyde (3a): IR (KBr, ν_{max}): 3500 (NH), 3012 (Ar-CH), 1647 (C=O), 1600 (C=N), 1595 (C=C), 1217 (N-N). ^{1}H NMR ($CDCl_3$, 200.13 MHz): δ 7.75-7.80 (m, 5H, C_6H_5), 8.10 (d, 1H, =CH), 9.85 (s, 1H, CHO), 11.00 (s, 1H, NH). ^{13}C NMR ($CDCl_3$, 50.32 MHz): δ 113.73 (=C<), 127.58 (=CH), 128.50 (=CH), 129.00 (=CH), 130.04 (=CH), 140.00 (=CH), 140.37 (=C<), 180.00 (C=O). Anal. calcd. (found) % for $C_{10}H_8N_2O$: C, 69.79 (69.76); H, 4.72 (4.68); N, 16.31 (16.27)

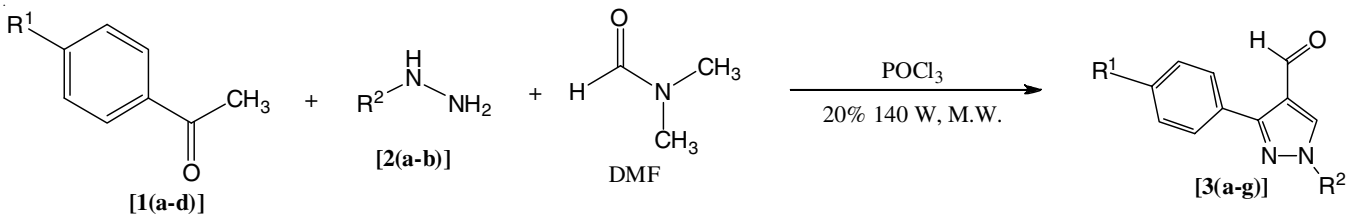
3-(4-Methoxy-phenyl)-1*H*-pyrazole-4-carbaldehyde (3b): IR (KBr, ν_{max}): 3500 (NH), 3012 (Ar-CH), 1577 (C=N), 1595 (C=C), 1230 (N-N), 1209 (OCH_3). ^{1}H NMR ($CDCl_3$, 200.13 MHz): δ 3.73 (s, 3H, CH_3), 7.5 (s, 1H, =CH), 6.83-7.37 (m, 4H, C_6H_4), 9.61 (s, 1H, CHO), 13.7 (s, 1H, NH). ^{13}C NMR ($CDCl_3$, 50.32 MHz): δ 56.00(OCH_3), 162.00 (=C<), 114.6 (2×CH), 128.0 (2×=CH), 128.8 (=C<), 150.0 (=C<), 104.0 (=C<), 134.0 (=C<), 190.0 (C=O), Anal. calcd. (found) % for $C_{11}H_{10}N_2O_2$: C, 65.39 (65.34); H, 5.04 (4.98); N, 13.89 (13.85).

3-(4-Methoxy-phenyl)-1-phenyl-1*H*-pyrazole-4-carbaldehyde (3c): IR (KBr, ν_{max}): 3012 (Ar-CH), 1595 (C=C), 1577 (C=N), 1230 (N-N), 1209 (OCH_3). ^{1}H NMR ($CDCl_3$, 200.13 MHz): δ 3.73 (s, 3H, CH_3), 7.28-7.30 (m, 5H, C_6H_5), 7.08 (d, 1H, =CH), 9.61 (s, 1H, CHO), 6.83-7.37 (m, 4H, C_6H_4). ^{13}C NMR ($CDCl_3$, 50.32 MHz): δ 56.00 (OCH_3), 162.00 (=C<), 114.6 (2×CH), 128.0 (2×=CH), 128.8 (=C<), 158.0 (=C<), 127.0 (=CH), 139.7 (=C<),118.8 (2×CH), 129.1 (2×=CH), 126.0 (=C<), 190.0 (C=O), Anal. calcd. (found) % for $C_{17}H_{14}N_2O_2$: C, 73.41 (73.37); H, 5.11 (5.07); N, 10.10 (10.07).

3-(4-Nitro-phenyl)-1*H*-pyrazole-4-carbaldehyde (3d): IR (KBr, ν_{max}): 3500 (NH), 3012 (Ar-CH), 1670 (C=O), 1595 (C=C), 1577 (C=N), 1421 (-NO_2), 1230 (N-N). ^{1}HNMR ($CDCl_3$, 200.13 MHz): δ 7.74-8.25 (m, 4H, C_6H_4), 7.05 (d, 1H, =CH), 9.61 (s, 1H, CHO), 13.07 (s, 1H, NH). ^{13}C NMR ($CDCl_3$, 50.32 MHz): δ 148.4 (=C<), 124.1 (2×CH), 127.9 (2×=CH), 142.6 (=C<), 150.0 (=C<), 134.0 (=CH), 104.0 (=C<),190.0 (C=O), Anal. calcd. (found) % for $C_{10}H_7N_3O_3$: C, 55.33 (55.30); H, 3.30 (3.25); N, 19.41 (19.35).

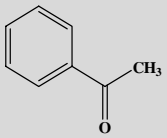
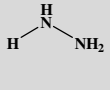
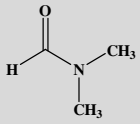
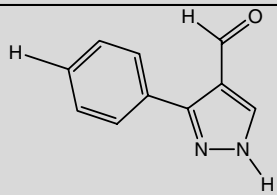
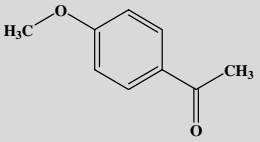
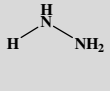
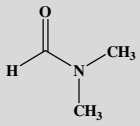
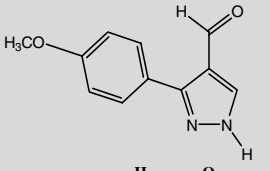
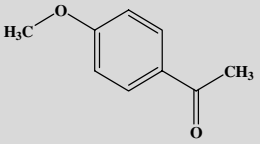
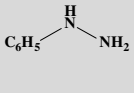
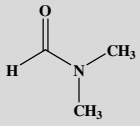
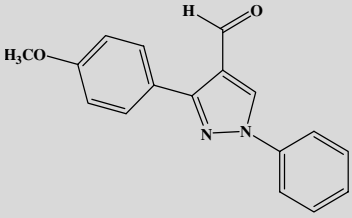
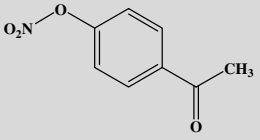
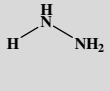
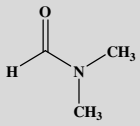
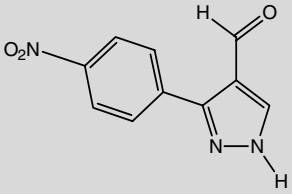
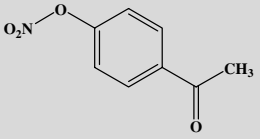
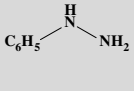
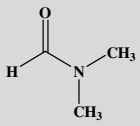
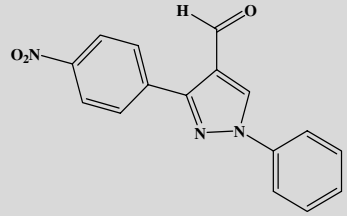
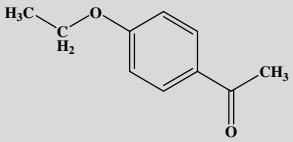
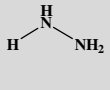
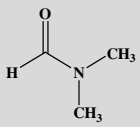
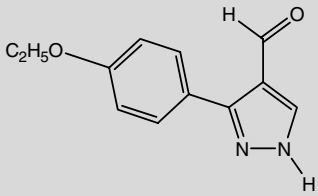
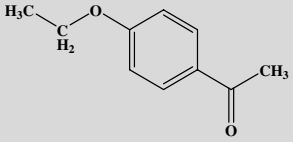
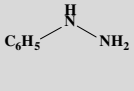
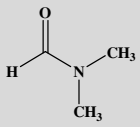
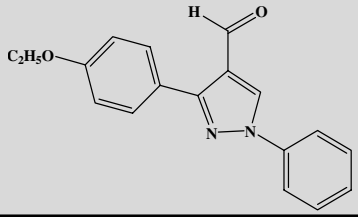
3-(4-Nitro-phenyl)-1-phenyl-1*H*-pyrazole-4-carbaldehyde (3e): IR (KBr, ν_{max}): 3012 (Ar-CH), 1670 (C=O), 1595 (C=C), 1577 (C=N), 1421 (-NO_2), 1230 (N-N). ^{1}H NMR ($CDCl_3$, 200.13 MHz): δ 7.74-8.25 (m, 4H, C_6H_4), 7.08 (d, 1H, =CH), 9.61 (s, 1H, CHO), 7.28-7.30 (m, 4H, C_6H_5). ^{13}C NMR ($CDCl_3$, 50.32 MHz): δ 148.4 (=C<), 124.1 (2×CH), 127.9 (2×=CH), 142.6 (=C<), 158.0 (=C<), 127.0 (=CH), 106.0 (=C<), 190.0 (C=O), 139.7 (=C<), 118.8 (2×CH), 129.1 (2×=CH), 126.0 (=C<), Anal. calcd. (found) % for $C_{16}H_{11}N_3O_3$: C, 65.57 (65.53); H, 3.83 (3.78); N, 14.38 (14.33).

3-(4-Ethoxy-phenyl)-1*H*-pyrazole-4-carbaldehyde (3f): IR (KBr, ν_{max}): 3500 (NH), 3012 (Ar-CH), 1670 (C=O), 1595 (C=C), 1577 (C=N), 1230 (N-N), 1117 (C-O). ^{1}H NMR ($CDCl_3$, 200.13 MHz): δ 1.33 (s, 3H, CH_3), 3.98 (s, 2H, CH_2), 6.83-7.37 (m, 4H, C_6H_4), 7.05 (d, 1H, =CH), 9.61 (s, 1H, CHO),



Scheme-I: Synthesis of 1-substituted-3-aryl-1*H*-pyrazole-4-carbaldehydes

TABLE-1
PREPARATION OF SUBSTITUTED PYRAZOLES UNDER MICROWAVE IRRADIATION

Comp.	Substrate 1	Substrate 2	Substrate 3	Product	Time (min)	m.p. (°C)	Yield (%)
3a					4	116-117	83
3b					4	124-125	75
3c					4	176-178	78
3d					5	139-140	79
3e					5	184-185	84
3f					5	271-272	82
3g					6	282-283	79

13.07 (s, 1H, NH). ^{13}C NMR ($CDCl_3$, 50.32 MHz): δ 14.3 (-CH_3), 65.1 (-OCH_2), 158.8 (=C<), 114.7 (2×CH), 127.6 (2×=CH), 128.1 (=C<), 150.0 (=C<), 134.0 (=CH), 104.0 (=C<),190.0 (C=O). Anal. calcd. (found) % for $C_{12}H_{12}N_2O_2$: C, 66.65 (66.61); H, 5.59 (5.54); N, 12.96 (12.94).

3-(4-Ethoxy-phenyl)-1-phenyl-1*H*-pyrazole-4-carbaldehyde (3g): IR (KBr, ν_{max}): 3012 (Ar-CH), 1670 (C=O), 1595 (C=C), 1577 (C=N), 1230 (N-N), 1117 (C-O). ^{1}HNMR ($CDCl_3$, 200.13 MHz): δ 1.33 (s, 3H, CH_3), 3.98 (s, 2H, CH_2), 6.83-7.37 (m, 4H, C_6H_4), 7.08 (d, 1H, =CH), 9.61 (s, 1H, CHO), 7.28-7.30 (m, 5H, C_6H_5). ^{13}C NMR ($CDCl_3$, 50.32 MHz): δ 14.3 (-CH_3), 65.1 (-OCH_2), 158.8 (=C<), 114.7 (2×CH), 127.6 (2×=CH), 128.1 (=C<), 150.0 (=C<), 127.0 (=CH), 106.0 (=C<), 190.0 (C=O), 139.7 (=C<), 118.8 (2×CH), 129.1 (2×=CH), 126.0 (=C<). Anal. calcd. (found) % for $C_{18}H_{16}N_2O_2$: C, 73.95 (73.91); H, 5.52 (5.49); N, 9.58 (9.54).

RESULTS AND DISCUSSION

Synthesis of various pyazoles *viz.* 1-substituted-3-aryl-1*H*-pyrazole-4-carbaldehydes derivatives (**3a-g**) were achieved

(**Scheme-I**). The synthesized compounds were characterized by analyzing their ^{1}H & ^{13}C NMR and IR bands. It was observed that substituted acetophenone condensation with substituted hydrazine and DMF yields 1-substituted-3-aryl-1*H*-pyrazole-4- carbaldehydes. The structures of the synthesized compounds (**3a-g**) were verified using the elemental analysis and IR spectra. An absorption band appeared at 1595 (C=C) in IR spectra, and in ^{1}H NMR, signals were obtained at 8.10 (d, 1H, =CH) and 9.85 (s, 1H, CHO), indicating the formation of desired products. Absorption bands observed at 1340 (C-N), 1230 (N-N) and 1577 (C=N) in the IR spectra and signal appearing at 13.07 (s, 1H, NH) in ^{1}H NMR confirmed that the structures correspond to 1-substituted-3-aryl-1*H*-pyrazole-4-carbaldehyde (**3a-g**).

QSAR Analysis of activities with PASS: The relationship of the synthesized structure with various biological activities was investigated through computer programme PASS. The structures of compounds (**3a-g**) were processed in software to predict their probabilities of being inactive [Pi] and active [Pa] for a biological activity set. Three activities *viz*. (i) aspulvinone dimethyl allyl transferase inhibitor; (ii) gluconate 2-dehydrogenase (acceptor) inhibitor and (iii) CYP2D15substrate, were predicted with top probability for the synthesized compounds (**3a-g**).

Aspulvinone dimethyl allyl transferase inhibitor: The enzyme named aspulvinone-edimethyl allyl transferase or dimethylallyl-diphosphate was used to catalyze a reaction of *Aspergillus terreus*. 2-Dimethylallyl diphosphate + aspulvinone E <=> 2 diphosphate + aspulvinone H. *Aspergillus terreus* poses a threat to humans and animals due to its total resistance towards amphotericin B, which is a crucial drug for fungal infections. The catalytic activities of the aforementioned enzyme can probably be inhibited in an organism by using the study compound.

Gluconate 2-dehydrogenase (acceptor) inhibitor: Gluconate 2-dehydrogenase (acceptor) (EC 1.1.99.3) is the enzyme catalyzing a chemical reaction that occurs in organisms such as *Campylobacter jejuni* and *Gluconobacter frateurii*. D-gluconate + acceptor 2-dehydro-D-gluconate + reduced acceptor *C. jejuni* and naturally occupies the digestive tract of numerous bird species and is frequently associated with poultry. The catalytic activities of the aforementioned enzyme can probably be inhibited in an organism by using the study compound.

CYP2D15 substrate: CYP2D15 is used exclusively to catalyze dextromethorphan O-demethylation in the metabolism of dog liver drugs. Compounds may serve as substrates to this protein in dogs. However, according to predictions, for the three activities, the derivatives of the series are moderately active. Among the derivatives, **3a** exhibits the highest Pa for CYP2D15 substrate and the highest aspulvinone dimethyl allyl transferase inhibitor activities. Whereas, compound **3f** is having highest Pa for gluconate 2-dehydrogenase (acceptor) inhibitor activity as shown in Table-2.

TABLE-2
PREDICTIONS OF BIOLOGICAL ACTIVITIES BY PASS

Comp.	Aspulvinone dimethyl allyl transferase inhibitor	Gluconate 2-dehydrogenase (acceptor) inhibitor	CYP2D15 substrate
	Pa	Pa	Pa
3a	0.570	0.532	0.527
3b	0.441	0.479	0.404
3c	0.423	0.612	0.369
3d	0.431	0.609	0.401
3e	0.358	0.529	0.269
3f	0.314	0.627	0.304
3g	0.285	0.523	0.269

Conclusion

The synthesis of 1-substituted-3-aryl-1*H*-pyrazole-4-carbaldehydes was reported. All the synthesized derivatives were analyzed through IR, NMR (^{1}H & ^{13}C) and mass spectral data. The synthesized compounds were screened to determine their antimicrobial properties. These compounds exhibit considerable potential against fungal and bacterial strains. Compound **3d** exhibits a high potential for inhibition and can act as a potent antimicrobial agent.

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