Biointerface Research in Applied Chemistry
Open-Access Journal (ISSN: 2069-5837)

Article
Volume 15, Issue 2, 2025, 27
https://doi.org/10.33263/BRIAC152.027

Nickel Promoted Green and One Pot Reaction Process: Construction of Pyrazoles Derivatives

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Received: 12.10.2024; Accepted: 4.01.2025; Published: 15.04.2025

Abstract: Through a one-pot multi-component approach, we accomplished a nickel-promoted simple, new, and efficient protocol for constructing pyrano[2,3-c] pyrazoles. Various aldehydes are treated under optimized reaction conditions via condensation and addition reactions to provide final compounds 5a-j in good to high yield. Mechanistic studies have been discussed in this methodology.

Keywords: nickel catalyst; one-pot reaction; pyrazoles, green approach; anti-cancer activity.

1. Introduction

In recent decades, both industrial scientists and academic people have prepared heterocyclic compounds using multi-component reactions [1,2]. Generally, single organic compounds can be prepared through multi-component reactions where a minimum of three or more reacting components participate in a proper manner. These are efficient approaches to constructing a library of heterocyclic molecules [3-7]. In this connection, synthetic ability [8-10] variability and convergency are most important for multi-component reactions.

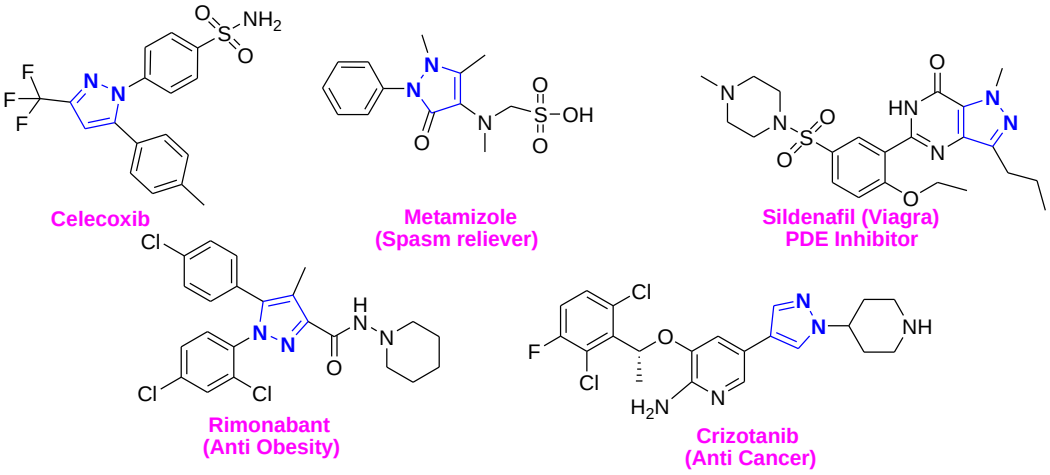


Figure 1. Biologically significant pyrazole scaffolds.

In synthetic organic chemistry, pyrazole derivatives are of wide importance [11] in the pharmaceutical industry, and they are efficient intermediates for the preparation of various

biological compounds (Figure 1) [12]. Generally, pyrazole compounds bear anti-cancer [13], insecticidal [14], anti-inflammatory [15], anti-microbial, insecticidal, fungicidal, molluscicidal [16], and analgesic properties [17], and they also inhibit human Chk1 kinase [18].

In recent years, pyrazoles [19-22] were constructed through two components [23], three components [24], and four variables [25]. However, many reports have involved toxic catalysts. For example, hexadecyl dimethyl benzyl ammonium chloride [26], basic ionic liquids, and others were used in the previous literature. On the other hand, it was prepared under catalyst-free conditions at high temperatures [27]. In addition, the reactions took longer, identified various byproducts, required harsh temperatures, and yielded less of the desired product. Thus, to overcome the above disadvantages, a newer method is desired. Many researchers have focused on developing novel approaches that may replace the existing method. In this connection, they developed eco-friendly protocols using green solvents, ionic liquids, supercritical fluids [28], and furious phases [29]. In this regard, we would like to establish nickel catalyzed simple and general multi-component approach for the preparation of pyrazoles in green solvent.

2. Material and Methods

2.1. Material.

All the required chemicals hydrazine hydrate, aromatic aldehydes, ethyl 3-oxobutanoate, malononitrile, nickel iodide with K_3PO_4, K_2CO_3, NiBr, Ni_2CO_3, $NiSO_4$ x $5H_2O$, $Ni(OAc)_2$ x H_2O, $NiCl_2$ x $2H_2O$, triethylamine, DABCO, hexane, 1,4 dioxane, toluene, DMF, methanol, ethanol, ethyl acetate solvents were purchased from Merk and used without further purification.

2.2. Instruments.

NMR: BRUKER 400 MHz, Model: ASCEND 400 MHz. (Chemical shift values are reported as values in ppm relative to TMS ($\delta = 0$) as internal standard. Multiplications using the abbreviations s = singlet, d = doublet, m = multiplet), GC: Perkin Elmer Clarus 600C Mass Spectrometer. MS: Perkin Elmer Clarus 680C Gas Chromatograph. FT-IR: Shimadzu IR Affinity-1 Fourier Transform Infrared spectrophotometer, Melting points of synthesized compounds were determined by Melting point apparatus.

2.3. Method.

The title compounds (5a-j) were synthesized by using hydrazine hydrate 2 (1 mmol), aromatic aldehydes 3 (1 mmol), ethyl 3-oxobutanoate 1 (1 mmol), malononitrile 4 (1 mmol) with K_3PO_4 (212 mg, 1 eq), assisted with NiI catalyst at 60°C in the presence of EtOH. A cyclohexane ethyl acetate mixture (70:30) is used as an eluent to monitor the reaction through TLC. The reaction mixture was transferred into the separating funnel, and the organic layer was collected in the round bottom flask. This organic layer is evaporated by a rotary evaporator and purified by CC (column chromatography) to get a pure final product.

3. Results and Discussion

Initially, we started the standardization using model substrates like ethyl 3-oxobutanote 1, benzaldehyde 3, malononitrile 4, and hydrazine hydrate 2 at 60°C using a Nickel source as

a catalyst with various solvent bases. No reaction proceeded without solvent (row 1 in Table 1). Thus, the solvent effect on the response has been studied. In this connection, the reaction with the 1,4-dioxane solvent provided final molecule 5a in 25% yield (row 2 in table 1). Whereas other solvents like toluene, DMF, and THF were tested for this reaction, they have provided final product 5a in 20%, 40%, and 60% yields, respectively (rows 3-5 in Table 1). It might be the reason that the starting material in solvents is solubilized less.

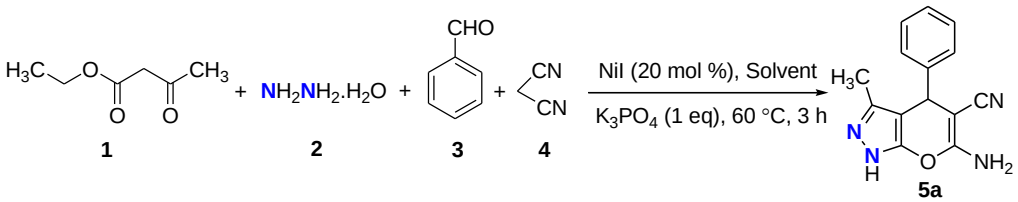


Table 1. Solvent standardization for the synthesis of pyrazoles[a].

S. No	Solvent	Time (hr)	Yield (%)[b] (5a)
1	-	8	0
2	1,4-Dioxane	8	25
3	toluene	8	20
4	Dimethylformamide	6	60
5	Tetrahydrofuran	6	40
6	Methanol	3	72
7	Ethanol	2	75
8[c]	Ethanol	18	Trace

[a] Conditions: 1 (1 mmol), 2 (1 eq), 3 (1 eq), and 4 (1 eq), NiI (0.2 eq), K_2CO_3 (1 eq), sol (4 mL), 2-18 h; [b] Purified yield; [c] Room temperature.

The reaction with MeOH provided the target compound **5a** in 72% yield (row 6 in Table 1); on the other hand, EtOH gave the final product **5a** in 75%, and it took less time (row 7 in table 1) comparatively the reaction with MeOH. Generally, heat may be released on the catalytic surface in a high polar medium, which enhances the rate of intermediate production and, thus, increases product yield. In this regard, we have concluded that K_3PO_4 (row 3 in Table 2) was a better base than other bases during base optimization. In addition, inorganic bases have shown promising activity compared to organic bases like Et_3N, pyridine, and DABCO. Generally, organic bases have a lower essential nature than inorganic bases. Therefore, they don't activate the catalytic surface, and thus, the rate of the reaction may be reduced. Furthermore, the reaction with the absence of base has not obtained any final product, which indicates base is a necessary component for proceeding with this method (Table 2, entry 8). Later, the activity of nickel sources was tested, and acceptably, Ni (I) catalysts produced the desired molecule 5a in 75% yield (Table 3, entries 1-3), while the activity of Ni (II) sources was much less towards this reaction. At the same time, a lower yield was obtained with a lower amount of catalyst NiI (10 mol %) (row 7 in Table 3).

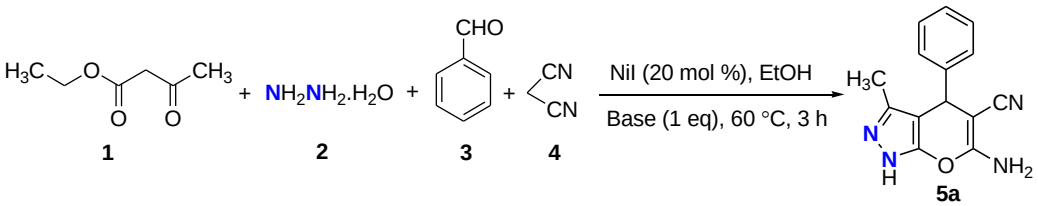


Table 2. Standardization of base[a].

S. No	Base	Time (h)	Yield (%)[b] (5a)
1	K_2CO_3	2	65
2	Cs_2CO_3	2	70

S. No	Base	Time (h)	Yield (%)[b] (5a)
3	K_3PO_4	2	75
4	Na_2CO_3	5	60
5	Triethylamine	8	-
6	Py	8	-
7	DABCO	8	-
8[c]	-	12	-

[a] Conditions: 1 (1 mmol), 2 (1 eq), 3 (1 eq), and 4 (1 eq), NiI (0.2 eq), base (1 eq), ethanol (4 mL), 2-12 h; [b] Purified yield; [c] Absence of base.

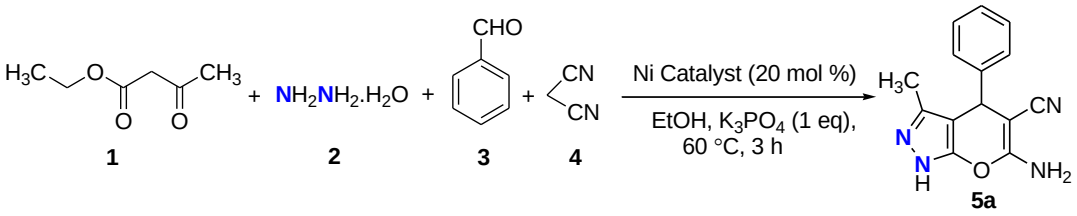


Table 3. Standardization of catalyst[a].

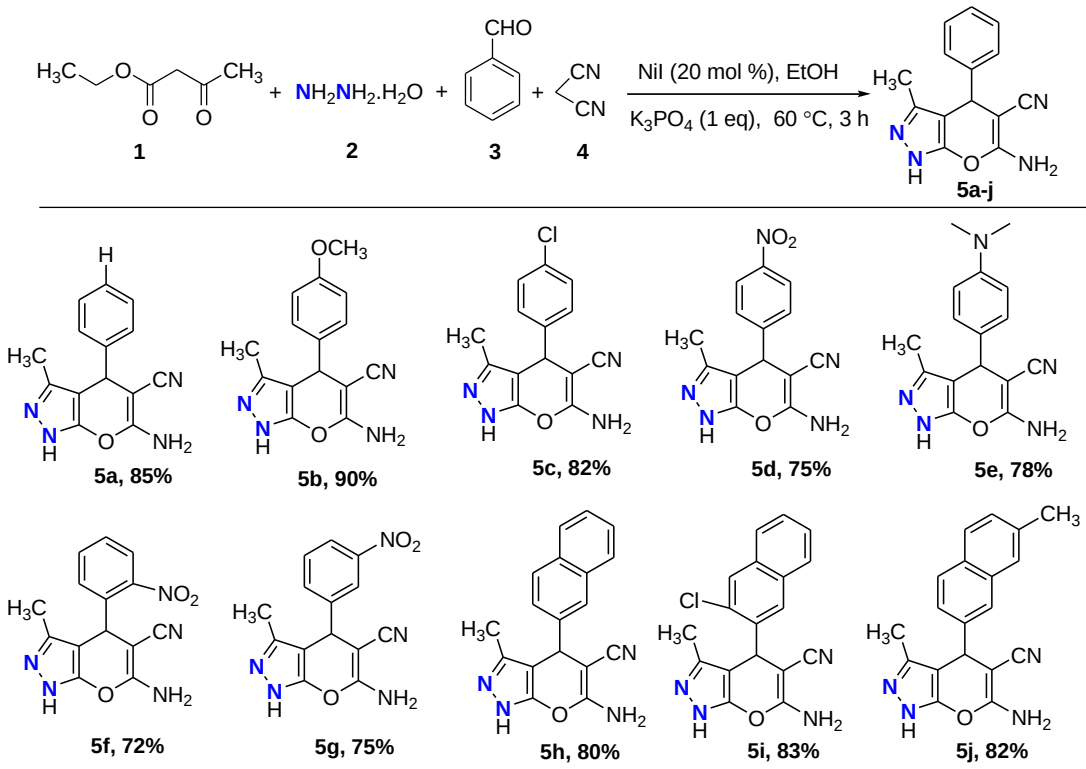
S. No	Catalyst	Time (h)	Yield (%)[b] (5a)
1	NiI	2	75
2	NiBr	2	75
3	NiCl	2	75
4	$NiSO_4$ x $5H_2O$	7	15
5	$Ni(OAc)_2$ x H_2O	7	12
6	$NiCl_2$ x $2H_2O$	8	15
7[c]	NiI	10	35
8	-	10	NIL

[a] Conditions: 1 (1 mmol), 2 (1 eq), 3 (1 eq), and 4 (1 eq), Ni catalyst (0.2 eq), K_3PO_4 (1 eq), ethanol (4 mL), 2-10 h; [b] Purified yield; [c] 10 mol % Ni sources used.

The control experiment has confirmed that no reaction proceeded without a Ni source (row 8 in Table 3). From these results, we strongly believe that the catalyst role is important for this reaction. Ni (I) source (0.2 eq), K_3PO_4 (1 eq), and ethanol as solvent were the standard conditions for this methodology.

We have started the exploration substrate scope with established standardization conditions (Scheme 1). Library of aldehydes participated to provide corresponding desired molecules 5a-j in good to high yield. Benzaldehyde-bearing substituents like 4-OCH_3, 4-Cl, 4-NO_2, and 4-$N(CH_3)_2$ carried out the reaction to get final molecules 5b-e in 75-90% yields. On the other hand, benzaldehyde bearing EWG like 2-NO_2 and 3-NO_2 gave expected products 5f-g in 72-75% yields. Other aldehydes like naphthaldehyde, 3-methyl naphthaldehyde, and 2-chloroquinolinaldehyde readily undergo reaction to get pyrazole molecules 5h-j in good yields.

As per experimental conditions, we have provided a mechanistic pathway for the synthesis of desired products (Figure 2). Here, initially, Ni initially coordinates with the keto group of ethylaceto acetate to get complex A by reacting with hydrazine. Later, complex A may produce B *via* intra-molecular. Nucleophilic addition using base [30]. The intermediate B undergoes dissociation to produce ethanol by product, and the in situ generated product coordinates with Ni to provide the complex C. That reacts with 2-benzylidene malononitrile D to give complex E *via* consecutive condensation (Knoevenagel) and addition (Michael). Finally, the complex E follows tautomerization to produce the expected molecule.



Scheme 1. Substrate scope for the synthesis of pyrazoles.

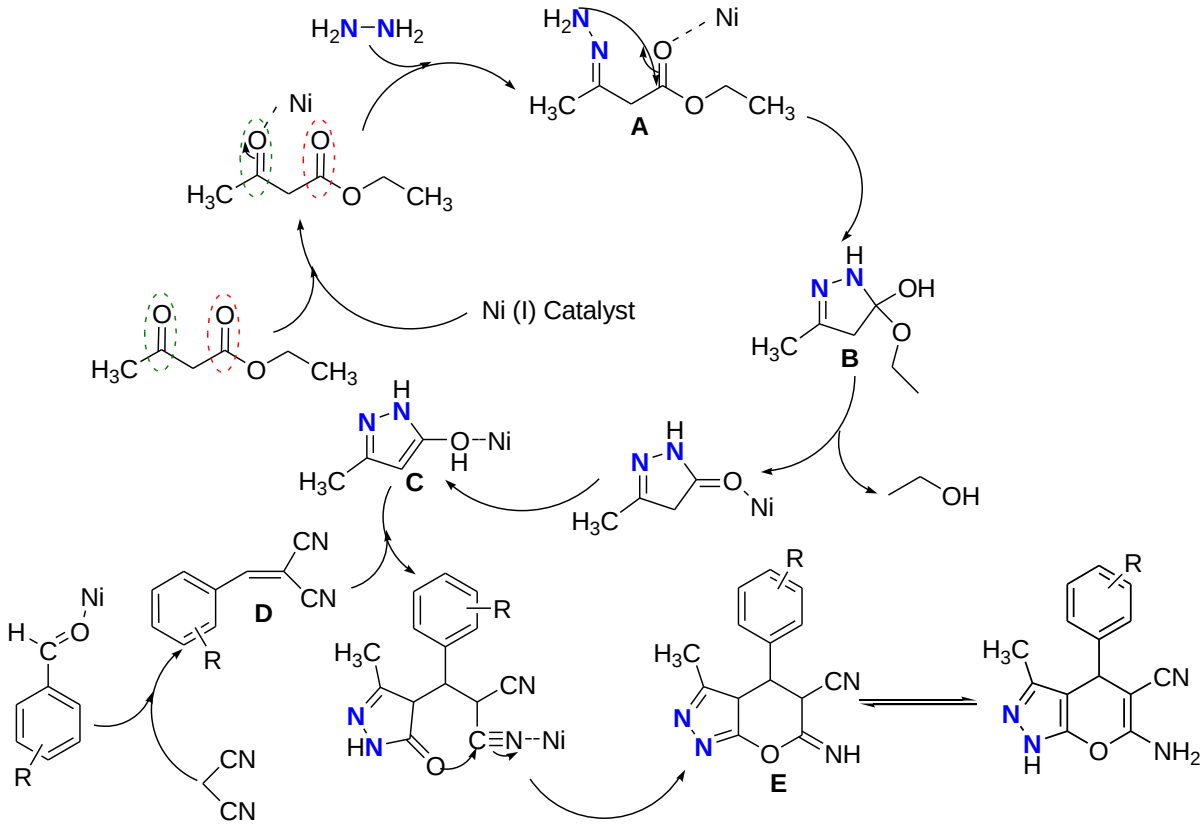


Figure 2. Plausible mechanism for the construction of pyrazoles.

Later, the cytotoxicity of pyrazole derivatives was examined (Table 4). The biological activity of resulted molecules was performed with an MTT assay on human SKOV-3 cells and PC-3 cells. Desired molecules showed good activity (performing IC_{50} varies between 6.9-100 µM). Depending on SAR studies, EWG (methyl and methoxy groups on aryl rings) revealed favorable activity 6.9-10.9 µM. Compound 5c has shown better cytotoxicity than compounds

5j and 5b. However, aryl without substitution exhibited moderate activity. Very unfortunately, the activity completely falls down in the case of nitro substrate molecules (5d, 5f, and 5g). From the above results, we would like to conclude that the desired molecule with EDG enhances the activity [31] while resulting compounds with EWG showed lower activity.

Table 4. Conduction of cytotoxicity of resulted molecules (5a-j).

Molecule	IC_{50}	
	PC-3	SKOV3
5a	35.5 ± 0.24	11.5 ± 0.16
5b	8.3 ± 0.13	10.9 ± 0.21
5c	12.8 ± 0.11	15.6 ± 0.29
5d	>100	>100
5e	9.8 ± 0.22	12.4 ± 0.17
5f	>100	>100
5g	>100	>100
5h	34.5 ± 0.36	52.9 ± 0.41
5i	24.6 ± 0.15	>100
5j	7.5 ± 0.11	6.9 ± 0.14
Doxorubicin (Standard)	1.1	0.8

3.1. Chemical characterization of compounds.

6-NH_2-5-CN-3-Me-4-Ph-dihydropyranopyrazole (5a): white solid; Yield (85%); Melting Point: 239-241°C; IR (KBr, υ_{max}, cm^{-1}): 3372- 3169 (N-H), 2192 (C≡N), 1160 (C-O-C). Proton NMR (400 Megahertz): δ_H 1.78 (3Hydrogen, singlet), 4.59 (1Hydrogen, singlet), 6.87 (2Hydrogen, br, singlet), 7.16-7.33 (5Hydrogen, multiflet), 12.10 (1Hydrogen, singlet). Carbon NMR (100 Megahertz): δ_C 9.7, 36.2, 57.2, 97.6, 120.7, 126.7, 127.4, 128.4, 135.5, 144.4, 154.7, 160.8; [M+1] = 253.

6-NH_2-5-CN-3-Me-4-OMePh-dihydropyranopyrazole (5b): yellow solid; Yield (90%); Melting Point: 209-211°C; IR (KBr, υ_{max}, cm^{-1}): 3482-3225 (N-H), 2191 (C≡N), 1052 (C-O-C). Proton NMR (400 Megahertz): δ_H 1.78 (3Hydrogen, singlet), 3.73 (3Hydrogen, singlet), 4.54 (1Hydrogen, singlet), 6.83 (2Hydrogen, br, singlet), 6.86-7.09 (4Hydrogen, multiflet), 12.08 (1Hydrogen, singlet). Carbon NMR (100 Megahertz): δ_C 9.7, 35.4, 55.0, 57.6, 97.9, 113.7, 120.8, 128.5, 135.5, 136.5, 154.7, 158.0, 160.7. [M+1] = 283.

6-NH_2-5-CN-3-Me-4-ClPh-dihydropyranopyrazole (5c): yellow solid; Yield (82%); Melting Point: 226-228°C; IR (KBr, υ_{max},cm^{-1}): 3479-3235 (N-H), 2193 (C≡N), 1071 (C-O-C). Proton NMR (400 Megahertz): δ_H 1.79 (3Hydrogen, singlet), 4.64 (1Hydrogen, singlet), 6.94 (2Hydrogen, br, singlet), 7.19-7.40 (4Hydrogen, doublet), 12.14 (1H, singlet). Carbon NMR (100 Megahertz): δ_C 9.7, 35.6, 56.8, 97.2, 120.6, 128.4, 129.4, 131.2, 135.7, 143.5, 154.7, 160.9. [M+1] =287.

6-NH_2-5-CN-3-Me-4-NO_2Ph-dihydropyranopyrazole (5d): yellow solid; Yield (75%); Melting Point: 247-248°C; IR (KBr, υ_{max},cm^{-1}): 3477-3228 (N-H), 2196 (C≡N), 1048 (C-O-C). Proton NMR (400 Megahertz): δ_H 1.80 (3 Hydrogen, s), 4.83 (1 Hydrogen, singlet), 7.06 (2 Hydrogen, br, singlet), 7.47 (2 Hydrogen, doublet, J = 8.8 Hz), 8.21 (2 Hydrogen, doublet, J = 8.4 Hz), 12.21 (1 Hydrogen, singlet). Carbon NMR (100 Megahertz): δ_C 9.7, 35.9, 56.0, 96.6, 120.5, 123.9, 128.8, 135.9, 146.4, 152.1, 154.7, 161.2. [M+1] = 298.

6-NH_2-5-CN-3-Me-4-(*N*, *N*- diMePh)-dihydropyranopyrazole (5e): yellow solid; Yield (78%); Melting Point: 203-205°C; IR (KBr, υ_{max}, cm^{-1}): 3384- 3304 (N-H), 2189 (C≡N), 1139

(C-O-C). Proton NMR (400 Megahertz): δ_H 1.79 (3 Hydrogen, singlet), 2.86 (6 Hydrogen, singlet), 4.45 (1 Hydrogen, singlet), 6.65 (2 Hydrogen, d, *J* = 8.4 Hz), 6.76 (2 Hydrogen, br, singlet), 6.96 (2 Hydrogen, doublet, *J* = 8.8 Hz), 12.04 (1 Hydrogen, singlet). Carbon NMR (100 Megahertz): δ_C 9.8, 35.4, 58.0, 98.2, 112.3, 120.9, 128.0, 132.0, 135.5, 149.2, 154.8, 160.5. [M+1] = 296.

6-NH_2-5-CN-3-Me-2-NO_2Ph-dihydropyranopyrazole (5f): white solid; Yield (72%); Melting Point: 191-193°C; IR (KBr, υ_{max},cm^{-1}): 3414-3314 (N-H), 2186 (C≡N), 1048 (C-O-C). Proton nmr (400 Megahertz): δ_H 1.77 (3 Hydrogen, singlet), 5.07 (1Hydrogen, singlet), 7.04 (2 Hydrogen, br, singlet), 7.31-7.87 (4 Hydrogen, doubledoublet), 12.22 (1 Hydrogen, singlet). Carbon NMR (100 Megahertz): δ_C 9.5, 31.4, 56.1, 96.4, 120.3, 123.6, 128.3, 131.3, 133.4, 135.8, 137.6, 149.2, 155.0, 161.2. [M+1] = 298.

6-NH_2-5-CN-3-Me-3-NO_2Ph-dihydropyranopyrazole (5g): white solid; Yield (75%); Melting Point: 225-238°C; IR (KBr, υ_{max}, cm^{-1}): 3473-3224 (N-H), 2194 (C≡N), 1043 (C-O-C). Proton NMR (400 Megahertz): δ_H 1.81 (3 Hydrogen, singlet), 4.88 (1 Hydrogen, singlet), 7.06 (2 Hydrogen, br, singlet), 7.63-8.14 (4 Hydrogen, multiflet), 12.2 (1 Hydrogen, singlet). Carbon NMR (100 Megahertz): δ_C 9.8, 35.6, 56.2, 96.7, 120.5, 121.8, 122.0, 130.2, 134.4, 135.9, 146.8, 147.9, 154.7, 161.1. [M+1] = 298.

6-NH_2-5-CN-3-Me-napthyl-dihydropyranopyrazole (5h): white solid; Yield (80%); Melting Point: 219-220°C; IR (KBr, υ_{max},cm^{-1}): 3402-3313 (N-H), 2192 (C≡N), 1050 (C-O-C). Proton NMR (400 Megahertz): δ_H 1.54 (3 Hydrogen, singlet), 5.42 (1 Hydrogen, singlet), 6.91 (2 Hydrogen, br, singlet), 7.37-8.20 (7 Hydrogen, multiflet), 12.07 (1 Hydrogen, singlet). Carbon NMR (100 Megahertz): δ_C 9.7, 57.5, 98.1, 120.6, 123.2, 125.5, 125.8, 126.9, 127.5, 128.8, 130.7, 133.7, 135.5, 154.8, 160.8. [M+1] = 303.

6-NH_2-5-CN-3-Me-2-Clnapthyl-dihydropyranopyrazole (5i): white solid; Yield (83%); Melting Point: 199-201°C; IR (KBr, υ_{max}, cm^{-1}): 3448-3254 (N-H), 2183 (C≡N), 1044 (C-O-C). Proton NMR (400 Megahertz): δ_H 1.78 (3 Hydrogen, singlet), 5.20 (1 Hydrogen, singlet), 7.54 (2 Hydrogen, br, singlet), 7.56-8.63 (5 Hydrogen, multiflet), 12.0 (1 Hydrogen, singlet). Carbon NMR (100 Megahertz): δ_C 9.6, 48.7, 93.8, 116.7, 120.4, 125.5, 125.9, 127.7, 127.9, 130.6, 130.8, 135.5, 136.7, 137.1, 139.5, 140.2, 156.7, 161.5. [M+1] = 337.

6-NH_2-5-CN-3-Me-7-Menapthyl-dihydropyranopyrazole (5j): white solid; Yield (82%); Melting Point: 241-243°C; IR (KBr, υ_{max}, cm^{-1}): 3482-3256 (N-H), 2190 (C≡N), 1056 (C-O-C). Proton NMR (400 Megahertz): δ_H 1.75 (3 Hydrogen, singlet), 3.86 (3 Hydrogen, singlet), 4.72 (1 Hydrogen, singlet), 6.91 (2 Hydrogen, br, singlet), 7.14-7.82 (6 Hydrogen, multiflet), 12.11 (1 Hydrogen, singlet). Carbon NMR (100 Megahertz): δ_C 9.7, 36.3, 55.2, 57.3, 97.6, 105.9, 118.6, 120.8, 125.5, 126.3, 127.3, 128.2, 129.1, 133.3, 135.8, 139.3, 154.8, 157.2, 160.8. [M+1] =333.0

4. Conclusion

We have accomplished a Ni-promoted one-pot reaction for constructing pyrazoles under moderate conditions in the presence of ethanol. Various aldehydes readily undergo the reaction to get the corresponding final product 5a-j in good to high yield. The following compounds, 5c, 5b, 5e, 5j, are showing good inhibiting action against the SK-OV-3 and PC-3

cancer cell lines, and this is mainly due to the electron-donating nature of the substituents (-CH_3, -OCH_3) in the above molecule as per SAR studies.

Funding

The authors are highly thankful to Gitam for their constant support.

Acknowledgments

The author, Dr. Sannapaneni Janardan, is highly thankful to the Dept of Chemistry, GSS, Gitam Deemed to be University, for the constant support.

Conflict of Interest

The authors declare that there is no conflict of interest.

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