Heterocyclic Letters
Vol. 13| No.4|811-816|Aug-Oct|2023
ISSN : (print) 2231–3087 / (online) 2230-9632
CODEN: HLEEAI
http://heteroletters.org

SYNTHESIS OF NOVEL PYRAZOLINE INTERMEDIATE AS POTENT PHARMACEUTICAL AGENT

Suresh Dhakhda[b], Girin Baxi[a], Raj Gusai[a],Ashvin Hadiyal[a] and Ajay Rathod[a*]

[a]*Department of Chemistry, KSKV Kachchh University, Bhuj (370015), Gujarat, India*
[b]*Department of Chemistry, Rai school science,RaiUniversity Ahmedabad (382260), Gujarat*
[*]*Corresponding Author: ajayrathod.chem@gmail.com*

ABSTRACT:
Pyrazole is a very potent pharmaceutical base moiety. Many researchers have been focusing on pyrazole integrated molecules for novel drug design. Currently we have synthesized active pharmaceutical scaffolds of 2-chloro-1-(5-(phenyl)-4,5-dihydro-3-p-tolylpyrazol-1-yl)ethanone. These intermediate can be used as a precursor of lead compounds. Novel Chemical entities were characterized by FT-IR, Mass, ^{1}HNMR and ^{13}Carbon NMR Spectra. Antioxidant properties of all new chemical entity were evaluated using DPPH method.

KEYWORDS: Pyrazole , Novel Intermediate , Antioxidant evaluation

INTRODUCTION:

Pyrazole base moieties possess a broad spectrum of biological activities[I]. Pyrazole scaffolds are havingversatile properties such as anti-inflammatory[II,] antibacteral[III,] antitumor[IV], antagonist[V], antiangiogenic[VI], antiinfluenza[VII], antidepressant[VIII].Pyrazole conatainingLonazolac, sulphaphenazole,celecoxib, deracoxib drugs readily available in the market[IX]. Now days, many active molecules are facing resistance toward fungal, bacteria, cancer cells, MTB[X]. Currently we have synthesized bioactive scaffolds of 2-chloro-1-(5-(phenyl)-4,5-dihydro-3-p-tolylpyrazol-1-yl)ethanonetoovercame Drug resistance. These novel molecules have active sites to acts as precursor of highly potent pharmaceutical agents. Novel intermediates were characterized through MS, Infra-Red, protonNMR and 13Carbon NMR Spectrum. Antioxidant properties of intermediates were investigated through DPPH method[XI].

EXPERIMENTAL

Material and Methods:

Methyl acetophenone, benzaldehydes, hydrazine and chloroacetylchloride were purchased from Merck. Reaction was monitored through TLC (Hexane: Ethyl acetate; 70:30). Infra-red spectra were recorded through Bruker spectrophotometer. ^{1}H NMR ^{13}CarbonNMR spectra were obtained through400 MHz Bruker spectrophotometer (in $CDCl_3$)

General procedure:

Synthesis of chalcones[XII](A1-10)

P-methyl acetophenone (20mmol), different aldehydes (20 mmol) and NaOH (25 mmol) were grinded in mortar at 30^0 C for 20mins. Solid was washed with water to eliminate excess NaOH .Resulting chalcones were filtered and recrystallized with ethanol. Yield 85% - 86%

Synthesis of Pyrazolinederivatives[XIII](B1-10)

Compound A1-10 (15mmol) and hydrazine hydrate (20mmol) were dissolved in ethanol in FBF. Reaction mixture was refluxed for 11 hours. Then ethanol was removed through distillation to get pyrazole. Solid were washed with water to eliminate excess hydrazine.It was further dissolved in dichloro methane. (15 mmol) chloro acetyl chloride was added at 5^0C and stirred for 7 to 8 hours at room temperature. Solid were achieved through distillation and recrystallized by ethanol.

2-chloro-1-(4,5-dihydro-5-phenyl-3-p-tolylpyrazol-1-yl)ethanone(B_1**):**

yellow solid, yield 68%, M.P.187^0C;M. Formula :$C_{18}H_{17}ClN_2O$; FT-IR(cm^{-1}, KBr): 1640 (C=O amide), 1514 (C=C str- Ar ring), ^{1}HNMR(400 MegaHz ,δ ppm) : 2.43 (s,CH_3), 2.10 (d, CH_2) , 4.84 (t, CH), 7.08-7.26(9H, m, Aromatic-H) ; ^{13}CarbonNMR (400 MegaHz ,δ ppm): 24.33,38.7,58.49,127.44,141.10,144.24,152.35, 166.28 Mass : M^{++} 314

2-chloro-1-(5-(4-chlorophenyl)-4,5-dihydro-3-p-tolylpyrazol-1-yl)ethanone(B_2**):**

yellow solid, yield 73%, M.P. 160^0 C; M. Formula :$C_{18}H_{16}Cl_2N_2O$; FT-IR(cm^{-1}, KBr): 1650 (C=O amide), 1518 (C=C str- Ar ring) , ^{1}HNMR(400 MegaHz ,δ ppm) : 2.48 (s, CH_3), 2.21 (d, CH_2) , 4.94 (t, CH), 7.11-7.52 (8H, m, Aromatic-H) ; ^{13}CarbonNMR (400 MegaHz ,δ ppm): 24.40, 38.77, 58.49, 127.63,140.90,145.24, 152.95, 166.08 Mass : M^{++} 348

2-chloro-1-(5-(2-chlorophenyl)-4,5-dihydro-3-p-tolylpyrazol-1-yl)ethanone (B_3**)**

Pale yellow solid, yield 62%, M.P.140^0C; M. Formula :$C_{18}H_{16}Cl_2N_2O$; FT-IR(cm^{-1}, KBr): 1635 (C=O amide), 1518 (C=C str- Ar ring) , ^{1}HNMR(400 MegaHz ,δ ppm) : 2.40(s, CH_3), 2.15 (d, CH_2) , 4.89 (t, CH), 7.10-7.58(8H, m, Aromatic-H) ; ^{13}CarbonNMR (400 MegaHz ,δ ppm): 24.30,38.66,58.40,126.90,141.90, 144.54, 152.05, 165.30 Mass : M^{++} 348

2-chloro-1-(4,5-dihydro-5-(4-nitrophenyl)-3-p-tolylpyrazol-1-yl)ethanone(B_4**)**

yellow solid, yield 65%, M.P. 190^0 C; M. Formula :$C_{18}H_{16}ClN_3O_3$; FT-IR(cm^{-1}, KBr): 1652 (C=O amide), 1528 (C=C str- Ar ring) , ^{1}HNMR(400 MegaHz ,δ ppm) : 2.32 (s, CH_3), 2.11 (d, CH_2) , 4.99 (t, CH), 7.12-8.23(8H, m, Aromatic-H) ; ^{13}CarbonNMR (400 MegaHz ,δ ppm): 24.48,38.32, 58.39, 129.94 ,133.25, 146.10, 149.24, 153.24, 166.15 Mass : M^{++} 359

2-chloro-1-(4,5-dihydro-5-(3-nitrophenyl)-3-p-tolylpyrazol-1-yl)ethanone(B_5**)**

yellow solid, yield 65%, M.P. 190^0 C; M. Formula :$C_{18}H_{16}ClN_3O_3$; FT-IR(cm^{-1}, KBr): 1652 (C=O amide), 1528 (C=C str- Ar ring) , ^{1}HNMR(400 MegaHz ,δ ppm) : 2.32 (s, CH_3), 2.11 (d, CH_2) , 4.99 (t, CH), 7.12-8.23 (8H, m, Aromatic-H) ; ^{13}CarbonNMR (400 MegaHz ,δ ppm): 24.44, 38.95, 57.99, 129.50 ,133.15, 144.38, 148.35, 152.98, 166.05 Mass : M^{++} 359

2-chloro-1-(5-(4-(dimethylamino)phenyl)-4,5-dihydro-3-p-tolylpyrazol-1-yl)ethanone(B_6**)**

white solid, yield 75%, M.P. 152^0 C; M. Formula :$C_{20}H_{22}ClN_3O$; FT-IR(cm^{-1}, KBr): 1664 (C=O amide), 1520 (C=C str- Ar ring) , ^{1}HNMR(400 MegaHz ,δ ppm) : 2.38, 3.04 (s, CH_3),

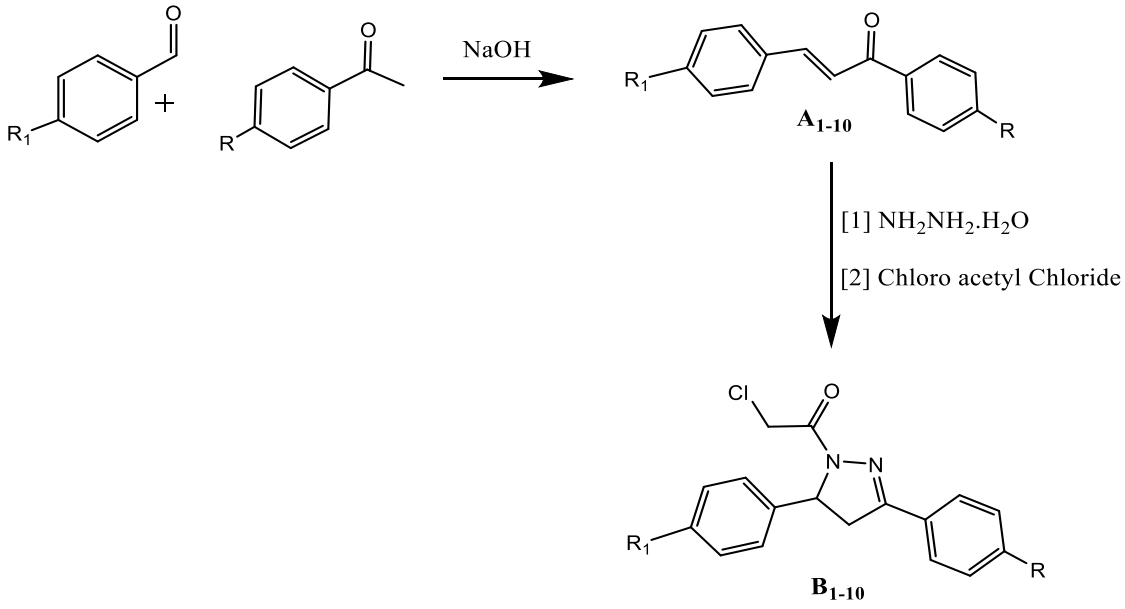
2.12 (d, CH_2) , 4.97 (t, CH), 6.90-7.40(8H, m, Aromatic-H) ; ^{13}CarbonNMR (400 MegaHz ,δ ppm): 23.90 , 39.07, 43.65, 59.16,126.98, 115.84, 140.80, 144.24, 153.15, 166.73 Mass : M^{++} 357

2-chloro-1-(4,5-dihydro-3,5-dip-tolylpyrazol-1-yl)ethanone(B_7**)**
white solid, yield 74%, M.P. 164^0 C; M. Formula :$C_{19}H_{19}ClN_2O$; FT-IR(cm^{-1}, KBr): 1690 (C=O amide), 1533 (C=C str- Ar ring) , ^{1}HNMR(400 MegaHz ,δ ppm) : 2.40, 2.42 (s, CH_3), 2.08 (d, CH_2) , 5.04 (t, CH), 7.03-7.46 (8H, m, Aromatic-H) ; ^{13}CarbonNMR (400 MegaHz ,δ ppm): 24.80,39.24, 58.63,127.44, 141.87, 145.12, 153.05, 166.45 Mass : M^{++} 328

2-chloro-1-(4,5-dihydro-5-(4-methoxyphenyl)-3-p-tolylpyrazol-1-yl)ethanone(B_8**)**
white solid, yield 69%, M.P. 171^0 C; M. Formula :$C_{19}H_{19}ClN_2O_2$; FT-IR(cm^{-1}, KBr): 1633 (C=O amide), 1545 (C=C str- Ar ring) , ^{1}HNMR(400 MegaHz ,δ ppm) : 2.38 (s, CH_3), 3.79 (s, OCH_3), 2.00 (d, CH_2) , 4.78 (t, CH), 6.82-7.36 (8H, m, Aromatic-H) ; ^{13}CarbonNMR (400 MegaHz ,δ ppm): 24.43,38.47, 55.40, 59.13, 114.25, 128.75, 132.18, 142.25,,159.40, 167.13 Mass : M^{++} 344

2-chloro-1-(4,5-dihydro-5-(3,4-dimethoxyphenyl)-3-p-tolylpyrazol-1-yl)ethanone(B_9**)**
white solid, yield 63%, M.P. 175^0 C; M. Formula :$C_{20}H_{21}ClN_2O_3$; FT-IR(cm^{-1}, KBr): 1636 (C=O amide), 1528 (C=C str- Ar ring) , ^{1}HNMR(400 MegaHz ,δ ppm) : 2.39 (s, CH_3), 3.78 (s, OCH_3) , 2.00 (d, CH_2) , 4.81 (t, CH), 6.61-7.44(7H, m, Aromatic-H) ; ^{13}CarbonNMR (400 MegaHz ,δ ppm): 24.50, 38.73, 58.78,115.12, 128.52,141.10, 148.62, 152.79, 166.52 Mass : M^{++} 374

2-chloro-1-(4,5-dihydro-5-(4-bromophenyl)-3-p-tolylpyrazol-1-yl)ethanone(B_{10}**)**
red solid, yield 75%, M.P.152^{0}C; M. Formula :$C_{18}H_{16}BrClN_2O$; FT-IR(cm^{-1}, KBr): 1658 (C=O amide), 1533 (C=C str- Ar ring) , ^{1}HNMR(400 MegaHz ,δ ppm) : 2.54 (s, CH_3), 2.05 (d, CH_2) , 4.98 (t, CH), 6.91-7.56 (8H, m, Aromatic-H) ; ^{13}CarbonNMR (400 MegaHz ,δ ppm): 24.46, 38.90, 58.89, 120.65, 128.35, 132.14, 141.53, 152.24, 166.68 Mass:M= 390 M^{+4} 394



Scheme 1

Compound	R	R_1
B_1	4-CH_3	H
B_2	4-CH_3	4-Cl
B_3	4-CH_3	2-Cl
B_4	4-CH_3	4-NO_2
B_5	4-CH_3	3-NO_2
B_6	4-CH_3	N(CH_3)$_2$
B_7	4-CH_3	4-CH_3
B_8	4-CH_3	4-OCH_3
B_9	4-CH_3	3,4-diOCH_3
B_{10}	4-CH_3	4-Br

Antioxidant Evaluation:

Antioxidant evaluation was carried out by DPPH scavenging method[XIV]. 200, 150, 100, 50 µg/ml solution of compound B_{1-10}were prepared using CH_3OH in cuvette.,2 mL sample were mixed with 2 mL 0.004% (W/V) DPPH and allowed to stand for 60 min for interactions. The absorbance was recorded at 517 nm using a Perkin– Elmer Lambda 25 UV–Vis spectrophotometer. Ascorbic acid was used as reference standard with same concentrations.The radical-scavenging activity of the tested samples, expressed as percentage inhibition of DPPH, was calculated according to the formula: % of Inhibition = $(A_0-A_t)/A_o$ * 100

RESULTS AND DISCUSSION:

The antioxidant evaluation confirms the good to moderate potential as antioxidants. In current investigation, novel molecules **B_5** and **B_4**have shown excellent activity due to CH_3at para position at phenyl ring as well as nitro group. B_5 and B_4 gave **78.24%, 70.18** % inhibition respectively. **B_8**possess methyl and methoxy substitution and **B_{10}**possess methyl and halide groups which areresponsible moderate activity with **63.14%, 55.34**% respectively. All other molecules have shown moderate to mild activity.

Comp. code	**% inhibition**			
	50 µg/ml	100 µg/ml	150 µg/ml	200 µg/ml
B_1	14.25	34.27	39.56	45.35
B_2	17	34.58	39.25	46.5
B_3	16.5	34.58	40.03	46.12
B_4	30.52	56.32	63.22	70.18
B_5	31.26	60.87	70.33	78.24
B_6	14.34	30.69	38.32	45
B_7	15.02	31.46	39.25	46.23
B_8	24.42	44.12	55.14	63.14
B_9	20.56	39.25	47.35	54.2
B_{10}	20.8	37.69	47.04	55.34
Ascorbic acid	56.32	92.22	95.45	100

Table 1: Antioxidant activity

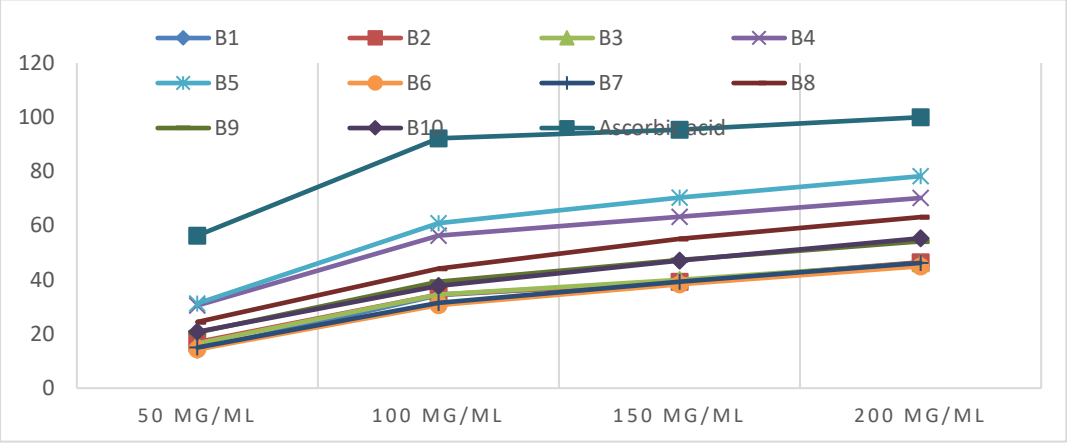


Figure 1: Antioxidant evaluation of $B_{1\text{-}10}$ at various concentrations. Vit. C used as reference (% Inhibition vs concentration)

CONCLUSION

In search of novel drug intermediate, we have efficiently synthesized bioactive derivatives of 2-chloro-1-(5-(phenyl)-4,5-dihydro-3-p-tolylpyrazol-1-yl)ethanone and characterized with the various spectroscopy techniques. All potent molecules show excellent antioxidant activities. **B_5** and **B_4**have shown highest inhibition. These molecules will be useful as a drug intermediate, because of having active chloro methylene group as well as its potential toward microorganism.

ACKNOWLEDGMENTS

Authors are grateful to KSKV Kachchh Univeristy for laboratory and analysis facilities. Authors are also grateful to SAIF Punjab Univeristy for providing analysis facilities.

CONFLICT OF INTERESTS

Authors conveystatement of no conflicted interest.

REFERENSES:

I. Sangani C. B., Mungra D. C., Patel M. P. & Patel R. G.; Synthesis and in vitro antimicrobial screening of new pyrano [4, 3-b] pyrane derivatives of 1H-pyrazole; *Chinese Chemical Letters*; (2012), ***23***(1), 57-60.

II. El-Moghazy S. M., Barsoum F. F., Abdel-Rahman H. M., & Marzouk A. A.; Synthesis and anti-inflammatory activity of some pyrazole derivatives; *Medicinal Chemistry Research*; (2012), ***21***, 1722-1733.

III. Rahimizadeh M., Pordel M., Bakavoli M., Rezaeian S., Sadeghian A.; Synthesis and antibacterial activity of some new derivatives of pyrazole; *World Journal of Microbiology and Biotechnology*; (2010), ***26***, 317-321.

IV. Park H. J., Lee K., Park S. J., Ahn B., Lee J. C., Cho H., & Lee K. I.; Identification of antitumor activity of pyrazole oxime ethers; *Bioorganic & medicinal chemistry letters;* (2005), ***15***(13), 3307-3312.

V. Lan R., Liu Q., Fan P., Lin S., Fernando S. R., McCallion D., Makriyannis A.; Structure− activity relationships of pyrazole derivatives as cannabinoid receptor antagonists; *Journal of medicinal chemistry*;(1999), ***42***(4), 769-776.

VI. Christodoulou M. S., Liekens S., Kasiotis K. M., Haroutounian S. A.; Novel pyrazole derivatives: synthesis and evaluation of anti-angiogenic activity; *Bioorganic & medicinal chemistry*; (2010), ***18***(12), 4338-4350.

VII. Shih S. R., Chu T. Y., Reddy G. R., Tseng S. N., Chen H. L., Tang W. F., Horng J. T.; Pyrazole compound BPR1P0034 with potent and selective anti-influenza virus activity; *Journal of biomedical science*; (2010), ***17***(1), 1-9.

VIII. Abdel-Aziz M., Abuo-Rahma G. E. D. A., Hassan A. A.; Synthesis of novel pyrazole derivatives and evaluation of their antidepressant and anticonvulsant activities; *European journal of medicinal chemistry*; (2009), ***44***(9), 3480-3487.

IX. Ebenezer O., Shapi M., Tuszynski J. A.; A review of the recent development in the synthesis and biological evaluations of pyrazole derivatives; *Biomedicines*;(2022), ***10***(5), 1124

X. Tortorano A. M., PrigitanoA., Morroni G., Brescini L., Barchiesi F.; Candidemia: evolution of drug resistance and novel therapeutic approaches; *Infection and Drug Resistance*, (2021), 5543-5553.

XI. Ghasempour L., Asghari S., Tajbakhsh M., Mohseni M.; Preparation of New Spiropyrazole, Pyrazole and Hydantoin Derivatives and Investigation of Their Antioxidant and Antibacterial Activities; *Chemistry & Biodiversity*; (2021), ***18***(9), e2100197.

XII. Rateb N. M., Zohdi H. F.; Atom-efficient, solvent-free, green synthesis of chalcones by grinding; *Synthetic Communications;* (2009), ***39***(15), 2789-2794.

XIII. Kavitha N. V., Divekar K., Priyadarshini B., Gajanan S., Manjunath M.; Synthesis and antimicrobial activities of some new pyrazole derivatives; *Der pharma chemical*; (2011), ***3***(4), 55-62

XIV. Mihailovic N., Markovic V., Matic I. Z., Stanisavljevic N. S., Jovanovic Z. S., Trifunovic S., Joksovic L.; Synthesis and antioxidant activity of 1, 3, 4-oxadiazoles and their diacylhydrazine precursors derived from phenolic acids; *RSC advances*; (2017), ***7***(14), 8550-8560

Received on August 12, 2023.