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Eco-friendly Synthesis of Some New Benzylidene-iminothiazolyl-pyrazol-3-ol Derivatives *via* One-Pot Multicomponent Reaction and Evaluation of Antioxidant Activities

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ABSTRACT

In present work, one-pot multicomponent reaction (MCR) route for the synthesis of benzylidene-iminothiazolyl-pyrazol-3-ol derivatives (**5a-p**) by reacting ethyl cyanoacetate (**1**), substituted benzaldehyde (**2a-c**), thiosemicarbazide (**3**) and substituted phenacyl bromide (**4a-g**). This reaction proceeds by using bleaching earth clay (BEC) (pH 12.5) in PEG-400 as a green reaction media. All the synthesized compounds were characterized by IR, ^{1}H NMR, ^{13}C NMR and mass spectral data. The pharmacological investigation of the synthesized compounds suggest that most of them showed good antioxidant activity.

KEYWORDS

Pyrazole, Thiazoles, Ethyl cyanoacetate, Benzaldehyde, Phenacyl bromide, Thiosemicarbazide, Antioxidant activities.

INTRODUCTION

The compounds from the family of heterocycles play an important key role in the field of pharmaceutical. In all of this pyrazoles and thiazoles attend the outstanding position in heterocyclic family due to their biological aspects. Literature study divulged that pyrazole derivatives have been implemented as an antimicrobial [1], antiviral [2], anticancer [3], antileishmanial [4], antimalarial [5] and dual antimicrobial–anti-inflammatory agents [6]. Apart from this, the recent studies on the potential of pyrazole confess that it acts as anticancer agents [7,8].

Thiazoles are the another important class of heterocycles as they have extensive spectrum of bioactivity. The recent studies report that thiazole nucleus is a leading topic in the modern drug synthesis due to its wide range of applications in medicinal region. The pharmaceutical review focus on the thiazole scaffolds which is successfully employed as a bioactive agent such as anti-inflammatory [9], schizophrenia [10], antimicrobial [11], HIV infections [12], hypnotics [13], anticancer [14], antifungal [15] and antioxidant activities [16]. Derivatives of thiazole explain their beneficial in various disease like anti-Alzheimer activity [17] and anxiety disorders [18]. Evolution of thiazole skeleton was studied time to time which realizes it's important in therapeutic use as a neuroprotective agents

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[19] and anticonvulsant agent [20,21]. Some selected anticancer compounds having pyrazole and thiazole scaffold are displayed in Fig. 1.

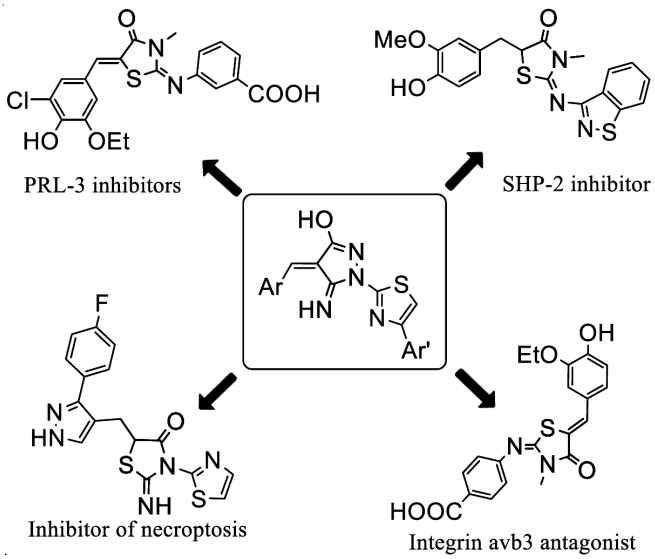


Fig. 1. Anticancer molecules containing pyrazole and thiazole scaffold

As a part of our research work to synthesize the novel heterocyclic scaffold acts as bioactive agents [22-27] and from the above study here we design and synthesize a new compound by the combination of pyrazole and thiazole moiety predicting the curative pharmaceutical agent. This hybridization leads to enhance the bioactivity of the newly formed molecule as such observe in many cases of recent study [28]. In present work, the synthesis of 1-(4-(-substituted phenyl)thiazol-2-yl)-4-(-substituted benzylidene)-5-imino-4,5-dihydro-1*H*-pyrazol-3-ol was carried by simple, convenient, efficient and eco-friendly one-pot multicomponent method. This type of method-ology exhausted the disadvantages of the conventional methods and supports the principle of green chemistry. The newly synthesized compounds were screened for their antioxidant activity.

EXPERIMENTAL

Melting points were determined by open capillary method and are uncorrected. The chemicals and solvents used were of laboratory grade and purified prior to use. Bleaching earth clay (BEC) was a gift from Supreme Silicones, Pune, India. Completion of the reaction was monitored by thin-layer chromatography on precoated sheets of silica gel-G (Merck, Germany) using iodine vapors for detection. IR spectra were recorded (in KBr pallets) on Shimadzu spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were recorded (in DMSO-d_6) on Bruker Avance-400 MHz spectrometer using TMS as an internal standard. The mass spectra were recorded on EI-Shimazdu-GC-MS spectrometer.

General procedure for the synthesis of (*E*)-4-(4-substituted benzylidene)-1-(4-(4-substitutedphenyl)thiazol-2-yl)-5-imino-4,5-dihydro-1*H*-pyrazol-3-ol (5a-p): A mixture of substituted aldehyde (1.00 mmol), ethylcyano acetate (1.00 mmol), thiosemicarbazide (1.00 mmol), substituted phenacyl bromide (1.00 mmol) and BEC (10 wt.%) was stirred in PEG-400 at 70-80 ºC for 1-2 h. After completion of reaction (monitored by TLC), the catalyst was isolated by simple filtration and the reaction mixture was poured into ice cold water and neutralized with dil. HCl. The separated solid was filtered off, dried and recrystallized by chloroform to get the pure product.

1-(4-(4-Chlorophenyl)thiazol-2-yl)-4-(4-fluorobenzylidene)-5-imino-4,5-dihydro-1*H*-pyrazol-3-ol (5a): IR (KBr, ν_{max}, cm^{-1}): 3416 (-OH), 3186 (-NH), 1604 (C=N), 1233 (C-S-C), 1092 (C-O-C); ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 12.19 (s, 1H, OH), 8.04 (s, 1H, -NH), 7.98 (s, 1H, C_5 of thiazol), 7.86 (d, *J* = 11 Hz, 2H, Ar-H), 7.72 (q, *J* = 18 Hz, 2H, Ar-H), 7.48 (d, *J* = 11 Hz, 2H, Ar-H), 7.40 (s, 1H, C=H), 7.28 (d, *J* = 23 Hz, 2H, Ar-H); ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 173.56, 162.42, 152.94, 140.29, 139.21, 138.76, 135.15, 134.56, 131.90, 130.85, 129.82, 129.31, 128.60, 128.28, 127.19, 115.98, 115.76, 104.53; EI-MS: 397 [M$^+$]; Elemental analysis: calcd. (found) % for $C_{19}H_{12}N_4OSClF$: % C, 57.22 (57.19); H, 3.03 (3.07); N, 14.05 (14.02); S, 8.04 (8.06).

4-(4-Fluorobenzylidene)-5-imino-1-(4-(3-nitrophenyl)thiazol-2-yl)-4,5-dihydro-1*H*-pyrazol-3-ol (5c): IR (KBr, ν_{max}, cm^{-1}): 3475 (-OH), 3307 (-NH), 1637 (C=N), 1229 (C-S-C), 1131(C-O-C); ^{1}H NMR: (400 MHz, DMSO-d_6, δ, ppm): 12.02 (s, 1H, -OH), 8.13 (d, *J* = 11 Hz, 2H, Ar-H), 8.02 (s, 1H, -NH), 7.82 (s, 1H, C_5 of thiazole), 7.42 (m, *J* = 18 Hz, 4H, Ar-H), 7.36 (s, 1H, =CH), 7.31 (d, *J* = 8 Hz, 2H, Ar-H), 7.24 (d, *J* = 8 Hz, 2H, Ar-H); ^{13}C NMR: (100 MHz, DMSO-d_6, δ, ppm): 170.81, 165.24, 152.09, 142.32, 137.02, 136.87, 134.11, 133.96 131.24, 130.78, 130.02, 127.84, 127.14, 126.04, 123.36, 120.35, 117.25, 116.41, 108.06; EI-MS: 409 [M$^+$]; Elemental analysis: calcd. (found) % for $C_{19}H_{12}N_5O_3SF$: % C, 55.74 (55.78); H, 2.95 (2.99); N, 17.11 (17.14); S, 7.83 (7.82).

4-(4-Chlorobenzylidene)-1-(4-(4-chlorophenyl)thiazol-2-yl)-5-imino-4,5-dihydro-1*H*-pyrazol-3-ol (5f): IR (KBr, ν_{max}, cm^{-1}): 3480 (-OH), 3132 (-NH), 1618 (C=N), 1223 (C-S-C), 1132 (C-O-C); ^{1}H NMR (400 MHz, DMSO-d_6, TMS, δ, ppm): 12.14 (s, 1H, -OH), 8.36 (s, 1H, -NH), 8.09 (s, 1H, C_5 thiazole), 7.92 (d, *J* = 8 Hz, 2H, Ar-H), 7.84 (d, *J* = 8 Hz, 2H, Ar-H), 7.34 (m, *J* = 20 Hz, 4H, Ar-H), 7.22 (s, 1H, C=H); ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 168.59, 163.84, 161.37, 148.53, 146.03, 140.66, 140.16, 130.71, 130.68, 128.05, 127.97, 126.00, 123.62, 115.53, 115.31, 107.63; EI-MS: 416 (M$^+$); Elemental analysis: calcd. (found) % for $C_{19}H_{12}N_4OSCl_2$: C, 54.95 (54.92); H, 2.91 (2.88); N, 13.49 (13.48); S, 7.72 (7.76).

4-(4-Chlorobenzylidene)-5-imino-1-(4-(3-nitrophenyl)thiazol-2-yl)-4,5-dihydro-1*H*-pyrazol-3-ol (5i): IR (KBr, ν_{max}, cm^{-1}): 3456 (-OH), 3171 (N-H), 1600 (C=N), 1211 (C-S-C), 1131 (C-O); ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 12.74 (s, 1H, -OH), 8.12 (s, 1H, -NH), 7.97 (s, 1H, C_5 of thiazole), 7.68 (m, *J* = 22 Hz, 4H, Ar-H), 7.51 (d, *J* = 10 Hz, 2H, Ar-H), 7.38 (s, 1H, =CH), 7.26 (d, *J* = 10 Hz, 2H, Ar-H); ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 170.49, 154.68, 152.46, 150.84, 139.76, 138.56, 134.01, 133.22, 131.61, 129.78, 128.79, 128.14, 126.49, 126.03, 124.57, 123.81, 122.33, 120.14, 108.71; EI-MS: 425 [M+]; Elemental analysis: calcd. (found) % for $C_{19}H_{12}N_5O_3SCl$: % C, 53.59 (53.57); H, 2.84; (2.88) N, 16.45 (16.48); S, 7.53 (7.56).

5-Imino-4-(4-nitrobenzylidene)-1-(4-(*p*-tolyl)thiazol-2-yl)-4,5-dihydro-1*H*-pyrazol-3-ol (5m): IR (KBr, ν_{max}, cm^{-1}):

3491 (-OH), 3186 (-NH), 1632 (C=N), 1236 (C-S-C), 1132 (C-O-C); ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 12.74 (s, 1H, -OH), 8.37 (s, 1H, -NH), 8.13 (m, *J* = 20 Hz, 4H, Ar-H), 7.92 (s, 1H, C_5 of thiazole), 7.65 (d, *J* = 8 Hz, 2H, Ar-H), 7.53 (d, *J* = 8 Hz, 2H, Ar-H), 7.12 (s, 1H, =CH), 2.13 (s, 3H, -CH_3); ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 172.56, 153.84, 152.64, 149.72, 139.52, 138.45, 134.89, 133.56, 132.87, 131.02, 130.98, 130.18, 129.63, 128.33, 126.38, 125.94, 124.22, 124.75, 106.82, 23.79; EI-MS: 405 [M$^+$]; Elemental analysis: calcd. (found) % for $C_{20}H_{15}N_5O_3S$: % C, 59.25 (59.28); H, 3.73 (3.71); N, 17.27 (17.30); S, 7.91 (7.89).

1-(4-(4-Bromophenyl)thiazol-2-yl)-5-imino-4-(3-nitrobenzylidene)-4,5-dihydro-1*H*-pyrazol-3-ol (5o): IR (KBr, ν_{max}, cm^{-1}): 3416 (-OH), 3236 (-NH), 1616 (C=N), 1196 (C-S-C), 1088(C-O-C); ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 12.14 (s, 1H, -OH), 8.11 (s, 1H, NH), 7.98 (s, 1H, C5), 7.83 (d, *J* = 8 Hz, 2H, Ar-H), 7.81 (d, *J* = 8 Hz, 2H, Ar-H), 7.41 (m, *J* = 20 Hz, 4H, Ar-H), 7.22 (s, 1H, =CH); ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 168.68, 153.12, 152.64, 147.12, 131.24, 130.78, 130.02, 127.84, 127.14, 126.02, 123.36, 119.38, 108.06; EI-MS: 470 [M$^+$]; Elemental analysis calcd. (found) % for $C_{19}H_{12}N_5O_3SBr$: C, 48.52 (84.55); H, 2.57 (2.60); N, 14.89 (14.92); S, 6.82 (6.85).

Antioxidant activity: In the present study, *in vitro* DPPH (1,1-diphenyl-2-picryl-hydrazyl), OH and SOR (superoxide anion) radical scavenging assay was utilized [29,30] to evaluate the antioxidant potential of substituted benzylidene-imino-thiazolyl-pyrazol-3-ol derivatives with respect to standard ascorbic acid using spectrophotometer.

DPPH radical scavenging assay: The synthesized compound was added to 10^{-4} M ethanolic solution of DPPH for the preparation of solution having equimolar concentration (0.5-1.00 mM). After incubation (30 min) at room temperature the sample absorbance was measured on spectrophotometrically at 517 nm. Ascorbic acid (AA) was used as standard.

OH radical scavenging assay: For the generation of OH radicals, the ferric ion (Fe^{3+})/AA system was used. The OH radical detection being carried out by measuring the amount of formaldehyde generated from the oxidation of DMSO. The reaction mixture contain 0.1 mM EDTA, 167 mM Fe^{3+}, 33 mM DMSO in phosphate buffer (50 mM pH 7.4), 0.05-0.1 mL individual of benzylidene-iminothiazolyl-pyrazol-3-ol derivatives (0.5-1 mM) solution. The reaction was initiated by the addition of ascorbic acid (150 mL, 10 mM in phosphate buffer). The reaction was terminated by using trichloroacetic acid (17% w/v). The generated formaldehyde was detected spectrophotometrically at 412 nm. For comparative study ascorbic acid (1 mM) was used as reference compound.

Superoxide anion radical (SOR) scavenging assay: The superoxide anion radical was generated by PMS/NADH system. Afterward the superoxide anion was made to diminish NBT, which yields a chrogenic products having λ_{max} at 560 nm. The radical scavenging activities, which are concentration dependent were performed separately. The reaction cocktail contain NBT (300 mM), NADH (936 mM), PMS (120 mM) and individual concentration of substituted benzylidene-iminothiazolyl-pyrazol-3-ol derivatives (0.5-1 mM) in Tris-HCl (buffer 100 mM, pH 7.4). The reaction was initiated by the addition of PMS to the reaction mixture. After incubation period (5 min) at room temperature the reaction mixture was read at 560 nm by using Thermo Make Automatic Ex-Microplate Reader (M51118170).

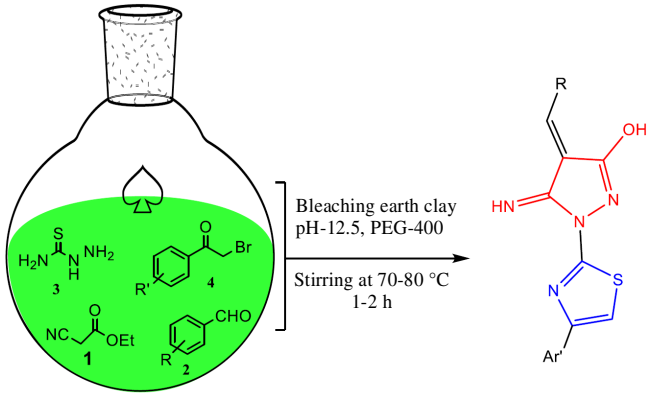
The percentage activity of DPPH, OH$^\bullet$ and SOR radical scavenging activity was calculated by using the following equation:

$$\text{Activity } (\%) = 1 - \frac{T}{C} \times 100$$

where; T = absorbance of the test sample and C = absorbance of the standard sample.

RESULTS AND DISCUSSION

The synthetic route of the title compound was shown in **Scheme-I**. The one-pot condensation of ethyl cyanoacetate (**1**), substituted benzaldehyde (**2a-c**), thiosemicarbazide (**3**) and substituted phenacyl bromide (**4a-g**) in bleaching earth clay (BEC) and PEG-400 as a green path to endeavor the title compound (**5a-p**) in quantitative yield. Initially, *in situ* Knoevenagel condensation of active methylene group of ethyl cyanoacetate (**1**) with substituted benzaldehyde (**2a-c**) in presence of catalytic amount of BEC in PEG-400 to form an intermediate, which when react with thiosemicarbazide (**3**) followed by substituted phenacyl bromide (**4a-g**) gave the title compounds (**5a-p**). The adequate spectral data confirmed the structure of the final compounds. In IR spectrum, compound **5a** exhibited strong stretching vibration band at 3416 cm^{-1} due to –OH functional group and stretching vibration at 3186 cm^{-1} is due to –NH functional group. The ^{1}H NMR spectrum of the compound **5a** showed a singlet displayed in more downfield region at δ 12.19 ppm indicate the –OH group. Another singlet at δ 8.04 ppm attributed to the –NH proton. Apart from this the remaining protons showed in their respective aromatic region at δ 7.89-7.25 ppm. The mass spectrum of compound **5a** displayed at 397 due to [M+]. The tenable reaction mechanism is outlined in **Scheme-I**.



Scheme-I: Synthetic route of benzylidene-imino-thiazolyl-pyrazol-3-ol derivatives **(5a-p)**

The model reaction was optimized to establish the optimum condition of the sundry reaction parameter. Initially, the reaction was carried out in solvent and catalyst free medium to offer the green path for the reaction route. But, it is observed

TABLE-1
OPTIMIZATION EXPERIMENT

Entry	Catalyst (mol/wt%)	Solvent	Temp. (°C)	Time (h)[a]	Yield of **2**[b] (%)
1	No catalyst	PEG-400	RT	24	0
2	No catalyst	PEG-400	80	24	0
3	Potassium hydroxide	PEG-400	70	> 3	40
4	Sodium ethoxide	PEG-400	70	> 3	50
5	Potassium carbonate	PEG-400	80	> 4	30
6	Triethyl amine	PEG-400	80	> 4	45
7	BEC (1 wt%)	PEG-400	80	2.0	70
8	BEC (5 wt%)	PEG-400	80	1.5	85
9	BEC (10 wt%)	PEG-400	80	1.5	89
10	BEC (20 wt%)	PEG-400	80	2.0	80

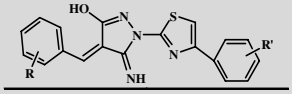
[a]Reaction progress monitored by TLC; [b]Yields refer to isolated yield; BEC = Bleaching earth clag.

that the reaction was not proceed in room temperature or even at high temperature. Furthermore, the model reaction was carried out in various basic catalysts such as potassium hydroxide, sodium ethoxide, potassium carbonate, triethylamine and BEC. This study reveals that BEC is the effective catalyst for the reaction from the side of green media and yield percentage. Results summarized in Table-1 also showed the influences of BEC catalyst concentration on the reaction. A 10 wt.% gave the maximum yield (89% entry 9, Table-1) as compared to 1 and 5 wt.% of the catalyst.

After optimizing the reaction conditions, the generality and scope of the present MCRs are verified. Noticeably a variety of substituted benzaldehyde such as 4-chloro, 4-fluoro, 4-nitro, 3-nitro underwent smooth coupling with different phenacyl bromide, thiosemicarbazide and ethyl cyanoacetate. The phenacyl bromide covers 4-chloro, 4-bromo, 4-nitro, 3-nitro substituent which underwent coupling with substituted benzaldehyde, thiosemicarbazide and ethyl cyanoacetate to give the corresponding benzylidene-iminothiazolyl-pyrazol-3-ol derivatives **(5a-p)** in satisfactory yield (Table-2).

The possible mechanism for the desire reaction is outlined in **Scheme-II**. The reaction is initiated by the BEC (pH 12.5) as a basic catalyst between ethyl cyanoacetate and substituted benzaldehyde to form the intermediate, which then captured by thiosemicarbazide and finally cyclized by substituted phenacyl bromide to gives rise the target compound benzylidene-iminothiazolyl-pyrazol-3-ol derivatives in good to admirable yield.

TABLE-2
SYNTHESIS OF BENZYLIDENE-IMINO-THIAZOLYL-PYRAZOL-3-OL DERIVATIVES **(5a-p)**

Compd.			Yield (%)	m.p. (°C)
	R	R'		
5a	-4F	-4Cl	84	151-153
5b	-4F	-4NO_2	83	165-167
5c	-4F	-3NO_2	81	157-159
5d	-4F	-4Br	85	160-162
5e	-4F	-4Me	80	166-168
5f	-4Cl	-4Cl	84	162-164
5g	-4Cl	-4F	81	149-151
5h	-4Cl	-4NO_2	87	159-161
5i	-4Cl	-3NO_2	85	162-164
5j	-4Cl	-4Br	87	160-162
5k	-4NO_2	-3NO_2	89	155-157
5l	-4NO_2	-4Br	86	161-163
5m	-4NO_2	-4Me	82	177-179
5n	-3NO_2	-3NO_2	88	158-160
5o	-3NO_2	-4Br	87	156-158
5p	-3NO_2	-4Me	82	172-174

Antioxidant assay: The initiative screening of 1-(4-(-substituted phenyl)thiazol-2-yl)-4-(-substituted benzylidene)-5-imino-4,5-dihydro-1*H*-pyrazol-3-ol derivatives (**5a-p**) for their antioxidant potential was assessed by the DPPH, OH• and SAR radical scavenging assay (Fig. 2). Antioxidants are known for their recognized proton radical scavenging action. Results of the present study evidently demonstrate that all conjugate hybrids have potential to interact with stable free radical DPPH, which shows their efficacy as effective radical scavenging ability. Compounds **5b**, **5d**, **5g**, **5k**, **5l**, **5n** and **5o** exhibited antioxidant property closer to standard ascorbic acid (85.17%), whereas rest of the compounds showed moderate radical scavenging activity.

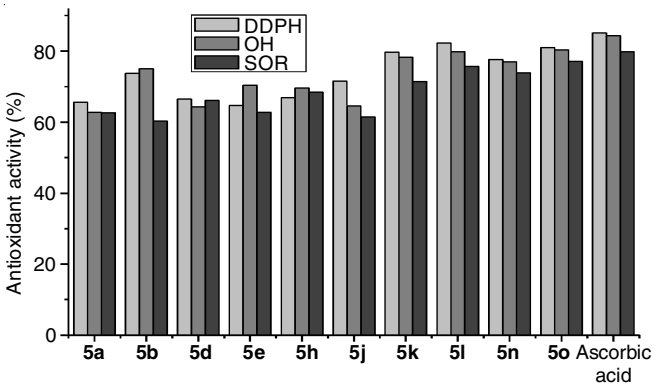
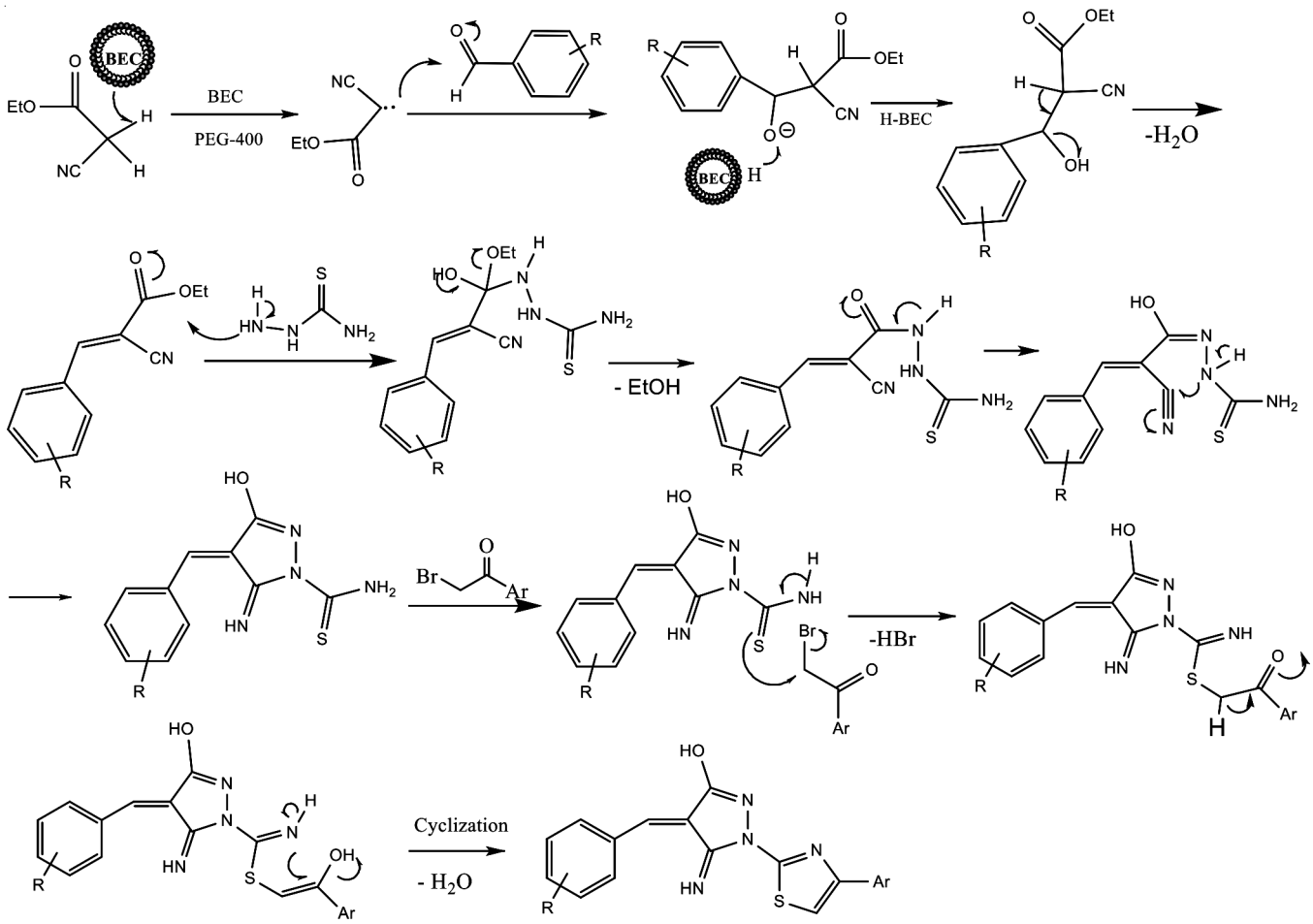


Fig. 2. Graphical representation of antioxidant screening of representative compounds [the results summarized are the mean values of the three independent experiments]

The most prevalent and reactive free radical molecule known is the hydroxyl (OH•) radicals. It frequently leads to react with neighboring molecule within one billionth of second by stealing the hydrogen atom. Generally it affects each kind of molecules which are available in living organism. The OH• radical may react with the physiologically relevant biomolecules like sugar, amino acids, phospholipids, DNA bases and organic acids, which may influence the normal physiological function of cells. From the results, it was observed that compounds **5b**, **5d**, **5k**, **5l**, **5n** and **5o** exhibited the improved OH•



Scheme-II: Possible mechanism for the BEC catalyzed synthesis of benzylidene-imino-thiazolyl-pyrazol-3-ol derivatives **(5a-p)**

radical scavenging activity. The profile of SOR radical scavenging activities indicate that compounds **5b**, **5d**, **5k**, **5l**, **5n** and **5o** exhibit very strong SOR radical scavenging activity as compared to standard ascorbic acid whereas the rest compounds displayed moderate SOR radical scavenging activities.

Conclusion

In summary, a simple, efficient, practical and green method for one pot synthesis of benzylidene-iminothiazolyl-pyrazol-3-ol derivatives (**5a-p**) in presence of bleaching earth clay (BEC) (pH 12.5) and PEG-400. The synthesized compounds were screened for antioxidant activity. The present procedure follows the advantages like eco-friendly in nature, less reaction time, convenient work-up, improved product yield and recyclability of catalyst. Thus it may be proven to be useful and improved than the existing method.

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