ARTICLE

Design, Synthesis, Characterization, Anti-Inflammatory and Antioxidant Evaluation of Certain Novel Pyrazoline Derivatives Containing Imidazo[2,1-*b*]thiazole Moiety

V.D. Sonawane[1,2,✉], B.D. Sonawane[3], M.J. Dhanavade[4], K.D. Sonawane[4] and R.B. Bhosale[1,✉]

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ABSTRACT

In present study, a novel series of substituted imidazo[2,1-*b*]thiazole pyrazoline derivatives (**2a-e**) and (**3a-e**) from the reference compound imidazo[2,1-*b*]thiazole chalcones (**1a-e**) in PEG-400 by using hydrazine hydrate and phenyl hydrazine was synthesized. Characterization of newly synthesized compounds was done using IR and ^{1}H NMR. Further, imidazo[2,1-*b*]thiazole pyrazoline derivatives were subjected to check their *in vitro* antioxidant activities at a concentration of 0.5 mmol/L in methanol. Compounds **2c**, **2d**, **3c**, **3d** and **3e** showed comparatively good activity than standard drug diclofenac. The anti-inflammatory activity of compounds **2c**, **2d**, **2e**, **3c**, **3d** and **3e** were comparable with standard drug. Similarly, all these compounds possess good antioxidant activity as compared to ascorbic acid (vitamin C); compared to the value of DPPH and SOD antioxidant activity 44.18 % and 74.07 %, respectively. These synthesized compounds exhibited a good anti-inflammatory and antioxidant activities hence might be useful in future drug designing studies.

KEYWORDS

Imidazo[2,1-*b*]thiazole chalcones, Imidazo[2,1-*b*]thiazole pyrazolines, Anti-inflammatory activity, Antioxidant activity.

INTRODUCTION

Currently, a research is focused on finding alternative synthetic route for the insertion of a hetero-atom into the heterocyclic compound which are having various biological activities [1,2]. The science and pharmacology for these heterocyclic compounds are studied to improve its medicinal value to make various biological active drugs. Pyrazolines is one of the best nitrogen containing five membered heterocycles compounds having various biological activities. Furthermore, the related heterocycles show different sorts of pharmacological activities on living as well as non-living things. Keeping these facts into consideration heterocycles compounds were used to make different medicinal drugs. These drugs can be mainly used as anti-inflammatory, antioxidant, antiviral, antifungal, antibacterial, antitubercular, antitumor, insecticidal and antiparasitic agent [3-9]. Pyrazoline sorted nitrogen holding heterocycles, is well known compound for its use in the field of research and

Author affiliations:

[1]Organic Chemistry Research Laboratory, School of Chemical Sciences, Punyashlok Ahilyadevi Holkar Solapur University, Solapur-413255, India
[2]Department of Chemistry, K.R.P. Kanya Mahavidyalaya, Islampur-415409, India
[3]Department of Chemistry, Karmaveer Bhaurao Patil Mahavidyalaya, Pandharpur-413304, India
[4]Department of Microbiology, Shivaji University, Kolhapur-416004, India

✉To whom correspondence to be addressed:

E-mail: vikassonawane8672@gmail.com; bhosale62@yahoo.com

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development of therapeutically active agents. The comp-ounds with pyrazole ring exhibit good pharmaceutical importance because of ease of synthesis. Hence, the current study is mainly focused on the synthesis of compounds containing pyrazole ring.

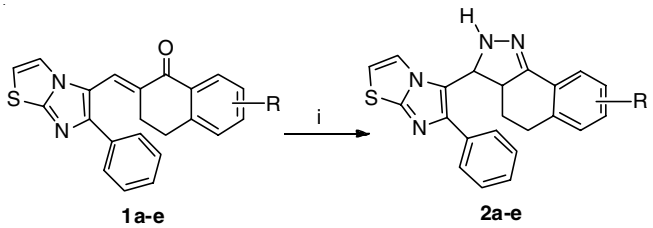
Literature survey supported the use of pyrazoles as anti-tumor, analgesic agent [10], anti-inflammatory [11,12], anti-tubercular [13] and antimicrobial agent [14]. The PEG solvents have many advantages such as cost-effective, easily accessible, compatible and stable at high temperature, water soluble and recyclable [11,12]. However synthesis of pyrazolines in PEG medium might be good in pharmaceutical studies. Here we have emphasized on using PEG-400 as only the solvent which would be the priority of green chemistry as eco-friendly solvent [15,16]. In present study, we have synthesized novel moieties of imidazo[2,1-*b*]thiazole pyrazoline derivatives by using imidazo[2,1-*b*]thiazole chalcones in PEG-400. Further efforts were made to assess their antioxidant and anti-inflammatory activities.

EXPERIMENTAL

Accurate melting points of synthesized imidazo[2,1-*b*]-thiazole pyrazoline derivatives were determined. KBr disk method was used to record IR spectra on FT-IR spectrometer (Perkin-Elmer). ^{1}H NMR spectra were recorded in $CDCl_3$ solvent with the help of Varian-NMR-mercury 300 MHz spectrometer.

Chemical shifts in δ ppm and coupling constants (*J*) in Hertz were determined. Analytical grade reagents and solvents were used. To monitor a reaction, thin layer chromatography (TLC) was performed by using silica gel coated plates. The imidazo[2,1-*b*]thiazole pyrazoline derivatives were synthesized according to the reported method [17,18].

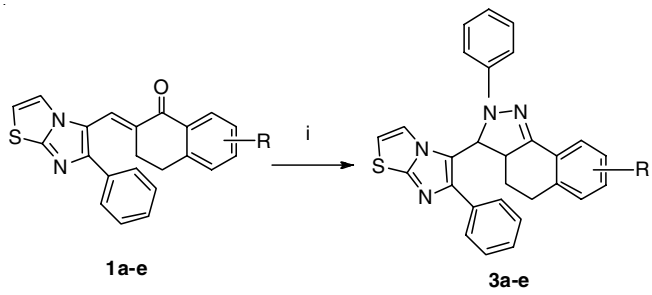
Synthesis of imidazo[2,1-*b*]thiazole pyrazoline derivatives (2a-e): Imidazo[2,1-*b*]thiazole chalcones (**1a-e**) (1 mmol) was taken in two necked round bottom flask fitted with water condenser and dissolved in PEG-400 (15 mL) and stirred at room temperature. Another solution of hydrazine hydrate (1 mmol) and 40 % NaOH (2 mL) was prepared and this solution was added dropwise to the above made solution of PEG-400 and imidazo[2,1-*b*]thiazole chalcones, heated for about 4-5 h at 70-80 ºC. The progress of the reaction was monitored by TLC. A reaction mixture was then cooled to room temperature and poured into ice pieces with constant stirring. The precipitate obtained was filtered and washed with distilled water for 2-3 times and dried. The solid product was purified by recrystallization using ethanol to form expected pure derivatives of pyrazoline (**2a-e**) (**Scheme-I**).



Reagents and conditions: (i) $NH_2.NH_2.H_2O$, PEG-400, Δ 70-80 °C, 4-5 h

Scheme-I: Synthesis of imidazo[2,1-*b*]thiazole pyrazoline derivatives (**2a-e**)

Synthesis of imidazo[2,1-*b*]thiazole phenyl pyrazoline derivatives (3a-e): Imidazo[2,1-*b*]thiazole chalcones (**1a-e**) (1 mmol) was taken two necked round bottom flask fitted with water condenser and dissolved in PEG-400 (15 mL) and stirred at room temperature. Another solution of phenyl hydrazine (1 mmol) and 40 % NaOH (2 mL) was prepered and this solution was added dropwise to a solution of PEG-400 and imidazo[2,1-*b*]thiazole chalcones and finally heated for about 4-5 h at 70-80 ºC. A progress of the reaction was monitored by TLC and then a reaction mixture was cooled to room temperature and poured into ice pieces with constant stirring. The precipitate obtained was filtered and washed with distilled water for 2-3 times and dried. The solid product was purified by recrystallization using ethanol to form expected pure derivatives of imidazo[2,1-*b*]thiazole phenyl pyrazoline (**3a-e**) (**Scheme-II**).



Reagents and conditions: (i) $Ph.NH_2.H_2O$, PEG-400, Δ 70-80 °C, 4-5 h

Scheme-II: Synthesis of imidazo[2,1-*b*]thiazole phenyl pyrazoline derivatives (**3a-e**)

Spectral data

3-(6-Phenylimidazo[2,1-*b*][1,3]thiazol-5-yl)-3,3a,4,5-tetrahydro-2*H*-benzo[*g*]indazole (2a): m.p.: 125 °C; m.f.: $C_{22}H_{18}N_4S$; m.w.: 370.47; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.1 (d, 1H); δ 1.8 (m, 2H); δ 2.7 (t, 2H); δ 7.2 (d, 1H); δ 7.1 (d, 1H); δ 7.6 (d, 1H); δ 7.0 (s, 1H); δ 2.1 & 1.8 (d, 2H); δ 3.9 (t, 1H); δ 7.9 (d, 1H); δ 7.4 (d, 1H); δ 7.4 (d, 1H); δ 7.3 (d, 1H); δ 7.2 (d, 1H).

3-(6-Phenylimidazo[2,1-*b*][1,3]thiazol-5-yl)-3,3a,4,5-tetrahydro-2*H*-benzo[*g*]indazol-7-ol (2b): m.p.: 127 °C; m.f.: $C_{22}H_{18}N_4OS$; m.w.: 462.57; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.1 (d, 1H); δ 1.7 (m, 2H); δ 2.6 (t, 2H); δ 6.6 (d, 1H); δ 5.0 (s, 1H) due to -OH; δ 6.6 (d, 1H); δ 7.5 (d, 1H); δ 7.0 (s, 1H); δ 2.1 & δ 1.8 (d, 2H); δ 3.9 (t, 1H); δ 7.9 (d, 1H); δ 7.4 (d, 1H); δ 7.4 (d, 1H); δ 7.3 (d, 1H); δ 7.2 (d, 1H).

7-Methoxy-3-(6-phenylimidazo[2,1-*b*][1,3]thiazol-5-yl)-3,3a,4,5-tetrahydro-2*H*-benzo[*g*]indazole (2c): m.p.: 150 °C; m.f.: $C_{29}H_{24}N_4OS$; m.w.: 476.59; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.1 (d, 1H); δ 1.7 (m, 2H); δ 2.6 (t, 2H); δ 6.7 (d, 1H); δ 3.7 (s, 1H); δ 6.6 (d, 1H); δ 7.5 (d, 1H); δ 7.0 (s, 1H); δ 2.1 & δ 1.8 (d, 2H); δ 3.9 (t, 1H); δ 7.9 (d, 1H); δ 7.4 (d, 1H); δ 7.4 (d, 1H); δ 7.3 (d, 1H); δ 7.2 (d, 1H).

7-Ethoxy-3,3a,4,5-tetrahydro-3-(6-phenylimidazo[2,1-*b*]thiazol-5-yl)-2*H*-benzo[*g*]indazole (2d): m.p.: 130 °C; m.f.: $C_{30}H_{26}N_4OS$; m.w.: 490.62; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.1 (d, 1H); δ 1.7 (m, 2H); δ 2.6 (t, 2H); δ 6.6 (d, 1H); δ 1.3 (t, 3H); δ 3.9 (q, 2H); δ 6.6 (d, 1H); δ 7.5 (d, 1H); δ 7.0 (s, 1H); δ 2.1 & δ 1.8 (d, 2H); δ 3.9 (t, 1H); δ 7.9 (d, 1H); 7.4 (d, 1H).

3-(6-Phenylimidazo[2,1-*b*][1,3]thiazol-5-yl)-2,3,3a,4-tetrahydroindeno[1,2-*c*]pyrazole (2e): m.p.: 171 °C; m.f.: $C_{27}H_{24}N_4S$; m.w.: 436.57; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.1 (d, 1H); δ 1.7 (m, 2H); δ 2.6 (t, 2H); δ 7.2 (d, 1H); δ 7.1 (d, 1H); δ 7.6 (d, 1H); δ 7.0 (s, 1H); δ 2.5 (d, 1H); 2.7 (d, 2H); δ 3.9 (d, 1H); δ 7.9 (d, 1H); δ 7.4 (d, 1H); δ 7.4 (d, 1H); δ 7.3 (d, 1H); δ 7.2 (d, 1H).

3,3a,4,5-Tetrahydro-2-phenyl-3-(6-phenylimidazo[2,1-*b*]thiazol-5-yl)-2*H*-benzo[*g*]indazol (3a): m.p.: 147 °C; m.f.: $C_{28}H_{26}N_4S$; m.w.: 450.50; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.1 (d, 1H) & δ 1.7 (m, 2H); δ 2.6 (t, 2H); δ 7.2 (d, 1H) & δ 7.1 (d, 1H); δ 7.6 (d, 1H); δ 7.0 (s, 1H); δ 2.1 & 1.8 (d, 2H); δ 3.9 (t, 1H); δ 6.4 (d, 1H); δ 7.0 (d, 1H); δ 6.5 (d, 1H); δ 7.9 (d, 1H); δ 7.4 (d, 1H); δ 7.4 (d, 1H); δ 7.3 (d, 1H); δ 7.2 (d, 1H).

3,3a,4,5-Tetrahydro-2-phenyl-3-(6-phenylimidazo[2,1-*b*]thiazol-5-yl)-2*H*-benzo[*g*]indazol-7-ol (3b): m.p.: 137 °C; m.f.: $C_{28}H_{22}N_4OS$; m.w.: 462.57; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.1 (d, 1H) & δ 1.7 (m, 2H); δ 2.6 (t, 2H); δ 6.6 (d, 1H); δ 5.0 (s, 1H); δ 6.6 (d, 1H); δ 7.5 (d, 1H); δ 7.0 (s, 1H); δ 2.1 & 1.8 (d, 2H); δ 3.9 (t, 1H); δ 6.4 (d, 1H); δ 7.0 (d, 1H); δ 6.5 (d, 1H); δ 7.9 (d, 1H); δ 7.4 (d, 1H); δ 7.4 (d, 1H); δ 7.3 (d, 1H); δ 7.2 (d, 1H).

3,3a,4,5-Tetrahydro-7-methoxy-2-phenyl-3-(6-phenylimidazo[2,1-*b*]thiazol-5-yl)-2*H*-benzo[*g*]indazole (3c): m.p.: 167 °C; m.f.: $C_{29}H_{24}N_4OS$; m.w.: 476.59; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.1 (d, 1H) & δ 1.7 (m, 2H); δ 2.6 (t, 2H); δ 6.7 (d, 1H); δ 3.7 (s, 1H); δ 6.6 (d, 1H); δ 7.5 (d, 1H); δ 7.0 (s, 1H); δ 2.1 & 1.8 (d, 2H); δ 3.9 (t, 1H); δ 6.43 (d, 1H); δ 7.0 (d, 1H); δ 6.5 (d, 1H); δ 7.9 (d, 1H); δ 7.4 (d, 1H); δ 7.4 (d, 1H); δ 7.3 (d, 1H); δ 7.2 (d, 1H).

7-Ethoxy-3,3a,4,5-tetrahydro-2-phenyl-3-(6-phenylimidazo[2,1-*b*]thiazol-5-yl)-2*H*-benzo[*g*]indazole (3d): m.p.: 135 °C; m.f.: $C_{30}H_{26}N_4OS$; m.w.: 490.62; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.1 (d, 1H); δ 1.7 (m, 2H); δ 2.6 (t, 2H); δ 6.6 (d, 1H); δ 1.3 (t, 3H); δ 3.9 (q, 2H); δ 6.6 (d, 1H); δ 7.5 (d, 1H); δ 7.0 (s, 1H); δ 2.1 & 1.8 (d, 2H); δ 3.9 (t, 1H); δ 6.4 (d, 1H); δ 7.0 (d, 1H); δ 6.5 (d, 1H); δ 7.9 (d, 1H); δ 7.4 (d, 1H); δ 7.4 (d, 1H); δ 7.3 (d, 1H); δ 7.2 (d, 1H).

2,3,3a,4-Tetrahydro-2-phenyl-3-(6-phenylimidazo[2,1-*b*]thiazol-5-yl)indeno[1,2-*c*]pyrazole (3e): m.p.: 171 °C; m.f.: $C_{27}H_{24}N_4S$; m.w.: 436.57; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.1 (d, 1H); δ 1.7 (m, 2H); δ 2.6 (t, 2H); δ 7.2 (d, 1H); δ 7.1 (d, 1H); δ 7.6 (d, 1H); δ 7.0 (s, 1H); δ 2.5 (d, 1H); 2.7 (d, 2H); δ 3.9 (d, 1H); δ 6.4 (d, 1H); δ 7.0 (d, 1H); δ 6.5 (d, 1H); δ 7.9 (d, 1H); δ 7.4 (d, 1H); δ 7.4 (d, 1H); δ 7.3 (d, 1H); δ 7.2 (d, 1H).

Antioxidant activity of different substituted imidazo[2,1-*b*]thiazole pyrazoline derivatives: The synthesized derivatives of imidazo[2,1-*b*]thiazole pyrazolines were evaluated for their antioxidant properties.

DPPH radical scavenging activity: The DPPH assay was performed using Kumar *et al*. [19] and Manzocco *et al*. [20], as a reference method with slight modification. A newly synthesized substituted imidazo[2,1-*b*]thiazole pyrazolines in 1 mM concentration was mixed with 3 mL of DPPH reagent (0.5 mmol/L in methanol solution). After incubation at 37 ºC for 30 min, an absorbance was measured at 517 nm [21]. The percentage of scavenging activity was calculated as follows:

$$\text{Inhibition } (\%) = \frac{A_{control} - A_{test}}{A_{control}} \times 100$$

where, $A_{control}$ = absorbance of DPPH, A_{test} = absorbance of reaction mixture (DPPH with sample).

Scavenging of superoxide radical by alkaline DMSO: To a reaction mixture containing 1 mL of alkaline DMSO, 0.3 mL of sample and standard was added in DMSO at various concentrations followed by addition of 0.1 mL of 4-nitroblue tetrazolium chloride to give a final volume of 1.4 mL. The absorbance was measured at 560 nm [22,23].

Anti-inflammatory activity: The *in vitro* anti-inflammatory activity was assessed using protein denaturation method. In this protocol, a reaction mixture was prepared using 0.4 mL egg albumin (fresh hen′s egg), 5.6 mL phosphate buffer saline (pH 6.4) and 4 mL synthetic derivatives (1 mM). Then this reaction mixture was incubated for 15 min at 37 ºC. After incubation period, it was heated again at 70 ºC for 5 min. Finally it was cooled and further its absorbance was measured at 660 nm. The demineralized water was used as a control. An absorbance of standard drug diclofenac (1mM) was used as reference. The protein denaturation percentage was calculated using following formula:

$$\text{Inhibition } (\%) = \frac{A_{control} - A_{sample}}{A_{control}} \times 100$$

where, A_{sample} = absorbance of sample; $A_{control}$ = absorbance of control.

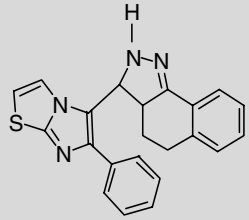
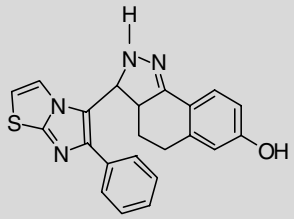
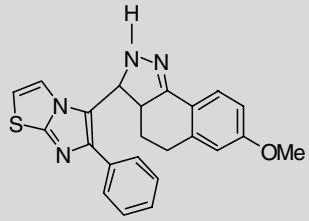
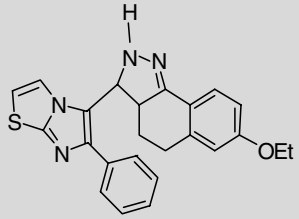
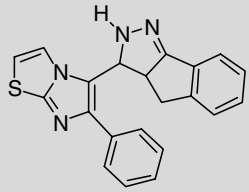
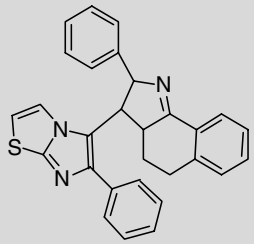
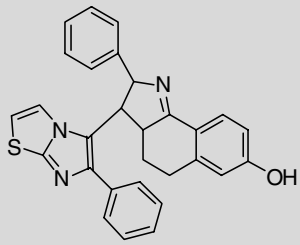
RESULTS AND DISCUSSION

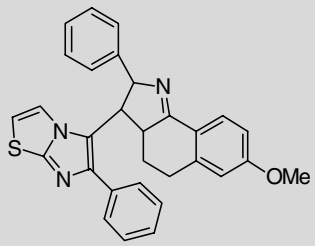
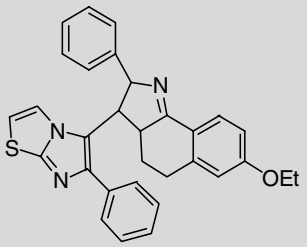
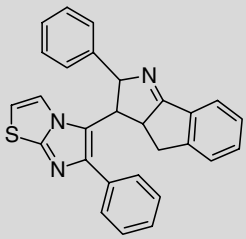
In this work, substituted imidazo[2,1-b]thiazole pyrazoline derivatives (**2a-e** and **3a-e**) have been synthesized successfully by using imidazo[2,1-*b*]thiazole chalcones (**1a-e**) which were prepared by Claisen-Schmidt condensation method of various substituted tetralones and imidazo-thiazole aldehyde in PEG-400 as green solvent [17]. The purity of newly synthesized imidazo[2,1-*b*]thiazole pyrazoline derivatives was assessed by TLC and melting point analysis. All the synthesized imidazo-[2,1-*b*]thiazole pyrazolines were characterized using IR and ^{1}H NMR analysis.

Antioxidant activity: Substituted imidazo[2,1-*b*]thiazole pyrazoline derivatives (**2a-e** and **3a-e**) were evaluated for their antioxidant activities. Substituted imidazo[2,1-*b*]thiazole pyrazoline derivatives shows potent antioxidant activities by DPPH and SOD assay. These antioxidant activity results are shown in Table-1 revealed that imidazo[2,1-*b*]thiazole pyrazoline derivatives containing aromatic imidazo[2,1-*b*]thiazole moiety is mainly responsible for its antioxidant activity. In addition, pyrazoline moiety and different substitution on the tetralone B ring (substituent hydroxyl, mehtoxy and ethoxy) might also be responsible for its antioxidant activity.

Particularly, pyrazoline derivatives **2a**, **2b** and **2e** showed a moderate percentage and compounds **2c**, **2d**, **3c**, **3d** and **3e** showed a potent antioxidant activity (Table-1). Almost all the pyrazoline derivatives indicates moderate to good antioxidant as compared with standard ascorbic acid (vitamin C). The DPPH and SOD method gives 44.18 and 74.07 % antioxidant activity respectively (Table-1). The results revealed that antioxidant potential of synthesized pyrazoline derivatives were found to be comparable with standard vitamin C even at lower concentration with consistent results in agreement with earlier report [22].

TABLE-1
ANTIOXIDANT AND ANTI-INFLAMMATORY ACTIVITIES DATA OF SYNTHESIZED SUBSTITUTED IMIDAZO[2,1-*b*]THIAZOLE PYRAZOLINE DERIVATIVES

Compound No.	Substituted pyrazoline derivatives	Antioxidant activity (%)		Anti-inflammatory activity (%)
		DPPH	SOD	
2a		54.21	43.18	50.55
2b		60.13	64.38	53.21
2c		64.38	70.89	61.58
2d		63.01	69.18	59.72
2e		50.35	46.79	59.81
3a		63.12	44.44	55.37
3b		58.88	42.85	59.40

3c		67.18	72.55	65.38
3d		65.73	70.85	61.54
3e		70.65	68.17	70.25
Vitamin C	–	44.18	74.07	–
Dichlorofenac	–	–	–	90.21

Anti-inflammatory activity: Synthesized imidazo[2,1-*b*]-thiazole pyrazolines were assessed for their anti-inflammatory activity. The results (Table-1) revealed that imidazo[2,1-*b*]-thiazole pyrazolines possess good anti-inflammatory activity. Imidazo[2,1-*b*]thiazole pyrazolines (**2c**, **2d**, **2e**, **3c**, **3d** and **3e**) showed higher anti-inflammatory activity (Table-1) due to the methoxy and ethoxy substitution on tetralone and indanone B ring, and in comparison with standard drug dichlorofenac showed 90.21 % anti-inflammatory activity.

Conclusion

In this work, a novel series of imidazo[2,1-*b*]thiazole pyrazolines was synthesized, characterized and evaluated for their antioxidant and anti-inflammatory activities. The yields of the synthesized imidazo[2,1-*b*]thiazole pyrazolines were found to be in the appropriate range. Almost all the synthesized imidazo-[2,1-*b*]thiazole pyrazolines showed potent antioxidant and anti-inflammatory activities. The antioxidant properties of imidazo-[2,1-*b*]thiazole pyrazolines when tested using two different methods *viz*. DPPH and SOD assay showed better activities. An enhanced activity was might be due to the presence of hydroxyl, methoxy, ethoxy substituent present in frame work of imidazo[2,1-*b*]thiazole pyrazolines structure. Hence, imidazo-[2,1-*b*]thiazole pyrazolines structure can becomes potent scavenger of DPPH and SOD assay which may be responsible for their good antioxidant activity. Thus, it can be concluded that modified imidazo[2,1-*b*]thiazole pyrazolines showed a significant biological evaluation as anti-inflammatory and antioxidant agents. However, a further evaluation of these derivatives has to be evaluated for the cytotoxicity, antidiabetic and anticancer activity.

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