A green and efficient protocol for the synthesis of dihydropyrano[2,3-c]pyrazole derivatives via a one-pot, four component reaction by grinding method

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ABSTRACT

An efficient grinding protocol for the synthesis of dihydropyrano[2,3-c]pyrazole derivatives from acetylene ester, hydrazine hydrate, aryl aldehydes and malononitrile under solvent free conditions has been achieved with excellent yields. The structures of the synthesized compounds were deduced by spectroscopic techniques and the compounds were further evaluated for their in vitro antioxidant and antimicrobial activities.

Introduction

Pollution is a major universal problem of today, so one of the interesting challenges for synthetic organic chemists is designing organic reactions by following simple and eco-friendly protocol. This has been established that solvent free one-pot reactions are effective toward organic transformation avoiding harmful organic solvents. Kumar et al. have reported a catalytic and solvent free multi-component reaction involving the grinding the components. Multi-component reactions (MCRs) are ecofriendly process as they obey green chemistry principles. MCR has emerged as an efficient green tool for the synthesis of simple and complex building blocks, thus allowing the generation of several bonds in a single operation with offer significant advantages such as convergence, facile automation, no time consuming workup, easy purification processes, atom economy, low cost, shorter reaction time and minimum wastage, replacement of volatile organic solvents by...
non-flammable, non-volatile, non-toxic and economical “green solvents” [8].

A number of methods have been reported for the synthesis of dihydro[2,3-c]pyranopyrazoles employing different catalysts such as ionic liquids [9,10], organic bases [11–14], amberlyst [15], glycine [16], per-6-amino-β-cyclodextrin [17], and iodine [18]. Zonouz et al. have reported a one pot four component reaction under non-catalytic green synthesis of pyranopyrazole in water [19]. Many recent reports have confirmed that pyranopyrazole derivatives are of great importance class of heterocyclic compounds with natural and synthetic molecules [20]. They exhibited numerous biological activities such as antimicrobial [21,22], antibacterial [23], anticancer [24], analgesic and anti-inflammatory [25,26] properties. Pyrazole ring fused heterocycles have also been identified as anti HIV agents [27]. Presence of pyran skeleton is central core in a number of natural products [28]. In the area of catalytic transformations, organocatalysts are metal free simple organic molecules that are able to function as potent and selective catalyst for large transformations. L-Proline is simple amino acid and its derivatives were effectively useful in much organic transformation, such as asymmetric aldol reaction [29], Mannich reaction [30] and Michael reaction [31]. Hence we have chosen L-proline catalyst for this reaction condition.

As part of our attempt to develop biologically important pyranopyrazole by a new synthetic method, a detailed literature survey revealed that only few numbers of grinding methods published for synthesis of pyranopyrazole [17]. A large number of catalysts stimulated this transformation at various reaction conditions [5,15,32–37] (Table 1, entry 1–8). The above mentioned results indicate that L-proline proved to be an efficient catalyst for this conversion. We report a green protocol for synthesis of dihydro[2,3-c]pyrazole derivatives from acetylene ester, hydrazine hydrate, aryl aldehydes and malononitrile in the presence of L-proline under solvent free conditions. Our methodology has advantages such as atom economy, short reaction time, no time consuming workup, no hazardous solvent and no column chromatography purification. The reaction gave quantitative yields and products formed smoothly under green reaction conditions. Here we could evaluate the anti-oxidant and anti-microbial activities of synthesized compounds (5a–m) at different concentrations.

### Experimental

#### General consideration

All the chemicals were purchased from Aldrich and Alfa-aesar used without any further purification. The 1H and 13C NMR spectra were recorded on a Bruker (Avance) 300 MHz NMR instrument using TMS as internal standard either CDCl3 or DMSO-d6 as solvent. Chemical shifts are given in parts per million (δ-scale) and the coupling constants are given in hertz (Hz). Silica gel-G plates (Merck) were used for thin layer chromatography (TLC) analysis with a mixture of petroleum ether (60–80 °C) and ethyl acetate as eluent. The single crystal X-ray data were collected on Bruker APEX II diffractometer with Mo Kα (λ = 0.71073 Å) radiation. Mass spectra were recorded in LCQ Fleet mass spectrometer, Thermo Fisher Instruments Limited, US. Electrospray ionization mass spectrometry (ESI-MS) analysis was performed in the positive ion and negative ion mode on a liquid chromatography ion trap. FTIR spectra were recorded in Shimadzu FTIR-8400S spectrometer.

#### General procedure for the synthesis of pyranopyrazole derivatives 5a–m

A mixture of aryl aldehyde (1 mmol), malononitrile (1 mmol) and 10% mol L-proline was added in mortar and ground continuously, after 2 min hydrazine hydrate (1 mmol) and diethyl acetylenedicarboxylate (1.2 mmol) were added. The mixture was ground until completion of the reaction was monitored by TLC (10 min). The syrup formed was washed with water and filtered through the filtration flask to afford the pure product without further purification.

**Ethyl-6-amino-5-cyano-4-phenyl-2,4-dihydro[2,3-c]pyrazole-3-carboxylate (5a)**

White solid; mp: 208–210 °C; yield: (79%). IR (KBr) (vmax/cm−1): 3410, 3302, 2362, 2195, 1707, 1635. 1H NMR (300 MHz, CDCl3): δ 7.26–7.13 (m, 5H), 6.08 (s, 2H), 4.81 (s, 1H), 4.11 (q, J = 6.0 Hz, 2H), 1.08 (t, J = 6.0 Hz, 3H). 13C NMR (75 MHz, CDCl3): δ 159.5, 158.0, 155.3, 143.9, 129.1, 127.6, 126.9, 126.1, 119.7, 103.0, 60.3, 59.7, 36.7, 13.3 ppm. MS m/z 309.3 (M−1).

**Ethyl-6-amino-5-cyano-4-(p-tolyl)-2,4-dihydro[2,3-c]pyrazole-3-carboxylate (5b)**

Greenish solid; mp: 212–214 °C; yield (80%). IR (KBr) (vmax/cm−1): 3458, 3275, 2922, 2195, 1707, 1635. 1H NMR (300 MHz, CDCl3): δ 7.11–7.08 (d, J = 9.0 Hz, 2H), 7.06–7.03 (d, J = 9.0 Hz, 2H), 4.83 (s, 1H), 4.72 (s, 2H), 4.17 (q, J = 6.0 Hz, 2H), 2.31 (s, 3H), 1.14 (t, J = 6.0 Hz, 3H). 13C NMR (75 MHz, CDCl3): δ 159.5, 158.3, 155.3, 141.0, 135.8, 129.3, 128.5, 127.0, 120.0, 103.4, 60.7, 60.3, 36.5, 20.6, 13.5 ppm. MS m/z 325.2 (M+1).

### Table 1 Comparison of our results with the previous literature reported work.

| Entry | Catalyst | Solvent  | Reaction conditions | Time  | Yield (%) | References |
|-------|----------|----------|---------------------|-------|-----------|------------|
| 1     | DIPEA    | EtOH     | reflux              | 45 min| 93        | [5]        |
| 2     | Amberlyst A21 | EtOH | reflux              | 30 min| 90        | [15]       |
| 3     | L-Proline | EtOH     | reflux              | 4 h   | 81        | [32]       |
| 4     | Urea     | EtOH–Water | reflux              | 6 h   | 91        | [33]       |
| 5     | Imidazole | Water    | 80 °C               | 30 min| 90        | [34]       |
| 6     | Barium hydroxide | Water | reflux              | 1.5 h | 93        | [35]       |
| 7     | γ-Alumina | Water    | reflux              | 30 min| 90        | [36]       |
| 8     | L-Proline | Ethanol  | reflux              | 10 min| 91        | [37]       |
| 9     | L-Proline | –        | Grinding            | 10 min| 93        | Present     |
**Table 2** Optimization of the reaction conditions.

| Entry | Catalyst | Catalytic amount (mol %) | Reaction condition | Solvent | Time | Yield (%) |
|-------|----------|--------------------------|--------------------|---------|------|-----------|
| 1     | –        | –                        | rt                 | Water   | 10 h | 0         |
| 2     | –        | –                        | Reflux             | Water   | 5 h  | 67        |
| 3     | –        | –                        | Grinding           | Solvent free | 10 min | 40       |
| 4     | L-Proline | 2                        | Grinding           | Solvent free | 10 min | 65       |
| 5     | L-Proline | 5                        | Grinding           | Solvent free | 10 min | 76       |
| 6     | L-Proline | 10                       | Grinding           | Solvent free | 10 min | 81       |
| 7     | L-Proline | 15                       | Grinding           | Solvent free | 10 min | 93       |
| 8     | L-Proline | 10                       | Reflux             | Water   | 1 h  | 88        |
| 9     | P-TSA    | 10                       | Grinding           | Solvent free | 10 min | 84       |
| 10    | SnCl₂    | 10                       | Grinding           | Solvent free | 10 min | 58       |
Table 3  Synthesis of pyrano[2,3-c]pyrazole derivatives (5a–m).

| Entry | Aromatic aldehydes | Products | Yield (%) |
|-------|--------------------|----------|-----------|
| 1     | ![Aromatic aldehyde 1](image1) | ![Product 5a](image2) | 79        |
| 2     | ![Aromatic aldehyde 2](image3) | ![Product 5b](image4) | 80        |
| 3     | ![Aromatic aldehyde 3](image5) | ![Product 5c](image6) | 69        |
| 4     | ![Aromatic aldehyde 4](image7) | ![Product 5d](image8) | 88        |
| Entry | Aromatic aldehydes | Products | Yield (%) |
|-------|--------------------|----------|-----------|
| 5     | ![Structure 5e](image) | ![Structure 5e](image) | 93        |
| 6     | ![Structure 5f](image) | ![Structure 5f](image) | 65        |
| 7     | ![Structure 5g](image) | ![Structure 5g](image) | 69        |
| 8     | ![Structure 5h](image) | ![Structure 5h](image) | 82        |
| 9     | ![Structure 5i](image) | ![Structure 5i](image) | 88        |

(continued on next page)
Table 3 (continued)

| Entry | Aromatic aldehydes | Products | Yield (%) |
|-------|---------------------|----------|-----------|
| 10    | ![Structure](image) | ![Structure](image) | 72        |
| 11    | ![Structure](image) | ![Structure](image) | 78        |
| 12    | ![Structure](image) | ![Structure](image) | 81        |
| 13    | ![Structure](image) | ![Structure](image) | 92        |

Ethyl-6-amino-5-cyano-4-(2-methoxyphenyl)-2,4-dihydropyrano[2,3-c]pyrazole-3-carboxylate (5j)
Yellow solid; mp: 188–190 °C; yield (72%). IR (KBr) ($\nu_{\text{max}}$/cm$^{-1}$): 3441, 2991, 2193, 1718, 1633. $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 7.17 (d, $J = 6.0$, Hz, 1H), 6.98–6.77 (m, 3H), 6.20 (s, 2H), 5.17 (s, 1H), 4.08 (q, $J = 7.2$, Hz, 2H), 3.77 (s, 3H), 1.06 (t, $J = 7.2$, Hz, 3H). $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ 160.3, 158.2, 156.4, 156.1, 132.1, 128.8, 128.4, 127.4, 120.0, 119.9, 110.7, 103.2, 60.2, 58.3, 55.1, 31.2, 13.2 ppm. MS m/z 393.3 (M$^+$–1).

Ethyl-6-amino-5-cyano-4-(4-hydroxy-3-methoxyphenyl)-2,4-dihydropyrano[2,3-c]pyrazole-3-carboxylate (5k)
Yellow solid; mp: 182–184 °C; yield: (78%). IR (KBr) ($\nu_{\text{max}}$/cm$^{-1}$): 3346, 2973, 2192,1716,1633. $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 7.17 (d, $J = 6.0$, Hz, 1H), 6.98–6.77 (m, 3H), 6.20 (s, 2H), 5.17 (s, 1H), 4.08 (q, $J = 7.2$, Hz, 2H), 3.77 (s, 3H), 1.06 (t, $J = 7.2$, Hz, 3H). $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ 160.3, 158.2, 156.4, 156.1, 132.1, 128.8, 128.4, 127.4, 120.0, 119.9, 110.7, 103.2, 60.2, 58.3, 55.1, 31.2, 13.2 ppm. MS m/z 393.3 (M$^+$–1).

(d, $J = 6.0$ Hz, 2H), 6.64 (d, $J = 6.0$ Hz, 2H), 4.62 (s, 1H), 4.10 (q, $J = 6.0$ Hz, 2H), 1.09 (t, $J = 6.0$ Hz, 3H).
One pot green synthesis of dihydropyrano[2,3-c]pyrazole

(300 MHz, CDCl3): δ 9.44 (s, 1H), 6.77 (d, J = 8.0 Hz, 1H), 6.64 (s, 1H), 6.60 (d, J = 8.0 Hz, 1H), 5.60 (s, 2H), 4.76 (s, 1H), 4.14 (q, J = 7.2 Hz, 2H), 3.81 (s, 3H), 1.13 (t, J = 7.2 Hz, 3H). 13C NMR (75 MHz, CDCl3): δ 101.4, 60.5, 56.1, 36.1, 13.3 ppm.

101.4, 60.5, 56.1, 36.1, 13.3 ppm.

159.7, 157.4, 155.0, 151.7, 146.7, 144.7, 135.8, 129.5, 120.2, 119.9, 114.4, 110.5, 103.6, 60.9, 60.8, 55.7, 36.7, 13.8 ppm.

158.5, 152.4, 146.8, 144.7, 135.8, 129.5, 120.2, 119.9, 114.4, 110.5, 103.6, 60.9, 60.8, 55.7, 36.7, 13.8 ppm.

151.7, 115.2, 114.5, 114.0, 104.9, 61.8, 55.9, 55.4, 36.4, 14.1 ppm. MS m/z 355.3 (M–1).

Ethyl-6-amino-5-cyano-4-(4-methoxyphenyl)-2,4-dihydropyrano[2,3-c]pyrazole-3-carboxylate (5l)

Yellow solid; mp: 206–208 °C; yield (81%). IR (KBr) (vmax/cm–1): 3350, 2985, 2196, 1726, 1635. 1H NMR (300 MHz, CDCl3): δ 10.59 (s, 1H), 7.10 (d, J = 9.0 Hz, 2H), 7.07 (d, J = 9.0 Hz, 2H), 4.82 (s, 1H), 4.71 (s, 2H), 4.19 (d, J = 6.9 Hz, 2H), 3.78 (s, 3H), 1.15 (t, J = 6.9 Hz, 3H). 13C NMR (75 MHz, CDCl3): δ 164.9, 159.0, 135.8, 133.5, 130.0, 128.75, 115.2, 114.5, 114.0, 104.9, 61.8, 55.9, 55.4, 36.4, 14.1 ppm. MS m/z 341.2 (M+1).

Ethyl-6-amino-5-cyano-4-(4-nitrophenyl)-2,4-dihydropyrano[2,3-c]pyrazole-3-carboxylate (5n)

Yellow solid; mp: 210–212 °C; yield (92%). IR (KBr) (vmax/cm–1): 3491, 2987, 2200, 1726, 1635. 1H NMR (300 MHz, CDCl3): δ 13.86 (s, 1H), 8.16 (d, J = 9.0 Hz, 2H), 7.39 (d, J = 9.0 Hz, 2H), 7.19 (s, 2H), 4.95 (s, 1H), 4.09 (q, J = 6.0 Hz, 2H), 1.08 (t, J = 6.0 Hz, 3H). 13C NMR (75 MHz, DMSO-d6): δ 159.7, 157.4, 155.0, 151.7, 146.7, 128.8, 128.3, 123.1, 119.0, 101.4, 60.5, 56.1, 36.1, 13.3 ppm. MS m/z 356.1 (M–1).

Spectral data additional

Ethyl-6-amino-5-cyano-4-(isobutyl)-2,4-dihydropyrano[2,3-c]pyrazole-3-carboxylate (5m)

White solid; mp: 148–150 °C; yield (63%). 1H NMR (300 MHz, CDCl3): δ 13.67 (s, 1H), 4.56 (q, J = 6.9 Hz, 2H), 4.23 (d, J = 10.2 Hz, 1H), 4.01 (t, J = 9.3 Hz, 1H), 2.20 (t, J = 11.7 Hz, 1H), 1.68 (t, J = 7.2 Hz, 1H), 1.50 (t, J = 6.9 Hz, 3H). 13C NMR (75 MHz, CDCl3): δ 160.5, 159.7, 112.3, 112.0, 103.2, 62.9, 39.5, 35.1, 27.4, 25.8, 23.3, 20.8, 13.9 ppm.

Results and discussion

To optimize the reaction conditions, 4-fluorobenzaldehyde, diethylacetylene dicarboxylate, hydrazine hydrate, and malononitrile with L-proline were selected as the model substrates. In the beginning, synthesis of pyranopyrazole was carried out without catalyst and solvent (Table 2, entries 1–3). The results were not encouraging due to longer reaction time, lower yield and tedious purification process. This result suggests that catalyst plays an important role in this reaction. Subsequently, the same reaction has been done with different catalysts (t-proline, p-toluene sulfonic acid, SnCl2) under different reaction conditions. The reaction was also performed with different quantities of t-proline (Table 2, entries 4–8). The best result was obtained with 10 mol% t-proline in 10 min (Table 2, entry 6). On increasing the amount of catalyst, there was no improvement of yield (Table 2, entry 7). While 15 mol% t-proline, 10 mol% t-proline, PTSA, SnCl2 afforded a yield 90%, 88%, 84%, 58% respectively (Table 2, entries 7–10). t-proline proved to be the most efficient (Table 2, entry 6).

With optimized reaction conditions in hand, we started synthesizing dihydropyrano[2,3-c]pyrazole derivatives by grinding method as shown in Table 3. The scope of such sequence was next examined with various substituted aldehydes which afforded the corresponding dihydropyrano[2,3-c]pyrazole derivatives with different yields as listed in Table 3. As evident from Table 3, all the reactions proceeded comfortably and desired products were obtained in high to excellent yields. The reaction was also sensitive to the steric environment of the aromatic aldehyde, and decreases yields of the product (Table 3, entries 3 and 10). The structures of all synthesized products were confirmed by using spectroscopic techniques including NMR, LCMS and FT-IR. The structure of 5h was
confirmed by X-ray crystallography [38] Fig. 1. We have used various electron withdrawing or electron donating substituents in the ortho, meta and para positions on the ring of various aromatic aldehydes. Moreover maximum yields of the products were observed for aryl aldehydes with the electron withdrawing group on such as 4-chlorobenzaldehyde, 4-fluorobenzaldehyde, and 4-nitrobenzaldehyde, (Table 3, entries 4, 5, 13). Heteroaromatic aldehydes such as thiophene-2-carbaldehyde and furan-2-carbaldehyde participated in this reaction, affording respective products in moderate yields (Table 3, entries 6–7).

On the basis of the above result, a plausible mechanism for the formation of product 5 was described in Scheme 1 [37]. Initially, diethylacetylene dicarboxylate 1 and hydrazine hydrate 2 to afford intermediate I and removes EtOH as a side product. In the next step, Knoevenagel condensation between aryl aldehyde 3 with malononitrile 4 to formation of intermediate II. A subsequent Michael addition of intermediates I and II in the presence of L-proline follows by intramolecular cyclization and tautomerization leads to the formation of product 5 in Scheme 1. All the synthesized compounds were screened for their antimicrobial and antioxidant activity.

Biological evaluation

Antimicrobial activity

The bacterial strains used for the evaluations were Staphylococcus albus (ATCC 25923), Streptococcus pyogenes (ATCC 12384), Klebsiella pneumonia (ATCC 27736), Pseudomonas aeruginosa (ATCC 27853), Candida albicans (ATCC 66027). Amikacin and Ketoconazole are used as standard for antibacterial and antifungal substances respectively. Dimethyl sulfoxide (DMSO) was used as negative control.

All the synthesized compounds were screened for their in vitro antimicrobial activity against two gram positive bacteria (S. albus, S. pyogenes), two gram negative bacteria (K. pneumonia, P. aeruginosa) and antifungal assay against C. albicans with amikacin and ketoconazole as a standard. This study was carried out by agar well diffusion method to determine the zone of inhibition (mm) against four strains of microorganisms [39,40]. The antimicrobial screening results were
measured by the diameter of the inhibition zones, expressed in millimeters (mm) as shown in Table 4. Our investigation of antimicrobial data revealed that the compounds 5a, 5g, 5h, 5j, 5k, and 5l showed activity against S. albus, S. pyogenes, K. pneumonia, P. aeruginosa and C. albicans fungal strains. All the synthesized compounds (5a–m) showed activity against C. albicans.

### Antioxidant activity

In the present work, all the synthesized compounds were screened for their antioxidant activity against 2,2-diphenyl-1-picrylhydrazyl (DPPH) radical scavenger [41] using ascorbic acid as reference. All the compounds showed radical scavenging activity in the test concentration ranges (25–100 μg/ml). Results revealed that the compounds 5i and 5k showed better scavenging capacity, and other compounds 5a–h, 5j, 5l, and 5m showed moderate scavenging ability. The radical scavenging abilities have been shown in Table 5. These results revealed that the presence of hydroxyl groups in para positions of 5i and 5k extends the π-conjugation stabilizing the produced free radical [42].

### Conclusions

We have developed a simple, efficient, one pot and ecofriendly protocol for the synthesis of dihydropyrano[2,3-c]pyrazole derivatives (5a–m) under solvent free conditions. The highlight of this protocol was easy work up by simple filtration and recrystallization, short reaction times, no hazardous solvent and no column purification. The compounds 5i and 5k showed better scavenging activity against DPPH assay.

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### Table 4 Antimicrobial activity of dihydropyrano[2,3-c]pyrazole derivatives (5a–m).

| Compound | Staphylococcus albus Zone of inhibition (mm) 7 | Streptococcus pyogenes Zone of inhibition (mm) 9 | Klebsiella pneumonia Zone of inhibition (mm) 12 | Pseudomonas aeruginosa Zone of inhibition (mm) 3 | Candida albicans Zone of inhibition (mm) 5 |
|----------|-----------------------------------------------|-----------------------------------------------|-----------------------------------------------|-----------------------------------------------|-----------------------------------------------|
| 5a       | 17                                            | 7                                             | 9                                             | 12                                            | 3                                             |
| 5b       | 12                                            | R²                                            | R²                                            | 10                                            | 2                                             |
| 5c       | 12                                            | R²                                            | R²                                            | 10                                            | 3                                             |
| 5d       | R²                                            | R²                                            | R²                                            | R²                                            | 5                                             |
| 5e       | R²                                            | 4                                             | 10                                            | R²                                            | 8                                             |
| 5f       | R²                                            | R²                                            | 13                                            | 3                                             | 11                                            |
| 5g       | 7                                             | 9                                             | 5                                             | 4                                             | 9                                             |
| 5h       | 15                                            | 15                                            | 7                                             | 7                                             | 6                                             |
| 5i       | 22                                            | 13                                            | 15                                            | 12                                            | 8                                             |
| 5j       | 15                                            | 11                                            | 17                                            | 7                                             | 15                                            |
| 5k       | 10                                            | 8                                             | 12                                            | 9                                             | 10                                            |
| 5l       | 8                                             | 10                                            | 9                                             | 7                                             | 10                                            |
| 5m       | 11                                            | 9                                             | 13                                            | 8                                             | 9                                             |
| Control  | R²                                            | R²                                            | R²                                            | R²                                            | R²                                            |
| Standard | ––                                            | ––                                            | ––                                            | ––                                            | ––                                            |

a Sample concentration: 5 mg/mL, sample volume 100 μl/well.
b Results are calculated after subtraction of DMSO activity.
c Not active (R, inhibition zone < 2 mm); weak activity (2–8 mm); moderate activity (9–15 mm); strong activity (> 15 mm).
d Amikacin and Ketoconazole.

### Table 5 Antioxidant activity (DPPH assay) of dihydropyrano[2,3-c]pyrazole derivatives (5a–m).

| Compound | % Inhibition |
|----------|--------------|
|          | 25 μg/ml     | 50 μg/ml     | 75 μg/ml     | 100 μg/ml    |
| 5a       | 16.16 ± 0.03 | 25.54 ± 0.02 | 37.23 ± 0.05 | 48.45 ± 0.02 |
| 5b       | 13.12 ± 0.02 | 23.64 ± 0.03 | 34.86 ± 0.02 | 43.84 ± 0.01 |
| 5c       | 15.52 ± 0.04 | 25.13 ± 0.01 | 38.52 ± 0.02 | 47.69 ± 0.02 |
| 5d       | 15.86 ± 0.04 | 25.23 ± 0.02 | 36.14 ± 0.02 | 45.70 ± 0.02 |
| 5e       | 16.26 ± 0.01 | 25.17 ± 0.03 | 35.23 ± 0.02 | 46.81 ± 0.01 |
| 5f       | 14.54 ± 0.03 | 21.22 ± 0.04 | 25.31 ± 0.05 | 32.21 ± 0.05 |
| 5g       | 18.14 ± 0.02 | 26.46 ± 0.02 | 39.76 ± 0.01 | 42.11 ± 0.03 |
| 5h       | 14.14 ± 0.02 | 24.22 ± 0.03 | 30.52 ± 0.04 | 39.50 ± 0.03 |
| 5i       | 22.75 ± 0.03 | 30.46 ± 0.01 | 48.11 ± 0.01 | 60.65 ± 0.05 |
| 5j       | 17.24 ± 0.01 | 26.61 ± 0.04 | 38.54 ± 0.05 | 49.41 ± 0.05 |
| 5k       | 21.62 ± 0.03 | 27.42 ± 0.04 | 45.12 ± 0.04 | 57.82 ± 0.07 |
| 5l       | 17.64 ± 0.05 | 24.25 ± 0.05 | 34.36 ± 0.03 | 44.11 ± 0.04 |
| 5m       | 17.25 ± 0.04 | 28.41 ± 0.03 | 36.19 ± 0.04 | 45.64 ± 0.03 |
| Control  | ––            | ––            | ––            | ––            |
| Ascorbic acid | 29.34 | 55.84 | 90.07 | 98.85 |
Conflict of Interest

The authors have declared no conflict of interest.

Compliance with Ethics Requirements

This article does not contain any studies with human or animal subjects.

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