Received: 15 July 2019 | Revised: 27 September 2019 | Accepted: 7 October 2019

DOI: 10.1002/jhet.3786

ARTICLE

WILEY

A meglumine catalyst–based synthesis, molecular docking, and antioxidant studies of dihydropyrano[3, 2-*b*] chromenedione derivatives

G. Sravya[1] | G. Suresh[2] | Grigory V. Zyryanov[1,3] | A. Balakrishna[4] | K. Madhu Kumar Reddy[5] | C. Suresh Reddy[5] | C. Venkataramaiah[6] | W. Rajendra[6] | N. Bakthavatchala Reddy[1]

[1] Chemical Engineering Institute, Ural Federal University, Yekaterinburg, Russian Federation

[2] Anhui Provincial Engineering Technology Research Centre of New silicon-based materials, Bengbu University, Caoshan Road, 1866 Bengbu, Anhui, China

[3] I. Ya. Postovskiy Institute of Organic Synthesis, Ural Division of the Russian Academy of Sciences, 22 S. Kovalevskoy Street, Yekaterinburg, Russian Federation

[4] Chemistry Department, Rajeev Gandhi Memorial College of Engineering and Technology (Autonomous), Nandyal 518501Andhra Pradesh, India

[5] Department of Chemistry, Sri Venkateswara University, Tirupati 517 502Andhra Pradesh, India

[6] Division of Molecular Biology, Department of Zoology, Sri Venkateswara University, Tirupati 517502Andhra Pradesh, India

Correspondence
N. Bakthavatchala Reddy, Chemical Engineering Institute, Ural Federal University, Yekaterinburg 620002, Russian Federation.
Email: drbvreddyn@gmail.com

Abstract

A simple method was employed for the synthesis of dihydropyrano[3, 2-*b*] chromenedione derivatives (**4a-o)** in high yields by condensation of 5, 5-dimethylcyclohexane-1, 3-dione(**1**), different aromatic aldehydes (**2a-o**), and 5-hydroxy-2-(hydroxymethyl)-4*H*-pyran-4-one(**3**), using meglumine as a stable and reusable catalyst. Meglumine, an amino sugar, was employed as an environmentally benign catalyst, due to its splendid properties such as being inexpensive, recyclable, and biodegradable. The accomplished protocol employs low catalyst loading and easy work-up for the synthesis of 5-hydroxy-2-(hydroxymethyl)-4*H*-pyran-4-one derivatives. A great asset is that without any significant loss, the catalyst could be recovered and reused for extended synthetic steps. This offer huge advantage to overcome recyclability issues. Our synthesized compounds were analyzed by IR, ^{1}H, ^{13}C NMR, mass spectra and evaluated for their antioxidant properties by 1, 1-diphenyl-2-picryl hydrazyl radical (DPPH), hydrogen peroxide(H_2O_2), and nitric oxide (NO) scavenging methods. The correlation in exhibition of antioxidant activity was effective at all doses. The binding interactions and molecular docking studies for entitled compounds were studied against 3MNG protein; **4k** exhibited marked binding affinity with excellent docking score of −7.6 Kcal/mol and emerged as a lead compound.

1 | INTRODUCTION

The green chemistry is benign by its design and in being constantly increasing demand because of providing for pulling together environmental technologies and advanced tools that are environmentally friendly.[1] Despite in the development of wealthy advancements in synthetic reactions, multicomponent reactions (MCRs) have been recognized for its importance and are being helpful to chemists in research and development for enhancement of more efficient and ecofriendly methods for synthesizing simple and readily accessible starting materials that receive profound financial benefits. However, employing MCRs ranging from synthetic organic to green chemistry have made much progress in adopting a desirable ideal and green solvent, which is aided along

with the search for suitable efficient catalyst that should be natural, inexpensive, and nontoxic and also must be readily available. An efficient catalyst is concerned with additional benefits aiding the reaction, separation from the reaction and catalyst recycling.[2] The most challenging in chemistry is to have two or more different heterocyclic moieties in a single molecule, and this approach is fascinating and drawing much more attention because it can notably enhance the multifaceted pharmacological properties of the respective drug. Therefore, the development of simple and efficient reactions for synthesizing biologically potent molecules is an exciting goal in synthetic organic chemistry and green chemistry.[3–5]

Kojic acid derivatives have long fascinated the chemistry community since they are auxiliary scaffolds in the structures of a number of pharmaceutical products and also in distinguished new bioactive molecules with various promising pharmacological activities such as antimicrobial,[6] anti-inflammatory,[7] antimelanogenic,[8] tyrosinase inhibitory activities,[9,10] whitening agent,[11] antineoplastic,[12] anti-fungal and antibacterial,[13] depigmenting,[14] and anticonvulsant.[15] An important interest is dedicated by organic chemists for the production of 5-hydroxy-2-(hydroxymethyl)-4*H*-pyran-4-one derivatives in order to improve existing moieties or to create new ones. To date, a handful of synthetic approaches have been produced for the synthesis of 5-hydroxy-2--(hydroxymethyl)-4*H*-pyran-4-one derivatives. In recent years, several reports revealed the usage of $InCl_3$,[16] $FeCl_3$-SiO_2,[17] and alums as catalysts[18] in a safe and effective manner in the synthesis of 2-(hydroxymethyl)-7, 7-dimethyl-10-aryl-7, 8-dihydropyrano[3, 2-*b*]chromene-4, 9(6H, 10H)-diones improved the yields enormously. Due to the fact that, various synthetic transformations have been indulged with some drawbacks in applications of expensive, water-bigoted and nonrecyclable catalysts. Present improvement of an effective, inexpensive, reliable, ecofriendly, cost-effective green chemistry synthetic approaches for synthesis of kojic acid derivatives is of incredible interest and is highly recommended.

Owing to the harmful effects of synthetic catalysts on the environment, many ecofriendly green catalysts have been recently introduced as an alternative in organic synthesis due to it being safe, cheap, and nontoxic in nature and are presently receiving prominent courtesies. Therefore, from the point of green chemistry, we have selected meglumine as an appropriate green catalyst for present chemical methodology. Meglumine, or D-(-)-*N*-methylglucamine, is an amino sugar (derived from sorbitol) consisting a molecular formula $C_7H_{17}NO_5$ with a pKa value of 9.6 (Figure 1).

It contains secondary amino group and four primary and secondary hydroxyl groups and is able to facilitate

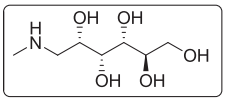
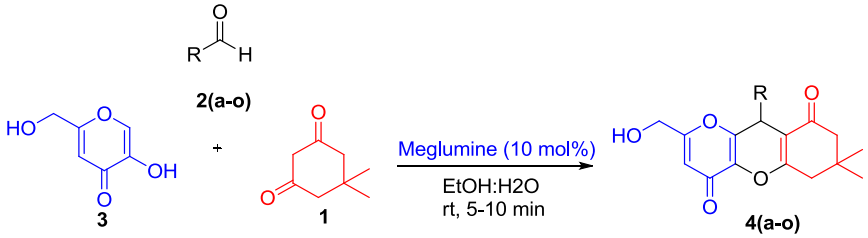
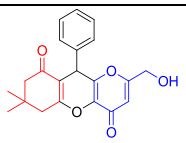
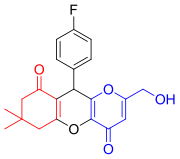
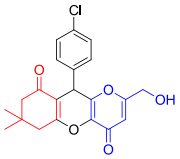
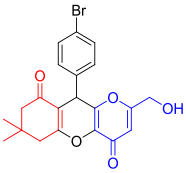
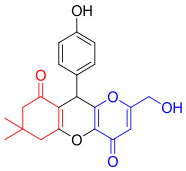
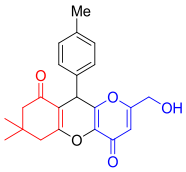
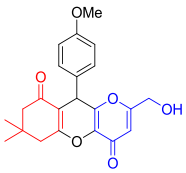


FIGURE 1 Structure of meglumine

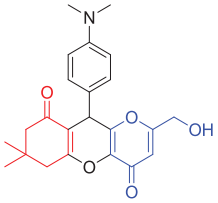
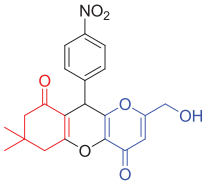
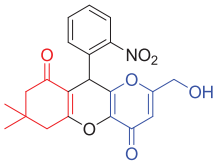
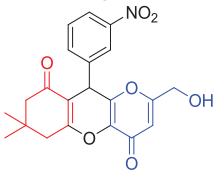
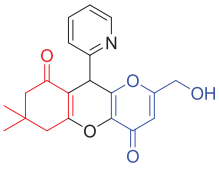
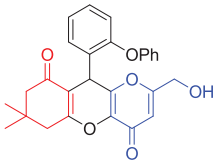
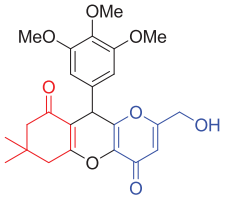
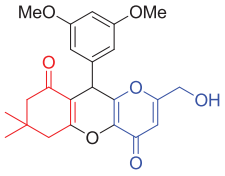
both electrophilic and nucleophilic substitution of reactants because of its ability to form hydrogen bond and to donate lone pair of electrons. It is an FDA approved excipient in pharmaceuticals and in medicine. Meglumine has astonishing physical and chemical properties such as low toxicity, biocompatibility and biodegradability, low cost, and noncorrosive nature. As a functional excipient, it acts as a counterion. It may help to enhance active pharmaceutical ingredient stability and solubility in formulation studies. Besides its availability, meglumine can be applied in different administration routes (eg, oral, intravenous). The main benefits of using meglumine catalyst are high yields of products, short reaction times, broad substrate scope, and carrying out reactions at room temperature. On the basis of its outstanding traits, meglumine has been proven as a notable candidate for several organic transformations. Thus, such selective catalysts play a prominent role for the establishment of sustainable chemistry.

Inferable from the malicious impacts of volatile organic solvents, recently, a few green solvent systems have been projected as substituent reaction media. Water stands out among the most stunning endowments of nature. It has possessed an imperative noticeable quality as a green medium in organic synthesis because of it being sheltered, modest, ecofriendly, and nonharmful.[19] Likewise, a result of superior qualities such as high reactant proficiency, nontoxic nature, and ease and simple reusing biodegradable material has additionally been accepting an ever-increasing number of considerations. The development of MCRs in water using biodegradable material as catalyst is progressing towards advancement of green chemistry. Scientific reports to date disclose that no synthetic protocols have been attempted for synthesizing dihydropyrano[3, 2-*b*]chromenedione derivatives mediated by meglumine as catalyst under ethanol:water mixture solvent conditions. Environmentally benign selective catalytic reactions are urgently needed in the pharmaceutical and chemical industries; therefore, our fundamental objective is to produce a greener technology that is simple, cleansed, and more effective than conventional reaction.[20–22] Centering our research interests on the development of efficient ecofriendly methodology, the versatility of meglumine as catalyst was extended for the synthesis of 5-hydroxy-2-(hydroxymethyl)-4*H*-pyran-4-one derivatives successfully via a new, fast, and profitable process in good yields.[23–25] Our newly synthesized



Entry	R	Product	Time (min)	Yield (%)[a]
2a	C_6H_5	 4a	10	85
2b	4-FC_6H_4	 **4b**	7	90
2c	4-ClC_6H_4	 **4c**	6	91
2d	4-BrC_6H_4	 **4d**	8	86
2e	4-OHC_6H_4	 **4e**	6	90
2f	4-MeC_6H_4	 **4f**	7	90
2g	4-$OMeC_6H_4$	 **4g**	5	92

SCHEME 1 Meglumine catalyzed synthesis of dihydropyrano[3, 2-*b*]chromenediones 4(a-o). [a]Isolated yields. [b]Catalyst was reused five times [Color figure can be viewed at wileyonlinelibrary.com]

2h	4-N,N$(CH_3)_2C_6H_4$	 **4h**	8	90
2i	4-$NO_2C_6H_4$	 **4i**	6	84
2j	2-$NO_2C_6H_4$	 **4j**	8	89
2k	3-$NO_2C_6H_4$	 **4k**	5	94, 94, 93, 93, 92[b]
2l	2-Pyridyl	 **4l**	9	90
2m	2-$OPhC_6H_4$	 **4m**	7	89
2n	3,4,5-$(OMe)_3C_6H_2$	 **4n**	6	92
2o	3,5-$(OMe)_2C_6H_3$	 **4o**	5	91

SCHEME 1 Continued

compounds were evaluated for their antioxidant activities, and docking studies provided valuable information that 3MNG protein exhibits effective binding interaction against the active compound.

2 | RESULTS AND DISCUSSION

In the panorama of meglumine catalyzed MCRs, the simplification, feasibility, and practicality were thoroughly investigated by opting few parameters such as scrutinizing the effects and performance of various catalysts. A model reaction was employed by setting various conditions such as catalyst loading, optimization of the reaction conditions for conducting successful one-pot three component method for the synthesis of dihydropyrano [3, 2-*b*]chromenediones **4(a-o)** by reaction of dimedone **(1)**, various aldehydes **2(a-o)** and kojic acid **(3)** under EtOH:H_2O system at room temperature (Scheme 1).

TABLE 1 Influence of catalyst loading on the synthesis of dihydropyrano [3, 2-b] chromenedione derivatives 4(a-o)[a]

Entry	Catalyst (mol%)	Time (min)	Yield (%)[b]
1	No	120	30
2	K_2CO_3	60	35
3	Et_3N	60	42
4	DMAP	60	38
5	L-Proline	60	40
6	Chitosan	50	24
7	β-CD	40	32
8	Ascorbic acid	50	34
9	Citric acid	60	38
10	CuI	60	30
11	Meglumine (2)	5	80
12	Meglumine (5)	5	85
13	Meglumine (10)	5	94
14	Meglumine (15)	5	92
15	Meglumine (20)	5	92

[a]Reaction of 3-nitro benzaldehyde (1 mmol), dimedone (1mmol) and kojic acid (1 mmol).

[b]Isolated yields.

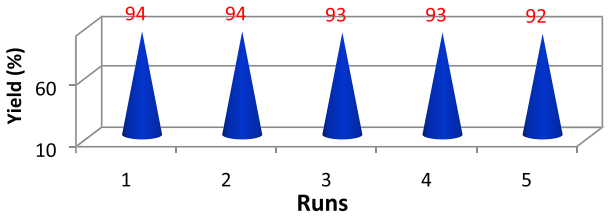
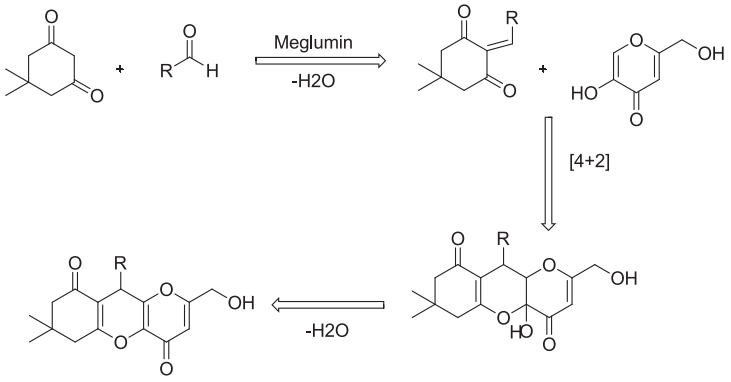


FIGURE 2 Reusability of meglumine catalyst in the synthesis of **4k** [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 2 The in vitro antioxidant activity of 4(a-o) in DPPH method.

Compound	Concentration (μg/mL)			
	50 (μg/mL)	75 (μg/mL)	100 (μg/mL)	IC_{50} (μg/mL)
4a	64.02±0.12	66.59±0.32	68.84±0.38	39.05±0.028
4b	67.32±0.09	69.74±0.14	71.70±0.66	37.13±0.031
4c	56.74±0.14	58.52±0.24	60.38±0.32	44.06±0.016
4d	55.32±0.12	56.24±0.20	59.20±0.30	45.19±0.014
4e	65.04±0.11	67.69±0.34	69.94±0.29	38.43±0.031
4f	54.98±0.10	55.84±0.32	58.92±0.24	45.47±0.008
4g	52.86±0.12	54.80±0.22	57.98±0.20	47.29±0.012
4h	65.35±0.15	68.32±0.32	70.54±0.38	38.25±0.029
4i	59.64±0.14	61.54±0.24	63.90±0.14	41.91±0.023
4j	74.33±0.11	76.34±0.18	78.54±0.20	33.63±0.032
4k	75.32±0.13	77.36±0.26	79.31±0.24	33.19±0.016
4l	58.86±0.08	60.72±0.22	62.54±0.11	42.47±0.006
4m	50.45±0.12	52.32±0.31	53.84±0.21	49.55±0.030
4n	51.28±0.09	53.42±0.21	55.64±0.32	48.75±0.021
4o	49.98±0.12	51.86±0.14	52.72±0.22	50.02±0.011
Ascorbic acid	73.23±0.10	75.22±0.13	77.34±0.35	34.04±0.008

Values were the means of three replicates ± SD



SCHEME 2 A plausible reaction mechanism

In order to evaluate the supremacy of meglumine, a comparative study based on selecting and using different catalysts were carried and the results are précised in Table 1. To evaluate the prominence of catalyst in this three-component process, the reaction was first executed in the absence of catalyst and only negligible yields of 30% of entitled product was perceived even after long intervals of time (Table 1, entry 1). Moreover in the presence of potassium carbonate, triethylamine, DMAP, and L-proline, the reaction gave 35%, 42%, 38%, and 40% isolated yield of product after 1 hour, respectively (Table 1, entries 2-5). In addition, chitosan, β-cyclodextrin (β-CD), ascorbic acid, citric acid, and CuI could also turn this conversion; however, no improvement was observed (Table 1, entries 6-10). However, these catalysts were less effective. We then tested the reaction in the presence of meglumine. Meglumine was found to be the excellent catalyst for this process, and the desired product **4k** was formed in 94% yield in just 5 minutes (Scheme 1, entry 2k). We believe that meglumine plays a vital role for the formation of product; this is due to the stabilization of the corresponding intermediates and transition states by hydrogen bonding of multiple hydroxyl groups present within the structure of meglumine. All the synthesized compounds were characterized by ^{1}H, ^{13}C-NMR, and LC-MS, and all the spectral information were in fine agreement with the anticipated structures.

A detailed schematic representation of the reaction mechanism showing the catalytic activity of meglumine in the synthesis of the final products **4(a-o)** has been proposed in Scheme 2. While the reaction was ongoing, we were confident about the formation of tricyclic intermediate, which on dehydration lead to the desired product by Knoevenagel–hetero-Diels-Alder reaction.[26]

The foremost benefit of solid catalysts is their recyclability. The risk of recycling and reusing the meglumine catalyst was studied in the three-component reaction between 3-nitrobenzaldehyde, dimedone, and kojic acid (Figure 2).

At the point when the reaction was finished, the catalyst was recovered, and further, the filtrate was dried under decreased weight, and recuperated catalyst was

TABLE 3 The in vitro antioxidant activity of 4(a-o) in H_2O_2 method.

	Concentration (μg/mL)		
Compound	**50 (μg/mL)**	**75 (μg/mL)**	**100 (μg/mL)**
4a	65.42±0.18	67.54±0.22	69.62±0.40
4b	69.92±0.24	70.53±0.34	73.84±0.43
4c	58.34±0.22	61.20±0.30	64.58±0.37
4d	57.98±0.16	60.84±0.22	62.96±0.34
4e	67.22±0.32	68.25±0.18	71.34±0.42
4f	55.86±0.18	58.90±0.24	61.24±0.36
4g	54.92±0.16	57.86±0.22	60.96±0.32
4h	67.62±0.19	68.64±0.30	70.52±0.34
4i	64.74±0.30	66.82±0.62	68.96±0.42
4j	75.85±0.45	78.32±0.64	80.24±0.37
4k	77.65±0.32	79.40±0.28	80.72±0.26
4l	60.24±0.16	63.68±0.20	65.90±0.38
4m	52.98±0.18	56.84±0.22	59.96±0.40
4n	53.42±0.14	57.65±0.24	60.26±0.36
4o	51.94±0.12	55.68±0.22	59.86±0.32
Ascorbic acid	75.28±0.19	77.29±0.09	79.20±0.12

Values were the means of three replicates ± SD

TABLE 4 The in vitro antioxidant activity of 4(a-o) in NO method.

	Concentration (μg/mL)		
Compound	**50 (μg/mL)**	**75 (μg/mL)**	**100 (μg/mL)**
4a	68.20±0.14	70.92±0.24	72.40±0.32
4b	70.72±0.26	72.80±0.35	74.80±0.16
4c	66.62±0.18	69.10±0.20	70.12±0.34
4d	65.96±0.16	68.89±0.22	69.90±0.30
4e	69.62±0.22	71.86±0.18	73.92±0.24
4f	65.84±0.14	68.76±0.22	69.60±0.28
4g	64.86±0.12	66.90±0.24	68.97±0.26
4h	70.33±0.20	72.62±0.16	74.75±0.16
4i	67.42±0.18	69.86±0.24	71.24±0.20
4j	78.92±0.36	80.66±0.12	83.70±0.28
4k	79.04±0.38	82.40±0.15	84.36±0.32
4l	66.86±0.16	69.22±0.22	70.34±0.34
4m	59.92±0.14	60.76±0.24	63.67±0.26
4n	63.20±0.12	64.34±0.22	66.54±0.32
4o	58.98±0.18	59.86±0.32	61.78±0.36
Ascorbic acid	77.11±0.31	79.86±0.43	81.36±0.34

Values were the means of three replicates ± SD

TABLE 5 Antioxidant activity of the compounds 4k and 4j at 10 min.

Compound	**10 min**	**20 min**	**30 min**
4j	74.41	74.50	74.61
4k	75.37	75.42	75.69

Time intervals by DPPH scavenging method.

washed twice with diethyl ether (2 mL) and reused in the next run after drying. The catalyst was reused for four to five runs, and in each and every individual reaction, the target compounds were formed in yields (94% to 92%) in their respective reaction times. As can be noticed, a slight deactivation of morphology of catalyst surface and the work up process lead to the loss of the yield, which is negligible.

2.1 | Antioxidant activities of title compounds 4(a-o)

All the compounds were subjected for antioxidant activity by DPPH (Table 2),[27,28] H_2O_2 (Table 3),[29] and nitric oxide methods (Table 4).[30,31] These dihydropyrano[3, 2-*b*]chromenediones **4(a-o)** compounds have one free hydroxyl group and two carbonyl groups bonded to the

TABLE 6 Bonding characterization of synthesized compounds 4(a-o)

S. No	Compound	Rank	Binding energy (K calmol^{-})	Binding interaction	Bond Length(A^{O})	Bond Angle (^{o})	Bond Type
Std	**DTT**	R	- 4.6	Gly 82 CA....OH	2.5	137.7	H- don
				Gly 17 CA.....OC	2.7	113.6	H- acc
Std	**BHT**	R	- 5.2	Arg 86 CZ ....OC	2.1	113.2	H- acc
1	**4a**	6	- 6.5	Gly 92 CA ....OH	2.4	113.2	H- acc
				Val 94 CA .... HO	2.0	120.9	H- don
				Ala 90 CA .... HO	2.7	119.1	H- don
				Arg 86 CZ ....OC	2.2	120.8	H- acc
2	**4b**	3	- 6.7	Gly 92 CZ ....HO	2.1	113.2	H- don
				Arg 86 CA ....OC	2.4	120.8	H- acc
3	**4c**	9	- 6.4	Glu 16 CB ....OC	2.6	116.4	H- acc
4	**4d**	10	- 6.4	Val 70 CZ ....HO	2.3	120.8	H- don
5	**4e**	5	- 6.5	Arg 86 CZ ....OC	2.4	120.8	H- acc
				Gly 85 CA .....OC	2.7	113.4	H- acc
				Val 94 CA .... HO	1.8	120.8	H- don
				Gly 92 CA ....OH	2.3	113.2	H- acc
6	**4f**	11	- 6.4	Leu 96 CZ ....HO	2.4	121.0	H- don
				Leu 96 CZ ... HO	2.0	115.3	H- acc
				Glu 91 CB ....OC	2.5	115.7	H- acc
7	**4g**	12	- 6.4	Asp 109 CB ....HO	22.5	121.6	H- don
				Lys 126 CZ ....OH	2.3	92.1	H- acc
				Val 5 CA .... OC	2.0	115.3	H- acc
8	**4h**	4	- 6.5	Leu 96 CZ ....OH	2.1	115.3	H- acc
				Glu 91 CZ ....OH	2.3	115.7	H- acc
9	**4i**	7	- 6.5	Gly 17 CB ....OH	2.8	113.6	H- acc
				Asn 21 CZ ....ON	2.7	117.4	H- acc
10	**4j**	2	-6.9	Arg 86 CZ ....OC	2.2	120.8	H- acc
				Arg 86 CZ ....ON	2.1	117.9	H- acc
				Gly 92 CB ....OC	2.2	113.2	H- acc
11	**4k**	1	-7.6	Val 94 CZ .....HO	2.4	120.9	H- don
				Val 94 CB ....OH	2.7	123.2	H- acc
				Lys 93 CZ ....OH	2.7	114.8	H- acc
				Gly 92 CB ....OH	2.2	113.2	H- acc
				Arg 86 CB ....OC	2.4	117.9	H- acc
12	**4l**	8	-6.5	Arg 96 CZ ....OC	2.1	120.8	H- acc
				Gly 92 CB ....OH	2.5	113.2	H- acc
13	**4m**	14	-6.3	Glu 16 CD ....HO	2.3	118.7	H- don
14	**4n**	13	-6.4	Leu 96 CZ ....OH	2.2	115.3	H- acc
				Glu 91 CA ....OH	2.3	115.7	H- acc
15	**4o**	15	-6.3	Leu 96 CZ ....OH	2.1	115.3	H- acc
				Glu 91 CA ....OH	2.4	115.7	H- acc

aromatic ring; the antioxidant activity was magnificently displayed by this model of substitution to scavenge the free radicals effectively. The mean antioxidant values are shown in Figures S1 to S3.

The antioxidant activity was evaluated by inferring that a stable molecule DPPH forms on accepting an electron or a hydrogen and thus found application in the determination of radical scavenging. The dihydropyrano[3, 2-*b*] chromenediones **4(a-o)** gained the competency by donating one electron to scavenge the DPPH radical. When compared with standard ascorbic acid, **4j** and **4k** showed good radical scavenging activity for all the three methods; **4j** and **4k** displayed appreciable antioxidant activity. Both of these showed the highest activity because $-NO_2$ substituent, which affect the electron and hydrogen donating capacities, appears to be useful in inducing antioxidant activity. Since $-NO_2$ is highly electron withdrawing moiety, thereby electron density around aromatic ring moiety decreases and increases affinity towards oxygen derived free radicals and mobilizes ROS to be scavenged out of living system. This points to the fact that electron withdrawing substituent in **4j** and **4k** appears to prevent to some extent oxidative metabolic pathways in the living cells. Moreover, for the remaining compounds **4a**, **4b**, **4c**, **4d**, **4e**, **4f**, **4g**, **4h**, **4i**, **4l**, **4m**, **4n**, and **4o**, the order is as follows: **4b > 4h > 4e > 4a > 4i > 4l > 4c > 4d > 4f> 4g > 4n > 4m > 4o**. As per the data presented in Tables 2, 3 and 4, with the increase of the concentration, the radical scavenging activities by DPPH, hydrogen peroxide and nitric oxide methods also displayed higher values; **4j** and **4k** was measured at different concentrations and monitored the change in absorbance at 10, 20, and 30 minutes in DPPH method (Table 5). The results indicated that the antioxidant activity is independent of time even after 10-minute intervals of time.

2.2 | Molecular docking analysis

In order to prove the reputation of our target molecules, compounds **4(a-o)** with selective pharmacological target were tested for docking analysis against 3MNG protein

TABLE 7 Physicochemical properties of compounds 4(a-o)

Compound Rule	Mol. wt[a] ≤ 500	Mol. vol[b]	n-ROTB[c]	n- OHNH donor[d] ≤ 5	n-ON acceptor[e] ≤ 10	mi Log P[f] ≤ 5	TPSA (A° 2)[g]	Lipinski's violation ≤ 1	%ABS[h]
4a	380.2	326.6	5	0	8	3.32	82.46	0	92.5
4b	368.6	344.0	6	0	7	3.46	84.18	0	92.5
4c	339.8	363.4	5	0	8	3.18	86.42	0	95.3
4d	412.6	362.4	5	0	7	3.45	80.66	0	94.5
4e	440.4	303.9	5	0	8	3.65	86.12	0	84.7
4f	337.8	331.0	5	0	7	3.66	92.36	0	96.5
4g	330.6	313.3	5	0	7	4.40	88.14	0	90.5
4h	386.1	289.6	4	0	6	4.23	88.14	0	92.3
4i	414.2	316.6	5	0	6	4.10	86.12	0	96.4
4j	436.3	343.3	5	0	7	3.89	90.42	0	96.2
4k	360.1	340.0	5	0	7	3.46	82.86	0	94.6
4l	344.2	366.6	6	0	8	2.12	92.14	0	94.6
4m	360.8	386.1	6	0	5	3.14	84.44	0	94.4
4n	380.3	390.9	5	0	7	2.86	92.10	0	98.2
4o	386.1	388.8	5	0	7	3.84	91.18	0	98.6

[a]Molecular weight

[b]Molecular volume

[c]Number of rotatable bonds

[d]Number of hydrogen bond donors

[e]Number of hydrogen bond acceptors

[f]Logarithmic ratio of the octanol-water partitioning coefficient

[g]Topological polar surface area

[h]Percentage of absorption. %ABS = 109 - (0.345 9 TPSA)

of human being, which is a suitable target for antioxidant activity. The 3D structure of 3MNG protein (PDB id: 3MNG) was taken from the protein data bank, and the reference drugs such as dithiothreitol (DTT)and butylated hydroxytoluene (BHT)were from PubChem DrugBank. The docking results of the synthesized compounds such as **4a**, **4b**, **4c**, **4d**, **4e**, **4f**, **4g**, **4h**, **4i**, **4j**, **4k**, **4l**, **4m**, **4n**, and **4o** have significant binding modes, with dock scores of **−6.5**, **−6.7**, **−6.4**, **−6.4**, **−6.5**, **−6.4**, **−6.4**, **−6.5**, **−6.5**, **−6.9**, **−7.6**, **−6.5**, **−6.3**, **−6.4 and −6.3**, against 3MNG protein when compared with the control drugs, **DTT(-4.6)** and **BHT(-5.2),** respectively. The type of bonds and energy profiles of compounds **4(a-o)** along with reference drugs are mentioned in Table 6. Based on the dock scores, the title compounds **4(a-o)** fitted more stably into the binding pocket of 3MNG protein. All our newly synthesized compounds will be established as promising next generation drugs in treating several diseases associated with oxidative stress as effective antioxidative agents. Compounds **4c**, **4d**, **4m**, and **BHT** have shown effective hydrophobic interaction against 3MNG protein. The 3D modeled binding modes of title compounds within the binding domain of peroxiredoxins are shown in Figure S4.

2.3 | Bioavailability of compounds 4(a-o)

Bioavailability refers to the extent and rate at which the active moiety (drug or metabolite) enters systemic circulation, thereby accessing the site of action. The therapeutic efficacy of a drug will be determined once the drug/compound succeeded in ADMET liabilities. In addition, drug likeness is an important paradigm of a compound that optimizes the ADMET of a compound in mammalian body.[32] Considering the importance of drug likeness, the title compounds were screened for their ADMET and Lipinski Rule of Five. Fundamentals of Rule of Five are mentioned in Table 7. The compound which violates these rules more than one of the fundamentals will be prone to high probability of failure to exert drug-likeness.[33]

Topological polar surface area (TPSA) is a prominent considering factor in estimating the bioavailability of compounds. Compounds that exhibit TPSA ≥140 Å come under low bioavailability group.[34] The complete bioavailability properties of title compounds are summarized in Table 7. The compounds have good oral percentage of absorption and drug likeness with the valves ranging from 84.70% to 98.6% followed by different ADME predictions such as HIA% (96.14-99.98), $CaCO_2$ cell permeability (20.14-28.24), PPB% (≥90.46), and BBB (0.120-0.412). From the above-exhibited properties of compounds, it is concluded that all the title compounds have complied with the rules of ADME property (Table 8).

TABLE 8 Prediction of pharmacokinetic properties of compounds 4(a-o)

Compound	$CaCO_2$[a] permeability	HIA[b] (%)	PPB[c] (%)	BBB[d](Cbrain/Cblood)
4a	22.36	96.14	96.16	0.102
4b	24.18	96.26	94.28	0.113
4c	24.12	98.66	95.36	0.108
4d	22.86	98.12	92.38	0.116
4e	28.24	98.36	90.46	0.142
4f	24.86	98.69	96.88	0.186
4g	20.14	98.44	100.00	0.316
4h	21.14	99.36	96.16	0.213
4i	22.82	99.12	94.26	0.218
4j	22.60	98.64	96.12	0.316
4k	23.16	98.06	96.16	0.224
4l	24.64	99.98	94.46	0.346
4m	24.46	98.48	93.86	0.136
4n	28.12	98.41	92.12	0.318
4o	24.00	99.00	98.88	0.412

[a]Colon adenocarcinoma

[b]Human intestinal absorption

[c]Plasma protein binding

[d]Blood-brain barrier

3 | CONCLUSION

In summary, we have designed an efficacious, graceful, efficient, easy, ecofriendly, and straightforward synthesis for substituted dihydropyrano[3, 2-*b*]chromenedione derivatives (**4a-o)**, which are imperative precursors for various biologically active heterocyclic scaffolds. We have shown the versatility use of meglumine, an ecofriendly catalyst, for the synthesis of entitled compounds (**4a-o)** in excellent yields in shorter reaction time. Employing meglumine as catalyst has several advantages such as easy catalyst separation, minimal product contamination, and the distinct possibility of reuse and easily biodegradable in the environment to establish a more sustainable society. The results of the present study showed that all the kojic acid derivatives (**4a-o)** exhibited moderate to good antioxidant activities. Specifically, **4j** and **4k** compounds showed high inhibitory potency when compared with other compounds. Coincidentally, more robust series of compounds were developed especially by a careful consideration of ADMET approaches. Innovative

synthetic chemistry and prediction of the ADMET properties play a crucial role within the drug design method of advanced molecular architectures that may be effectively applied not only in the drug discovery setting but also on process scale and will continue hopefully provide inspiration to researchers worldwide within the continued discovery of the latest future medication.

4 | EXPERIMENTAL

All reagents were purchased from Sigma-Aldrich, Hyderabad, India, and used without further purification. Melting points were determined on Guna Mel-Temp apparatus (Tempo Instruments and Equip., Mumbai, India) and were uncorrected. The IR spectra were recorded on Bruker Alpha ECO-ATR FTIR (attenuated total reflection–Fourier transform infrared) interferometer with single reflection sampling module equipped with ZnSe crystal. ^{1}H, ^{13}C-NMR spectra were taken on Jeol JNM ECP 400 NMR instrument (Tokyo) at room temperature in DMSO-d_6 or $CDCl_3$ using tetramethylsilane (TMS) as internal standard. EI-Mass spectra were obtained on JEOL GCMATE II GC-MS spectrometer (Tokyo) at SAIF IIT-Madras, Chennai.

4.1 | General method for the preparation of dihydropyrano[3, 2-*b*]chromenedione derivatives 4(a-o)

In a dry 50 mL RB flask, a mixture of aldehyde (1.0 mmol), kojic acid (1.0 mmol), dimedone (1.1 mmol), and EtOH:H_2O (1:1 mL) were taken and then stirred at room temperature for 5 to 10 minutes along with meglumine (10 mol%). The progress of the reaction was monitored by TLC; after completion of the reaction, the precipitated product was filtered and washed with aqueous ethanol (5 mL). The crude product was purified by column chromatography (ethyl acetate-hexane, 7:3) on silica gel to get the pure substituted dihydropyrano[3, 2-*b*]chromenedione derivatives **4(a-o)**. The supplementary material contains complete spectral data for the new compounds **4(a-o)** (Figures S5-S25).

4.2 | 2-(Hydroxymethyl)-7, 7-dimethyl-10-phenyl-7, 8-dihydropyrano[3, 2-*b*]chromene-4, 9(6H, 10H)-dione (4a)

Solid, Yield: 85%, Mp: 183-186°C; ^{1}H-NMR (DMSO-d_6): δ 7.32-7.22 (m, 5H), 6.46 (s, 1H), 4.84 (s, 1H), 4.42-4.35 (m, 2H), 2.84-2.76 (m, 2H), 2.21-2.15 (m, 2H), 1.12 (s, 3H), 1.04 (s, 3H); ^{13}C-NMR (DMSO-d_6): δ 196.6, 170.3, 168.2, 163.6, 150.2, 140.2, 136.4, 129.1, 128.2, 127.7, 112.6, 112.0, 60.2, 50.4, 39.4, 38.5, 32.0, 29.2, 27.3; ESI-MS (*m*/*z*): 353 $[M + H]^+$. Anal. Calcd for $C_{21}H_{20}O_5$: C, 71.58; H, 5.72. Found: C, 71.53; H, 5.68.

4.3 | 10-(4-Fluorophenyl)-2-(hydroxymethyl)-7, 7-dimethyl-7, 8-dihydropyrano[3, 2-*b*]chromene-4, 9(6H, 10H)-dione (4b)

Solid, Yield: 90%, Mp: 161-164°C; ^{1}H-NMR (DMSO-d_6): δ 7.29-7.22 (m, 2H), 6.96-6.90 (m, 2H), 6.52 (s, 1H), 4.86 (s, 1H), 4.42-4.35 (m, 2H), 2.70-2.62 (m, 2H), 2.26-2.19 (m, 2H), 1.14 (s, 3H), 1.02 (s, 3H); ^{13}C-NMR (DMSO-d_6): δ 195.6, 170.4, 168.2, 165.6, 161.5, 150.2, 138.0, 136.6, 129.6, 129.2, 115.5, 114.4, 112.2, 112.0, 61.4, 50.6, 40.2, 38.6, 32.2, 28.5, 27.6; ESI-MS (*m*/*z*):371 $[M + H]^+$. Anal. Calcd for $C_{21}H_{19}FO_5$: C, 68.10; H, 5.17. Found: C, 68.06; H, 5.13.

4.4 | 10-(4-Chlorophenyl)-2-(hydroxymethyl)-7, 7-dimethyl-7, 8-dihydropyrano[3, 2-*b*]chromene-4, 9(6H, 10H)-dione (4c)

Solid, Yield: 91%, Mp: 203-206°C; ^{1}H-NMR (DMSO-d_6): δ 7.22-7.14 (m, 4H), 6.52 (s, 1H), 4.82 (s, 1H), 4.42-4.35 (m, 2H), 2.72-2.66 (m, 2H), 2.32-2.22 (m, 2H), 1.14 (s, 3H), 1.02 (s, 3H); ^{13}C-NMR (DMSO-d_6): δ 196.2, 170.6, 168.2, 164.2, 150.1, 138.6, 138.2, 132.8, 129.4, 129.6, 112.6, 111.2, 60.4, 50.2, 40.5, 38.2, 32.2, 28.4, 27.2; ESI-MS (*m*/*z*):387 $[M + H]^+$. Anal. Calcd for $C_{21}H_{19}ClO_5$: C, 65.20; H, 4.95. Found: C, 65.16; H, 4.89.

4.5 | 10-(4-Bromophenyl)-2-(hydroxymethyl)-7, 7-dimethyl-7, 8-dihydropyrano[3, 2-*b*]chromene-4, 9(6H, 10H)-dione (4d)

Solid, Yield: 86%, Mp: 198-201°C; ^{1}H-NMR (DMSO-d_6): δ 7.24-7.15 (m, 4H), 6.42 (s, 1H), 4.80 (s, 1H), 4.43-4.34 (m, 2H), 2.62-2.58 (m, 2H), 2.34-2.22 (m, 2H), 1.12 (s, 3H), 1.02 (s, 3H); ^{13}C-NMR (DMSO-d_6): δ 198.4, 180.9, 176.8, 154.9, 142.0, 140.9, 131.2, 129.9, 120.4, 113.5, 112.2, 111.4, 60.2, 51.2, 39.2, 34.5, 32.6, 27.2; ESI-MS (*m*/*z*): 431 $[M + H]^+$. Anal. Calcd for $C_{21}H_{19}BrO_5$: C, 58.48; H, 4.44. Found: C, 58.44; H, 4.41.

4.6 | 2-(Hydroxymethyl)-10-(4-hydroxyphenyl)-7, 7-dimethyl-7, 8-dihydropyrano[3, 2-*b*]chromene-4, 9(6H, 10H)-dione (4e)

Solid, Yield: 90%, Mp: 202-204°C; ^{1}H-NMR (DMSO-d_6): δ 7.20-7.14 (m, 4H), 6.48 (s, 1H), 4.74 (s, 1H), 4.40-4.32 (m, 2H), 2.79-2.74 (m, 2H), 2.35-2.20 (m, 2H), 1.10 (s, 3H), 1.01 (s, 3H); ^{13}C-NMR (DMSO-d_6): δ 198.6, 180.6, 177.2, 156.2, 155.2, 143.2, 136.2, 130.2, 115.2, 114.2, 112.2, 112.0, 60.5, 52.4, 38.4, 34.5, 32.8, 27.4; ESI-MS (*m*/*z*): 369 $[M + H]^+$. Anal. Calcd for $C_{21}H_{20}O_6$: C, 68.47; H, 5.47. Found: C, 68.44; H, 5.41.

4.7 | 2-(Hydroxymethyl)-7, 7-dimethyl-10-(p-tolyl)-7, 8-dihydropyrano[3, 2-*b*]chromene-4, 9(6H, 10H)-dione (4f)

Solid, Yield: 90%, Mp: 213-216°C; ^{1}H-NMR (DMSO-d_6): δ 7.24-7.12 (m, 2H), 6.79-6.73 (m, 2H), 6.46 (s, 1H), 4.80 (s, 1H), 4.40-4.34 (m, 2H), 2.76-2.68 (m, 2H), 2.34 (s, 3H), 2.22-2.16 (m, 2H), 1.12 (s, 3H), 1.02 (s, 3H); ^{13}C-NMR (DMSO-d_6): *δ* 196.0, 172.2, 168.4, 162.6, 152.2, 138.4, 137.5, 137.2, 129.2, 127.6, 112.4, 111.2, 60.4, 50.2, 40.4, 37.5, 32.2, 29.6, 27.0, 21.4; ESI-MS (*m*/*z*): 367 $[M + H]^+$. Anal. Calcd for $C_{22}H_{22}O_5$: C, 72.12; H, 6.05. Found: C, 72.06; H, 5.99.

4.8 | 2-(Hydroxymethyl)-10-(4-methoxyphenyl)-7, 7-dimethyl-7, 8-dihydropyrano[3, 2-*b*]chromene-4, 9(6H, 10H)-dione (4g)

Solid, Yield: 92%, Mp: 179-182°C, ^{1}H-NMR (DMSO-d_6): δ 7.20-7.14 (m, 2H), 7.04-6.98 (m, 2H), 6.44 (s, 1H), 4.84 (s, 1H), 4.38-4.32 (m, 2H), 3.74 (s, 3H), 2.71-2.60 (m, 2H), 2.36-2.30 (m, 2H), 1.12 (s, 3H), 1.04 (s, 3H); ^{13}C-NMR (DMSO-d_6): δ 196.4, 172.2, 168.4, 162.6, 160.0, 152.4, 136.8, 132.6, 130.0, 115.4, 112.2, 130.4, 60.2, 55.2, 51.2, 41.0, 36.4, 32.2, 29.6, 27.2; ESI-MS (*m*/*z*): 383$[M + H]^+$. Anal. Calcd for $C_{22}H_{22}O_6$: C, 69.10; H, 5.80. Found: C, 69.06; H, 5.76.

4.9 | 10-(4-(Dimethylamino)phenyl)-2-(hydroxymethyl)-7, 7-dimethyl-7, 8-dihydropyrano[3, 2-*b*]chromene-4, 9(6H, 10H)-dione (4h)

Solid, Yield: 90%, Mp: 178-180°C, ^{1}H-NMR (DMSO-d_6): δ 7.02-6.88 (m, 4H), 6.40 (s, 1H), 4.64 (s, 1H), 4.33-4.28 (m, 2H), 3.12 (s, 6H), 2.73-2.60 (m, 2H), 2.32-2.23 (m, 2H), 1.09 (s, 3H), 1.02 (s, 3H); ^{13}C-NMR (DMSO-d_6): δ198.2, 180.9, 177.2, 156.1, 150.2, 142.8, 132.0, 128.6, 114.2, 112.4, 112.8, 111.5, 60.4, 52.4, 42.2, 39.2, 34.2, 33.4, 27.2; ESI-MS (*m*/*z*): 396 $[M + H]^+$. Anal. Calcd for $C_{23}H_{25}NO_6$: C, 69.86; H, 6.37; N, 3.54. Found: C, 69.76; H, 6.32; N, 3.50.

4.10 | 2-(Hydroxymethyl)-7, 7-dimethyl-10-(4-nitrophenyl)-7, 8-dihydropyrano[3, 2-*b*]chromene-4, 9(6H, 10H)-dione (4i)

Solid, Yield: 84%, Mp: 194-196°C; ^{1}H-NMR (DMSO-d_6): δ 8.12-7.78 (m, 4H), 6.28 (s, 1H), 4.59 (s, 1H), 4.30-4.24 (m, 2H), 2.74-2.66 (m, 2H), 2.32-2.21 (m, 2H), 1.11 (s, 3H), 1.04 (s, 3H); ^{13}C-NMR (DMSO-d_6): δ198.6, 181.4, 176.9, 155.4, 149.2, 145.2, 142.8, 127.4, 124.6, 114.5, 112.8, 112.0, 60.2, 52.2, 39.2, 33.8, 32.8, 27.4; ESI-MS (*m*/*z*): 398 $[M + H]^+$. Anal. Calcd for $C_{21}H_{19}NO_7$: C, 63.47; H, 4.82; N, 3.52. Found: C, 63.40; H, 4.79; N, 3.49.

4.11 | 2-(Hydroxymethyl)-7, 7-dimethyl-10-(2-nitrophenyl)-7, 8-dihydropyrano[3, 2-*b*]chromene-4, 9(6H, 10H)-dione (4j)

Solid, Yield: 89%, Mp: 190-192°C; ^{1}H-NMR (DMSO-d_6):δ 7.05-6.95 (m, 4H), 6.34 (s, 1H), 4.82 (s, 1H), 4.29-4.21 (m, 2H), 2.70-2.61 (m, 2H), 2.29-2.19 (m, 2H), 1.12 (s, 3H), 1.04 (s, 3H); ^{13}C-NMR (DMSO-d_6): δ 194.6, 170.0, 168.6, 164.2, 149.8, 138.0, 137.2, 132.5, 130.6, 129.4, 128.6, 127.4, 111.6, 110.0, 58.8, 49.6, 45.0, 34.2, 31.6, 28.6, 27.2; ESI-MS (*m*/*z*): 398 $[M + H]^+$. Anal. Calcd for $C_{21}H_{19}NO_7$: C, 63.47; H, 4.82; N, 3.52. Found: C, 63.40; H, 4.79; N, 3.49.

4.12 | 2-(hydroxymethyl)-7, 7-dimethyl-10-(3-nitrophenyl)-7, 8-dihydropyrano[3, 2-*b*]chromene-4, 9(6H, 10H)-dione (4k)

Solid, Yield: 94%, Mp: 212-214°C; ^{1}H-NMR (DMSO-d_6): δ 8.17-8.02 (m, 2H), 7.62-7.50 (m, 2H), 6.82 (s, 1H), 4.86 (s, 1H), 4.45-4.30 (m, 2H), 2.77-2.66 (m, 2H), 2.33-2.21 (m, 2H), 1.16 (s, 3H), 1.04 (s, 3H); ^{13}C-NMR (DMSO-d_6): δ 196.6, 171.2, 168.5, 164.2, 150.4, 147.6, 143.0, 138.4, 134.2, 130.6, 124.5, 122.4, 112.6, 112.2, 60.4, 50.6, 40.4, 38.2, 32.6, 28.6, 27.4; ESI-MS (*m*/*z*): 398 $[M + H]^+$. Anal. Calcd for $C_{21}H_{19}NO_7$: C, 63.47; H, 4.82; N, 3.52. Found: C, 63.40; H, 4.79; N, 3.49.

4.13 | 2-(hydroxymethyl)-7, 7-dimethyl-10-(pyridin-2-yl)-7, 8-dihydropyrano[3, 2-*b*] chromene-4, 9(6H, 10H)-dione (4l)

Solid, Yield: 90%, Mp: 196-198°C; ^{1}H-NMR (DMSO-d_6): δ 8.20-7.70 (m, 4H), 6.34 (s, 1H), 4.40-4.32 (m, 2H), 4.26 (s, 1H), 2.73-2.59 (m, 2H), 2.35-2.20 (m, 2H), 1.14 (s, 3H), 1.07 (s, 3H); ^{13}C-NMR (DMSO-d_6): δ 198.8, 181.6, 177.9, 159.2, 155.2, 149.0, 142.8, 137.2, 124.6, 121.5, 114.4, 113.2, 112.0, 60.4, 52.6, 39.4, 34.2, 32.6, 27.2; ESI-MS (*m*/*z*): 354 $[M + H]^+$. Anal. Calcd for $C_{20}H_{19}NO_5$: C, 67.98; H, 5.42; N, 3.96; Found: C, 67.88; H, 5.39; N, 3.89.

4.14 | 2-(hydroxymethyl)-7, 7-dimethyl-10-(2-phenoxyphenyl)-7, 8-dihydropyrano[3, 2-*b*]chromene-4, 9(6H, 10H)-dione (4m)

Solid, Yield: 89%, Mp: 191-194°C; ^{1}H-NMR (DMSO-d_6): δ 7.48-7.28 (m, 5H), 7.05-6.87 (m, 4H), 6.50 (s, 1H), 4.83 (s, 1H), 4.44-4.30 (m, 2H), 2.64-2.59 (m, 2H), 2.40-2.35 (m, 2H), 1.16 (s, 3H), 1.08 (s, 3H); ^{13}C-NMR (DMSO-d_6): δ 196.2, 171.2, 168.6, 164.4, 152.2, 150.6, 148.2 136.2, 135.4, 128.6, 122.4, 121.6, 113.4, 106.6, 60.6, 50.2, 40.6, 37.6, 32.6, 29.4, 27.0; ESI-MS (*m*/*z*): 445 $[M + H]^+$. Anal. Calcd for $C_{27}H_{24}O_6$: C, 72.96; H, 5.44. Found: C, 72.89; H, 5.41.

4.15 | 2-(hydroxymethyl)-7, 7-dimethyl-10-(3, 4, 5-trimethoxyphenyl)-7, 8-dihydropyrano[3, 2-*b*] chromene-4, 9(6H, 10H)-dione (4n)

Solid, Yield: 92%, Mp: 173-176°C; ^{1}H-NMR (DMSO-d_6): δ 6.84-6.52 (m, 3H), 6.38 (s, 1H), 4.82 (s, 1H), 4.40-4.34 (m, 2H), 3.82 (s, 6H), 3.80 (s, 3H), 2.64-2.60 (m, 2H), 2.30-2.22 (m, 2H), 1.14 (s, 3H), 1.06 (s, 3H); ^{13}C-NMR (DMSO-d_6): δ 196.2, 170.6, 168.4, 164.2, 152.8, 150.6, 138.0, 136.3, 112.6, 106.5, 60.4, 60.1, 55.4, 50.6, 40.4, 38.6, 32.5, 29.4, 27.2; ESI-MS (*m*/*z*): 443 $[M + H]^+$. Anal. Calcd for $C_{24}H_{26}O_8$: C, 65.15; H, 5.92. Found: C, 65.08; H, 5.86.

4.16 | 10-(3, 5-dimethoxyphenyl)-2-(hydroxymethyl)-7, 7-dimethyl-7, 8-dihydropyrano[3, 2-*b*]chromene-4, 9(6H, 10H)-dione (4o)

Solid, Yield: 91%, Mp: 157-160°C; ^{1}H-NMR (DMSO-d_6): δ 7.16-7.12 (m, 2H), 6.80-6.74 (m, 1H), 6.30 (s, 1H), 4.72 (s, 1H), 4.26-4.10 (m, 2H), 3.72 (s, 6H), 2.64-2.48 (m, 2H), 2.25-2.10 (m, 2H), 1.10 (s, 3H), 1.04 (s, 3H); ^{13}C-NMR (DMSO-d_6): δ 195.2, 169.4, 168.2, 163.4, 154.2, 150.4, 137.0, 136.5, 132.4, 129.5, 129.6, 124.2, 111.6, 111.0, 59.0, 54.2, 53.4, 49.4, 44.5, 37.0, 31.6, 28.2, 26.6; ESI-MS (*m*/*z*): 413 $[M + H]^+$. Anal. Calcd for $C_{23}H_{24}O_7$: C, 66.98; H, 5.87; Found: C, 66.92; H, 5.81.

4.17 | Biology

Peroxiredoxins (Prxs) are a class of abundant thiol peroxidases that degrade hydroperoxides to water. Peroxiredoxins are an important antioxidant protein that is involved in the protection of proteins from oxidative damage caused by reactive oxygen species (ROS). The ROS were generated as the result of the reduction of molecular oxygen by DTT to superoxide and H_2O_2, which were further reduced to hydroxyl radicals in the presence of trace amounts of contaminating metal (iron or copper) ions. Prxs contain an active site of cysteine that is sensitive to oxidation by H_2O_2. Mammalian cells express six Prx isoforms that are localized to various cellular compartments. The Prxs have a remarkably high catalytic efficiency that makes them a dominant player in cell-wide peroxide reduction. The accumulation of oxidized Prxs may indicate disruption of cellular redox homeostasis. The biochemical properties of the Prxs make them suitable as endogenous biomarkers of oxidative stress in mammals. Monitoring the oxidative state of Prxs provides insight into disturbances of cellular redox homeostasis and complements the use of exogenous probes of oxidative stress. In the present study, title compounds **4(a-o)** have been evaluated for their antioxidant activity against peroxiredoxins using molecular docking approach.

4.18 | Antioxidant activity

All the entitled compounds **4(a-o)** were screened for their antioxidant property by DPPH, H_2O_2, and NO methods at three different concentrations 50, 75, and 100 μg/mL. Ascorbic acid was used as reference standard drug to compare antioxidant activities.

4.19 | Experimental procedure for antioxidant activity of compounds 4(a-o)

4.19.1 | DPPH radical scavenging activity

This assay is based on the activity of the scavenging ability of inhibitor substances toward the stable radical. The hydrogen atom or electron contribution capability of the compounds was measured from the decolorizing of the purple colored methanol solution of 1, 1-diphenyl-2-picryl hydrazyl radical (DPPH). The spectrophotometric

method uses the stable radical DPPH as a reagent. To methanol solution of DPPH (4 mL of 0.004% w/v), 1 mL of different concentrations of the experiment compounds (50, 75, and 100 μg/mL) in methanol were added. The absorbance was read against blank at 517 nm after a 30-minute incubation period at room temperature. Ascorbic acid was used as the standard. The percent of inhibition (I %) of free radical production from DPPH was calculated by the following equation:

$$\%\text{of scavenging} = \left[\left(A_{\text{control}} - A_{\text{sample}}\right)/A_{\text{control}}\right] \times 100,$$

where A_{control} is the absorbance of the control reaction (containing all reagents except the test compounds) and A_{sample} is the absorbance of the test compound (containing methanolic DPPH and test compound). Tests were carried out in triplicate.

4.19.2 | Hydrogen peroxide (H_2O_2) scavenging activity

All the cellular processes are influenced by a biologically important, nonradical ROS, which are key components in such as hydrogen peroxide (H_2O_2). A solution of H_2O_2 (40 mm) prepared in phosphate buffer (pH 7.4) was employed to test the compound scavenging ability by H_2O_2 method. It was optimized by taking 50, 75, and 100 μg/mL concentrations of the test compounds in 3.4 mL phosphate buffer were added to H_2O_2 solution (0.6 mL, 40 mm). Ascorbic acid was used as the standard. The absorbance value of the reaction mixture was recorded at 230 nm. The percent scavenging of H_2O_2 was calculated by the following equation.

$$\%\text{of scavenging} = \left[\left(A_{\text{control}} - A_{\text{sample}}\right)/A_{\text{control}}\right] \times 100,$$

where A_{sample} is the absorbance of the test compound (containing all reagents and test compound). A_{control} is the absorbance of the control reaction (containing all reagents except the test compounds). Tests were carried out in triplicate.

4.19.3 | Nitricoxide (NO) scavenging activity

Sodium nitroprusside (5μM) in phosphate buffer pH 7.2 was incubated with different concentrations (50, 75, and 100 μg/mL) of test compounds dissolved in a suitable solvent (methanol), and tubes were incubated at 25°C for 2 hours. The compound sodium nitroprusside is known to decompose in aqueous solution at physiological pH (7.2) producing NO. Under aerobic conditions, NO reacts with oxygen to produce stable products (nitrate and nitrite). The quantities of which can be determined using Griess reagent. Scavengers of nitric oxide compete with oxygen leading to reduced production of nitrite ions. Control experiment was conducted with equal amount of solvent in an identical manner. At intervals, 0.5 mL of incubation solution was taken and diluted with 0.5 mL of Griess reagent (1% sulfanilamide, 0.1% *N*-naphthyl ethylene diamine di hydrochloride and 2% *o*-phosphoric acid dissolved in distilled water). The absorbance of the chromophore formed during diazotization of nitrite with sulfanilamide and subsequent *N*-naphthyl ethylene diamine dihydrochloride was read at 546 nm. The experiment was run in triplicate. Nitric oxide scavenging activity was calculated by the following equation.

$$\%\text{of scavenging} = \left[\left(A_{\text{control}} - A_{\text{sample}}\right)/A_{\text{control}}\right] \times 100,$$

where A_{control} is the absorbance of the control reaction (containing all reagents except the test compounds) and A_{sample} is the absorbance of the test compound (containing all reagents and test compound). Tests were carried out in triplicate.

4.20 | In silico studies

Molecular docking studies[35] were carried against 3MNG protein along with the reference drugs DTT and BHT using Pyrx 2010.12 docking module. To get the stable conformer of the target protein, the 3D structure of protein was protonated and subjected to energy minimization using the MMFF94x force field. Flexible docking module was employed, and the binding site residues of inhibitor were softened and highlighted using "Site Finder" module of Pymol software. Pyrx 2010.12 with default parameters was used for docking analysis, and a maximum of 10 conformations of each compound were allowed for consideration. After that, the docking profiles of protein-ligand complexes were done using Pymol viewer tool (www.pymol.org). The 3D structure of peroxiredoxins (**PDB: 3MNG**) and the reference drugs such as DTT (PubChem ID 446094) and BHT (PubChem ID 31404) were downloaded from the RCSB protein DataBank and PubChem. The atomic coordinates of the protein was estranged, and geometry optimization was done using Argus Lab 4.0.1.[36] The chemical structure of compounds were prepared using ChemBioDraw and converted all the ligands into Pdbqt file format and atomic coordinates were generated using Pyrx 2010.12.[32] The active sites are the coordinates of the ligand in the original target protein grids, and these active binding sites of target protein were analysed using the Drug Discovery Studio version 3.0, and 3D Ligand Site virtual tools were used as

analysing tools for the prediction of active binding sites of target protein.[37]

4.21 | In silico ADME prediction

ADMET stands for Absorption, Distribution, Metabolism, Excretion and Toxicity. The prediction of the ADME properties plays an important role in the drug design process because these properties account for the failure of about 60% of all drugs in the clinical phases. Different ADME properties such as molecular weight and volume, H-bond types, rotatable bonds, topological polar surface area (TPSA), and violation of Lipinski Rule of Five were determined to the compounds using Molinspiration online property toolkit. In addition, the percentage of HIA, PPB, $CaCO_2$ permeability, and blood-brain barrier (BBB) were also determined by using ADMET online server (http://preadmet.bmdrc.org/).[37]

ACKNOWLEDGMENTS

The authors G. Sravya and N. Bakthavatchala Reddy are thankful to Ural Federal University, Yekaterinburg, Russia, for postdoctoral fellowship.

ORCID

G. Sravya https://orcid.org/0000-0002-6249-3870
C. Suresh Reddy https://orcid.org/0000-0002-9804-9683
N. Bakthavatchala Reddy https://orcid.org/0000-0003-2039-9277

REFERENCES AND NOTES

[1] (a) R. A. Sheldon, *Green Chem.* **2007**, *9*, 1273. (b) H. Ahankar, A. Ramazani, K. Stlepokura, T. Lis, S. W. Joo, *Green Chem.* **2016**, *18*, 3582. (c) Q. Chen, E. J. Beckman, *Green Chem.* **2008**, *10*, 934. (d) D. Q. Shi, S. Zhang, Q. Y. Zhuang, X. S. Wang, S. J. Tuand, H. W. Hu, *Chin J Chem* **2003**, *21*, 680; (e) S. Iravani, *Green Chem.* **2011**, *13*, 2638. (f) T. H. Istvan, T. A. Paul, *Chem. Rev.* **2007**, *107*, 2167. (g) R. B. N. Baig, R. S. Varma, *Chem. Soc. Rev.* **2012**, *41*, 1559.

[2] H. Bienayme, C. Hulme, G. Oddon, P. Schmitt, *Chem. A Eur. J.* **2000**, *6*, 3321.

[3] A. Nefzi, J. M. Ostresh, R. A. Houghten, *Chem. Rev.* **1997**, *97*, 449.

[4] L. A. Thompson, *Curr. Opin. Chem. Biol.* **2000**, *4*, 324.

[5] A. Domling, *Curr. Opin. Chem. Biol.* **2002**, *6*, 306.

[6] M. D. Aytemir, U. Calis, M. Ozalp, *Arch. Pharm.* **2004**, *337*, 281.

[7] H. S. Rho, S. M. Ahn, D. S. Yoo, M. K. Kim, D. H. Cho, J. Y. Cho, *Bioorg. Med. Chem. Lett.* **2010**, *20*, 6569.

[8] H. S. Rho, H. S. Baek, S. M. Ahn, D. H. Kim, I. S. Chang, *Bull Korean Chem Soc* **2008**, *29*, 1569.

[9] J. M. Noh, S. Y. Kwak, D. H. Kim, Y. S. Lee, *Biopolymers* **2007**, *88*, 300.

[10] S. M. Ahn, H. S. Rho, H. S. Baek, Y. H. Joo, Y. D. Hong, S. S. Shin, Y. H. Park, S. N. Park, *Bioorg. Med. Chem. Lett.* **2011**, *21*, 7466.

[11] D. H. Kim, J. S. Hwang, H. S. Baek, K. J. Kim, B. G. Lee, I. Chang, H. H. Kang, O. S. Lee, *Chem. Pharm. Bull.* **2003**, *51*, 113.

[12] L. Novotny, P. Rauko, M. Abdel-Hamid, A. Vachalkova, *Neoplasma* **1999**, *46*, 89.

[13] B. V. S. Reddy, M. R. Reddy, C. Madan, K. P. Kumar, M. S. Rao, *Bioorg. Med. Chem. Lett.* **2010**, *20*, 7507.

[14] J. C. Cho, H. S. Rho, H. S. Baek, S. M. Ahn, B. Y. Woo, Y. D. Hong, J. W. Cheon, J. M. Heo, S. S. Shin, Y. H. Park, K. D. Suh, *Bioorg. Med. Chem. Lett.* **2012**, *22*, 2004.

[15] M. D. Aytemir, B. Oezcelik, *Eur. J. Med. Chem.* **2010**, *45*, 4089.

[16] B. V. Subba Reddy, M. Ramana Reddy, G. Narasimhulu, J. S. Yadav, *Tetrahedron Lett.* **2010**, *51*, 5677.

[17] W. L. Li, J. Y. Liang, T. B. Wang, Y. Q. Yang, *Collect Czech Chem Commun* **2011**, *76*, 1791.

[18] W. L. Li, L. Q. Wu, F. L. Yan, *J. Braz. Chem. Soc.* **2011**, *22*, 2202.

[19] J. Yang, H. Q. Li, M. H. Li, J. J. Peng, Y. L. Gu, *Adv Synth Catal* **2012**, *354*, 688.

[20] C. Syama Sundar, K. U. Maheswara Rao, N. Bakthavatchala Reddy, M. V. N. Reddy, S. Siva Prasad, C. Suresh Reddy, *Cat. Sci. Technol.* **2012**, *2*, 1382.

[21] N. Bakthavatchala Reddy, K. U. Maheswara Rao, C. SyamaSundar, S. K. Nayak, C. SureshReddy, *Heterocycl Commun* **2012**, *18*, 53.

[22] G. Sravya, G. V. Zyryanov, A. Balakrishna, K. Madhu Kumar Reddy, C. SureshReddy, G. MallikarjunaReddy, A. Camilo Jr., J. R. Garcia, N. BakthavatchalaReddy, *Phosphorus Sulfur Silicon Relat Elem* **2018**, *193*, 562.

[23] R. Y. Guo, Z. M. An, L. P. Mo, R. Z. Wang, H. X. Liu, S. X. Wang, Z. H. Zhang, *ACS Comb. Sci.* **2013**, *15*, 557.

[24] S. Zhang, Y. C. Luo, X. Q. Hu, Z. Y. Wang, Y. M. Liang, P. F. Xu, *J. Org. Chem.* **2015**, *80*, 7288.

[25] X. T. Li, Y. H. Liu, X. Liu, Z. H. Zhang, *RSC Adv.* **2015**, *5*, 25625.

[26] A. Venkatesham, R. Srinivasa Rao, K. Nagaiah, J. S. Yadav, G. Roopa Jones, S. J. Basha, B. Sridhar, A. Addlagatta, *Med. Chem. Commun.* **2012**, *3*, 652.

[27] M. Burits, F. Bucar, *Phytother. Res.* **2000**, *14*, 323.

[28] M. Cuendet, K. Hostettmann, O. Potterat, W. Dyatmiko, *Helv. Chim. Acta* **1997**, *80*, 1144.

[29] R. J. Ruch, S. J. Cheng, J. E. Klaunig, *Carcinogenesis* **1989**, *10*, 1003.

[30] L. C. Green, D. A. Wagner, J. Glogowski, P. L. Skipper, J. S. Wishnok, S. R. Tannenbaum, *Anal. Biochem.* **1982**, *126*, 131.

[31] L. Marcocci, J. J. Maguire, M. T. Droy-Lefaix, L. Packer, *Biochem Biophys ResCommun* **1994**, *201*, 748.

[32] E. F. Pettersen, T. D. Goddard, C. C. Huang, G. S. Couch, D. M. Greenblatt, E. C. Meng, T. E. Ferrin, *J. Comput. Chem.* **2004**, *25*, 1605.

[33] Y. H. Zhao, M. H. Abraham, J. Lee, A. Hersey, N. C. Luscombe, G. Beek, B. Sherborne, I. Cooper, *Pharm. Res.* **2002**, *19*, 1446.

[34] G. Walkinshaw, C. M. Waters, *Neuro Sci* **1994**, *63*, 975.

[35] G. M. Morris, R. Huey, W. Lindstrom, M. F. Sanner, R. K. Belew, D. S. Goodsell, A. J. Olson, *J. Comput. Chem.* **2009**, *30*, 2785.

[36] E. Ter Haar, J. T. Coll, D. A. Austen, H. M. Hsiao, L. Swenson, J. Jain, *Nat. Struct. Biol.* **2001**, *8*, 593.

[37] G. Vistoli, A. Pedretti, B. Testa, *Drug Discov. Today* **2008**, *13*, 285.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

How to cite this article: Sravya G, Suresh G, Zyryanov GV, et al. A meglumine catalyst–based synthesis, molecular docking, and antioxidant studies of dihydropyrano[3, 2-*b*]chromenedione derivatives. *J Heterocyclic Chem*. 2020;57:355–369. https://doi.org/10.1002/jhet.3786