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ARTICLE

Lewis acid–catalyzed green synthesis and biological studies of pyrrolo[3,4-*c*]pyrazoles in aqueous medium

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Abstract

An environmentally benign approach in aqueous medium by means of Lewis acid catalyst affords a wide spectrum of pyrazoline derivatives in satisfactory yields. [3+2] cycloaddition reactions of substituted azomethine-*N*-imines to maleimide in aqueous medium at relatively high concentrations of Lewis acid catalyst have emerged as an environment friendly alternative to conventional solvents. Promising catalytic activity has been revealed by Lewis acid like Cu $(NO_3)_2$ in aqueous medium. The obvious features of this synthetic protocol were short reaction time, high efficiency, less hazardous synthesis by benign solvent, catalysis, modest workup, and a clean reaction methodology.

1 | INTRODUCTION

Aqueous organic reactions are inexpensive, nonhazardous, and nontoxic[1–10] in the green chemistry approach.[11] Organic reactions in water have high environmental acceptability and availability.[12,13] However, the reactivity and selectivity cannot be achieved in case of traditional organic solvents.[14]

The endorsement of catalytic chemical reactions contributes to the progress of unconventional mechanisms by allowing the substitution of organic solvents with water.[15–19] In recent years, eco-green features have recognized [3+2] cycloaddition reactions in aqueous medium, as an innovative green alternative to conventional solvents in scientific research.[17–23] Micellar catalysts in basic medium have been used for in situ generation of 1,3-dipoles,[24] which possess a variety of pharmacological activities such as antidepressant,[25–28] anticonvulsant,[27,28] antitumor,[29] protein kinase *C* inhibitor,[30] anticancer,[31,32] anti-inflammatory,[33] antiepileptic, antimicrobial,[34] inhibitors of alkaline phosphatase,[35] antiamoebic[36] and antiandrogenic,[37] antibiotic,[38] and antioxidant.[39] Oxidized low-density lipoproteins (LDLs) have a major role in the development of atherosclerosis.[40] Treatment of hypoxic-ischemic encephalopathy[41] in neonates and paraquat poisoning[42] using pyrazolin-5-one derivatives have been reported. Fipronil and zaleplon are widely used as pesticides and sedatives, respectively.[43] Many pyrazole derivatives have exhibited remarkable biological activities like analgesic, antipyretic,[44,45] antifilarial,[46] immunosuppressive,[47] antineoplastic, hypoglycemic, and antidiabetic activities.[48–50] Broggini et al[51] reported the use of promoter Ag_2CO_3. Afterwards, Bonini et al[52] used Ag_2CO_3 with Sc $(OTf)_3$ for the 1,3-dipolar cycloaddition reactions of in situ generated nitrilimines with functionalized acetylenes. In current years, hydrotalcites (HTs) served as a better approach in the reactions with Lewis base, Brønsted base, or acid-base sites.[53] HTs have been reported in base-catalyzed cycloaddition reactions for the synthesis of isoxazoles and tetrazoles.[54] Synthesis of 1,4,2-dioxazoles in aqueous media by employing β-cyclodextrin nanoreactor and 2-amino-4*H*-chromene derivatives using MOF-5 as catalyst under solvent-free conditions has been developed as a green alternative method for producing most important class of heterocyclic compounds.[55,56] A considerable number of methods towards the formation of heterocyclics using green catalysts and solvent-free conditions under microwave and ultrasonic irradiations have also been reported in recent years.[57,58] One-pot synthesis of propanamide derivatives in aqueous solvent under catalyst-free environment using ultrasonic irradiations has been reported as a successful method in achieving the green chemistry objectives.[59] Eco-friendly synthesis of efficient and recyclable nanocatalysts and their usage in heterocyclic synthesis have been investigated successfully.[60,61] 1,3-Dipolar cycloaddition reactions of nitrilimine with *N*-benzylmaleimide in conventional solvents using base has been reported by our group previously.[62] Vinyltriphenylphosphonium salts on the Michael

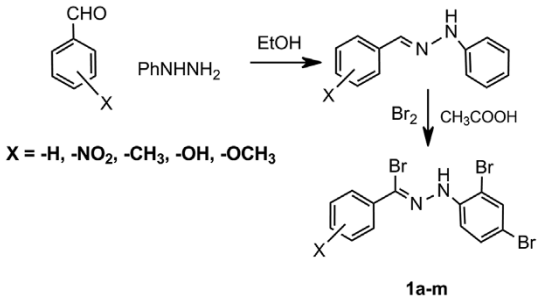
addition lead to the formation of stabilized phosphorus ylides that produce various heterocyclic compounds to take part in intramolecular Wittig reaction.[63] A green procedure for the synthesis of biologically important quinoxaline derivatives in the presence of two novel heterogeneous Lewis acid catalysts at ambient temperature has been reported in literature.[64] Lewis acid-promoted chemical reactions appreciably contribute to the development of new reaction strategies by allowing the replacement of hazardous organic solvents with environmentally safe and inexpensive solvents such as water to reduce the generation of toxic waste.[65,66] Benzopyrano[3,2-*c*]chromene-6,8-dione derivatives have been synthesized through an eco-friendly approach using Cu (II)-Schiff base/SBA-15 in solvent-free conditions, and 2,4,5-trisubstituted imidazoles have been synthesized using $CoFe_2O_4$ magnetic nanoparticles as benign catalyst.[67,68]

2 | RESULTS AND DISCUSSION

2.1 | Chemistry

The present scheme is a convenient and facile approach for the in situ generation of nitrilimines by treating the respective hydrazonyl bromides **1a**-**m** (Scheme 1) and *N*-cyclohexyl maleimide **2** (Scheme 2) with an excess of triethylamine in different solvents as reported in literature.[69] Table 1 shows that no reaction has been observed in the absence of Lewis acid catalyst in aqueous medium and that poor yield has been obtained on heating the reactants in solvent-free and catalyst-free conditions. However, lower yields have been obtained with cosolvents under catalyst-free conditions consuming more time, while on adding varied quantities of Cu (II) salts as catalyst, the reactions occurred smoothly on mild heating consuming less time and providing higher yields. It has been found that yield obtained with Cu $(NO_3)_2$ in water was quite high and promoted the Lewis acid–catalyzed cycloaddition reactions in aqueous medium (Scheme 3, Table 2). The proposed structure of compounds **3a**-**m** has been characterized through spectroscopic techniques IR, ^{1}H-NMR, $^{[13]}$C-NMR, ^{1}H,^{1}H correlation spectroscopy (COSY) (Figure 1), and electrospray ionization–mass spectrometry (ESI-MS).

All the stereoisomers exhibited an analogous trend in their IR spectra. However, as a representative case, the IR spectrum of compound **3e** shows two absorption bands owing to the symmetric and asymmetric carbonyl stretching vibrations of succinimide moiety.[70,71] In IR spectrum, two carbonyl bands of succinimide moiety coupled with each other and hence redistributed their energies, showing the appearance of one strong band in the region of 1703 cm^{-1} $\nu_{sym.}$(C═O) and another shoulder band in the region of 1774 cm^{-1} $\nu_{asymm.}$(C═O). Absorption bands at 1603 cm^{-1} (C═N stretching vibrations of the pyrazole ring) and 1575 cm^{-1} (aromatic C═C double-bond skeletal stretching vibrations) confirm the cycloaddition between nitrilimine and *N*-cyclohexyl maleimide. ^{1}H-NMR spectra compound **3e** shows aromatic multiplets in the range of δ 7.19-7.81 (7H), and doublets at δ 5.78 (C_{6a}-H, *J* = 10.08 Hz) and δ 4.89 (C_{3a}-H, *J* = 10.04 Hz), respectively, on mutual coupling of protons C_{3a}-H and C_{6a}-H. Downfield shift appeared in C_{6a}-H owing to electronegative nitrogen atom,



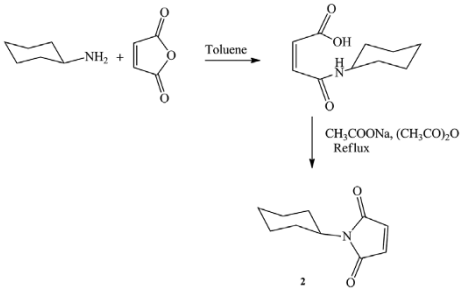
SCHEME 1 Schematic diagram describing the synthesis of hydrazonyl bromides **1a**-**m**

whereas proton of the cyclohexyl ring directly attached to nitrogen atom shows multiplet in the range of δ 3.83-3.89 owing to coupling with the neighboring protons, while a multiplet in the range of δ 2.02-1.09 (10H) and a singlet at δ 2.59 (3H) has been assigned to aliphatic protons of cyclohexyl moiety and methyl protons, respectively. Compound **3e** displays characteristic signals at δ 166.72 and 166.70 (C═O of succinimide moiety), δ 141.40 (C_3 of C═N), δ 137.06 (C-1′ of the dibromophenyl ring), δ 132.57 (C-3′), δ 126.45 (C-2″), δ 124.36-110.93 (aromatic carbons), δ 56.55 (carbon atom of *N*-cyclohexyl moiety directly attached to the nitrogen atom of succinimide moiety), δ 49.66 (C_5-pyrazoline), δ 47.26 (C_4-pyrazoline), δ 18.10 (CH_3), and δ 23.48-19.57 (carbon atoms of cyclohexyl moiety).

2.2 | Biology

2.2.1 | In vitro inhibition of advanced glycation end-product formation activity

Synthesized compounds **3a**-**m** were tested for their in vitro inhibition of advanced glycation end-product formation activity.[72] It was suggested that compounds **3b**, **3c**, and **3d** having strong electron-withdrawing nitro groups (−M and −I effects) on the *C*-phenyl ring were more potent (Table 3). Among these compounds, compound **3c** having *m*-NO_2 substitution on *C*-phenyl moiety was more potent owing to strong electron-withdrawing power. **3m** and **3k** with *p*-OCH_3 and *o*-OCH_3 group on *C*-phenyl moiety were least active owing to weaker electron-withdrawing power of the methoxy group at *para*



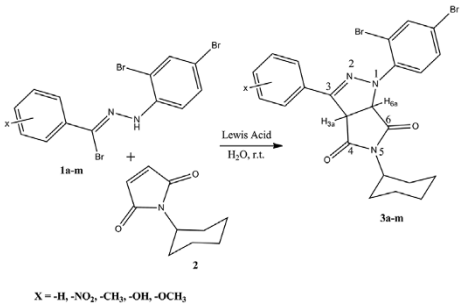
SCHEME 2 Schematic diagram describing the synthesis of *N*-cyclohexyl maleimide **2**

TABLE 1 Optimization of the reaction condition[a] for 1, 3-dipolar cycloaddition reaction of **1a** with *N*-cyclohexyl maleimide **2**

Entry	Catalyst	Solvent	Yield,[b] %	Time, h
1	$(C_2H_5)_3N$	THF	58	5
2		CH_2Cl_2	48	6
3		1,4-Dioxane	53	7
4		H_2O	55	6
5	Cu $(NO_3)_2$	THF	72	4
6		CH_2Cl_2	69	6
7		1,4-Dioxane	63	6
8		H_2O	84	2
9	$CuCl_2{\cdot}2H_2O$	THF	72	6
10		CH_2Cl_2	63	6
11		1,4-Dioxane	58	6
12		H_2O	80	3
13	Cu $(OAc)_2$	THF	65	7
14		CH_2Cl_2	53	8
15		1,4-Dioxane	45	8
16		H_2O	72	5
17	$CuCO_3$	THF	69	6
18		CH_2Cl_2	64	7
19		1,4-Dioxane	58	7
20		H_2O	70	4
21	No catalyst	H_2O	NR[c]	-
22	-	-	7[d]	9
23	-	H_2O/*t*-BuOH[e]	25	8
24	-	EtOH/AcOH[e]	32	9
25	-	CH_2Cl_2/AcOH[e]	18	10
26	-	CH_3CN/AcOH[e]	15	9

Abbreviation: THF, tetrahydrofuran.
[a]Reaction condition: **1a** (5 mmol), **2** (30 mmol), solvent (100 mL).
[b]Isolated yield after recrystallization.
[c]No reaction was observed.
[d]Reflux/solvent-free.
[e]Cosolvent (20 mL)/reflux, Et_3N (3.3 mmol), other Lewis acid catalyst (0.05 mmol).

and *ortho* positions (owing to +M effect along with −I effect). The methoxy group at the *meta* position on the *C*-phenyl ring **3l** that exhibited that strong electron-withdrawing power (−I effect) was also an active antiglycating agent, and the potency was comparable with that of aminoguanidine. Compounds **3h**, **3i**, and **3j** with strong electron-donating hydroxyl group (+M and −I effects) at the *ortho* and *para* positions on the *C*-phenyl ring were less active (owing to +M effect along with −I effect). Compounds **3e**, **3f**, and **3g** having moderate electron-donating methyl group on the *C*-phenyl ring and unsubstituted compound **3a** were reasonable antiglycating agents, while compounds **3m** and **3k** with high electron-donating power, viz, *p*-OCH_3 and *o*-OCH_3, were found to be the least potent among all synthesized compounds **3a**-**m**. The graphical representation of the data and IC_{50} values in μ*M* is also shown in Figure 2.



SCHEME 3 Schematic diagram describing the Lewis acid–catalyzed synthesis of variously substituted compounds **3a**-**m** in aqueous media

2.2.2 | Antioxidant activity

The radical scavenging activity (RSA) (%) at various concentrations (0.25, 0.54, 0.88, 1.37, 2.50, 5.00, and 7.50 μg/mL) and IC_{50} of synthesized compounds **3a**-**m** are depicted in Table 4.[73] All tested compounds **3a**-**m** have shown remarkable in vitro antioxidant activity as than did standard antioxidant (butylated hydroxytoluene [BHT]) (Figures 3 and 4). It was very clear from our present findings that the highest scavenging activity was observed in compound **3c** (electron-withdrawing group [EWG] at the *meta* position) and the least scavenging activity was observed in compound **3g** (electron-donating group [EDG] at the *para* position), whereas compounds **3b**, **3c**, and **3d** with nitro substitution were more active than their unsubstituted counterparts. The moderate activity has been shown by compounds **3h**, **3i**, and **3j** having hydroxy group in the aromatic ring. It was interesting to note that the *C*-phenyl ring of pyrazoline having EWG showed maximum antioxidant activity.

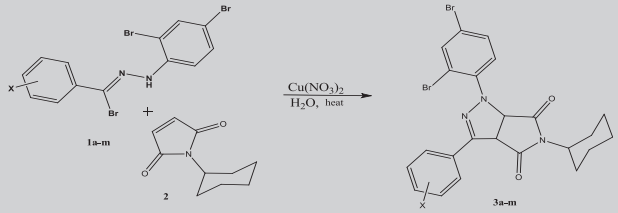
3 | EXPERIMENTAL

Melting points reported are uncorrected. IR spectra were obtained using PerkinElmer RXIFT infrared spectrophotometer (manufactured at Buckinghamshire, England). ^{1}H-NMR, ^{13}C-NMR spectra, and ^{1}H,^{1}H-COSY spectra were obtained at 400 MHz on BRUKER spectrometer (manufactured at Fallanden, Switzerland). Waters Micromass Q-T of Micro (ESI) spectrometer (manufactured at Vernon Hills, IL, USA) was used to obtain electrospray ionization mass spectra. Elementar Vario MICRO cube CHN analyzer (Frankfurt, Germany) was used for elemental analysis. Glass plates coated with silica gel-G and silica gel (100-200 mesh, Loba Chemie Pvt Ltd Mumbai, Maharashtra, India) suspended in methanol-chloroform (1:2) were used for thin-layer chromatography (TLC) and column chromatography.

3.1 | General procedure for synthesis of substituted benzaldehyde-2′,4′-dibromophenyl hydrazonyl bromide 1a-m

The reaction mixture of phenyl hydrazone (0.1 mol) in cold glacial acetic acid (100 mL) and acetous bromine (0.3 mol/30 mL of glacial acetic acid) on continuous stirring for 3 to 4 hours gave hydrazonyl bromide derivatives **1a**-**m** in good yield.

TABLE 2 Synthesis of cycloadducts **3a**-**m** by 1,3-dipolar cycloaddition reactions of **1a**-**m** with *N*-cyclohexyl maleimide **2** using Cu $(NO_3)_2$



X = -H, -NO_2, -CH_3, -OH, -OCH_3

Compound	X	mp,°C	Time, h	Yield,[a] %
3a	**H**	**168-169**	**2**	**84**
3b	2-NO_2	240-243	2	78
3c	3-NO_2	210-215	1.5	82
3d	4-NO_2	172-173	2	75
3e	2-CH_3	162-163	3	83
3f	3-CH_3	142-144	3	67
3g	4-CH_3	185-187	2.5	78
3h	2-OH	225-227	1.5	84
3i	3-OH	192-193	2.5	71
3j	4-OH	200-203	2	77
3k	2-OCH_3	212-214	2	82
3l	3-OCH_3	182-184	3	70
3m	4-OCH_3	185-187	2.5	76

Note. **1a**-**m** (5 mmol), **2** (30 mmol), and catalyst (10 mol %).
[a]Isolated yield of pure compound after recrystallization.

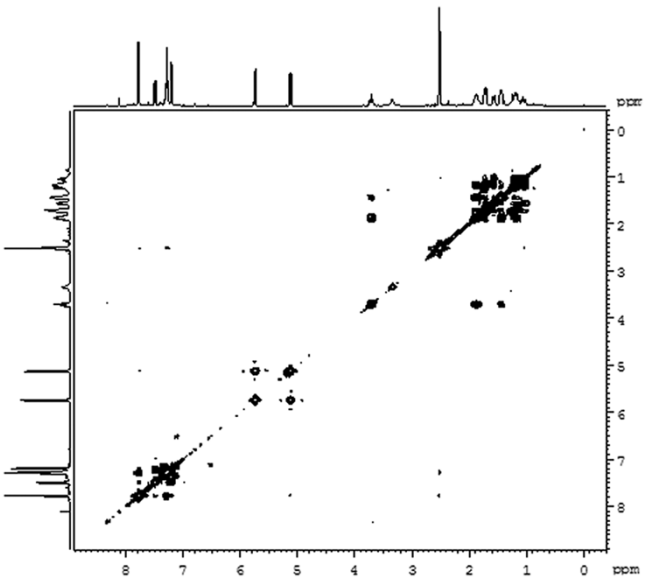


FIGURE 1 $^1H,^1H$-COSY spectrum of compound **3e**. COSY, correlation spectroscopy

TABLE 3 Advanced glycation end-product formation inhibitory activity of synthesized compounds **3a**-**m**

Compound	X	IC_{50}, μ*M*
3a	H	65.19 ± 2.20
3b	2-NO_2	16.60 ± 1.52
3c	3-NO_2	10.66 ± 0.90
3d	4-NO_2	14.56 ± 0.24
3e	2-CH_3	52.85 ± 1.10
3f	3-CH_3	94.30 ± 3.91
3g	4-CH_3	68.67 ± 2.61
3h	2-OH	122.67 ± 5.23
3i	3-OH	107.67 ± 3.61
3j	4-OH	135.67 ± 4.65
3k	2-OCH_3	235.67 ± 5.23
3l	3-OCH_3	37.53 ± 0.83
3m	4-OCH_3	266.37 ± 5.65
Aminoguanidine	-	40.54 ± 2.04

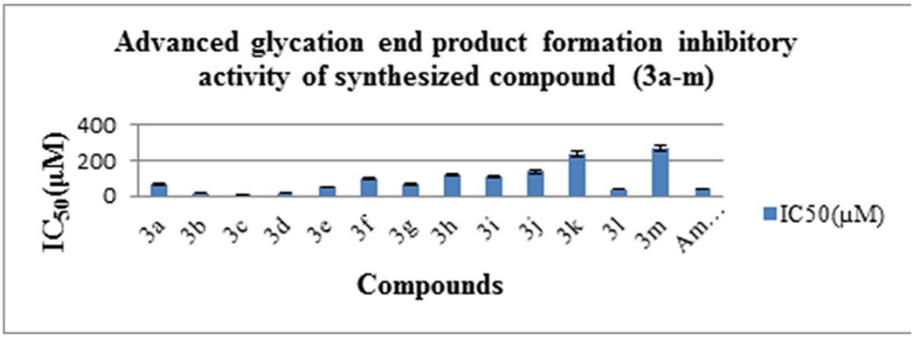


FIGURE 2 Graphical representation of IC_{50} values (μ*M*) for the advanced glycation end-product formation inhibitory activity of synthesized compounds **3a**-**m** relative to the standard drug aminoguanidine [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 4 Percentage of in vitro radical scavenging activity of synthesized compounds (**3a**-**m**)

	Concentration, μg/mL							
Compound	0.25	0.54	0.88	1.37	2.50	5.00	7.50	IC_{50}
3a	17.04	23.02	30.05	44.04	55.04	65.03	74.03	0.48
3b	11.04	23.06	31.03	41.07	56.04	64.01	76.00	0.46
3c	0.56	18.09	26.05	35.02	44.03	53.03	76.03	0.44
3d	9.05	24.08	36.07	53.08	65.08	78.09	83.04	0.45
3e	2.07	17.05	28.07	45.03	59.04	62.09	83.04	0.52
3f	12.02	21.06	33.07	45.09	59.08	76.06	86.08	0.56
3g	15.07	24.08	36.09	49.08	62.04	77.03	89.05	0.59
3h	7.05	18.04	27.05	41.03	54.07	62.04	86.04	0.49
3i	18.05	22.02	31.05	40.04	54.04	66.03	78.03	0.48
3j	7.09	19.04	33.01	43.06	52.04	67.03	79.02	0.49
3k	11.04	16.07	32.09	36.04	53.04	63.05	81.06	0.51
3l	9.04	16.04	30.09	41.03	52.07	67.07	77.04	0.52
3m	15.06	28.07	39.05	42.04	53.02	66.03	79.03	0.52
BHT[a]	-	4.62	11.56	23.12	30.11	44.71	55.22	5.37

Note. - indicates no activity.
[a]Butylated hydroxytoluene as standard substance.

3.2 | General procedure for synthesis of *N*-cyclohexyl maleimide 2

N-Cyclohexyl maleanilic acid was obtained by stirring 20 mmol of maleic anhydride in 25 mL of diethyl ether and cyclohexyl aniline in 5 mL of diethyl ether at room temperature, which was refluxed with a solution of anhydrous sodium acetate (0.65 g, 8 mmol) in acetic anhydride (6.7 mL) for 1.5 hours afforded *N*-cyclohexyl maleimide **2**.

3.3 | General procedure for cycloaddition in triethylamine

Triethylamine (3.3 mmol) was added dropwise to the cold reaction mixture of substituted benzaldehyde-2′,4′-dibromophenyl hydrazonyl bromide derivatives **1a**-**m** (5 mmol) and *N*-cyclohexyl maleimides **2** (30 mmol) in 100 mL of solvent. The reaction mixture was stirred at room temperature till completion as evidenced by TLC to give cycloadducts **3a**-**m**.

3.4 | General procedure for Lewis acid–catalyzed cycloaddition in water

Cu $(NO_3)_2$ was allowed to dry by heating under vacuum. The reaction mixture of 5 mmol of corresponding hydrazonyl bromides **1a**-**m**, 30 mmol of *N*-cyclohexyl maleimide **2** in 100 mL of deionized water, and 0.05 mmol of dried Cu $(NO_3)_2$ was placed in a round-bottom flask set in an oil bath for 1.5 to 2.0 hours under an inert atmosphere of nitrogen. Stir the reaction mixture on magnetic stirrer till completion, as directed by TLC. After removal of the solvent under reduced pressure dichloromethane was added to the reaction mixture. Remove undissolved catalyst by filtration. Cycloadducts **3a**-**m** were obtained by column chromatography on silica gel using hexane-ethyl acetate mixture as eluent.

3.4.1 | 2′,4′-Dibromophenyl-5-cyclohexyl-3-phenyl-3*a*,4,6,6*a*-tetrahydro-1*H*,5*H*-pyrrolo[3,4-*c*]pyrazole-4,6-dione (3a)

Compound obtained as white solid, yield 84%; mp 168-169°C; IR (KBr pellets, υ_{max}/cm^{-1}): 1709 (C═O), 1781 (C═O), 1609 (C═N), 1565 (C═C); ^{1}H-NMR (400 MHz, DMSO-d_6): δ 5.82 (d, 1H, *J* = 10.28 Hz, H_{6a}), 4.87 (d, 1H, *J* = 10.24 Hz, H_{3a}), 7.81-7.19 (m, 8H, Ar–H), 3.74-3.68 (m, 1H, CH cyclohexyl), 2.20-1.09 (m, 10H, $5CH_2$ cyclohexyl); ^{13}C-NMR (100 MHz, DMSO-d_6): δ 172.46, 172.08, 149.65, 145.55, 135.02, 134.69, 131.62, 130.26, 129.87, 128.07, 117.20, 116.08, 113.48, 52.60, 50.45, 41.28, 28.87, 28.80, 23.66, 20.53, 20.19; MS (ESI): *m*/*z* = 531(M)$^+$; Anal Calcd (%) for $C_{23}H_{21}N_3O_2Br_2$: C, 51.98; H, 3.95; N, 7.90. Found: C, 52.17; H, 3.93; N, 7.92.

3.4.2 | 2′,4′-Dibromophenyl-5-cyclohexyl-3-(2″-nitrophenyl)-3*a*,4,6,6*a*-tetrahydro-1*H*,5*H*-pyrrolo[3,4-*c*]pyrazole-4,6-dione (3b)

Compound obtained as brownish solid, yield 78%; mp 240-243°C; IR (KBr, υ_{max}/cm^{-1}): 1706 (C═O), 1778 (C═O), 1604 (C═N), 1563 (C═C); ^{1}H-NMR (400 MHz, $CDCl_3$): δ 5.72 (d, 1H, *J* = 10.20 Hz, H_{6a}), 4.71 (d, 1H, *J* = 10.20 Hz, H_{3a}), 7.88-7.19 (m, 7H, Ar–H), 3.89-3.83 (m, 1H, CH cyclohexyl), 1.92-1.02 (m, 10H, $5CH_2$ cyclohexyl); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 172.63, 172.42, 148.72, 146.87, 144.90, 136.07, 135.28, 132.68, 131.28, 130.46, 126.12, 123.34, 118.26, 117.18,

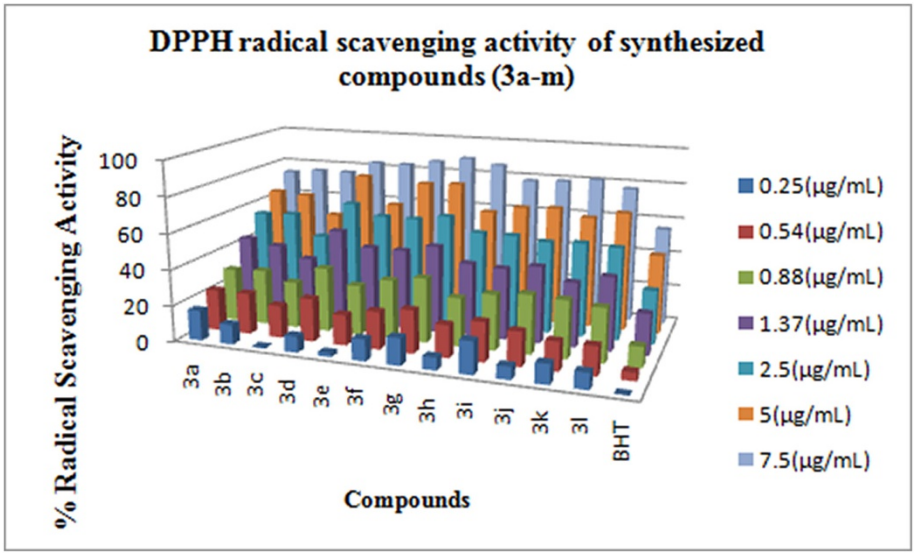


FIGURE 3 Graphical presentation of in vitro DPPH radical scavenging activity of compounds **3a**-**m** relative to the standard antioxidant BHT. BHT, butylated hydroxytoluene [Color figure can be viewed at wileyonlinelibrary.com]

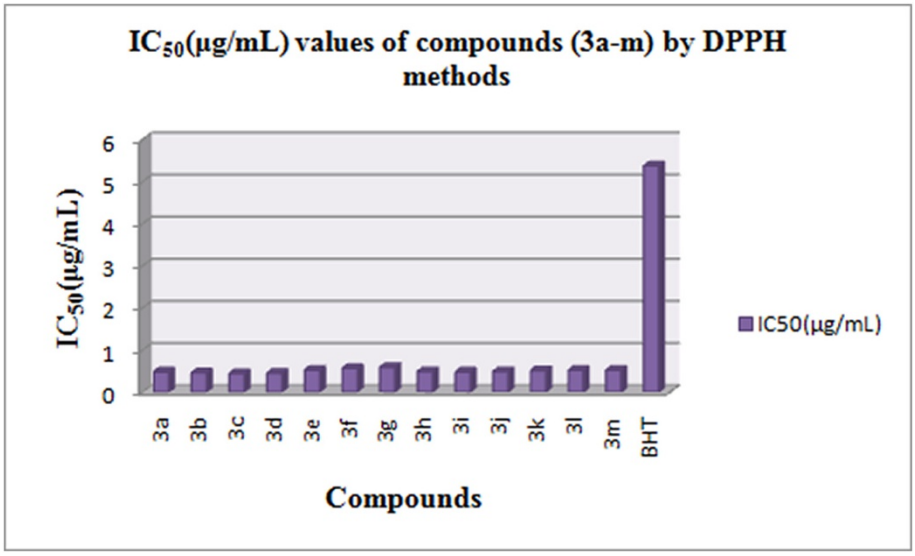


FIGURE 4 Graphical presentation of the IC_{50} values (µg/mL) for the antioxidant activity of compounds **3a**-**m** measured at various concentrations [Color figure can be viewed at wileyonlinelibrary.com]

114.29, 52.64, 50.98, 40.05, 29.73, 29.71, 26.85, 26.45, 24.39; MS (ESI): *m*/*z* = 576 $(M)^+$; Anal Calcd (%) for $C_{23}H_{20}N_4O_4Br_2$: C, 47.92; H, 3.47; N, 9.72. Found: C, 47.88; H, 3.45; N, 9.70.

3.4.3 | 2′,4′-Dibromophenyl)-5-cyclohexyl-3-(3″-nitrophenyl)-3*a*,4,6,6*a*-tetrahydro-1*H*,5*H*-pyrrolo[3,4-*c*]pyrazole-4,6-dione (3c)

Compound obtained as brownish solid, yield 82%; mp 210-215°C; IR (KBr, υ_{max}/cm^{-1}): 1705 (C═O), 1781 (C═O), 1608 (C═N), 1562 (C═C); ^{1}H-NMR (400 MHz, DMSO-d_6): δ 5.79 (d, 1H, *J* = 10.48 Hz, , H_{6a}), 5.32 (d, 1H, *J* = 10.48 Hz, H_{3a}), 7.89-7.17 (m, 7H, Ar–H), 3.87-3.78 (m, 1H, CH cyclohexyl), 2.00-1.00 (m, 10H, $5CH_2$ cyclohexyl); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 171.80, 171.62, 149.72, 147.87, 145.90, 135.07, 134.88, 133.66, 130.48, 129.72, 125.14, 123.33, 117.56, 116.78, 113.22, 52.44, 50.77, 42.15, 28.74, 28.65, 25.64, 25.45, 21.42; MS (ESI): *m*/*z* = 576$(M)^+$; Anal Calcd (%) for $C_{23}H_{20}N_4O_4Br_2$: C, 47.92; H, 3.47; N, 9.72. Found: C, 47.75; H, 3.46; N, 9.76.

3.4.4 | 2′,4′-Dibromophenyl-3-(4″-nitrophenyl)-5-cyclohexyl-3*a*,4,6,6*a*-tetrahydro-1*H*,5*H*-pyrrolo[3,4-*c*]pyrazole-4,6-dione (3d)

Compound obtained as white solid, yield 75%; mp 172-173°C; IR (KBr, υ_{max}/cm^{-1}): 1699 (C═O), 1771 (C═O), 1609 (C═N), 1577 (C═C); ^{1}H-NMR (400 MHz, $CDCl_3$): δ 5.74 (d, 1H, *J* = 10.40 Hz, H_{6a}), 4.75 (d,

1H, *J* = 10.36 Hz, H_{3a}), 8.02-7.15 (m, 7H, Ar–H), 3.79-3.62 (m, 1H, CH cyclohexyl), 1.98-1.08 (m, 10H, $5CH_2$ cyclohexyl); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 173.18, 172.32, 150.23, 149.24, 144.53, 141.16, 135.59, 131.26, 129.68, 122.12, 117.25, 116.28, 113.28, 52.78, 50.44, 42.02, 28.75, 28.71, 25.35, 24.95, 21.33; MS (ESI): *m/z* = 576 $(M)^+$; Anal Calcd (%) for $C_{23}H_{20}N_4O_4$ Br_2: C, 47.92; H, 3.47; N, 9.72. Found: C, 47.72; H, 3.42; N, 9.80.

3.4.5 | 2′,4′-Dibromophenyl-5-cyclohexyl-3-(2″-methylphenyl)-3*a*,4,6,6*a*-tetrahydro-1*H*,5*H*-pyrrolo[3,4-*c*]pyrazole-4,6-dione (3e)

Compound obtained as white solid, yield 83%; mp 162-163°C; IR (KBr, υ_{max}/cm^{-1}): 1703 (C═O), 1774 (C═O), 1603 (C═N), 1575 (C═C); ^{1}H-NMR (400 M Hz, DMSO-d_6): δ 5.78 (d, 1H, *J* = 10.08 Hz, H_{6a}), 4.89 (d, 1H, *J* = 10.04 Hz, H_{3a}), 7.81-7.19 (m, 7H, Ar–H), 3.83-3.89 (m, 1H, CH cyclohexyl), 2.02-1.1.09 (m, 10H, $5CH_2$ cyclohexyl), 2.59 (s, 3H, CH_3); ^{13}C-NMR (100 MHz, DMSO-d_6): δ 166.72, 166.70, 141.40, 137.06, 132.57, 130.50, 126.45, 126.09, 124.36, 124.00, 123.41, 120.50, 120.48, 112.91, 110.93, 56.55, 49.66, 47.26, 23.48, 23.28, 20.44, 20.39, 19.57, 18.10; MS (ESI): *m/z* = 545$(M)^+$; Anal Calcd (%) for $C_{24}H_{23}N_3O_2Br_2$: C, 52.84; H, 4.22; N, 7.70. Found: C, 52.90; H, 4.20; N, 7.66.

3.4.6 | 2′,4′-Dibromophenyl-5-cyclohexyl-3-(3″-methylphenyl)-3*a*,4,6,6*a*-tetrahydro-1*H*,5*H*-pyrrolo[3,4-*c*]pyrazole-4,6-dione (3f)

Compound obtained as white solid, yield 67%; mp 142-144°C; IR (KBr, υ_{max}/cm^{-1}): 1706 (C═O), 1782 cm^{-1} (C═O), 1603 (C═N), 1575 (C═C); ^{1}H-NMR (400 MHz, DMSO-d_6): δ 5.68 (d, 1H, *J* = 10.00 Hz, H_{6a}), 5.17 (d, 1H, *J* = 10.00 Hz, H_{3a}), 8.01-7.02 (m, 7H, Ar–H), 3.79-3.64 (m, 1H, CH cyclohexyl), 1.99-1.00 (m, 10H, $5CH_2$ cyclohexyl), 2.56 (s, 3H, CH_3); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 172.72, 172.60, 149.45, 145.65, 137.50, 135.35, 132.45, 130.45, 130.20, 128.37, 127.20, 125.54, 117.25, 116.28, 113.18, 52.67, 50.23, 44.29, 24.40, 24.24, 20.47, 20.36, 19.70, 18.20; MS (ESI): *m/z* = 545$(M)^+$; Anal Calcd (%) for $C_{24}H_{23}N_3O_2Br_2$: C, 52.84; H, 4.22; N, 7.70. Found: C, 53.05; H, 4.20; N, 7.72.

3.4.7 | 2′,4′-Dibromophenyl-5-cyclohexyl-3-(4″-methylphenyl)-3*a*,4,6,6*a*-tetrahydro-1*H*,5*H*-pyrrolo[3,4-*c*]pyrazole-4,6-dione (3g)

Compound obtained as white solid, yield 78%; mp 185-187°C; IR (KBr, υ_{max}/cm^{-1}): 1706 (C═O), 1781 (C═O), 1597 (C═N); 1572 (C═C); ^{1}H-NMR (400 MHz, DMSO-d_6): δ 5.76 (d, 1H, *J* = 10.40 Hz, H_{6a}), 4.67 (d, 1H, *J* = 10.38 Hz, H_{3a}), 8.00-7.10 (m, 7H, Ar–H), 3.84-3.77 (m, 1H, CH cyclohexyl), 2.01-1.00 (m, 10H, $5CH_2$ cyclohexyl), 2.53 (s, 3H, CH_3); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 172.04, 171.68, 148.50, 143.72, 140.64, 135.58, 131.90, 131.09, 129.22, 129.12, 117.75, 116.72, 113.11, 52.53, 50.12, 42.28, 23.68, 23.44, 20.98, 20.56, 19.92, 18.32; MS (ESI): *m/z* = 545$(M)^+$; Anal Calcd (%) for $C_{24}H_{23}N_3O_2Br_2$: C, 52.84; H, 4.22; N, 7.70. Found: C, 53.02; H, 4.30; N, 7.62.

3.4.8 | 2′,4′-Dibromophenyl-5-cyclohexyl-3-(2″-hydoxyphenyl)-3*a*,4,6,6*a*-tetrahydro-1*H*,5*H*-pyrrolo[3,4-*c*]pyrazole-4,6-dione (3h)

Compound obtained as white solid, yield 84%; mp 225-227°C; IR (KBr, υ_{max}/cm^{-1}): 1700 (C═O), 1780 (C═O), 1601 (C═N), 1575 cm^{-1} (C═C); ^{1}H-NMR (400 MHz, DMSO-d_6): δ 5.81 (d, 1H, *J* = 10.24 Hz, H_{6a}), 4.79 (d, 1H, *J* = 10.24 Hz, H_{3a}), 7.92-7.10 (m, 7H, Ar–H), 3.83-3.79 (m, 1H, CH cyclohexyl), 2.00-1.02 (m, 10H, $5CH_2$ cyclohexyl), 9.02 (s, 1H, OH); ^{13}C-NMR (100 MHz, DMSO-d_6): δ 173.04, 172.78, 159.50, 148.77, 144.34, 135.52, 132.80, 131.10, 129.80, 122.56, 119.93, 117.25, 116.98, 116.52, 113.81, 52.32, 50.62, 42.18, 28.62, 28.58, 23.32, 23.98, 20.82; MS (ESI): *m/z* = 547 $(M)^+$; Anal Calcd (%) for $C_{23}H_{21}N_3O_3Br_2$: C, 50.46; H, 3.84; N, 7.68. Found: C, 50.17; H, 3.85; N, 7.62.

3.4.9 | 2′,4′-Dibromophenyl-5-cyclohexyl-3-(3″-hydroxyphenyl)-3*a*,4,6,6*a*-tetrahydro-1*H*,5*H*-pyrrolo[3,4-*c*]pyrazole-4,6-dione (3i)

Compound obtained as white solid, yield 71%; mp 192-193°C; IR (KBr, υ_{max}/cm^{-1}): 1702 (C═O), 1775 (C═O), 1603 (C═N), 1572 (C═C); ^{1}H-NMR (400 MHz, $CDCl_3$): δ 5.67 (d, 1H, *J* = 10.40 Hz, H_{6a}), 4.89 (d, 1H, *J* = 10.40 Hz, H_{3a}), 7.77-6.88 (m, 7H, Ar–H), 3.89-3.83 (m, 1H, CH cyclohexyl), 2.10-1.04 (m, 10H, $5CH_2$ cyclohexyl), 9.01 (s, 1H, OH); ^{13}C-NMR (100 MHz, DMSO-d_6): δ 172.44, 171.82, 158.80, 149.87, 143.24, 136.58, 135.70, 130.78, 129.65, 121.68, 118.73, 117.55, 116.78, 114.32, 112.61, 52.38, 50.52, 41.48, 28.52, 28.35, 23.12, 23.08, 20.92; MS (ESI): *m/z* = 547$(M)^+$; Anal Calcd (%) for $C_{23}H_{21}N_3O_3Br_2$: C, 50.46; H, 3.84; N, 7.68. Found: C, 50.49; H, 3.83; N, 7.60.

3.4.10 | 2′,4′-Dibromophenyl-5-cyclohexyl-3-(4″-hydroxyphenyl)-3*a*,4,6,6*a*-tetrahydro-1*H*,5*H*-pyrrolo[3,4-*c*]pyrazole-4,6-dione (3j)

Compound obtained as white solid, yield 77%; mp 202-203°C; IR (KBr, υ_{max}/cm^{-1}): 1700 (C═O), 1777 (C═O), 1603 (C═N), 1574 (C═C); ^{1}H-NMR (400 MHz, $CDCl_3$): δ 5.72 (d, 1H, *J* = 10.34 Hz, H_{6a}), 4.79 (d, 1H, *J* = 10.34 Hz, H_{3a}), 7.89-7.03 (m, 7H, Ar–H), 3.82-3.74 (m, 1H, CH cyclohexyl), 1.92-0.90 (m, 10H, $5CH_2$ cyclohexyl), 9.09 (s, 1H, OH); ^{13}C-NMR (100 MHz, DMSO-d_6): δ 172.74, 172.38, 160.20, 148.97, 143.94, 135.32, 131.60, 130.04, 125.90, 117.35, 116.66, 116.27, 113.85, 52.63, 50.82, 41.59, 27.93, 27.88, 23.20, 23.18, 18.82; MS (ESI): *m/z* = 547$(M)^+$; Anal Calcd (%) for $C_{23}H_{21}N_3O_3Br_2$: C, 50.46; H, 3.84; N, 7.68. Found: C, 50.47; H, 3.73; N, 7.65.

3.4.11 | 2′,4′-Dibromophenyl-5-cyclohexyl-3-(2″-methoxyphenyl)-3*a*,4,6,6*a*-tetrahydro-1*H*,5*H*-pyrrolo [3,4-*c*]pyrazole-4,6-dione (3k)

Compound obtained as white solid, yield 82%; mp 212-214°C; IR (KBr, υ_{max}/cm^{-1}): 1704 (C═O), 1777 (C═O), 1598 (C═N); 1576 (C═C); ^{1}H-NMR (400 MHz, $CDCl_3$): δ 5.28 (d, 1H, *J* = 10.40 Hz, H_{6a}), 4.35 (d, 1H, *J* = 10.38 Hz, H_{3a}), 8.20-7.62 (m, 7H, Ar–H), 3.79-3.66 (m, 1H, CH cyclohexyl), 2.00-1.08 (m, 10H, $5CH_2$ cyclohexyl), 3.63 (s, 3H, OCH_3); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 173.10, 172.68, 160.20, 149.97, 144.44, 135.72, 132.62, 131.70, 130.04, 122.34, 117.98, 117.15, 116.56, 114.28, 112.83, 56.43, 52.17, 50.28, 40.68, 29.42, 29.07, 27.32, 24.62, 24.48; MS (ESI): *m*/*z* = 561(M)$^+$; Anal Calcd (%) for $C_{24}H_{23}N_3O_3Br_2$: C, 51.34; H, 4.10; N, 7.49. Found: C, 51.36; H, 4.12; N, 7.46.

3.4.12 | 2′,4′-Dibromophenyl-5-cyclohexyl-3-(3″-methoxyphenyl)-3*a*,4,6,6*a*-tetrahydro-1*H*,5*H*-pyrrolo [3,4-*c*]pyrazole-4,6-dione (3l)

Compound obtained as white solid, yield 70%; mp 182-184°C; IR (KBr, υ_{max}/cm^{-1}): 1703 (C═O), 1779 (C═O), 1600 (C═N), 1566 (C═C); ^{1}H-NMR (400 MHz, $CDCl_3$): δ 5.67 (d, 1H, *J* = 10.00 Hz, H_{6a}), 4.79 (d, 1H, *J* = 10.02 Hz, H_{3a}), 7.78-7.12 (m, 7H, Ar–H), 3.88-3.81 (m, 1H, CH cyclohexyl), 2.02-0.92 (m, 10H, $5CH_2$ cyclohexyl), 3.62 (s, 3H, OCH_3); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 172.70, 172.48, 159.26, 149.77, 144.24, 135.92, 135.32, 131.92, 129.84, 122.44, 117.28, 116.35, 116.26, 113.08, 112.92, 56.63, 52.57, 50.38, 41.78, 29.32, 29.09, 26.52, 23.62, 23.28; MS (ESI): *m*/*z* = 561(M)$^+$; Anal Calcd (%) for $C_{24}H_{23}N_3O_3Br_2$: C, 51.34; H, 4.10; N, 7.49. Found: C, 51.38; H, 4.16; N, 7.41.

3.4.13 | 2′,4′-Dibromophenyl-5-cyclohexyl-3-(4″-methoxyphenyl)-3*a*,4,6,6*a*-tetrahydro-1*H*,5*H*-pyrrolo [3,4-*c*]pyrazole-4,6-dione (3m)

Compound obtained as white solid, yield 76%; mp 185-187°C; IR (KBr, υ_{max}/cm^{-1}): 1703 (C═O), 1778 (C═O), 1601 (C═N), 1576 (C═C); ^{1}H-NMR (400 MHz, $CDCl_3$): δ 5.57 (d, 1H, *J* = 10.00 Hz, H_{6a}), 4.92 (d, 1H, *J* = 10.02 Hz, H_{3a}), 7.88-7.10 (m, 7H, Ar–H), 3.89-3.82 (m, 1H, CH cyclohexyl), 2.02-0.90 (m, 10H, $5CH_2$ cyclohexyl), 3.63 (s, 3H, OCH_3); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 172.90, 172.42, 163.40, 149.72, 145.34, 135.81, 131.88, 130.23, 117.24, 116.56, 114.48, 112.89, 56.62, 52.78, 50.17, 41.28, 29.66, 29.45, 26.20, 23.89, 23.82; MS (ESI): *m*/*z* = 561(M)$^+$; Anal Calcd (%) for $C_{24}H_{23}N_3O_3Br_2$: C, 51.34; H, 4.10; N, 7.49. Found: C, 51.42; H, 4.24; N, 7.46.

4 | CONCLUSIONS

The contemporary reassessment of Diels-Alder reactions in aqueous medium is a new synthetic approach for [3+2] cycloaddition reactions of hydrazonyl bromides and substituted maleimides under Cu (II) salts' catalytic conditions without using volatile organic solvents. The vital role of these cycloadducts as aldose reductase inhibitors and antioxidants is prejudiced by the relative positions of electron-withdrawing/electron-donating substituents on the *C*-phenyl ring. The compounds with less activated rings are more significant as potent aldose reductase inhibitors.

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