Res Chem Intermed (2016) 42:5353–5366
DOI 10.1007/s11164-015-2371-0

Microwave assisted synthesis of ring junction heterocyclic antioxidants

Rajesh Sompalle[1] · **Selvaraj Mohana Roopan**[1]

Received: 9 August 2015 / Accepted: 19 November 2015 / Published online: 26 November 2015

Abstract A series of 6,7-dihydro-[1,2,4]triazolo[5,1-*b*]quinazolin-8(5*H*)-ones, **4a–o** were synthesized via a one-pot, multicomponent reaction in the presence of water as a solvent under microwave irradiation using ceric ammonium nitrate as an oxidizing agent. This techno-chemical method provides a rapid construction of higher molecules in short duration with high yield. The adopted method was carried out in the presence of water without catalyst and yielded the compounds without any side products, and thus further purification of compounds by column chromatography was not required. All the synthesized compounds, **4a–o** were screened for their 2,2-diphenyl-1-picrylhydrazyl radical scavenging activity. All the compounds, **4a–o** possessed moderate antioxidant activity when compared to their standard antioxidant (ascorbic acid).

Keywords Heterocycles · Dihydro-triazolo-quinazolinones · Multi-component assembly process · Microwave irradiation · Antioxidant activity

Introduction

In the twenty-first century, research in the field of chemistry has been directed towards the green chemical approach, thereby decreasing the usage of organic solvents, byproducts, and reaction time [1, 2]. Recently, development of environmentally

Electronic supplementary material The online version of this article (doi:10.1007/s11164-015-2371-0) contains supplementary material, which is available to authorized users.

✉ Selvaraj Mohana Roopan
mohanaroopan.s@gmail.com; mohanaroopan.s@vit.ac.in

[1] Chemistry of Heterocycles and Natural Product Research Laboratory, Organic Chemistry Division, School of Advanced Sciences, VIT University, Vellore, Tamilnadu 632 014, India

benign synthetic methodologies have become an urgent need for several organic synthesis and chemical transformations [3].

The Multi-Component Assembly Process (MCAP) is a process in which more than two starting materials were reacted to give a highly reactive single product [4, 5]. A few examples for MCAP are Mannich, Gewald, Biginelli, Hantzsch pyridine, Ugi, and Passerini reactions for the construction of *N*-heterocycles [6–8]. The MCAP is an advanced technique for the construction of complex moiety with the help of readily available starting material with high atom economy and selectivity [9, 10]. Microwave energy is considered one of the top most energy sources that will increase the reaction rates and reduce the reaction time [11]. Microwave (MW) irradiation reactions promote green chemistry principles such as high reaction rates, more economic value, easy work-up, good atom economy, and environment-friendly methods.

N-heterocycles are found commonly and abundantly present in plants and animals, and posses various properties such as therapeutic, nutraceutical, and deterrent [12–14]. Quinazolinone is a fused bicyclic scaffold construct that is present in nature and possess a variety of medicinally important properties such as anti-inflammatory [15], anticonvulsant [16], antioxidant [17], antitumor [18], antiviral [19], antitubercular [20, 21], diuretic [22, 23], sedative/hypnotic [24], antihypertensive [25], anticancer [26, 27], and antimicrobial activities [28–30]. An example of a ring junction *N*-heterocyclic compound is luotonin A, a quinazolinone-based ring junction nitrogen heterocycle [31], which is used as a traditional medicine to treat inflammation, abscesses, and rheumatism. Similarly, camptothecin and mappicine (Fig. 1) are two other alkaloids used in cancer treatment chemotherapy [32]. Similarly [1,2,4], triazoles also possess various pharmacological and biological properties such as anticholinergic, antihypertensive, anti-asthmatic, anti-inflammatory, diuretic, antibacterial, analgesic, and antifungal activities [33, 34]. The [1,2,4]triazoles are considered to be important structural scaffolds found in a large number of functionalized molecules with a wide variety of uses, including applications in medicinal chemistry, materials science, and organocatalysis, also found in medicinal drugs such as fluconazole, triazolam, rizatriptan, and alprazolam (Fig. 2). They also have medicinal activities, such as antifungal, anticonvulsant, analgesic, anxiolytic, antiemetic [35, 36]. Both moieties show individually promising properties. Hence, coupling of both bioactive components would lead to the introduction of a new, fused system. The literature reveals that [1,2,4]-triazolo- and [1,2,4]-triazino[4,3-*c*]quinazolines were used in the medical field for

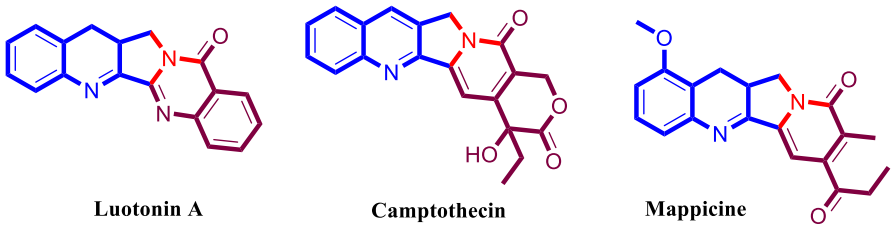


Fig. 1 Medicinally important alkaloids containing a nitrogen ring junction

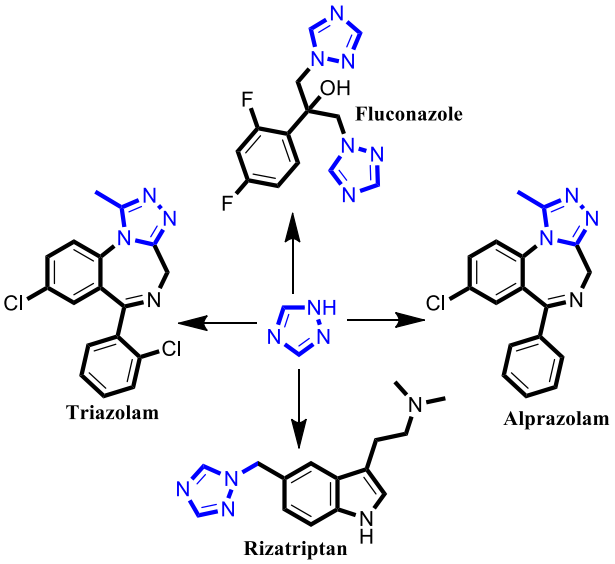


Fig. 2 Drugs containing [1,2,4]triazole nucleus

blood platelet aggregation inhibitors, antidepressants, analgesics, and antihistaminics [37, 38]. Based on the importance of triazolo and quinazolinone, we have decided to synthesize triazolo-quinazolinone as a hybrid molecule.

Free radicals are single group of atoms with an odd number of electrons, which are responsible for large number of diseases in the biological system of the human body, including neural disorders, Parkinson's disease, cardiovascular disease, ulcerative colitis, mild cognitive impairment, Alzheimer's disease, atherosclerosis, aging, and liver disease [39]. The formation of free radicals are due to oxidation in the body, and are initiators of a chain reaction and often damage/death to a cell. Antioxidants are chemicals that inhibit the oxidation process of other molecules, even at relatively small concentrations, and thus damage of key cell components can be prevented by removing free radical intermediates [40, 41].

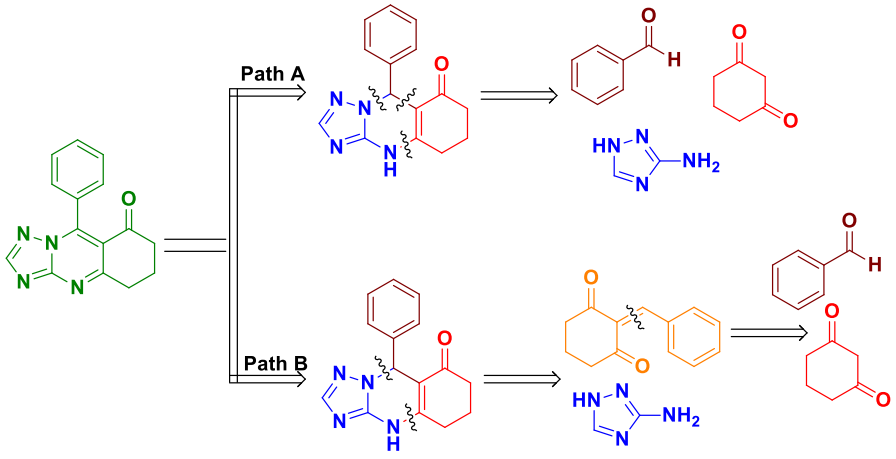
There are several strategies reported for synthesis of dihydro-triazolo-quinazolinones. The most common protocol is the condensation of 3-amino-1,2,4-triazole and substituted aldehyde with cyclic β-diketone in the presence of different catalysts followed by an oxidation process using many oxidizing agents under various solvents. The synthesis of dihydro-triazolo-quinazolinones is usually carried out by condensing the starting materials in the presence of heteropolyacids [42] or in the presence of chitosan and acetic acid under reflux conditions [43]. This can also be achieved by the following methods: molecular iodine using acetonitrile as solvent under reflux conditions [44], sulfamic acid and acetonitrile under reflux conditions [45], dimethylformamide under MW irradiation conditions [46], boric acid and ethyl acetate as solvent [47], silica gel and dichloromethane as solvent under MW irradiation conditions [48], ionic liquids [49], Nafion-H using polyethylene glycol-400 under reflux conditions [50] followed by oxidative aromatization in the

presence of *p*-chloranil using chlorobenzene under reflux conditions [46]. Moreover, these synthetic protocols are associated with several drawbacks such as having multiple steps, use of organic solvents, tedious experimental protocol, expensive catalysts, prolonged reaction times, and unsatisfactory yields. Hence, in relevance to the present research, there appears to be no prior instant procedure for the synthesis of dihydro-triazolo-quinazolinones under ecofriendly conditions.

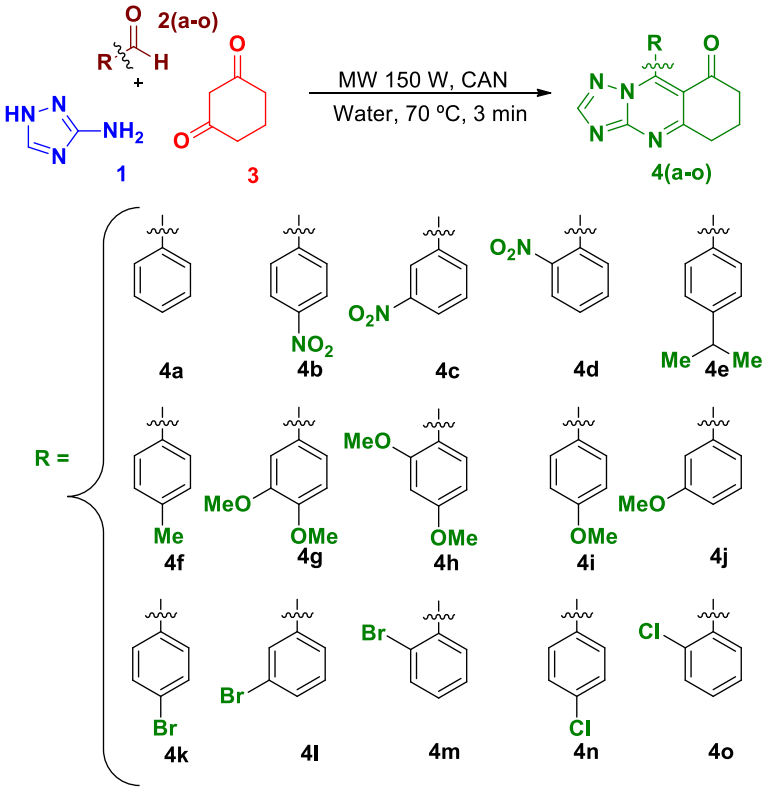
Results and discussion

While various methods are involved for synthesizing the dihydro-triazolo-quinazolinones, the chemistry arena is shifted towards the development of ecofriendly and economically attractive greener synthetic methodologies [51, 52]. By considering all the above-mentioned loopholes, we have put our efforts to develop an environmentally benign protocol. Microwave irradiation has been applied to form dihydro-triazolo-quinazolinones in a short time with excellent yields. We have identified two possible retro-synthetic pathways to synthesize the dihydro-triazolo-quinazolinone, outlined in Scheme 1. Among the two retrosynthetic pathways, we prefer path A because it has fewer number of steps, low cost, and easily available starting materials. The experimental procedure is simple and easy to access, and we have synthesized compounds, **4a–o** (Scheme 2) with excellent isolated yields. The advantage of the present protocol over other reported methods are that it uses water as a green solvent instead of hazardous organic solvents, as well as shorter reaction time, a simple experimental procedure without expensive catalysts, and excellent yields [42–50].

We have optimized the reaction conditions for compound, **4a** with respect to different methodologies (Table 1). Initially, we started the reaction in the absence of water, but we found no progress in the reaction. Our second option was to carry out



Scheme 1 Reterosynthetic pathway to 9-phenyl-6,7-dihydro-[1,2,4]triazolo[5,1-*b*]quinazolin-8(5*H*)-one, **4a** synthesis



Scheme 2 Synthesis of 9-phenyl substituted-6,7-dihydro-[1,2,4]triazolo[5,1-*b*]quinazolin-8(5*H*)-ones, **4a–o**

the same reaction in both the conventional and non-conventional sources in the presence of water. In the conventional method, we operated the reaction at various temperatures, 50, 70, 100, and 150 °C, for 1 h and we could not find a positive response. Then we chose the non-conventional energy sources such as MW irradiation, ultrasonic (US) energy, and ultraviolet (UV) energy. From the optimization, the MW conditions with 300 W at 90 °C for 3 min show 70 % of product formation. To increase the yield of the isolated product **4a**, we fine-tuned the reaction conditions by varying power, temperature, and mole ratio of ceric ammonium nitrate (CAN) (Table 2). From the above optimization, we observed that 150 W at 70 °C for 3 min with 1.5 equiv of CAN was found to be the optimized conditions.

DPPH radical scavenging activity

The radical scavenging activity of dihydro-triazolo-quinazolinones, **4a–o** was evaluated with 2,2-diphenyl-1-picrylhydrazyl (DPPH) assays. DPPH is widely used to evaluate the antioxidant activity of natural products as well as synthetic

Table 1 Optimizing the method for the synthesis of compound, **4a**

S. no.	Conventional		Non-conventional				Reaction status
	Time (h)	Temp (°C)	MW (W)	UV (nm)	Time (min)	Temp (°C)	
1	10	rt	–	–	–	–	NR
2	10	70	–	–	–	–	NR
3	8	100	–	–	–	–	NR
4	–	–	300	–	3	90	70 % EP
5	–	–		365	20	–	NR
6	–	–		312	20	–	NR
7	–	–		262	20	–	NR
8	–	–		–	20	–	NR

[a] All the reactions were carried out in 1:1:1 equivalence of **1, 2, 3**, and 2 eq of CAN in the presence of aqueous medium

[b] *MW* Microwave, *US* Ultrasound, *UV* Ultraviolet, *NR* No reaction, *EP* Expected product. The optimal conditions are shown by bold letters

Table 2 Optimization of the reaction parameters with respect to power, temperature, and CAN for the synthesis of compound, **4a**

S. no.	Power (W)	Time (min)	Temp (°C)	Mole ratio of CAN	Yield (%)[b]
1	100	12	55	2	57
2	150	3	70	2	94
3	200	3	70	2	82
4	250	3	70	2	78
5	150	15	70	0.5	Trace
6	150	15	70	1	62
7	150	3	70	1.5	94
8	150	3	80	1.5	87

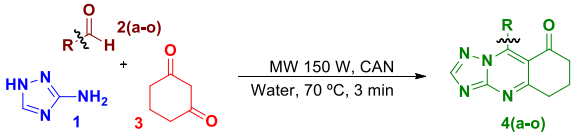
To scrutinize the scope of this reaction, a variety of substituted aromatic aldehydes were subjected to this reaction and it was shown in Table 3. It is evident that all the substituted aromatic aldehydes afford their corresponding products with good yield

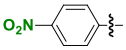
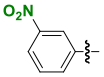
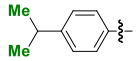
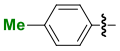
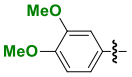
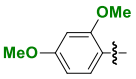
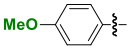
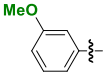
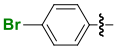
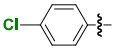
[a] Trace = Product formation in TLC. The optimal conditions are shown by bold letters

[b] Isolated yields

molecules [53]. DPPH is a well known radical scavenger, with maximum absorption at 517 nm in ethanol. DPPH shows a deep violet colour in solution form, and it becomes colourless or pale yellow when it gains the electron or hydrogen from an oxidant, becoming a more stable molecule with decrease in the absorbance [54]. The IC_{50} values of dihydro-triazolo-quinazolinones, **4a–o** in terms of the scavenging of DPPH radicals are given in Table 4. The results demonstrated that all dihydro-triazolo-quinazolinones, **4a–o** exhibit moderate activity. Among the all compounds, **4e** and **4f** shown good activity when compared with the standard ascorbic acid.

Table 3 Synthesis of 9-phenyl-6,7-dihydro-[1,2,4]triazolo[5,1-*b*]quinazolin-8(5*H*)-ones, **4a–o**



Entry	R	Product	M. P (°C)	Yield (%)[a]
1		**4a**	198–200	94
2		**4b**	168–170	86
3		**4c**	182–184	88
4		**4d**	206–208	85
5		**4e**	171–174	93
6		**4f**	200–202	92
7		**4g**	164–166	90
8		**4h**	214–216	92
9		**4i**	194–196	91
10		**4j**	190–192	93
11		**4k**	242–244	90
12		**4l**	198–200	88
13		**4m**	252–254	89
14		**4n**	220–222	91
15		**4o**	242–244	87

[a] Isolated yields

Table 4 DPPH radical scavenging activities of dihydro-triazolo-quinazolinones, **4a–o**

Entry	Compounds	% inhibition at different concentrations (mM)				IC_{50}
		0.001	0.002	0.003	0.004	
1	**4a**	50.71	66.55	77.98	82.64	0.8032
2	**4b**	49.24	58.32	64.01	69.49	0.9807
3	**4c**	50.18	60.02	69.51	76.08	0.9128
4	**4d**	49.6	58.41	68.56	75.28	1.0219
5	**4e**	50.22	66.68	74.8	80.91	0.7864
6	**4f**	51.72	66.79	75.05	85.17	0.7176
7	**4g**	48.01	59.5	68.73	73.34	1.0924
8	**4h**	51.71	58.14	72.41	83.44	1.0275
9	**4i**	50.29	57.01	69.29	76.32	1.0570
10	**4j**	49.11	57.41	66.98	73.67	1.0896
11	**4k**	48.64	60.28	67.35	77.78	1.0811
12	**4l**	49.21	60.91	75.28	86.66	1.0812
13	**4m**	48.62	69.65	71.14	72.18	1.0322
14	**4n**	50.14	59.02	67.82	78.34	1.0220
15	**4o**	49.08	58.74	63.33	70.32	1.0114
16	**Std**	58.09	67.7	79.16	97.62	0.5758

[a] *Std* = Ascorbic acid

Experimental section

Materials and methods

The reagents used for the reactions were commercially procured and used without further purification. The completion of the reaction were monitored by TLC. All the **MW** reactions were carried out in a UWave-1000 **MW**·Uv·Us Synthesis/Extraction Reactor. IR spectrum was recorded on a SHIMADZU Infrared spectrophotometer (400–4000 cm^{-1}; resolution: 1 cm^{-1}) using KBr pellets. The ^{1}H NMR (at 400 MHz) and ^{13}C NMR (at 100 MHz) were analysed using a Bruker Avance 400 Mz spectrometer in $CDCl_3$ solution with TMS as an internal standard. Chemical shift values (δ) were expressed in parts per million (ppm). The abbreviations are as follows: s, singlet; d, doublet; t, triplet; m, multiplet. The melting points were measured on an Elchem Microprocessor-based DT apparatus using an open capillary tube and are corrected with standard benzoic acid. The ESI–MS data were obtained using high resolution mass spectroscopy (HRMS).

General procedure for synthesis of dihydro-triazolo-quinazolinones, 4a–o

Equimolar quantities of 3-amino-1,2,4-triazole, **1** (10 mmol), substituted benzaldehyde, **2a–o** (10 mmol), 1,3-cylohexanedione, **3** (10 mmol) were mixed and

irradiated at 150 W for 60 s. About 15 mmol of ceric ammonium nitrate was dissolved in 10 mL of water, and this was added to the reaction mixture dropwise. Further, it was subjected to MW irradiation for another 2 min at 150 W. The reaction process was monitored by TLC. The reaction mass was washed with water to get 9-phenyl susbtitued-6,7-dihydro-[1,2,4] triazolo[5,1-*b*]quinazolin-8(5*H*)-ones, **4a–o**.

DPPH radical scavenging assay

The radical scavenging activity was carried out by the reported method [55]. Briefly, 1 mL of 0.1 mM DPPH in DMSO was added to 2.5 mL of synthesized samples, **4a–o,** at different concentrations (0.001, 0.002, 0.003, 0.004 mM) and placed for incubation for 30 min at room temperature. The absorbance of incubated solutions and control (without sample) were measured using a Hitachi U2910 spectrophotometer at 517 nm. Ascorbic acid was used as a standard antioxidant. The percentage inhibition was calculated according to the following formula.

$$\% \text{ Inhibition } = [A_0 - A_t/A_0] \times 100$$

here A_0 is the absorbance of control and A_t is the absorbance of tested samples at particular time. The antioxidant activity was expressed as IC_{50}. IC_{50} is the half minimal inhibitory concentration of a substance or drug.

The yields of all the synthesized compounds, **4a–o,** are summarized in Table 3 and the spectral data are given below.

9-phenyl-6,7-dihydro-[1,2,4] triazolo[5,1-b]quinazolin-8(5H)-one, ***4a***

Pale yellow solid; mp 198–200 °C; IR (KBr, υ_{max}/cm^{-1}): 3030, 2856, 1687, 1593, 1577, 1485, 736; ^{1}H NMR (400 MHz, $CDCl_3$): $\boldsymbol{\delta}$ (ppm), 2.23–2.29 (m, CH_2, 2H), 2.74 (t, $J = 6.4$ Hz, CH_2, 2H), 3.35 (t, $J = 6$ Hz, CH_2, 2H), 7.42–7.44 (m, ArH, 2H), 7.56–7.62 (m, ArH, 3H), 8.46 (s, ArH, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\boldsymbol{\delta}$ (ppm), 20.6 (CH_2), 34.4 (CH_2), 40.0 (CH_2), 115.7, 128.4 (2C), 128.6 (2C), 129.5, 130.8, 151.3, 154.8 (N–HC=N), 157.9, 169.31, 194.8 (C=O). HRMS: *m/z* calcd for $C_{15}H_{12}N_4O$: 264.1011, found: 264.1010.

9-(4-nitrophenyl)-6,7-dihydro-[1,2,4] triazolo[5,1-b]quinazolin-8(5H)-one, ***4b***

Half white solid; mp 168–170 °C; IR (KBr, υ_{max}/cm^{-1}): 3051, 2852, 1695, 1589, 1525, 1489, 740; ^{1}H NMR (400 MHz, $CDCl_3$): $\boldsymbol{\delta}$ (ppm), 2.26–2.33 (m, CH_2, 2H), 2.76 (t, $J = 6.4$ Hz, CH_2, 2H), 3.39 (t, $J = 6.4$ Hz, CH_2, 2H), 7.61 (d, $J = 8.8$ Hz, ArH, 2H), 8.44 (t, $J = 8$ Hz, ArH, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\boldsymbol{\delta}$ (ppm), 20.5 (CH_2), 29.7 (CH_2), 34.3 (CH_2), 39.8, 115.6, 123.9 (2C), 129.7 (2C), 136.1, 148.6, 148.8, 154.8 (N–HC=N), 158.2, 169.3, 194.7 (C=O). HRMS: *m/z* calcd for $C_{15}H_{11}N_5O_3$: 309.0862, found: 309.0860.

5-(3-nitrophenyl)-8,9-dihydro-[1,2,4] triazolo[3,4-b]quinazolin-6(7H)-one, ***4c***

Half white solid; mp 182–184 °C; IR (KBr, υ_{max}/cm^{-1}): 3039, 2881, 1695, 1595, 1514, 744; ^{1}H NMR (400 MHz, $CDCl_3$): $\boldsymbol{\delta}$ (ppm), 2.27–2.33 (m, CH_2, 2H), 2.77 (t, $J = 6.4$ Hz, CH_2, 2H), 3.39 (t, $J = 6.4$ Hz, CH_2, 2H), 7.78–7.81 (m, ArH, 2H), 8.47 (s, ArH, 1H) 8.46 (m, ArH, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): $\boldsymbol{\delta}$ (ppm), 20.5 (CH_2), 34.4 (CH_2), 39.9 (CH_2), 115.7, 124.2, 125.4, 129.7, 131.1, 134.6, 148.2, 148.2, 154.8 (N–HC=N), 158.2, 169.3, 194.7 (C=O). HRMS: *m/z* calcd for $C_{15}H_{11}N_5O_3$: 309.0862, found: 309.0860.

9-(2-nitrophenyl)-6,7-dihydro-[1,2,4]triazolo[5,1-b]quinazolin-8(5H)-one, ***4d***

Half white solid; mp 206–208 °C; IR (KBr, υ_{max}/cm^{-1}): IR: 3030, 2856, 1697, 1589, 1516, 734; ^{1}H NMR (400 MHz, $CDCl_3$): $\boldsymbol{\delta}$ (ppm), 2.32–2.31 (m, CH_2, 2H), 2.70 (t, $J = 6.4$ Hz, CH_2, 2H), 3.38 (t, $J = 6.8$ Hz, CH_2, 2H), 7.31–7.33 (m, ArH, 1H), 7.78–7.87 (m, ArH, 2H), 8.42–8.48 (m, ArH, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): $\boldsymbol{\delta}$ (ppm), 20.6 (CH_2), 34.1 (CH_2), 39.4 (CH_2), 114.8, 125.2, 126.6, 129.5, 131.3, 134.6, 146.7, 149.1, 154.8 (N–HC=N), 158.1, 169.2, 195.1 (C=O). HRMS: *m/z* calcd for $C_{15}H_{11}N_5O_3$:: 309.0862, found: 309.0860.

9-(4-isopropylphenyl)-6,7-dihydro-[1,2,4]triazolo[5,1-b]quinazolin-8(5H)-one, ***4e***

Pale yellow solid; mp 172–174 °C; IR (KBr, υ_{max}/cm^{-1}): 3097, 2960, 2875, 1691, 1591, 729; ^{1}H NMR (400 MHz, $CDCl_3$): $\boldsymbol{\delta}$ (ppm), 1.33 (d, $J = 7.2$ Hz, $2 \times CH_3$, 6H), 2.23–2.29 (m, CH_2, 2H), 2.74 (t, $J = 6$ Hz, CH_2, 2H), 2.99–3.06 (m, CH, 1H), 3.34 (t, $J = 6.4$ Hz, CH_2, 2H), 7.38–7.45 (m, ArH, 4H), 8.47 (s, ArH, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\boldsymbol{\delta}$ (ppm), 20.6 (CH_2), 23.7 (CH_3, 2C), 34.1 (CH), 34.4 (CH_2), 40.0 (CH_2), 115.8, 126.6 (2C), 126.7, 128.7 (2C), 151.7, 151.8, 154.9 (N–HC=N), 157.9, 169.2, 195.0 (C=O). HRMS: *m/z* calcd for $C_{18}H_{18}N_4O$: 306.1481, found: 306.1480.

9-(p-tolyl)-6,7-dihydroS-[1,2,4]triazolo[5,1-b]quinazolin-8(5H)-one, ***4f***

Pale yellow solid; mp 200–202 °C; IR (KBr, υ_{max}/cm^{-1}): 3099, 2922, 1689, 1639, 1539, 1300, 748; ^{1}H NMR (400 MHz, $CDCl_3$): $\boldsymbol{\delta}$ (ppm), 2.22–2.29 (m, CH_2, 2H), 2.47 (s, CH_3, 3H), 2.74 (t, $J = 6.4$ Hz, CH_2, 2H), 3.34 (t, $J = 6$ Hz, CH_2, 2H), 7.33–7.40 (m, ArH, 4H), 8.45 (s, ArH, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\boldsymbol{\delta}$ (ppm), 20.6 (CH_2), 21.7 (CH_3), 34.4 (CH_2), 40.0 (CH_2), 115.7, 126.5 (2C), 128.5, 129.3 (2C), 141.3, 151.6, 154.8 (N–HC=N), 157.9, 169.2, 194.9 (C=O). HRMS: *m/z* calcd for $C_{16}H_{14}N_4O$: 278.1168, found: 278.1165.

9-(3,4-dimethoxyphenyl)-6,7-dihydro-[1,2,4]triazolo[5,1-b]quinazolin-8(5H)-one, ***4g***

Yellow solid; mp 164–166 °C; IR (KBr, υ_{max}/cm^{-1}): IR: 3105, 2835, 1697, 1633, 1593, 1458, 763; ^{1}H NMR (400 MHz, $CDCl_3$): $\boldsymbol{\delta}$ (ppm), 2.23–2.30 (m, CH_2, 2H),

2.76 (t, $J = 6.4$ Hz, CH_2, 2H), 3.34 (t, $J = 6$ Hz, CH_2, 2H), 3.9 (d, $J = 6.4$ Hz, 2 x OCH_3, 6H), 6.99 (d, $J = 1.6$ Hz, ArH, 1H), 7.03–7.08 (m, ArH, 2H), 8.46 (s, ArH, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): **δ** (ppm), 20.6 (CH_2), 34.5 (CH_2), 40.1 (CH_2), 55.9 (OCH_3), 56.0 (OCH_3), 110.8, 112.2, 115.7, 121.2, 122.3, 148.9, 151.2, 151.2, 154.9 (N–HC=N), 157.8, 169.2, 194.9 (C=O). HRMS: *m/z* calcd for $C_{17}H_{16}N_4O_3$: 324.1222, found: 324.1220.

9-(2,4-dimethoxyphenyl)-6,7-dihydro-[1,2,4]triazolo[5,1-b]quinazolin-8(5H)-one, ***4h***

Pale Yellow solid; mp 214–216 °C; IR (KBr, υ_{max}/cm^{-1}): IR: 3099, 2954, 1703, 1589, 1496, 790; ^{1}H NMR (400 MHz, $CDCl_3$): **δ** (ppm), 2.21–2.27 (m, CH_2, 2H), 2.70–2.75 (m, CH_2, 2H), 3.30–3.34 (m, CH_2, 2H), 3.7 (s, OCH_3, 3H), 3.89 (s, OCH_3, 3H), 6.59 (d, $J = 1.6$ Hz, ArH, 1H), 6.67–6.70 (m, ArH, 1H), 7.30 (t, $J = 8.4$ Hz, ArH, 1H), 8.44 (s, ArH, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): **δ** (ppm), 20.7 (CH_2), 34.3 (CH_2), 39.7 (CH_2), 55.5 (OCH_3), 55.6 (OCH_3), 99.0, 105.0, 111.2, 116.8, 130.6, 148.3, 155.0 (N–HC = N), 157.5, 158.0, 163.2, 168.5, 195.0 (C=O). HRMS: *m/z* calcd for $C_{17}H_{16}N_4O_3$: 324.1222, found: 324.1220.

9-(4-methoxyphenyl)-6,7-dihydro-[1,2,4]triazolo[5,1-b]quinazolin-8(5H)-one, ***4i***

Half white solid; mp 194–196 °C; IR (KBr, υ_{max}/cm^{-1}): 3015, 2954, 2835, 1693, 1608, 1589, 1496, 752; ^{1}H NMR (400 MHz, $CDCl_3$): **δ** (ppm), 2.24–2.29 (m, CH_2, 2H), 2.75 (t, $J = 6.4$ Hz, CH_2, 2H), 3.33 (t, $J = 6$ Hz, CH_2, 2H), 3.90 (s, OCH_3, 3H), 7.06–7.09 (m, ArH, 2H), 7.44–7.48 (m, ArH, 2H) 8.46 (s, ArH, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): **δ** (ppm), 20.6 (CH_2), 34.5 (CH_2), 40.1 (CH_2), 55.4 (OCH_3), 113.9, 115.6 (2C), 121.0, 131.0 (2C), 151.0, 154.9 (N–HC=N), 157.8, 161.7, 169.2, 195.1 (C=O). HRMS: *m/z* calcd for $C_{16}H_{14}N_4O_2$: 294.1117, found: 294.1115.

9-(3-methoxyphenyl)-6,7-dihydro-[1,2,4]triazolo[5,1-b]quinazolin-8(5H)-one, ***4j***

Half white solid; mp 190–192 °C; IR (KBr, υ_{max}/cm^{-1}): 3015, 2954, 2835, 1693, 1593, 1577, 1483, 750; ^{1}H NMR (400 MHz, $CDCl_3$): **δ** (ppm), 2.23–2.29 (m, CH_2, 2H), 2.74 (t, $J = 6.4$ Hz, CH_2, 2H), 3.35 (t, $J = 6.4$ Hz, CH_2, 2H), 3.84 (s, OCH_3, 3H), 6.96–6.98 (m, ArH, 2H), 7.11–7.14 (m, ArH, 1H), 7.50 (t, $J = 7.6$ Hz, ArH, 1H), 8.46 (s, ArH, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): **δ** (ppm), 20.6 (CH_2), 34.5 (CH_2), 40.0 (CH_2), 55.3 (OCH_3), 114.1, 115.8, 116.0, 120.3, 129.9, 130.7, 151.0, 154.8 (N–HC=N), 157.9, 159.6, 169.2, 194.6 (C=O). HRMS: *m/z* calcd for $C_{16}H_{14}N_4O_2$: 294.1117, found: 294.1115.

9-(4-bromophenyl)-6,7-dihydro-[1,2,4]triazolo[5,1-b]quinazolin-8(5H)-one, ***4k***

Half white solid; mp 242–244 °C; IR (KBr, υ_{max}/cm^{-1}): 3105, 2881, 1689, 1562, 1581, 1481, 750; ^{1}H NMR (400 MHz, $CDCl_3$): **δ** (ppm), 2.23–2.30 (m, CH_2, 2H), 2.75 (t, $J = 6.8$ Hz, CH_2, 2H), 3.35 (t, $J = 6.4$ Hz, CH_2, 2H), 7.32 (d, $J = 8.4$ Hz, ArH, 2H), 7.71 (d, $J = 8.4$ Hz, ArH, 2H), 8.46 (s, ArH, 1H); ^{13}C NMR (100 MHz,

$CDCl_3$): **δ** (ppm), 20.5 (CH_2), 34.4 (CH_2), 40.0 (CH_2), 115.6, 125.5 (2C), 128.3, 130.2 (2C), 131.9, 150.1, 154.8 (N–HC=N), 158.0, 169.2, 194.8 (C=O). HRMS: *m/z* calcd for $C_{15}H_{11}BrN_4O$: 342.0116, found: 342.0115.

9-(3-bromophenyl)-6,7-dihydro-[1,2,4]triazolo[5,1-b]quinazolin-8(5H)-one, ***4l***

Half white solid; mp 198–200 °C; IR (KBr, υ_{max}/cm^{-1}): 3051, 2854, 1687, 1602, 1591, 1471, 752; ^{1}H NMR (400 MHz, $CDCl_3$): **δ** (ppm), 2.24–2.30 (m, CH_2, 2H), 2.75 (t, $J = 6.4$ Hz, CH_2, 2H), 3.36 (t, $J = 6$ Hz, CH_2, 2H), 7.35–7.37 (m, ArH, 1H), 7.46 (t, $J = 8$ Hz, ArH, 1H), 7.55 (t, $J = 1.6$ Hz, ArH, 1H), 7.72–7.75 (m, ArH, 1H), 8.47 (s, ArH, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): **δ** (ppm), 20.5 (CH_2), 34.4 (CH_2), 39.9 (CH_2), 115.6, 122.6, 127.0, 130.1, 131.2, 131.4, 133.7, 149.4, 154.8 (N–HC=N), 158.1, 169.2, 194.6 (C=O). HRMS: *m/z* calcd for $C_{15}H_{11}BrN_4O$: 342.0116, found: 342.0115.

9-(2-bromophenyl)-6,7-dihydro-[1,2,4]triazolo[5,1-b]quinazolin-8(5H)-one, ***4m***

Half white solid; mp 252–254 °C; IR (KBr, υ_{max}/cm^{-1}): 3101, 2945, 1693, 1597, 1519, 1423, 750; ^{1}H NMR (400 MHz, $CDCl_3$): **δ** (ppm), 2.26–2.31 (m, CH_2, 2H), 2.68–2.82 (m, CH_2, 2H), 3.37–3.40 (m, CH_2, 2H), 7.28 (d, $J = 2$ Hz, ArH, 1H), 7.45–7.57 (m, ArH, 2H), 7.76–7.85 (m, ArH, 1H), 8.49 (s, ArH, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): **δ** (ppm), 20.6 (CH_2), 34.3 (CH_2), 39.6 (CH_2), 116.0, 121.0, 127.8, 129.0, 131.6, 131.8, 133.0, 149.2, 154.9 (N–HC=N), 158.2, 169.0, 194.4 (C=O). HRMS: *m/z* calcd for $C_{15}H_{11}BrN_4O$: 342.0116, found: 342.0116.

9-(4-chlorophenyl)-6,7-dihydro-[1,2,4]triazolo[5,1-b]quinazolin-8(5H)-one, ***4n***

Half white solid; mp 220–222 °C; IR (KBr, υ_{max}/cm^{-1}): 57, 2854, 1691, 1587, 1562, 1487,752; ^{1}H NMR (400 MHz, $CDCl_3$): **δ** (ppm), 2.23–2.30 (m, CH_2, 2H), 2.75 (t, $J = 6.4$ Hz, CH_2, 2H), 3.35 (t, $J = 6.4$ Hz, CH_2, 2H), 7.39 (d, $J = 8.4$ Hz, ArH, 2H), 7.55 (d, $J = 8.4$ Hz, ArH, 2H) 8.46 (s, ArH, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): **δ** (ppm), 20.5 (CH_2), 34.4 (CH_2), 40.0 (CH_2), 115.7, 127.8, 129.0 (2C), 130.1 (2C), 137.1, 150.1, 154.8 (N–HC=N), 158.0, 169.2, 194.8 (C=O). HRMS: *m/z* calcd for $C_{15}H_{11}ClN_4O$: 298.0621, found: 298.0620.

9-(2-chlorophenyl)-6,7-dihydro-[1,2,4]triazolo[5,1-b]quinazolin-8(5H)-one, ***4o***

Pale yellow solid; mp 242–244 °C; IR (KBr, υ_{max}/cm^{-1}): 3103, 2897, 1693, 1600, 1589, 1469, 704; ^{1}H NMR (400 MHz, $CDCl_3$): **δ** (ppm), 2.24–2.31 (m, CH_2, 2H), 2.68–2.82 (m, CH_2, 2H), 3.36–3.40 (m, CH_2, 2H), 7.21–7.31 (m, ArH, 1H), 7.47–7.61 (m, ArH, 3H), 8.48 (s, ArH, 1H,–NH); ^{13}C NMR (100 MHz, $CDCl_3$): **δ** (ppm), 20.6 (CH_2), 34.2 (CH_2), 39.6 (CH_2), 116.2, 127.2, 129.0, 129.6, 129.9, 131.6, 131.9, 148.0, 154.9 (N–HC=N), 158.1, 169.0, 195.5 (C=O). HRMS: *m/z* calcd for $C_{15}H_{11}ClN_4O$: 298.0621, found: 298.0620.

Conclusion

We have successfully reported a simple and green protocol for the synthesis of new dihydro-triazolo-quinazolinone derivatives, **4a–o,** by applying views of green chemistry. The reaction proceeds in a minimal reaction time, has good atom economy, is a simple experiment with easy work-up using a benign solvent such as water, and has a high conversion with good yields. In addition, these new derivatives were evaluated for their antioxidant activities and the results reveal that the compounds **4e** and **4f** showed promising free radical scavenging ability towards the DPPH.

Acknowledgments One of the authors, Dr. S. Mohana Roopan, thanks DST-FTYS Fast Track (No. SB/FT/CS-126/2012), Government of India, New Delhi, for providing the research grants. The authors wish to express their gratitude to SIF, VIT University, for NMR support. The other author, Mr. Rajesh Sompalle, wishes to thank the VIT University Management for providing RA fellowship and the infrastructure. Finally, we also thank Dr. G. Madhumitha, Assistant Professor, School of Advanced Sciences, VIT University, for granting access to the microwave instrumentation.

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