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Chapter

One-Pot-Condensation Reaction of Heterocyclic Amine, 1,3-Diketone and Aldehydes Using *In Situ* Generated Superoxide Ion: A Rapid Synthesis of Structurally Diverse Drug-Like Complex Heterocycles

Sundaram Singh and Savita Kumari

Abstract

A novel, convenient one-pot multicomponent synthesis of tetraheterocyclicbenzimidazolo/benzothiazolo quinazolin-1-one derivatives has been reported in the presence of tetraethylammonium superoxide under non-aqueous condition. The superoxide induced three-component reaction of various aromatic aldehydes, 2-aminobenzimadazole/2-aminobenzothiazole and dimedone/1,3- cyclohexanedione produced tetraheterocyclicbenzimidazolo/benzothiazolo quinazolin-1-one derivatives at room temperature under the mild reaction conditions. The tetraethylammonium superoxide has been generated by phase transfer reaction of potassium superoxide and tetraethylammonium bromide in dry DMF at room temperature. The present study extended the applicability of tetraethylammonium bromide as a phase transfer catalyst for the efficient use of superoxide ion in multi-component synthesis of structurally diverse drug-like complex heterocycles (quinazolines).

Keywords: superoxide ion, multicomponent reaction, Tetraethylammonium bromide, phase transfer catalyst, KO_2

1. Introduction

The importance of oxygen in sustaining life is unquestionable but the aerobic life-style is fraught with danger. However, some recent reports about oxygen toxicity have caused much concern among the whole scientific community. The oxygen toxicity is due to various reactive oxygen species (ROS) such as hydroxyl radical ($HO^{\bullet}$), superoxide anion radical $O_2^{\bullet -}$, and perhydroxyl radical. Hypochlorous acid (HOCl), hydrogen peroxide (H_2O_2), singlet oxygen and ozone are also included in this category, although they are not free radicals but can lead to free radical reaction. Out of all the reactive oxygen species, superoxide anion radical is probably the most important ROS, which has come to the forefront of current chemical and

biochemical research for the two reasons [1–4]. First superoxide ion as a biochemical species which causes many diseases such as cancer, ageing, inflammation, heart attack and lung injury, etc. More recently, it has been implicated to play a key role in both aging and cancer. Second superoxide ion as a novel reagent. Further from its elementary reactivity pattern, this anion radical has been recognized as a multipotent reagent, which acts as a base, nucleophile, oxidant and reductant. In view of these two points, superoxide research has become an area of interdisciplinary investigation [5–13].

Multi-component reactions (MCRs), in which multiple reactions are combined into one synthetic operation, have been used extensively to form carbon-carbon bonds in synthetic chemistry. Such reactions offer greater possibilities for molecular diversity per step with minimum reaction time, labor, cost, and waste production. The rapid assembly of molecular diversity utilizing MCRs has gained a great deal of attention, most notably for the construction of 'drug-like' libraries [14–20].

Quinazolines are very interesting heterocycles [21–25] as they serve as building blocks in numerous natural and synthetic products [26]. They exhibit a wide spectrum of biological and pharmacological activities such as propyl hydroxylase inhibitor [27], antidiabetics [28], anti-inflammatory [29], antiviral [30], antimicrobial [31], antineoplastic [32] and potent immunosuppressive agents [33]. Moreover, benzimidazolo quinazolines have also been an important class of heterocyclic compounds in drug research, as they are formed from both biodynamic heterosystems, benzimidazole and quinazoline, which have shown significant anticancer activities. Many useful methods, have been reported for synthesis of tetrahydrobenzoimidazo [2,1-b] quinazolin-1(2H)-ones ring system skeletons, such as the condensation of aminoazoles with benzylidene compounds, or three-component condensation of 2-aminobenzothiazole or 2-aminobenzimidazole and an aldehyde with cyclic 1,3-diketone. These reported methodologies produce good results in many cases [34, 35]. However, some of them suffer with certain limitations such as expensive catalysts, low yields of products, long reaction times, tedious procedures for preparations of catalysts, and tedious workup conditions [36–40]. Thus, there is enough room for further investigation in this direction. With a view to investigate the behavior of the superoxide ion in multicomponent organic synthesis, which is of importance in itself and further to assess its synthetic scope, the reaction of this novel reagent was studied.

2. Results and discussion

In continuation of our ongoing program on superoxide research and the synthesis of biologically active compounds, it is our current endeavor to extent the applicability of Et_4NO_2 for the synthesis of tetraheterocyclicBenzimidazolo/benzothiazolo quinazolin-1-one ring systems **4** by a one-pot three-component condensation reaction of various aromatic aldehydes **2** and 1,3-diketones **3** with 2-aminobenzimidazole/2-aminobenzothiazole **1** using tetraethylammonium superoxide under non aqueous conditions (**Figure 1**).

In order to achieve the optimum yield of the product, the effect of various parameters such as effect of solvents (DMF, DMSO, and CH_3CN) and molar proportion of the reactants were investigated in detail using benzaldehyde **2**, dimedone **3** with 2-aminobenzimidazole **1** as a model reaction.

To investigate the effect of solvents, the model reaction was carried out in different aprotic solvents. The results obtained clearly indicate that DMF was the best solvent among all investigated solvents in terms of product yield and the reaction time (**Table 1**).

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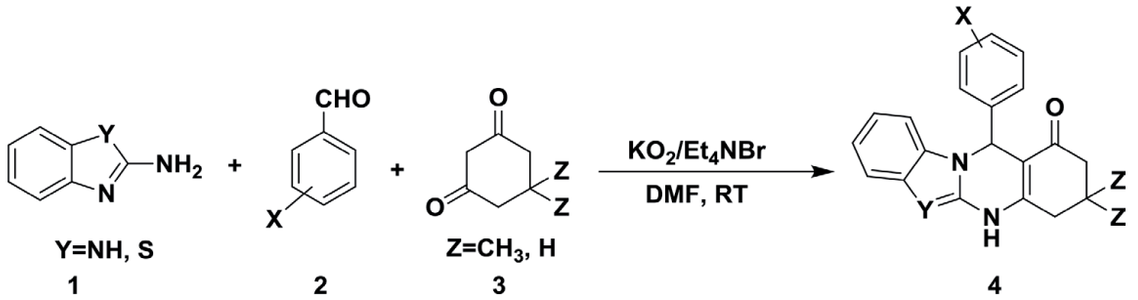


Figure 1.
One-pot synthesis of compounds **4** *by the three-component condensation reaction of various aldehydes and 1,3-diketones with 2-aminobenzimidazole/2-aminobenzothiazole under superoxide ion at room temperature.*

Entry	Solvents	Time	%Yield
1	Dichloromethane	12 h	Trace
2	Acetonitrile	8 h	70
3	Tetrahydrofuran	14 h	42
4	Dimethylsulfoxide	20 h	Trace
5	Dimethylformamide	6 h	88

Table 1.
Effect of solvents on the yield of the product 4a.

Entry	Reactants molar ratio					Product yield* (%)
	Benzaldehydes:dimidone:2-aminobezimidazole:KO_2:Et_4NBr					
1	1.0	1.0	1.0	1.0	1.0	40
2	1.0	1.0	1.0	1.0	0.5	38
3	1.0	1.0	1.0	1.0	0.25	28
4	1.0	1.0	1.0	2.5	1.25	69
5	**1.0**	**1.0**	**1.0**	**4.0**	**2.00**	**88**
6	1.0	1.0	1.0	6.0	3.00	90

**Isolated yield based on aldehyde.*
Optimized condition has been shown by bold letter (entry 5).

Table 2.
Effect of reactants molar ratio on the yield of product 4a.

In order to establish the reactants molar ratio on the yield of product the model reaction was carried out in different concentration of reactants (**Table 2**).

A perusal of the table clearly indicates the profound effect of the concentration of KO_2 and Et_4NBr on the yield of the product **4a**. As regards the ratio of KO_2 and Et_4NBr, it is evident from the entries 1, 2 and 3 that with the diminution of the concentration of Et_4NBr, the yield of product **4a** decreases. But as may be seen only a little difference in the yield of the product in the case of entries 1 and 2, the ratio of KO_2 and Et_4NBr was further kept to be 2:1. Therefore, in subsequent studies, the concentration of KO_2 has been increased manifold but the ratio of KO_2 and Et_4NBr was all along maintained to be 2:1. Furthermore, in case of entries 5 and 6, there is just a 2% increase in the yield of the product and for that 2% increase, the concentration of KO_2 and Et_4NBr have been increased

substantially (6 fold and 3 fold respectively). As a result, considering the high cost of KO_2 and Et_4NBr, the entry 5, with the reactants ratio **1:1:1:4:2**, has been selected as the optimum ratio.

The scope and limitations of this reaction were fully illustrated with various *ortho-, meta- and para-substituted* benzaldehydes in the presence of 2-aminobenzimidazole and 2-aminobenzothiazole.

As indicated in **Table 3**, the reaction proceeded efficiently with both electron-withdrawing and electron releasing *ortho-, meta- and para-*substituted benzaldehydes.

The products were identified by their physical and spectral data, which were in full agreement with the reported values.

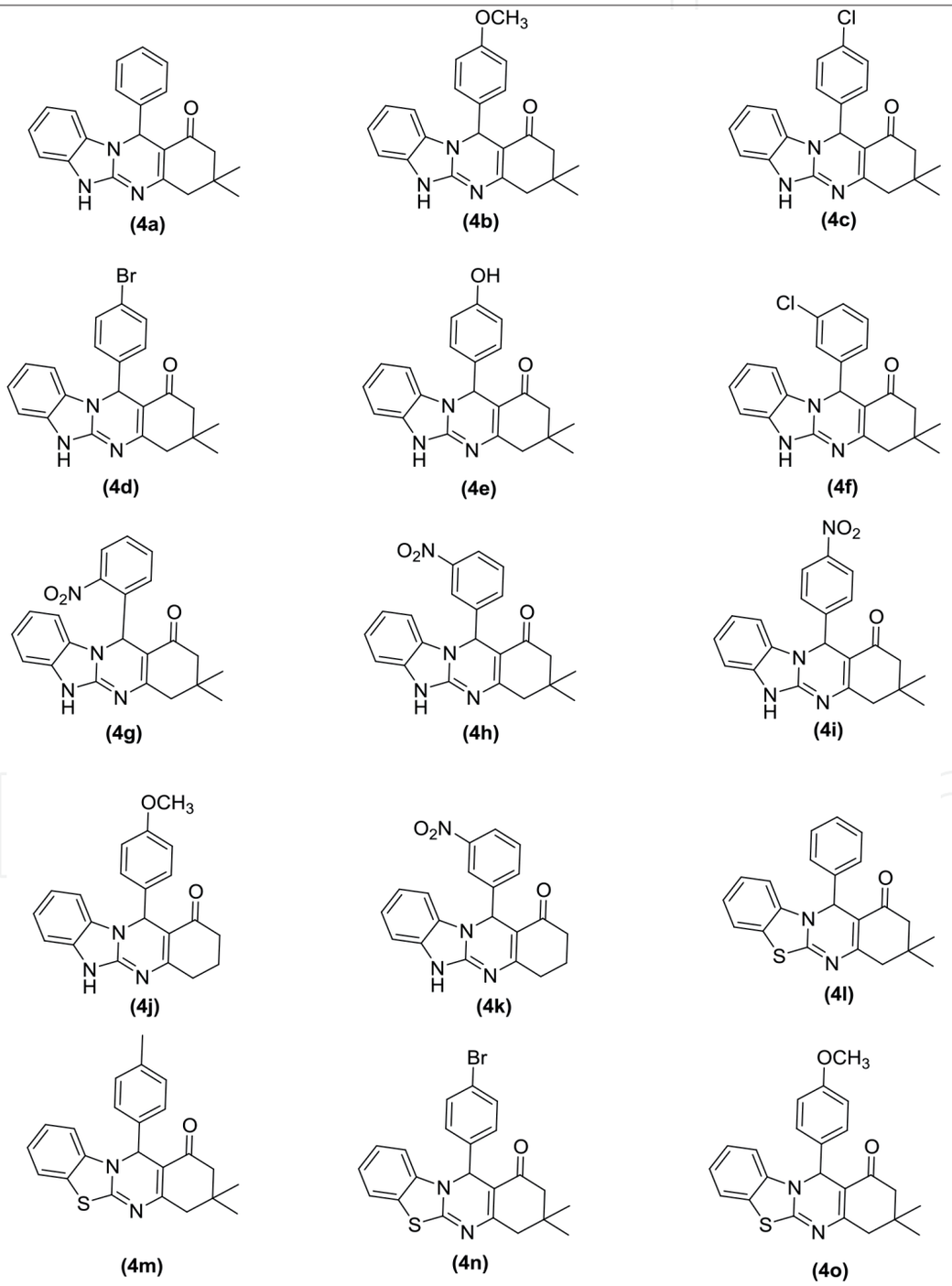


Table 3.
Synthesis of tetraheterocyclicbenzimidazolo/benzothiazolo quinazolin-1-ones.

2.1 Mechanism for the synthesis of tetraheterocyclicbenzimidazolo/benzothiazolo quinazolin-1-ones

The proposed mechanism for the formation of tetraheterocyclicbenzimidazolo/benzothiazolo quinazolin-1-ones ring system is given in **Figure 2**. The reaction was initiated by the abstraction of proton from 1,3-diketones **3** by tetraethylammonium superoxide which was *in situ* generated by the phase transfer reaction of potassium superoxide with tetraethylammonium bromide. Now, Knoevenagel condensation takes place between benzaldehyde **2** and subsequently, by dehydration, olefin 3-benzylidene-2,4-hexanedione **5** is produced. Then 2-aminobenzimidazole/2-aminobenzothiazole**1** is reacted with compound **5** through a Michael addition to produce a product of type **6** and after cyclisation to afford tetraheterocyclicbenzimidazolo/benzothiazolo quinazolin-1-one ring systems **4**.

Potassium superoxide (1.42 g, 0.02 mol) and tetraethylammonium bromide (2.10 g, 0.01 mol) were weighed under nitrogen atmosphere using an atmosbag and were transferred into a three-necked R. B. flask, dry DMF (20 mL) was added to it and the mixture was agitated magnetically for 15 min to facilitate the formation of tetraethylammoniumsuperoxide. To the stirred reaction mixture, dimedone (0.70 g, 0.005 mol) **3** were added. After 10 min, benzaldehyde (0.53 g, 0.005 mol) **2** and 2-aminobenzimidazole (0.665 g, 0.005 mmol) **1** were introduced, and the stirring was continued 6 h. After the reaction was over as indicated by TLC, mixture was treated with cold brine solution (2 mL) followed by saturated sodium hydrogen carbonate solution (2 mL) to decompose the unreacted KO_2. The mixture was then extracted with dichloromethane (3 × 15 mL) and the combined organic phase was dried over anhydrous Na_2SO_4, filtered, and evaporated to give the products **4a**, which were purified by column chromatography.

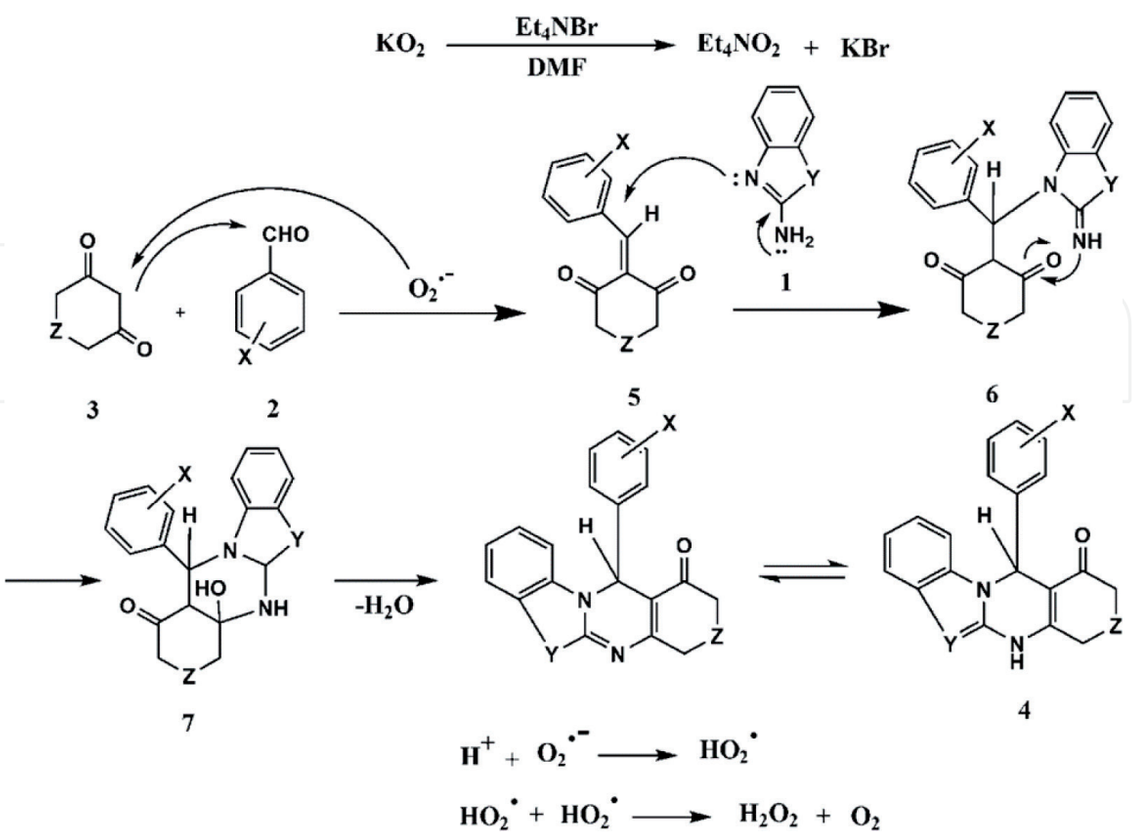


Figure 2.
*Plausible mechanism for the formation of tetraheterocyclicbenzimidazolo/benzothiazolo quinazolin-1-one derivatives (**4a-o**).*

All the products were characterized by IR and ^{1}H NMR (because of low solubility of compounds **4a-o**, ^{13}C NMR was not obtained).

3,3–Dimethyl–12–phenyl–3,4,6,12–tetrahydrobenzo[4,5]imidazo[2,1-b] quinazolin–1(2H)–one (4a): M.p. > 300°C; IR (KBr, υ = cm^{-1}) 3445, 2885, 1640, 1618, 1610, 1565 cm^{-1}; ^{1}H NMR (500 MHz, DMSO–d_6): δ = 11.16 (br. s, 1H, NH), 7.39–7.30 (m, 6H), 7.23 (d, J = 8.0 Hz, 1H), 7.07–7.04 (m, 1H), 6.98–6.95 (m, 1H), 6.44 (s, 1H), 2.26 (d, J = 16.0 Hz, 2H), 2.06 (d, J = 16.0 Hz, 2H), 1.06 (s, 3H), 0.92 (s, 3H). Anal. Calcd for $C_{22}H_{21}N_3O$: C, 76.94; H, 6.16; N, 12.24; O, 4.66. Found: C, 76.90; H, 6.20; N, 12.26; O, 4.64.

12–(4–Methoxyphenyl)–3,3–dimethyl–3,4,6,12–tetrahydrobenzo[4,5] imidazo[2,1-b]quinazolin–1(2H)–one (4b): M.p. > 300°C; IR (KBr, υ = cm^{-1}) 3391, 2850, 1670, 1644, 1610, 1590 cm^{-1};^{1}H NMR (500 MHz, DMSO–d_6): δ = 11.06 (br. s, 1H, NH), 7.36 (d, J = 8.0 Hz, 1H), 7.26–7.24 (m, 3H), 7.04 (t, J = 7.5 Hz, 1H), 6.95 (t, J = 7.5 Hz, 1H), 6.78 (d, J = 8.5 Hz, 2H), 6.36 (s, 1H), 3.65 (s, 3H), 2.64–2.52 (m, 2H), 2.25 (d, J = 16.0 Hz, 1H), 2.05 (d, J = 16.0 Hz, 1H), 1.06 (s, 3H), 0.94 (s, 3H). Anal Calcd for $C_{23}H_{23}N_3O_2$: C, 73.97; H, 6.21; N, 11.25; O, 8.57. Found: C, 73.92; H, 6.26; N, 11.23; O, 8.59.

12–(4–Chlorophenyl)–3,3–dimethyl–3,4,6,12–tetrahydrobenzo[4,5] imidazo[2,1-b] quinazolin–1(2H)–one (4c): M.p. > 300°C; IR (KBr, υ = cm^{-1}) 3440, 2934, 1655, 1650, 1613, 1580 cm^{-1}; ^{1}H NMR (500 MHz, DMSO–d_6): δ = 11.10 (br. s, 1H, NH), 7.36 (d, J = 7.5 Hz, 1H), 7.33 (d, J = 6.5 Hz, 2H), 7.24 (s, 2H), 7.15 (s, 1H), 7.04 (s, 1H), 6.95 (s, 1H), 6.41 (s, 1H), 2.63 (d, J = 16.0 Hz, 2H), 2.26 (d, J = 16.0 Hz, 2H), 1.06 (s, 3H), 0.93 (s, 3H). Anal. Calcd for $C_{22}H_{20}ClN_3O$: C, 69.93; H, 5.34; Cl, 9.38; N, 11.12; O, 4.23. Found: C, 69.90; H, 5.37; Cl, 9.34; N, 11.15; O, 4.24.

12–(4–Bromophenyl)–3,3–dimethyl–3,4,6,12–tetrahydrobenzo[4,5] imidazo[2,1-b] quinazolin–1(2H)–one (4d): M.p. >300°C; IR (KBr, υ = cm^{-1}) 3441, 2956, 1645, 1614, 1590, 1566 cm^{-1}; ^{1}H-NMR (500 MHz, DMSO-d_6): δ = 10.01 (br. s, 1H, NH), 6.99–7.89 (m, Ar–H), 6.43 (s, 1H), 2.59–2.67 (m, 2H), 2.20 (d, J = 16.00 Hz, 1H), 2.00 (d, J = 16.01 Hz, 1H) 1.05 (s, 3H), 0.94 (s, 3H). Anal. Calcd for $C_{22}H_{20}BrN_3O$: C, 62.57; H, 4.77; Br, 18.92; N, 9.95; O, 3.79. Found: C, 62.67; H, 4.86; Br, 18.80; N, 9.83; O, 3.90.

12–(4–Hydroxyphenyl)–3,3–dimethyl–3,4,6,12–tetrahydrobenzo[4,5] imidazo[2,1-b] quinazolin–1(2H)–one (4e): M.p. > 300°C; IR (KBr, υ = cm^{-1}) 3449, 2891, 1642, 1613, 1587, 1566 cm^{-1}; ^{1}H-NMR (500 MHz, DMSO-d_6) δ = 11.02 (br. s, 1H, NH), 9.33 (s, 1H, OH), 6.61–7.36 (m, 8H, Ar–H), 6.18 (s, 1H), 2.51–2.74 (m, 2H), 2.25 (d, J = 9.24 Hz, 1H), 2.05(d, J = 8.94 Hz, 1H), 1.07 (s, 3H), 0.96 (s, 3H), Anal. Calcd for $C_{22}H_{21}N_3O_2$: C, 73.52; H, 5.89; N, 11.69; O, 8.90. Found: C, 73.63; H, 5.97; N, 11.80; O, 8.71.

12–(3–Chlorophenyl)–3,3–dimethyl–3,4,6,12–tetrahydrobenzo[4,5] imidazo[2,1-b] quinazolin–1(2H)–one (4f) M.p. > 300°C; IR (KBr, υ = cm^{-1}) 3400, 2891, 1660, 1652, 1613, 1575 cm^{-1}; ^{1}H NMR (500 MHz, DMSO–d_6): δ = 11.18 (br. s, 1H, NH), 7.46 (s, 1H), 7.39 (d, J = 8.0 Hz, 1H), 7.30–7.21 (m, 5H), 7.06 (s, 1H), 6.98 (s, 1H), 6.46 (s, 1H), 2.58 (d, J = 16.0 Hz, 1H), 2.26 (d, J = 16.0 Hz, 1H), 2.08 (d, J = 16.0 Hz, 1H), 1.06 (s, 3H), 0.93 (s, 3H). Anal. Calcd for $C_{22}H_{20}ClN_3O$: C, 69.93; H, 5.34; Cl, 9.38; N, 11.12; O, 4.23. Found: C, 69.90; H, 5.37; Cl, 9.35; N, 11.14; O, 4.24.

3,3–Dimethyl–12–(2–nitrophenyl)–3,4,6,12–tetrahydrobenzo[4,5] imidazo[2,1-b]quinazolin–1(2H)–one (4 g): M.p. > 300°C; IR (KBr, υ = cm^{-1}) 3398, 2972, 1664, 1645, 1618, 1594 cm^{-1}; ^{1}H NMR (500 MHz, DMSO–d_6): δ = 11.18 (br. s, 1H, NH), 7.46 (s, 1H), 7.31–7.19 (m, 5H), 7.06 (t, J = 7.5 Hz, 1H), 6.98 (t, J = 7.5 Hz, 1H), 6.46 (s, 1H), 2.62 (d, J = 16.0 Hz, 1H), 2.55 (s, 1H), 2.26 (d, J = 16.0 Hz, 1H), 2.08 (d, J = 16.0 Hz, 1H), 1.06 (s, 2H), 0.93 (s, 2H). Anal. Calcd

for $C_{22}H_{20}N_4O_3$: C, 68.03; H, 5.19; N, 14.42; O, 12.36. Found: C, 68.07; H, 5.15; N, 14.46; O, 12.32.

3,3–Dimethyl–12–(3–nitrophenyl)–3,4,6,12–tetrahydrobenzo[4,5] imidazo[2,1-b]quinazolin–1(2H)–one (4 h): M.p. > 300°C; IR (KBr, υ = cm^{-1}) 3394, 2970, 1660, 1648, 1615, 1598 cm^{-1}; ^{1}H NMR (500 MHz, DMSO–d_6): δ = 11.26 (br. s, 1H, NH), 8.27 (s, 1H), 8.04 (d, J = 8.0 Hz, 1H), 7.73 (d, J = 7.5 Hz, 1H), 7.56 (t, J = 8.0 Hz, 1H), 7.40 (d, J = 8.0 Hz, 1H), 7.29 (d, J = 8.0 Hz, 1H), 7.07 (t, J = 7.5 Hz, 1H), 6.97 (t, J = 7.5 Hz, 1H), 6.65 (s, 1H), 2.27 (d, J = 16.0 Hz, 2H), 2.07 (d, J = 16.0 Hz, 2H), 1.06 (s, 3H), 0.91 (s, 3H). Anal. Calcd for $C_{22}H_{20}N_4O_3$: C, 68.03; H, 5.19; N, 14.42; O, 12.36. Found: C, 68.08; H, 5.14; N, 14.44; O, 12.34.

3,3–Dimethyl–12–(4–nitrophenyl)–3,4,6,12–tetrahydrobenzo[4,5] imidazo[2,1-b]quinazolin–1(2H)–one (4i): M.p. > 300°C; IR (KBr, υ = cm^{-1}) 3396, 2980, 1662, 1641, 1612, 1594 cm^{-1}; ^{1}H NMR (500 MHz, DMSO–d_6): δ = 11.27 (br. s, 1H, NH), 8.12 (d, J = 8.5 Hz, 2H), 7.61 (d, J = 9.0 Hz, 2H), 7.40 (d, J = 7.5 Hz, 1H), 7.23 (d, J = 8.0 Hz, 1H), 7.07 (t, J = 7.5 Hz, 1H), 6.96 (t, J = 7.5 Hz, 1H), 6.60 (s, 1H), 2.65 (d, J = 16.0 Hz, 1H), 2.54 (d, J = 16.0 Hz, 1H), 2.27 (d, J = 16.0 Hz, 1H), 2.06 (d, J = 16.0 Hz, 1H), 1.06 (s, 3H), 0.91 (s, 3H). Anal. Calcd for $C_{22}H_{20}N_4O_3$: C, 68.03; H, 5.19; N, 14.42; O, 12.36. Found: C, 68.04; H, 5.18; N, 14.40; O, 12.38.

12–(4–Methoxyphenyl)–3,4,6,12–tetrahydrobenzo[4,5]imidazo[2,1-b] quinazolin–1(2H)–one (4j): M.p. = 238–240°C; IR (KBr, υ = cm^{-1}) 3398, 2976, 1666, 1642, 1616, 1575 cm^{-1}; ^{1}H NMR (500 MHz, DMSO–d_6): δ = 11.07 (br. s, 1H, NH), 7.36 (d, J = 8.0 Hz, 1H), 7.26–7.22 (m, 3H), 7.06–7.01 (m, 1H), 6.95 (t, J = 7.2 Hz, 1H), 6.78 (d, J = 8.0 Hz, 2H), 6.37 (s, 1H), 3.65 (s, 3H), 2.68 (d, J = 5.0 Hz, 2H), 2.29 (dd, J = 10.5, 5.0 Hz, 1H), 2.22 (dd, J = 16.0, 5.0 Hz, 1H), 2.02–1.93 (m, 1H), 1.88–1.80 (m, 1H). Anal. Calcd for $C_{21}H_{19}N_3O_2$: C, 73.03; H, 5.54; N, 12.17; O, 9.26. Found: C, 73.01; H, 5.56; N, 12.14; O, 9.29.

12–(3–Nitrophenyl)–3,4,6,12–tetrahydrobenzo[4,5]imidazo[2,1-b]quinazolin–1(2H)–one(4 k): M.p. > 300°C; IR (KBr, υ = cm^{-1}) 3412, 2872, 2855, 1670, 1640, 1617, 1601 cm^{-1};^{1}H NMR (500 MHz, DMSO–d_6): δ = 11.28 (br. s, 1H, NH), 8.26 (s, 1H), 8.03 (d, J = 8.5 Hz, 1H), 7.70 (d, J = 7.5 Hz, 1H), 7.54 (t, J = 8.0 Hz, 1H), 7.40 (d, J = 8.0 Hz, 1H), 7.26 (d, J = 7.5 Hz, 1H), 7.06 (t, J = 7.4 Hz, 1H), 6.96 (t, J = 7.5 Hz, 1H), 6.66 (s, 1H), 2.40–2.18 (m, 2H), 1.93 (dd, J = 16.0, 2H);. Anal. Calcd for $C_{20}H_{16}N_4O_3$: C, 66.66; H, 4.48; N, 15.55; O, 13.32. Found: C, 66.64; H, 4.50; N, 15.53; O, 13.34.

3,3–Dimethyl–12–phenyl–2,3,4,12–tetrahydro–1H–benzo[4,5]thiazolo[2,3–b] quinazolin–1–one (4 l): M.p. = 208–210°C; IR (KBr, υ = cm^{-1}) 3428, 2965, 1680, 1655, 1589, 1516, 1370 cm^{-1}; ^{1}H NMR (500 MHz, DMSO–d_6): δ = 7.79 (d, J = 10.0 Hz, 1H), 7.43 (dd, J = 17.5, 7.7 Hz, 3H), 7.28 (dd, J = 16.0, 3H), 7.20 (dd, J = 16.0, 8.0 Hz, 2H), 6.51 (s, 1H), 2.47–2.36 (m, 2H), 2.24 (d, J = 16.0 Hz, 1H), 2.05 (d, J = 16.0 Hz, 1H), 1.02 (s, 3H), 0.86 (s, 3H). Anal. Calcd for $C_{22}H_{20}N_2OS$: C, 73.30; H, 5.59; N, 7.77; O, 4.44; S, 8.89. Found: C, 73.33; H, 5.56; N, 7.79; O, 4.41; S, 8.88.

3,3–Dimethyl–12–(4-methylphenyl)–2,3,4,12–tetrahydro–1H–benzo[4,5] thiazolo[2,3–b]quinazolin–1–one(4 m):

M.p. = 203–205°C. ^{1}H NMR (500 MHz, DMSO–d_6): δ = 7.49–7.47 (m, 1H), 7.34 (d, J = 8 Hz, 2H), 7.28–7.22 (m, 1H), 7.18–7.15 (m, 2H), 7.06 (d, J = 8 Hz, 2H), 6.47 (s, 1H), 2.49 (s, 2H), 2.28–2.17 (m, 5H), 1.09 (s, 3H), 0.97 (s, 3H). Anal. Calcd for $C_{23}H_{22}N_2OS$: C, 73.77; H, 5.92; N, 7.48; O, 4.27; S, 8.56. Found: C, 73.68; H, 5.71; N, 7.60; O, 4.35; S, 8.70.

3,3–Dimethyl–12–(4-bromophenyl)–2,3,4,12–tetrahydro–1H–benzo[4,5] thiazolo[2,3–b]quinazolin–1–one (4n): M.p. 182–184°C. ^{1}H NMR (500 MHz, DMSO–d_6): δ = 7.47 (d, J = 8 Hz, 1H), 7.37–7.28 (m, 5H), 7.19 (d, J = 8 Hz, 1H), 7.06

(d, J = 8 Hz, 1H), 6.45 (s, 1H), 2.47 (s, 2H), 2.29–2.20 (m, 2H), 1.07 (s, 3H), 0.91 (s, 3H), Anal. Calcd for $C_{22}H_{19}BrN_2OS$: C, 60.14; H, 4.36; Br, 18.19; N, 6.38; O, 3.64; S, 7.30. Found: C, 60.35; H, 4.49; Br, 18.37; N, 6.50; O, 3.80; S, 7.45.

3,3–Dimethyl–12–(4-methoxyphenyl)–2,3,4,12–tetrahydro–1H–benzo[4,5] thiazolo[2,3–b]quinazolin–1–one (4o): M.p. 87–88°C. ^{1}H NMR (500 MHz, DMSO–d_6): δ = 7.49–7.46 (m, 2H), 7.38 (d, J = 8 Hz, 2H), 7.23–7.07 (m, 2H), 6.74 (d, J = 8 Hz, 2H), 6.44 (s, 1H), 3.62 (s, 3H), 2.48 (s, 2H), 2.31–2.17 (m, 2H), 1.06 (s, 3H), 0.93 (s, 3H). Anal. Calcd for $C_{23}H_{22}N_2O_2S$: C, 70.74; H, 5.68; N, 7.17; O, 8.19; S, 8.21. Found: C, 70.89; H, 5.80; N, 7.35; O, 8.39; S, 8.40.

3. Conclusion

In conclusion, the reaction of *in situ* generated $O_2^{\bullet-}$ with imidazoles is able to mimic the *in vivo* biochemical reactions involved and corroborate the role of $O_2^{\bullet-}$ in living cells. Since the investigation has been performed at an ambient temperature in the presence of *in situ* generated $O_2^{\bullet-}$, the results may be easily correlated with those occurring at physiological temperatures in more complex biological counterparts.

A novel synthetic route has been developed for the synthesis of tetraheterocyclic benzimidazolo/benzothiazolo quinazolin-1-one ring systems using tetraethylammonium superoxide under non aqueous condition at room temperature (mild reaction condition) within 6 h. The yield of the products was obtained up to 88% without using any tedious purification process. The applicability of tetraethylammonium bromide as an inexpensive alternative to 18-crown-6 for superoxide ion generation has been extended in present report.

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Conflict of interest

No conflict of interest.

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