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Schiff's bases of quinazolinone derivatives: Synthesis and SAR studies of a novel series of potential anti-inflammatory and antioxidants

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ABSTRACT

A series of quinazolinone derived Schiff base derivatives **7**–**28** were synthesized and characterized as novel antioxidants and anti-inflammatory agents. The in vitro antioxidant activities of these compounds were evaluated and compared with commercial antioxidants ascorbic acid (AA), gallic acid (GA), butylatedhydroxytoluene (BHT), butylatedhydroxyanisole (BHA) employing 1,1-diphenyl-2-picryl-hydrazyl (DPPH) assay, 2,2-azinobis-(3-ethylbenzothiazoline-6-sufonic acid) (ABTS) assay and *N*,*N*-dimethyl-*p*-phenylenediamine dihydrochloride (DMPD) assay. The results revealed that IC_{50} of **17**, **18**, **23**, **24**, **25**, **27** and **28** were lower than the IC_{50} of standards in all the three performed antioxidant assays indicating good activities of these compounds. In addition, in vitro anti-inflammatory activity of the synthesized compounds were evaluated and the results demonstrate that the compounds **9**–**12** exhibited excellent anti-inflammatory activity. Preliminary structure–activity relationship revealed that the compounds **17**, **18**, **23**, **24**, **25**, **27** and **28** with electron donating moiety (OH, OCH_3) were found to be excellent antioxidants and compounds **9**, **10**, **11** and **12** with electron withdrawing moiety (Cl, NO_2) were found to be excellent anti-inflammatory agents.

The Schiff's base family is composed of natural products with critical pharmacophores.[1] It can be used as ideal lead structures to develop agrochemicals and medicines, including fungicide,[2] bactericide,[3] antivirals,[4] antioxidants,[5] antiproliferative[6] and antimicrobial drug.[7] Various natural alkaloids with critical pharmacophores contain quinazolinone groups. For example, febrifugine, isofebrifugine, thiabutazide, (−)-benzomalvin A, 2-(4-hydroxybutyl) quinazolin-4-one, and luotonin F were found in the plants, animals, and microorganisms.[8,9] Moreover, The quinazolinone nucleus and its derivatives have been extensively studied because of their wide range of pharmacological activities. As medicines, many of them display antitubercular,[10] anti-inflammatory,[11] anticonvulsant,[12] antidepressant,[13] antiulcer[14] and analgesic[15] activities.

Antioxidants play a vital role in the defense mechanism against oxidative damage induced by free radicals and reactive oxygen species (ROS). Balanced reactive oxygen species generation and detoxification in a normal cellular metabolism is important to keep the mammalian cells in healthy condition. When a cell fails to detoxify the excessive ROS generated as a result of damaging species or low level of antioxidants, they enter into a state of oxidative stress and is damaged.[16] High levels of ROS can cause damage to cell structure, nucleic acids, membrane lipids and proteins.[17] They also damage purine and pyrimidine bases of DNA molecule, thus leading to mutation.[18] Oxidative stress on a cell due to high concentration of ROS can leads to a variety of disorders including cancer, neurodegenerative disorder, atherosclerosis and aging.[19] Many studies have suggested that antioxidants or other compounds that can neutralize free radicals may be of pivotal interest in the prevention of vascular diseases and some forms of cancer.[20] The attachment of hydroxyl groups on the aromatic ring makes hydroxyl-substituted Schiff's bases the effective antioxidants, and potential drugs to prevent disease related to free radical damage. Recently, Liu and co-workers have reported the protective effects of hydroxyl-substituted Schiff's bases against free radical-induced peroxidation of triolein in micelles, haemolysis of human red cells, and oxidation of DNA.[21,22] Some of the recently reported[23–27] structures of the biologically active Schiff's bases are shown in Figure 1. The length of alkyl chain play an important role in deciding biological activities. The antioxidant activity of *p*-alkylaminophenols enhanced by elongation of alkyl chain.[28] Similarly anti-inflammatory activity of 2-amino-alcohols was enhanced by increasing the alkyl chain length.[29]

Non-steroidal anti-inflammatory drugs (NSAIDs) are the most commonly prescribed medications in the world. They are used for the treatment of pain, fever and inflammation, particularly arthritis.[30] Rheumatic diseases are the most prevalent causes of disability in European countries and non-steroidal anti-inflammatory

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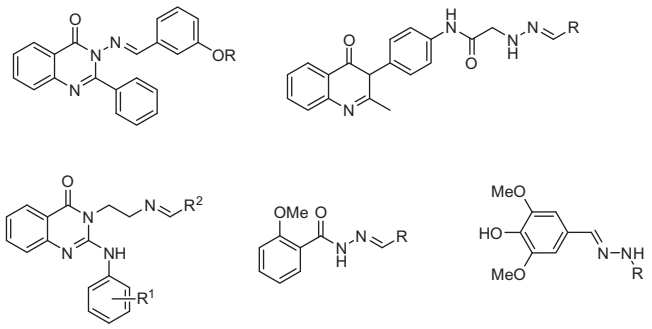


Figure 1. Structures of the biologically active Schiff's bases.

drugs (NSAIDs) are still the most commonly used remedies. Chronic use may cause several serious adverse effects, the most important one being gastric injury and renal complications. Gastro-intestinal (GI) damage from NSAIDs is generally attributed to two factors: local irritation by the direct contact of the free carboxylic acid (COOH) moiety of NSAIDs with GI mucosal cells (topical effect) and decreased tissue prostaglandin production in tissues.[31]

Based on the above facts and in continuation of our drug development program,[32–34] the present work involves the synthesis of a new series of quinazolinone derived Schiff's base derivatives as potential anti-inflammatory and antioxidants.

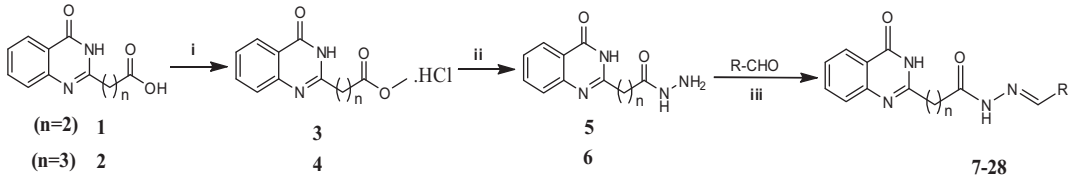
Synthesis of the desired compounds were achieved according to the steps illustrated in Scheme 1. 3-(4-Oxo-3,4-dihydroquinozolin-2-yl)propanoic acid (QZN 1) and 4-(4-oxo-3,4-dihydroquinozolin-2-yl)butanoic acid (QZN 2)[35–37] were methylated using trimethylsilylchloride (TMS-Cl) and methanol at room temperature,[41] which upon reaction with excess of hydrazine hydrate afforded the corresponding quinazolinone hydrazides (**5** and **6**).[42] The Schiff's bases (**7**–**28**) were obtained by reacting **5** and **6** with different aromatic aldehydes in presence of catalytic amount of glacial acetic acid.[43] All the derivatives were obtained in high yield and the methods employed are very simple. The structures of all the newly synthesized compounds including intermediates were confirmed by IR, ^{1}H NMR, ^{13}C NMR and mass spectral analysis (Supplementary material). The formation of methyl esters (**3** and **4**) were confirmed by the appearance of a singlet at 3.68 δ for OCH_3 and absence of COOH proton peak at 12.25 δ in ^{1}H NMR spectrum. In IR spectra, bands at 3310 and 3217 cm^{-1} for NH_2–NH groups indicates the conversion of methyl esters into hydrazides. The formation of Schiff's bases were confirmed by the presence of absorption at 1612–1630 cm^{-1} for imines, i.e., —N═CH— in IR spectra. The presence of all requisite peaks and absence of extraneous peaks in ^{1}H NMR and ^{13}C NMR confirms the structures.

In vitro antioxidant activities of all the synthesized compounds including intermediates were evaluated by (i) 1,1-diphenyl-2-picryl-hydrazyl (DPPH) assay which is a rapid and convenient technique for screening the antioxidant activities of the antioxidants, (ii) 2,2-azinobis-3-ethylbenzothiazoline-6-sufonic acid (ABTS) cation radical assay which is a conventional and excellent model for assessing the antioxidant activities of hydrogen donating and chain breaking antioxidants.[38] and (iii) *N,N*-dimethyl-*p*-phenylenediamine dihydrochloride (DMPD) cation radical assay which is similar to the DPPH radical scavenging assay. The values of IC_{50}, the effective concentration at which 50% of the radicals were scavenged, were calculated to evaluate the antioxidant activities. A lower IC_{50} value indicated greater antioxidant activity. IC_{50} values of lower than 10 mg/mL usually implied effective activities in antioxidant properties.[39] The IC_{50} of butylatedhydroxytoluene (BHT), butylatedhydroxyanisole (BHA), ascorbic acid (AA) and gallic acid (GA) was also determined for comparison. The results were shown in Table 1.

Most of the synthesized compounds showed potent antioxidant activities. Compounds **17**, **18**, **22**, **23**, **24**, **25**, **26**, **27** and **28** showed excellent radical scavenging activities with IC_{50} values 113, 95, 97, 104, 88, 85, 106, 81 and 78 μM/mL, respectively, in DPPH assay much better than the standard BHT (IC_{50} = 114 μM/mL). In $ABTS^+$ radical scavenging assay, the compounds **17**, **18**, **23**, **24**, **25**, **27** and **28** showed potent antioxidant activity with IC_{50} values 40, 50, 40, 50, 55, 35 and 40 μM/mL, respectively, which is much better than the commercial standards BHA (IC_{50} = 55 μM/mL), AA (IC_{50} = 65 μM/mL) and GA (IC_{50} = 60 μM/mL). The compounds **17**, **18**, **23**, **24**, **25**, **27**and **28** also exhibited striking antioxidant activity with IC_{50} values 105, 75, 50, 80, 80, 45 and 45 μM/mL, respectively, which is better than the standards BHA (IC_{50} = 155 μM/mL), AA (IC_{50} = 140 μM/mL) and GA (IC_{50} = 100 μM/mL) in DMPD assay. In all the three assays performed, the compounds **17**, **18**, **23, 24, 25, 27** and **28** showed excellent antioxidant activities with IC_{50} values much lower than the standards. The IC_{50} values of these compounds **17**, **18**, **23**, **24**, **25**, **26**, **27** and **28** were found to be in μg/mL level and much lower than 10 mg/mL demonstrating greater antioxidant activities of these compounds in all the three assays. On the basis of the above observation, compounds having –OH (phenolic) and $–OCH_3$ (anisole) groups in the phenyl ring (**17**, **18**, **23**, **24**, **25**, **27** and **28**) were found to be the most potent antioxidants. The compounds with electron withdrawing Cl and NO_2 substituents (**9**–**12**) showed least antioxidants activity.

All the synthesized compounds were also evaluated for their in vitro anti-inflammatory activity using known literature procedure in human erythrocytes.[40] A substantial number of compounds have been identified exhibiting excellent to moderate inhibitory activity compared to standard drug aspirin. IC_{50} was determined for the compounds showing more than 50% inhibition concentration (Table 1). The compounds **9**, **10**, **11** and **12** showed excellent activity with IC_{50} values 84, 67, 54 and 52 μM/mL, respectively, much better than the standard aspirin (IC_{50} = 166 μM/mL). Other compounds **17**, **18**, **23**, **24**, **27** and **28** showed moderate activity. It is evident from the results that the compounds bearing electron withdrawing groups Cl and NO_2 (**9**–**12**) are better anti-inflammatory agents.

In conclusion, we have designed and synthesized a series of quinazolinone derived Schiff's bases with different groups in benzene ring. Of all the compounds synthesized, compounds **17**, **18**, **23**, **24**, **25**, **27** and **28** with OH and OCH_3 groups in benzene ring (electron donating) exhibited stronger radical scavenging activities than BHT, BHA, AA and GA in all the three assays performed. Compounds **9**, **10**, **11** and **12** with Cl and NO_2 in benzene ring (electron withdrawing) demonstrated better anti-inflammatory activity



Scheme 1. Synthesis of final compounds **7**–**28**. Reagents and conditions: (i) TMS-Cl, MeOH, rt, 4 h, (ii) $NH_2NH_2{\cdot}H_2O$, EtOH, reflux, 16 h, (iii) EtOH, CH_3COOH, reflux, 7–8 h.

Table 1
Biological activities of the synthesized quinazolinone Schiff's base derivatives

Entry	Antioxidant activity[a]			Anti-inflammatory activity[a] IC_{50} (μM/mL)
	DPPH IC_{50} (μM/mL)	ABTS IC_{50} (μM/mL)	DMPD IC_{50} (μM/mL)	
1	1100 ± 4.49	—	—	—
2	1250 ± 2.56	—	—	—
3	862 ± 3.46	—	—	1163 ± 4.89
4	772 ± 6.95	280 ± 1.73	—	975 ± 2.16
5	—	—	—	—
6	—	—	—	—
7	734 ± 2.88	265 ± 2.08	—	—
8	568 ± 2.94	240 ± 2.18	—	—
9	381 ± 3.69	185 ± 2.08	—	84 ± 1.44
10	353 ± 3.10	—	—	67 ± 1.24
11	328 ± 2.88	220 ± 1.73	—	54 ± 1.88
12	316 ± 1.73	270 ± 3.36	—	52 ± 0.81
13	238 ± 2.15	105 ± 2.08	300 ± 2.44	—
14	214 ± 2.44	170 ± 1.73	—	—
15	214 ± 2.94	75 ± 2.94	—	—
16	247 ± 1.63	180 ± 1.24	280 ± 3.62	—
17	113 ± 1.28	40 ± 1.69	105 ± 2.15	255 ± 3.17
18	95 ± 1.63	50 ± 1.20	75 ± 2.15	300 ± 2.17
19	204 ± 2.74	95 ± 1.24	290 ± 2.94	—
20	236 ± 2.08	115 ± 1.28	280 ± 3.87	—
21	126 ± 1.73	105 ± 2.88	275 ± 2.64	530 ± 4.28
22	97 ± 1.69	135 ± 2.16	225 ± 2.05	524 ± 2.87
23	104 ± 1.41	40 ± 2.63	50 ± 1.73	261 ± 4.54
24	88 ± 1.24	50 ± 0.40	80 ± 1.63	277 ± 2.94
25	85 ± 1.28	55 ± 1.77	80 ± 2.05	682 ± 3.10
26	106 ± 2.88	60 ± 1.67	85 ± 2.08	613 ± 3.61
27	81 ± 1.69	35 ± 0.40	45 ± 1.41	203 ± 2.88
28	78 ± 1.20	40 ± 0.81	45 ± 1.69	183 ± 2.17
BHT	**114 ± 1.24**	—	—	—
BHA	—	**55 ± 0.20**	**155 ± 2.16**	—
AA	—	**65 ± 0.86**	**140 ± 1.69**	—
GA	—	**60 ± 1.63**	**100 ± 1.24**	—
Aspirin	—	—	—	**166 ± 1.24**

Bold values are represented as standard drugs.
Standards: BHT = butylatedhydroxytoluene; BHA = butylatedhydroxyanisole; AA = ascorbic acid; GA = gallic acid.
[a] Values are mean of three determinations, the ranges of which are <5% of the mean in all cases.

Table 2
Chemical structure and physical data of new Schiff's bases **7–28**

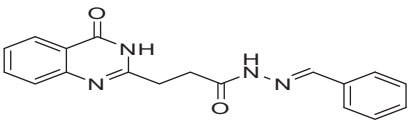
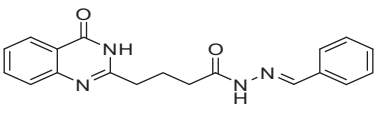
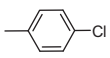
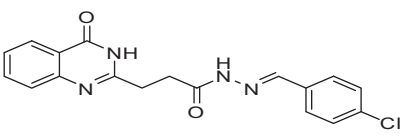
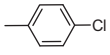
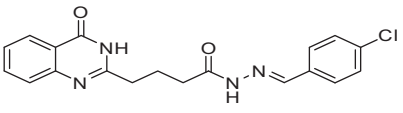
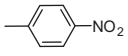
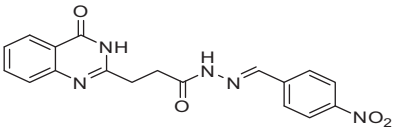
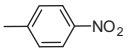
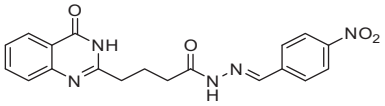
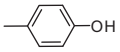
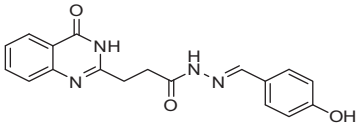
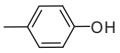
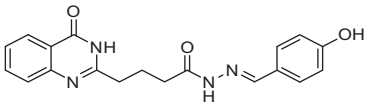
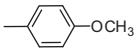
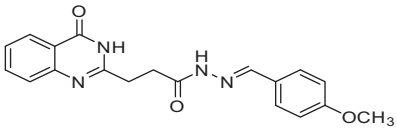
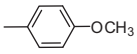
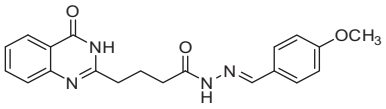
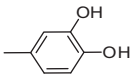
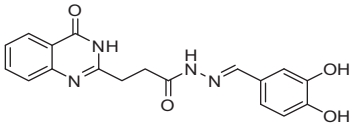
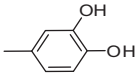
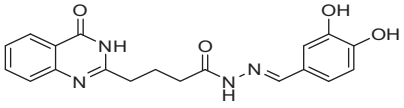
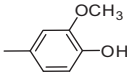
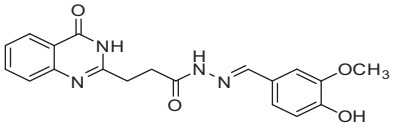
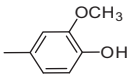
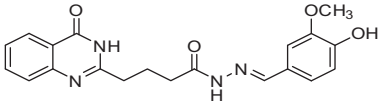
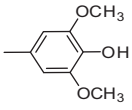
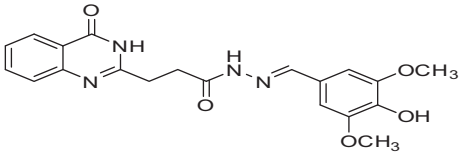
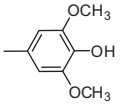
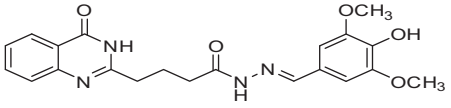
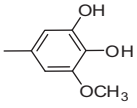
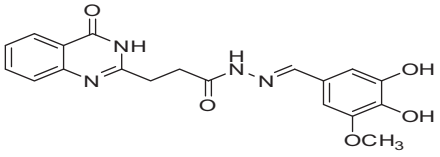
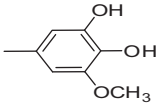
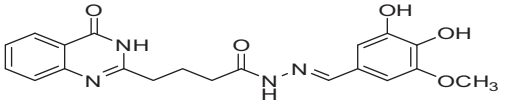
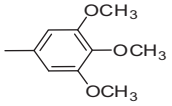
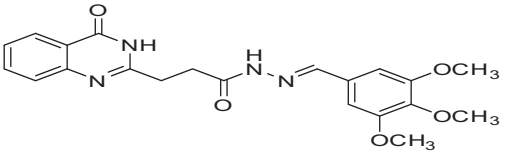
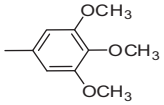
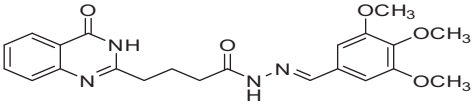
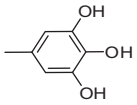
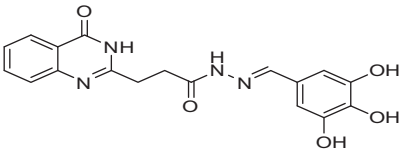
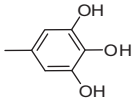
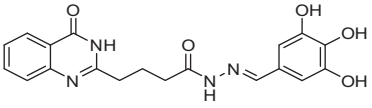
Entry	R	Structure	Yield (mg)	% age yield	Mp (°C)
7			305	89.18	242–244
8			281	92.13	206–207
9			320	84.40	221–223
10			422	87.01	229–230
11			201	85.53	235–238

Table 2 (*continued*)

Entry	R	Structure	Yield (mg)	% age yield	Mp (°C)
12			458	91.60	244–246
13			190	87.55	239–241
14			398	85.20	237–238
15			197	87.16	195–197
16			445	92.70	234–236
17			419	92.29	210–212
18			403	91.17	220–222
19			478	87.06	222–224
20			440	87.82	238–240
21			312	91.49	204–206
22			490	90.57	224–226
23			295	89.60	238–240
24			279	91.47	212–213

(*continued on next page*)

Table 2 (*continued*)

Entry	R	Structure	Yield (mg)	% age yield	Mp (°C)
25			277	85.98	198–201
26			495	88.55	204–206
27			271	90.63	229–231
28			248	89.88	210–212

than aspirin. Further studies on the relevant mechanism of action and the toxicity studies of these compounds are in progress.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bmcl.2015.01.010.

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41. *Experimental procedure for the synthesis of* **3** and **4**: To a solution of QZN 1 (0.02 mol, 4.36 g) and QZN 2 (0.02 mol, 4.64 g) separately in methanol (40 mL), trimethylsilylchloride (0.02 mol, 3.80 mL) was added slowly. The reaction mixture was stirred for 4 h to complete the reaction (monitored by TLC). The solvent was removed under reduced pressure and the resultant precipitate was washed with ice cold water and filtered to yield the desired products **3** (yield = 4.90 g, 91.41%, mp 184–185 °C) and **4** (yield = 5.20 g, 92.36%, mp 180–182 °C), respectively.
42. *Experimental procedure for the synthesis of* **5** and **6**: To a solution of **3** (0.015 mol, 4.02 g) and **4** (0.015 mol, 4.23 g) separately in ethanol (40 mL), hydrazine hydrate (0.020 mol, 0.97 mL) was added. The reaction mixture was refluxed for 16 h for completion of the reaction (monitored by TLC). The solvent was removed under reduced pressure and cooled by adding ice cold water. The resulting precipitate was filtered, washed with cold water and recrystallized

from ethanol to get the desired compounds **5** (yield = 2.90 g, 83.33%, mp 220–221 °C) and **6** (yield = 3.10 g, 84.01%, mp 224–226 °C), respectively.

43. *General procedure for the synthesis of Schiff's bases* (**7**–**28**): An equimolar amount of **5** (1 mmol) and **6** (1 mmol) was dissolved separately in ethanol (10 mL/g of compound) and treated with appropriate aldehydes (1 mmol) in the presence of catalytic amount of glacial acetic acid. The reaction mixtures were refluxed for 7–8 h and the completion of reaction was monitored by TLC. After completion of the reaction, the solvent was removed under reduced pressure and cooled by adding ice cold water. The resulting precipitate was filtered, washed with water and recrystallized from ethanol to obtain the desired Schiff's bases (**7**–**28**). The yields, % of yield and mp are shown in Table 2.