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Synthesis, Antifungal, and Antioxidant Evaluation of New Class of Thiazoloquinazoline Linked by Carbonyl with Nitrile, Phenylacrylonitrile, Pyrazole, Pyrazolo[1,5-*a*]pyrimidine and Triazolo[1,5-*a*]pyrimidine as Five and Six-Membered Heterocycles Derivatives

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Abstract—A specific route for the synthesis of a novel benzo[4,5]thiazolo[2,3-*b*]quinazoline (**IVa**–**e**), (**VIa**–**e**), (**VIIa**–**e**), (**VIIIa**–**e**), (**IXa**–**e**), and (**Xa**–**e**) derivatives, where established using thiazolo[2,3-*b*]quinazoline-3,6(5*H*,7*H*)-dione derivatives (**Ia**–**e**) as an efficient starting materials. The present report briefly outlines relevant synthetic methods employed for this class of new compounds and intensively reveals significant antifungal and antioxidant activities along with SAR studies. The results of this study indicate that the target compounds (**VIIa**–**e**) and (**VIIIa**–**e**) exhibited better antifungal activity at 100 μg/ml compared with standard Trifloxystrobin and Azoxystrobin, respectively while compounds (**IXa**–**f**) particularly compound (**IXd**) showed good antioxidant activity at 10 μg/mL. Structures of newly synthesized compounds were confirmed by elemental analysis and spectral IR, ^{1}H NMR and ^{13}C NMR.

Keywords: pyrido, pyrano, benzo, thiazolo and quinazoline

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INTRODUCTION

Phenylacrylonitriles, pyrazolo[1,5-*a*]pyrimidine, thiazolo[2,3-*b*]quinazoline and triazolo[1,5-a]pyrimidine and their related fused heterocyclic derivatives have long been of increasing interest in the field of synthetic organic and medicinal chemistry due to their synthetic feasibility and their incorporation into various types of therapeutically useful agents and are of paramount interest in the development of important pharmacophores in the drug discovery endeavor [1–20]. Nowadays several derivatives of pyrazolo[1,5-*a*]pyrimidine, thiazolo[2,3-*b*]quinazoline and triazolo[1,5-*a*]pyrimidine command much attention as privileged scaffolds comprising a vital class of heterocyclic structures possessing exciting and varied pharmacologic activities, such as anti-inflammatory [1, 21–27], anticancer [2, 28–33], antimicrobial, antituberculosis [34–37], anticonvulsant [2, 38–41], antimalarial [42–44], antihypertensive [45–47], HIV-1 inhibitors [48–51], COX-2 selective inhibitors [52–55], agents. In light of these facts and in order to arrive at a highly proficient synthetic approach for the construction of these type of compounds and as a continuation of our previous work in the synthesis of novel thiazoloquinazoline compounds with promising biological applications [56], we report herein the synthesis of new thiazoloquinazoline carbonyl-linked either with 3-amino-5-phenyl-1*H*-pyrazole, pyrazolo[1,5-*a*]pyrimidine or triazolo[1,5-*a*]pyrimidine derivatives using the reaction of intermediates (**VIa**–**e**) with hydrazine hydrate, 2-aminobenzimidazole, 3-methyl-5-amino pyrazole and 3-amino-1,2,4-triazole.

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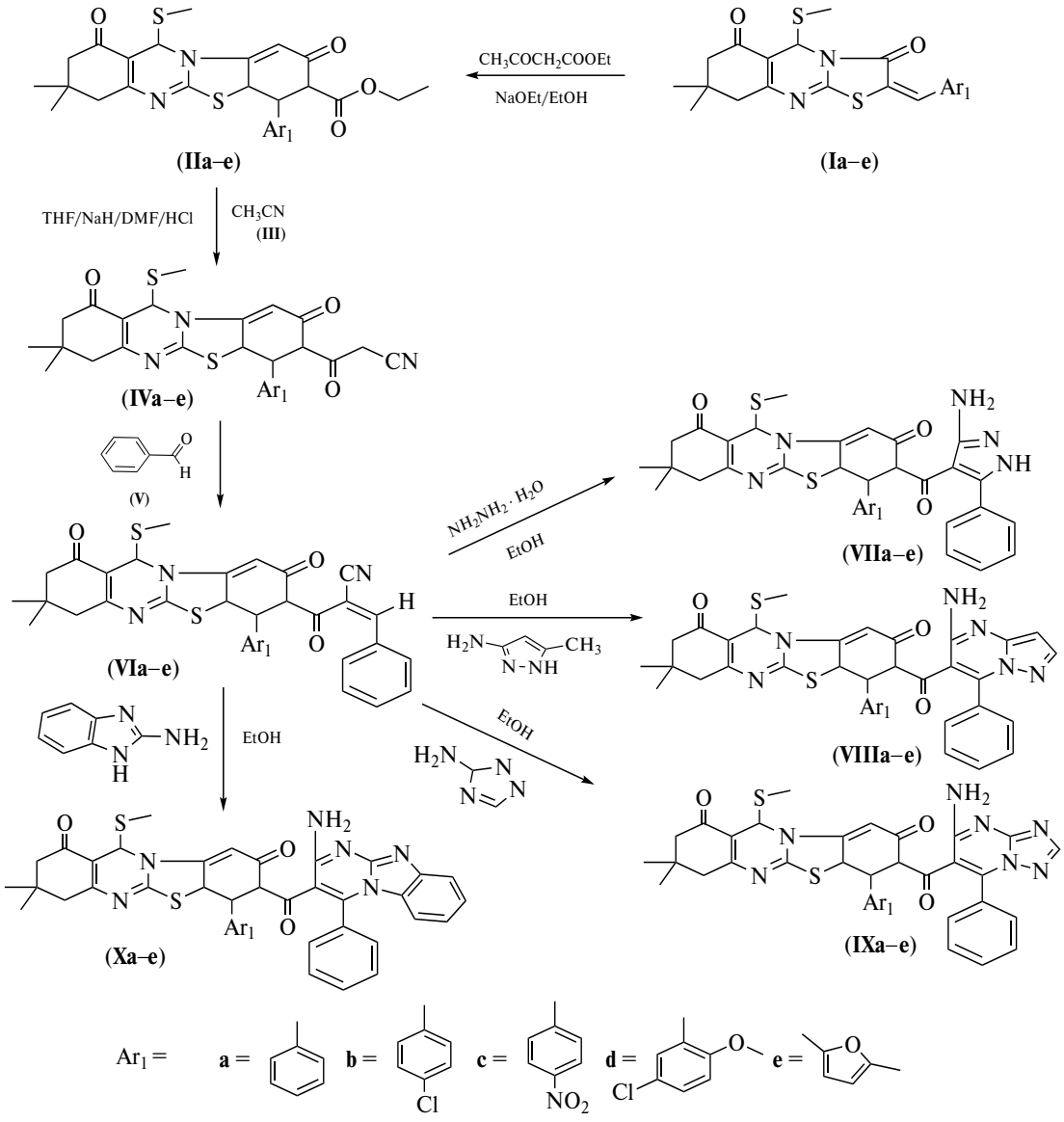
RESULTS AND DISCUSSION

Chemistry

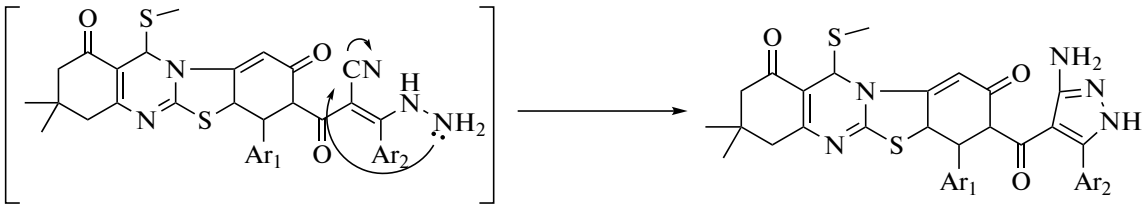
The desired starting material (**IIa**–**e**) were prepared in high yield as a part of our previous published work [55] by reacting thiazolo[2,3-*b*]quinazoline-3,6(5*H*,7*H*)-dione derivatives (**Ia**–**e**) with ethyl acetoacetate in a molar ratio 1 : 1 in the presence sodium ethoxide solution leads to the products (**IIa**–**e**) as shown in Scheme 1. The treatment of compounds (**IIa**–**e**) with MeCN, in the presence of sodium hydride, followed by acidification with HCl, it provided product derivatives (**IVa**–**e**) as presented in Scheme 1. The structures of compounds (**IVa**–**e**) were established on the basis of elemental analysis and spectral data. Thus the IR spectrum of compound (**IVa**), taken as a typical example of the synthesized series, exhibited a nitrile band at 2256 cm^{-1} a three strong carbonyls absorption bands at 1764, 1740, 1725 cm^{-1}. Its ^1H NMR spectra revealed a singlet signal at δ 2.44 ppm, assignable to the $-SCH_3$ group, a singlet at δ 3.98 ppm due to a new methylene protons and singlet at δ 7.04 ppm due to methine proton in addition to aromatic multiplet in the region δ 7.35–7.82 ppm. Its ^{13}C NMR spectrum showed signals at δ 12.06, 32.11, 116.36, 193.26, 195.14 and 199.57 ppm corresponding to $-SCH_3$, $-CH_2-$, –CN and three groups of –C=O carbons, respectively.



Scheme 1. Synthesis of benzo[4,5]thiazolo[2,3-*b*]quinazoline (**IVa**–**e**), (**VIa**–**e**), (**VIIa**–**e**), (**VIIIa**–**e**), (**IXa**–**e**), and (**Xa**–**e**).

The products (**VIa–e**) were formulated from treatment of compounds (**IVa–e**) with benzaldehyde under refluxing ethanol condition in the presence of piperidine as catalyst. The IR spectrum of compound (**VIa**), taken as a typical example of the prepared series, exhibited a nitrile band at 2247 cm^{-1} a three strong carbonyls absorption bands at 1760, 1745, and 1711 cm^{-1}. Its ^1H NMR spectra revealed a singlet signal at δ 2.53 ppm, assignable to the $-SCH_3$ group, the disappearance of methylene protons signals at 3.98 ppm and appearance of new singlet at δ 7.60 ppm was due to a new methine proton in addition to aromatic multiplet in the region δ 7.84–8.20 ppm for 10 protons. Its ^{13}C NMR spectrum showed signals at δ 11.46, 117.63, 192.30, 194.08 and 196.30 ppm corresponding to $-SCH_3$, –CN, and three groups of C=O carbons, respectively.

Treatment of each of compounds (**VIa–e**) with hydrazine hydrate in refluxing ethanol, afforded the corresponding pyrazole derivatives (**VIIa–e**) as shown in Scheme 1. The products formed via the non-isolable intermediates, which undergo intramolecular cyclization followed by dehydrogenation to give the corresponding derivatives (**VIIa–e**) as illustrated in Scheme 2. The formation of compounds (**VIIa**) taken as a typical example of the prepared series were ascertained by the appearance of characteristic bands of stretching vibration at 3310 and 3270 cm^{-1} for two amino groups, also showed three strong absorption bands at 1745, 1622, 1683 cm^{-1} due to –C=O groups. The ^1H NMR spectra of the same compound revealed the appearance of D_2O exchangeable signal at δ 8.25 ppm due to NH_2 protons and D_2O exchangeable signal at δ 11.75 ppm due to NH proton. The ^{13}C NMR spectrum for the same compound showed signals at δ 14.62, 192.20, 194.02 and 196.34 ppm corresponding to $-SCH_3$ and three groups of –C=O carbons, respectively. All the other carbons signals revealed at the expected regions.



(VIIa–e)

Scheme 2. The proposed mechanism for the formation of the products (**VIIa–e**).

However in similar manner and under the same condition, the compounds (**VIa–e**) reacted with 3-methyl-5-amino pyrazole afforded the corresponding pyrazolo[1,5-*a*]pyrimidine derivatives (**VIIIa–e**) as shown in Scheme 2. The IR spectra for compound (**VIIIa**) taken as a typical example of the prepared series, exhibited an absorption band at 3364 and 3211cm^{-1} due to two NH groups and three absorption bands at 1750, 1724 and 1616 cm^{-1} due to three carbonyls groups. Its ^1H NMR spectra revealed singlet signal at δ 2.41 ppm due to $-SCH_3$ protons and two duplet signals at δ 6.92 and δ 7.06 ppm due to pyrazole protons in addition to D_2O exchangeable signal at δ 8.85 ppm due to NH_2 protons. The ^{13}C NMR spectrum for the same compound showed signals at δ 13.12, 190.62, 192.32 and 195.14 ppm corresponding to $-SCH_3$ and three groups of –C=O carbons, respectively. All the others carbons signals revealed at the expected regions. When compounds (**VIa–e**) were treated with a 3-amino-1,2,4-triazole afforded the corresponding triazolo[1,5-*a*]pyrimidine derivatives (**IXa–e**) as shown in Scheme 2. The IR spectra for compound (**IXa**) taken as a typical example of the prepared series, exhibited an absorption bands at 3322 and 3240 cm^{-1} due to NH group and three absorotin bands at 1755, 1742 and 1668 cm^{-1} due to three carbonyls groups. Its ^1H NMR spectra revealed singlet signal at δ 2.38 ppm due to $-SCH_3$ protons and singlet signal at δ 6.92 ppm due to NH protons. The ^{13}C NMR spectrum for the same compound showed signals at δ 12.22, 190.28, 192.62 and 196.32 ppm corresponding to $-SCH_3$ and three groups of –C=O carbons, respectively. All the others carbons signals revealed at the expected regions.

Finally when compounds (**VIa–e**) were treated with 2-aminobenzimidazole in presence of piperidine, as catalyst, it afforded a product identified as benzo[4, 5]thiazolo[2,3-*b*]quinazoloine carbonyl linked by imidazo[1,2-*a*]pyrimidine (**Xa–e**) as illustrated in Scheme 2. The IR spectra for compound (**Xa**) taken as a typical example of the prepared series, exhibited an absorption bands at 3340 and 3223 cm^{-1} due to NH group and three absorotin bands at 1746, 1713 and 1690 cm^{-1} due to three carbonyls groups. Its ^1H NMR spectra revealed singlet signal at δ 2.52 ppm due to $-SCH_3$ protons and singlet signal at δ 8.60 ppm due to NH protons. The ^{13}C NMR spectrum for the same compound showed signals at δ 14.34, 190.18, 193.40 and 196.14 ppm corresponding to $-SCH_3$ and three

groups of –C=O carbons, respectively. All the others carbons signals revealed at the expected regions.

In Vitro Antifungal Activity of Target Compounds

Initially antifungal activities of newly compounds (**IIa–e**), (**IVa–e**), (**VIa–e**), (**VIIa–e**), (**VIIIa–e**), (**IXa–e**), and (**Xa–e**) against six common phytopathogens at 100 μg/mL were evaluated under the same conditions. The in vitro antifungal activity was evaluated by a mycelium growth rate method and the corresponding results were listed in (Table 1). Trifoxystrobin and Azoxystrobin were used as the positive control fungicides throughout the experiment. Noteworthy, the antifungal activities of target compounds against *Botrytis cinerea, Cercospora arachidicola*, and *Rhizoctonia cerealis* were generally better than that of *Alternaria solani*, *Gibberella zeae*, and *Sclerotinia sclerotiorum*. Especially, the target compounds (**VIIa–e**), (**VIIIa–e**), and (**IXa–e**) exhibited outstanding antifungal activity against *B. cinerea*, and *R. cerealis* at 100 μg/mL particularly compound (**IXc**) with the corresponding inhibition rates of 95%, which was superior to the other compounds and positive control fungicides Trifoxystrobin (94%) and Azoxystrobin (91%). This means that antifungal activity was dependent on the structure of the target compound (**IXc**) which has imidazo[1,2-*a*]pyrimidine scaffold linked to thiazolo[2,3-*b*]quinazoline scaffold which bearing 4-nitro phenyl ring. Despite the presence of imidazo[1,2-*a*]pyrimidine scaffold in target compound (**IXc**) playing the main role of activity against the *B. cinerea, C. arachidicola* and *R. cerealis* strains, it could be noted the positive effect of the nitro group at para position of phenyl ring for thiazolo[2,3-*b*]quinazoline scaffold in improving the inhibitory action of synthesized compound (**IXc**). Meanwhile, the intermediate compounds (**IVa, d**), (**VIa**), and target compounds (**IXa–e**) and (**Xa, d**) showed remarkable antifungal activities against *B. cinerea*, *C. orbiculare* and *G. zeae* at 100 μg/mL with the ranging inhibition rates between 55 to 82%, which were close to the positive control fungicides Trifoxystrobin (94, 79 and 85%) and Azoxystrobin (91, 73 and 80%) respectively.

Antioxidant Activity

DPPH radical scavenging assay has been widely used to measure the antioxidant activity of synthetic or extracts compounds based on their abilities to reduce radicals [23–26]. Accordingly, (DPPH·) 2,2-diphenyl-1-picryl-hydrazyl radical assays were used to assess the radical-scavenging ability of target compounds (**IIa–e**), (**IVa–e**), (**Va–e**), (**VIa–e**), (**VIIIa–e**), (**IXa–e**) and (**Xa–e**) (Table 2). Out of the 35 evaluated compounds for antioxidant activity only compounds (**IXa–e**) and (**Xa–e**) showed significant free radical scavenging ability. Majority of the tested compounds in these series showed low to moderate interaction with the DPPH radical at 10 μg/mL concentration. Maximum DPPH RSA was observed in compounds (**IXa–f**) derivatives particularly compound (**IXd**) ($p < 0.05$), which has a [1, 2, 4]triazolo[1,5-*a*]pyrimidine scaffold linked to thiazolo[2,3-*b*]quinazoline scaffold which bearing 5-chloro-2-methoxyphenyl ring (Table 2). The presence of large number of lone pair of electrons on this scaffold might favor the activity. The targeted compounds (**VIIIa**) and (**VIIb**) showed high to moderate radical scavenging activity, whereas the compounds (**IIa–e**), (**IVa–e**), and (**Va–e**) that contain few numbers of lone pair of electrons showed low radical scavenging activity. The maximum antioxidant activity was observed with evaluated compounds (**IXa–e**) and (**Xa–e**) in the following order (**IXb**) < (**Xb**) < (**VIIId**) < (**Xd**) < (**IXc**) < (**IXd**), which is comparable to that of standard vitamin C at similar concentration. The presence of both chloro and methoxy groups at positions 2 and 5 on the phenyl ring of triazolo[1,5-*a*]pyrimidine scaffold of compounds (**IXb–e**) may be the main reason behind enhancing the free radical scavenging of these derivatives. Also the presence of electron-withdrawing groups like chloro group or nitro group alone at position 4 on the same phenyl ring such as in the targeted derivatives (**IIb–c**), (**IVb–c**), (**Vb–c**), (**VIb–c**), (**VIIb–c**), (**VIIIb–c**), (**IXb–c**), and (**Xb–c**) may increase the radical scavenging activity to some extent according to the activity values recorded and illustrated in Table 2. Antioxidant activity of these compounds is related to their electron or hydrogen radical donating ability to DPPH radical so that they become stable diamagnetic molecules. This might be the reason for the higher antioxidant activity of the second series of compounds (**IXa–e**). On the other hand the free radical scavenging activity for the targeted compounds (**IIa–e**), (**IVa–e**), (**VIa–e**), and (**VIIa–e**) showed that the replacement of the triazolo[1,5-*a*]pyrimidine scaffold by another, such as -oxopropanenitrile, -phenylacrylonitrile, and -phenyl-1*H*-pyrazol-3-amine, may be the main reason that leads to the limitation of antioxidants activity of these compounds. Evaluation of anti-lipid peroxidation activity of new compounds was performed by the formation of thiobarbituric acid reactive species (TBARS) using egg yolk homogenate as lipid-rich media. The result showed that all newly synthesized compounds inhibited the ferric chloride-induced lipid peroxidation at 40 μg/mL concentration with a varying degree when compared with standard biological anti-oxidant vitamin E (Table 2). The maximum anti-lipid peroxidation inhibition was observed in target compounds (**VIIIa–e**), (**IXa–e**), and (**Xa–e**) particularly compound (**Xb**) ($p < 0.05$), which has high electron density releated to existence extra fused phenyl ring on imidazo[1,2-*a*]pyrimidine scaffold and a chloro group at position 4 of the phenyl ring in thiazolo[2,3-*b*]quinazoline scaffold (Table 2). However, the target compounds (**IVa–e**) and (**VIa–e**) showed low to mod-

Table 1. Antifungal activity of the synthesized compounds

Compounds	Inhibition (%) at 100 μg/mL					
	B. cinerea	*C. arachidicola*	*A. solani*	*G. zeae*	*S. sclerotiorum*	*R. cerealis*
(IIa)	30 ± 0.40	48 ± 1.33	19 ± 1.15	42 ± 0.23	55 ± 1.18	23 ± 0.80
(IIb)	64 ± 0.43	56 ± 0.66	27 ± 0.78	34 ± 1.14	52 ± 0.62	16 ± 0.26
(IIc)	64 ± 0.80	ND	ND	42 ± 0.25	49 ± 1.35	NA
(IId)	33 ± 1.24	44 ± 0.43	ND	33 ± 0.29	53 ± 0.29	NA
(IIe)	42 ± 0.35	24 ± 0.03	ND	34 ± 1.23	34 ± 1.03	NA
(IVa)	61 ± 1.04	40 ± 1.20	10 ± 0.40	41 ± 1.08	11 ± 0.18	30 ± 0.30
(IVb)	63 ± 1.76	38 ± 0.42	18 ± 1.15	49 ± 0.61	NA	38 ± 1.55
(IVc)	60 ± 0.80	42 ± 0.26	12 ± 0.38	36 ± 0.26	NA	22 ± 0.48
(IVd)	74 ± 1.07	44 ± 1.41	14 ± 1.10	45 ± 0.40	15 ± 0.30	34 ± 1.20
(IVe)	72 ± 1.36	54 ± 1.23	14 ± 1.39	21 ± 1.33	11 ± 1.13	40 ± 1.39
(VIa)	60 ± 1.23	39 ± 0.49	9 ± 1.09	38 ± 1.24	68 ± 0.28	29 ± 1.09
(VIb)	64 ± 1.54	45 ± 0.84	15 ± 1.25	32 ± 0.50	62 ± 0.22	35 ± 1.05
(VIc)	71 ± 1.10	53 ± 0.14	13 ± 1.33	39 ± 1.08	59 ± 1.30	43 ± 1.03
(VId)	69 ± 1.56	61 ± 0.62	9 ± 1.44	28 ± 1.60	68 ± 0.20	49 ± 1.42
(VIe)	73 ± 0.23	37 ± 0.77	NA	25 ± 0.18	55 ± 0.48	37 ± 0.87
(VIIa)	75 ± 0.60	49 ± 0.30	NA	42 ± 0.18	42 ± 0.12	80 ± 1.40
(VIIb)	81 ± 0.43	52 ± 0.44	29 ± 0.24	51 ± 0.33	63 ± 0.18	81 ± 0.64
(VIIc)	86 ± 0.12	50 ± 1.41	20 ± 1.31	58 ± 1.06	68 ± 0.46	67 ± 1.61
(VIId)	84 ± 0.15	63 ± 0.35	23 ± 1.05	47 ± 0.91	67 ± 0.41	53 ± 1.05
(VIIe)	73 ± 1.30	47 ± 0.70	27 ± 1.40	51 ± 1.50	81 ± 1.20	47 ± 1.10
(VIIIa)	74 ± 1.08	54 ± 0.34	44 ± 1.14	68 ± 1.41	78 ± 0.11	80 ± 1.44
(VIIIb)	67 ± 1.40	65 ± 0.85	41 ± 0.37	72 ± 1.31	72 ± 1.31	81 ± 0.37
(VIIIc)	64 ± 0.85	41 ± 0.27	42 ± 1.20	62 ± 1.20	72 ± 0.20	78 ± 1.20
(VIIId)	60 ± 0.23	43 ± 0.33	47 ± 1.13	68 ± 0.13	68 ± 0.43	57 ± 1.13
(VIIIe)	74 ± 0.43	54 ± 0.35	50 ± 1.75	54 ± 1.51	74 ± 1.21	51 ± 1.75
(IXa)	90 ± 0.61	53 ± 0.30	39 ± 1.52	ND	64 ± 0.53	58 ± 1.52
(IXb)	91 ± 0.81	68 ± 1.42	50 ± 1.35	ND	75 ± 1.19	64 ± 1.35
(IXc)	95 ± 1.09	75 ± 0.50	41 ± 0.40	ND	84 ± 1.25	88 ± 0.40
(IXd)	92 ± 1.13	61 ± 0.26	37 ± 1.36	ND	69 ± 1.33	53 ± 1.36
(IXe)	83 ± 0.42	50 ± 0.17	35 ± 1.18	ND	71 ± 0.43	55 ± 1.17
(Xa)	82 ± 0.61	34 ± 1.44	42 ± 0.54	58 ± 1.41	58 ± 1.21	74 ± 1.44
(Xb)	80 ± 1.25	45 ± 0.37	35 ± 0.22	52 ± 1.31	52 ± 0.60	65 ± 0.37
(Xc)	83 ± 1.09	40 ± 0.20	31 ± 1.24	61 ± 1.20	72 ± 1.40	71 ± 1.20
(Xd)	68 ± 0.27	47 ± 0.19	27 ± 1.14	48 ± 0.13	68 ± 0.63	65 ± 1.13
(Xe)	65 ± 0.13	36 ± 0.13	30 ± 1.13	58 ± 0.12	68 ± 0.55	67 ± 1.13
Trifloxystrobin	94 ± 1.20	79 ± 0.84	51 ± 0.68	85 ± 0.22	91 ± 0.72	84 ± 1.28
Azoxystrobin	91 ± 0.22	73 ± 0.26	45 ± 1.04	80 ± 0.45	97 ± 0.15	60 ± 0.14

NA, not active; ND, not determined. The data represent mean value (SEM).

Table 2. Antioxidant activity of synthesized novel series of the synthesized compounds

Compounds	DPPH radical scavenging activity (%) at 10 μg/mL	Anti-lipid peroxidation (%) at 40 μg/mL
(IIa)	NA	ND
(IIb)	38 ± 0.62	ND
(IIc)	57 ± 1.45	ND
(IId)	NA	ND
(IIe)	58 ± 1.38	ND
(IVa)	30 ± 1.18	26 ± 1.10
(IVb)	46 ± 0.21	33 ± 0.73
(IVc)	57 ± 0.56	31 ± 0.34
(IVd)	55 ± 0.35	48 ± 0.66
(IVe)	49 ± 1.13	34 ± 1.20
(VIa)	55 ± 1.24	30 ± 0.14
(VIb)	61 ± 0.71	36 ± 0.21
(VIc)	67 ± 1.58	42 ± 1.30
(VId)	72 ± 1.26	48 ± 0.16
(VIe)	60 ± 0.88	45 ± 0.14
(VIIa)	ND	ND
(VIIb)	63 ± 1.63	ND
(VIIc)	68 ± 1.56	ND
(VIId)	72 ± 0.81	ND
(VIIe)	ND	ND
(VIIIa)	60 ± 1.31	43 ± 1.10
(VIIIb)	68 ± 1.14	51 ± 0.32
(VIIIc)	73 ± 1.84	41 ± 0.51
(VIIId)	78 ± 0.63	49 ± 1.33
(VIIIe)	69 ± 1.43	49 ± 1.09
(IXa)	63 ± 1.13	53 ± 0.42
(IXb)	75 ± 1.63	57 ± 1.12
(IXc)	87 ± 1.15	48 ± 0.73
(IXd)	89 ± 1.87	52 ± 1.18
(IXe)	69 ± 1.63	41 ± 1.40
(Xa)	62 ± 1.63	47 ± 0.67
(Xb)	77 ± 1.15	61 ± 0.33
(Xc)	74 ± 1.87	53 ± 0.76
(Xd)	83 ± 1.63	55 ± 0.44
(Xe)	70 ± 1.63	45 ± 0.23
Vitamin C	94.5 ± 0.55	–
Vitamin E	–	72.1 ± 0.55

Antioxidant activities were expressed in percentage compared with standard vitamin and E, respectively. NA, not active; ND, not determined. The data represent mean value (SEM) of three duplicates.

erate anti-lipid peroxidation inhibition comparable to that of standard vitamin E at similar concentration.

EXPERIMENTAL

General Experimental Procedures

All melting points were measured on Thomas Hoover melting point apparatus and uncorrected. The infrared spectra were recorded in potassiumbromide disks on a Shimadzu 8300 spectrometer, in range 400–4000 cm^{-1}. An elemental analysis was carried out on an Elementorvairo-EL instrument. ^1H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded on Sea 400 (Bruker) using $CDCl_3$ and DMSO-d_6 as solvent and TMS as an internal reference. Chemical shifts are expressed in δ ppm units.

*Synthetic Procedures. General Procedurefor the Synthesis of Compounds (**IVa–e**)*

A three-necked, round bottomed flask (500 mL), equipped with a magnetic stirrer, thermometer, decanter and condenser was charged with the 1*H*-benzo[4,5]thiazolo[2,3-*b*]quinazolines **(IIIa–e)** (5 mmol), acetonitrile (0.21 g, 5 mmol), in dry THF. The mixture was stirred well then an equivalent weight of NaH and DMF were added and the mixture was then heated to 100°C for 2 h then left to cool. The formed solid was filtered off and washed with petroleum ether [56]. The formed salt was dissolve in ice-cold water and then acidified HCl to afford the corresponding compounds (**IVa–e**).

3-((8*R*)-3,3-Dimethyl-12-(methylthio)-1,9-dioxo-7-phenyl-2,3,4,6a,7,8,9,12-octahydro-1*H*-benzo[4,5]-thiazolo[2,3-*b*]quinazolin-8-yl)-3-oxopropanenitrile (IVa) was recrystallized from ethanol as white crystals (1.9 g, 77.34%). Mp 169–171°C. IR (KBr pellets, cm^{-1}) ν_{max}, 2256, (CN); 1764, 1740, 1725 (3C=O); ^1H NMR (400 MHz, DMSO-d_6); δ 1.23 (s, 3H, $-CH_3$); 1.25 (s, 3H, $-CH_3$); 1.94 (s, 2H, $-CH_2-$); 2.25 (s, 2H, $-CH_2-$); 2.50 (s, 3H, $-SCH_3$); 3.25 (m, 1H, –CH–Cyclohexene); 3.62 (m, 1H, –CH–Cyclohexene); 3.82 (m, 1H, –CH–Cyclohexene); 3.98 (s, 2H, $-CH_2$); 4.62 (s, 1H, –CH–); 7.04 (s, 1H, –C=CH–); 7.26–7.49 (m, 5H, ArH); ^{13}C NMR (100 MHz, DMSO-d_6); δ 12.06, 25.31, 26.18, 30.53, 32.11, 37.24, 47.13, 54.30, 60.17, 69.14, 104.20, 116.36, 124.30, 126.25, 127.10, 132.20, 146.76, 152.13, 156.22, 165.19, 193.26, 195.14, 199.57. Anal. calcd. for $C_{26}H_{25}N_3O_3S_2$: C, 63.52%; H, 5.13%, N, 8.55%. Found: C, 63.67%; H, 5.80%; N, 8.11%.

3-((8*R*)-7-(4-Chlorophenyl)-3,3-dimethyl-12-(methylthio)-1,9-dioxo-2,3,4,6a,7,8,9,12-octahydro-1*H*-benzo-[4,5]thiazolo[2,3-*b*]quinazolin-8-yl)-3-oxopropanenitrile (IVb) was recrystallized from ethanolas white crystals (2.1 g, 79.85%). Mp 181–183°C. IR (KBr pellets, cm^{-1}) ν_{max}, 2236, (CN); 1751, 1745, 1730 (3C=O); ^1H NMR (400 MHz, DMSO-d_6); δ 1.10 (s, 3H, $-CH_3$); 1.29 (s, 3H, $-CH_3$); 1.67 (s, 2H, $-CH_2-$); 2.20 (s, 2H, $-CH_2-$); 2.52 (s, 3H, $-SCH_3$); 3.30 (m, 1H, –CH–Cyclohexene); 3.60 (m, 1H, –CH–Cyclohexene); 3.84 (m, 1H, –CH–Cyclohexene); 3.97(s, 2H, $-CH_2$); 4.55 (s, 1H, –CH–); 7.10 (s, 1H, –C=CH–); 7.48 (d, J = 8.20 Hz, 2H, Ar); 7.64 (d, J = 8.20 Hz, 2H, Ar); ^{13}C NMR (100 MHz, DMSO-d_6); δ 11.46, 24.81, 26.32, 31.86, 32.24, 37.90, 47.28, 52.42, 60.51, 68.23, 103.40, 115.87, 126.44, 128.19, 128.80, 132.20, 145.63, 153.55, 155.84, 165.32, 193.14, 194.86, 199.66. Anal. calcd. for $C_{26}H_{24}ClN_3O_3S_2$: C, 59.36%; H, 4.60%, N, 7.99%. Found: C, 59.71%; H, 4.93%; N, 7.45%.

3-((8*R*)-3,3-Dimethyl-12-(methylthio)-7-(4-nitrophenyl)-1,9-dioxo-2,3,4,6a,7,8,9,12-octahydro-1*H*-benzo[4,5]thiazolo[2,3-*b*]quinazolin-8-yl)-3-oxopropanenitrile (IVc) was recrystallized from ethanol–hexane (1 : 2) as yellow crystals (2.2 g, 82.10%). Mp 181–183°C. IR (KBr pellets, cm^{-1}) ν_{max}, 2242, (CN); 1751, 1746, 1730 (3C=O); ^1H NMR (400 MHz, DMSO-d_6); δ 1.12 (s, 3H, $-CH_3$); 1.24 (s, 3H, $-CH_3$); 1.50 (s, 2H, $-CH_2-$); 2.23 (s, 2H, $-CH_2-$); 2.60 (s, 3H, $-SCH_3$); 3.32 (m, 1H, –CH–Cyclohexene); 3.64 (m, 1H, –CH–Cyclohexene); 3.80 (m, 1H, –CH–Cyclohexene); 3.94 (s, 2H, $-CH_2$); 4.60 (s, 1H, –CH–); 7.25 (s, 1H, –C=CH–); 7.50 (d, J = 8.20 Hz, 2H, Ar); 7.84 (d, J = 8.20 Hz, 2H, Ar);^{13}C NMR (100 MHz, DMSO-d_6); δ 11.10, 24.75, 26.55, 31.70, 32.17, 37.86, 47.48, 52.60, 60.47, 68.35, 103.34, 115.76, 125.24, 128.26, 132.08, 148.02, 153.54, 155.62, 157.33, 165.45, 191.60, 194.26, 199.50. Anal. calcd. for $C_{25}H_{24}N_4O_5S_2$: C, 58.19%; H, 4.51%, N, 10.44%. Found: C, 57.80%; H, 4.67%; N, 9.93%.

3-((8*R*)-7-(5-Chloro-2-methoxyphenyl)-3,3-dimethyl-12-(methylthio)-1,9-dioxo-2,3,4,6a,7,8,9,12-octahydro-1*H*-benzo[4,5]thiazolo[2,3-*b*]quinazolin-8-yl)-3-oxopropanenitrile (IVd) was recrystallizedfrom ethanol as white crystals (2.3 g, 82.73%). Mp 190–192°C. IR (KBr pellets, cm^{-1}) ν_{max}, 2260, (CN); 1759, 1743, 1728 (3C=O); ^1H NMR (400 MHz, DMSO-d_6); δ 1.12 (s, 3H, $-CH_3$); 1.23 (s, 3H, $-CH_3$); 1.46 (s, 2H, $-CH_2-$); 2.30 (s, 2H, $-CH_2-$); 2.56 (s, 3H, $-SCH_3$); 3.28 (m, 1H, –CH–Cyclohexene); 3.46 (m, 1H, –CH–Cyclohexene); 3.56 (m, 1H, –CH–Cyclohexene); 3.68 (s, 2H, $-CH_2$); 3.88 (s, 3H, $-OCH_3$); 4.54 (s, 1H, –CH–); 7.38 (s, 1H, –C=CH–); 7.46 (d, J = 4 Hz, 1H, Ar); 7.80 (d, J = 4Hz, 1H, Ar);7.96 (s, 1H, Ar); ^{13}C NMR (100 MHz, DMSO-d_6); δ 13.04, 20.50, 26.45, 31.50, 32.23, 37.76, 47.41, 51.06, 55.12, 59.44, 67.23, 103.20, 110.48, 116.32, 124.46, 125.33, 129.71, 132.08, 139.11, 151.46, 153.28, 157.66, 167.19, 192.43, 193.32, 199.48. Anal. calcd. for $C_{27}H_{26}ClN_3O_4S_2$: C, 58.32%; H, 4.71%, N, 7.56%. Found: C, 58.13%; H, 4.55%; N, 7.02%.

3-((8*R*)-7-(2,5-Dimethylfuran-3-yl)-3,3-dimethyl-12-(methylthio)-1,9-dioxo-2,3,4,6a,7,8,9,12-octahydro-1*H*-benzo[4,5]thiazolo[2,3-*b*]quinazolin-8-yl)-3-oxopropanenitrile (IVe) was recrystallized from ethanol-hexane (1 : 2) as white crystals (1.8 g, 70.59%). Mp 174–176°C. IR (KBr pellets, cm^{-1}) ν_{max}, 2258, (CN); 1763, 1746, 1715 (3C=O); ^{1}H NMR (400 MHz, DMSO-d_6); δ 1.16 (s, 3H, $-CH_3$); 1.27 (s, 3H, $-CH_3$); 1.58 (s, 2H, $-CH_2-$); 2.16 (s, 2H, $-CH_2-$); 2.50 (s, 3H, $-SCH_3$); 2.64 (s, 3H, $-CH_3$); 2.80 (s, 3H, $-CH_3$); 3.32 (m, 1H, –CH–Cyclohexene); 3.48 (m, 1H, –CH–Cyclohexene); 3.68 (m, 1H, –CH–Cyclohexene); 3.80(s, 2H, $-CH_2$); 3.94(s, 3H, $-CH_3$); 4.18 (s, 1H, –CH–); 6.20 (s, 1H, Ar), 7.40 (s, 1H, –C=CH); ^{13}C NMR (100 MHz, DMSO-d_6); δ 10.42, 11.43, 13.08, 20.32, 26.15, 30.64, 32.50, 38.36, 48.02, 51.64, 58.20, 65.12, 103.42, 108.33, 110.48, 116.24, 129.26, 132.50, 150.06, 155.38, 156.14, 165.17, 191.22, 193.42, 199.80. Anal. calcd. for $C_{26}H_{27}N_3O_4S_2$: C, 61.27%; H, 5.34%, N, 8.25%. Found: C, 59.78%; H, 5.83%; N, 8.69%.

General Procedure for the Synthesis of Compounds (VIa–e)

A mixture of 1*H*-benzo[4,5]thiazolo[2,3-*b*]quinazolines (**IVa–e**) (5 mmol), benzaldehyde (**V**) (0.50 g, 5 mmol) and a catalytic amount of piperidine (1 mL) in ethanol solvent (20 mL) stirred and refluxed for 4 h. Completion of the reaction was monitored by TLC. After completion the reaction, solventwas removed under reducedpressureto give crude product which was extracted with ethyl acetate (2 × 20 mL) followed by washing with water. Thecombined organic extracts were dried over anhydrous Na_2SO_4 and concentrated to give crudeproducts which were further purified by column chromatography by using ethylacetate : hexane (5 : 3) as solvent system to afford pure compounds **(VIa–e).**

(*Z*)-2-((8*S*)-3,3-Dimethyl-12-(methylthio)-1,9-dioxo-7-phenyl-2,3,4,6a,7,8,9,12-octahydro-1*H*-benzo-[4,5]thiazolo[2,3-*b*]quinazoline-8-carbonyl)-3-phenylacrylonitrile (VIa) was recrystallized from diluted ethanol as whitecrystals (2.4 g, 82.76%). Mp 154–156°C. IR (KBr pellets, cm^{-1}) ν_{max}, 2247, (CN); 1760, 1745, 1711 (3C=O); ^{1}H NMR (400 MHz, $CDCl_3$); δ 1.04 (s, 3H, $-CH_3$); 1.28 (s, 3H, $-CH_3$); 1.80 (s, 2H, $-CH_2-$); 2.34 (s, 2H, $-CH_2-$); 2.53 (s, 3H, $-SCH_3$); 3.30 (m, 1H, –CH–Cyclohexene); 3.54 (m, 1H, –CH–Cyclohexene); 3.87 (m, 1H, –CH–Cyclohexene); 4.33 (s, 1H, –CH–); 7.12 (s, 1H, –C=CH–); 7.60 (s, 1H, –C=CH–); 7.84–8.20 (m, 10H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$); δ 11.4 6, 25.23, 26.14, 30.40, 37.54, 47.18, 49.11, 59.58, 61.23, 103.41, 109.70, 117.63, 124.10, 126.05, 127.14, 128.20, 128.60, 132.13, 132.44, 133.50, 146.70, 151.36, 155.19, 156.67, 165.12, 192.30, 194.08, 196.30. Anal. calcd. for $C_{33}H_{29}N_3O_3S_2$: C, 68.37%; H, 5.04%, N, 7.25%. Found: C, 67.84%; H, 5.62%; N, 7.19%.

(*Z*)-2-((8*S*)-7-(4-Chlorophenyl)-3,3-dimethyl-12-(methylthio)-1,9-dioxo-2,3,4,6a,7,8,9,12-octahydro-1*H*-benzo[4,5]thiazolo[2,3-*b*]quinazoline-8-carbonyl)-3-phenylacrylonitrile (VIb) was recrystallized from ethanol as white crystals (2.8 g, 91.21%). Mp 161–163°C. IR (KBr pellets, cm^{-1}) ν_{max}, 2275, (CN); 1763, 1747, 1706 (3C=O); ^{1}H NMR (400 MHz, $CDCl_3$); δ 1.13 (s, 3H, $-CH_3$); 1.30 (s, 3H, $-CH_3$); 1.72 (s, 2H, $-CH_2-$); 2.23 (s, 2H, $-CH_2-$); 2.60 (s, 3H, $-SCH_3$); 3.14 (m, 1H, –CH–Cyclohexene); 3.28 (m, 1H, –CH–Cyclohexene); 3.65 (m, 1H, –CH–Cyclohexene); 4.50 (s, 1H, –CH–); 7.08 (s, 1H, –C=CH–); 7.12 (d, J = 4.30 Hz, 2H, Ar); 7.32–7.65 (m, 5H, ArH); 7.82 (d, J = 4.30 Hz, 2H, Ar); 7.94(s, 1H, –C=CH–); ^{13}C NMR (100 MHz, $CDCl_3$); δ 11.36, 24.48, 26.12, 31.25, 32.41, 37.73, 47.19, 52.33, 63.81, 104.10, 109.30, 116.52, 126.12, 127.36, 127.78, 128.25, 129.40, 131.49, 132.69, 133.06, 145.17, 153.15, 155.33, 157.29, 162.69, 193.11, 194.46, 197.19. Anal. calcd. for $C_{33}H_{28}ClN_3O_3S_2$: C, 64.53%; H, 4.60%, N, 6.84%. Found: C, 64.95%; H, 4.21%; N, 6.55%.

(*Z*)-2-((8*S*)-3,3-Dimethyl-12-(methylthio)-7-(4-nitrophenyl)-1,9-dioxo-2,3,4,6a,7,8,9,12-octahydro-1*H*-benzo[4,5]thiazolo[2,3-*b*]quinazoline-8-carbonyl)-3-phenylacrylonitrile (VIc) was recrystallized from ethanol as dark yellow crystals (2.9 g, 92.95%). Mp 193–195°C. IR (KBr pellets, cm^{-1}) ν_{max}, 2254, (CN); 1762, 1740, 1713 (3C=O); ^{1}H NMR (400 MHz, $CDCl_3$); δ 1.09 (s, 3H, $-CH_3$); 1.27 (s, 3H, $-CH_3$); 1.48 (s, 2H, $-CH_2-$); 2.29 (s, 2H, $-CH_2-$); 2.74 (s, 3H, $-SCH_3$); 3.06 (m, 1H, –CH–Cyclohexene); 3.32 (m, 1H, –CH–Cyclohexene); 3.71 (m, 1H, –CH–Cyclohexene); 4.66 (s, 1H, –CH–); 7.02 (s, 1H, –C=CH–); 7.24 (d, J = 7 Hz, 2H, Ar); 7.40–7.62 (m, 5H, ArH); 7.84 (d, J = 7 Hz, 2H, Ar); 7.91 (s, 1H, –C=CH–); ^{13}C NMR (100 MHz, $CDCl_3$); δ 12.12, 24.36, 26.18, 31.24, 39.66, 47.21, 52.27, 57.33, 63.74, 103.17, 109.63, 116.34, 121.56, 126.42, 127.55, 127.78, 129.18, 132.45, 133.37, 147.08, 154.30, 155.52, 156.36, 159.67, 165.20, 191.61, 194.30, 197.26. Anal. calcd. for $C_{33}H_{28}N_4O_5S_2$: C, 63.44%; H, 4.52%, N, 8.97%. Found: C, 63.13%; H, 4.35%; N, 8.41%.

(*Z*)-2-((8*S*)-7-(5-Chloro-2-methoxyphenyl)-3,3-dimethyl-12-(methylthio)-1,9-dioxo-2,3,4,6a,7,8,9,12-octahydro-1*H*-benzo[4,5]thiazolo[2,3-*b*]quinazoline-8-carbonyl)-3-phenylacrylonitrile (VId) was recrystallized from ethanol as white crystals (2.3 g, 71.43%). Mp 201–203°C. IR (KBr pellets, cm^{-1}) ν_{max}, 2264, (CN); 1748, 1723, 1684 (3C=O); ^{1}H NMR (400 MHz, $CDCl_3$); δ 1.19 (s, 3H, $-CH_3$); 1.30 (s, 3H, $-CH_3$); 1.42 (s, 2H, $-CH_2-$); 2.33 (s, 2H, $-CH_2-$); 2.60 (s, 3H, $-SCH_3$); 3.28 (m, 1H, –CH–Cyclohexene); 3.42 (m, 1H, –CH–Cyclohexene); 3.51 (m, 1H, –CH–Cyclohexene); 3.70 (s, 2H, $-OCH_3$); 4.62 (s, 1H, –

CH–); 7.43 (d, J = 4 Hz, 1H, Ar); 7.52 (d, J = 4 Hz, 1H, Ar); 7.64 (s, 1H, –C=CH–); 7.72–7.96 (m, 6H, ArH); 8.04 (s, 1H, –C=CH–); ^{13}C NMR (100 MHz, $CDCl_3$); δ 11.34, 18.93, 26.38, 31.64, 37.46, 47.11, 51.23, 55.41, 59.12, 64.63, 103.14, 110.50, 116.44, 118.43, 125.41, 127.11, 127.81, 128.36, 130.05, 133.61, 133.54, 136.20, 139.19, 151.30, 153.32, 154.28, 157.25, 161.98, 194.33, 195.27, 197.53. Anal. calcd. for $C_{34}H_{30}ClN_3O_4S_2$: C, 63.39%; H, 4.69%, N, 6.52%. Found: C, 63.19%; H, 4.50%; N, 6.32%.

(*Z*)-2-((8*S*)-7-(2,5-Dimethylfuran-3-yl)-3,3-dimethyl-12-(methylthio)-1,9-dioxo-2,3,4,6a,7,8,9,12-octahydro-1*H*-benzo[4,5]thiazolo[2,3-*b*]quinazoline-8-carbonyl)-3-phenylacrylonitrile (VIe) was recrystallized from ethanol–hexane (1 : 2) as white crystals (1.7 g, 56.86%). Mp 158–160°C. IR (KBr pellets, cm^{-1}) ν_{max}, 2250, (CN); 1756, 1735, 1720 (3C=O); ^{1}H NMR (400 MHz, $CDCl_3$); δ 1.03 (s, 3H, $-CH_3$); 1.22 (s, 3H, $-CH_3$); 1.62 (s, 2H, $-CH_2-$); 2.08 (s, 2H, $-CH_2-$); 2.54 (s, 3H, $-SCH_3$); 2.66 (s, 3H, $-CH_3$); 2.84 (s, 3H, $-CH_3$); 3.30 (m, 1H, –CH–Cyclohexene); 3.43 (m, 1H, –CH–Cyclohexene); 3.64 (m, 1H, –CH–Cyclohexene); 4.25 (s, 1H, –CH–); 5.80 (s, 1H, –C=CH); 7.20 (s, 1H, –C=CH); 7.40–7.82 (m, 5H, Ar) 7.94 (s, 1H, –C=CH); ^{13}C NMR (100 MHz, $CDCl_3$); δ 10.19, 11.32, 13.18, 20.55, 27.22, 30.47, 38.14, 45.92, 51.61, 58.20, 65.43, 103.40, 104.40, 111.30, 116.32, 126.12, 127.47, 128.33, 130.21, 132.25, 133.46, 147.86, 150.02, 151.48, 154.64, 159.11, 163.82, 190.39, 192.70, 194.66. Anal. calcd. for $C_{33}H_{31}N_3O_4S_2$: C, 66.31%; H, 5.23%, N, 7.03%. Found: C, 55.91%; H, 5.13%; N, 6.78%.

*General Procedurefor the Synthesis of Compounds (**VIIa–e**)*

An ethanolic solution of 1*H*-benzo[4,5]thiazolo[2,3-*b*]quinazoline (**VIa–e**) (5 mmol), and hydrazine hydrate (0.24 g, 5 mmol) hydrazine hydrate (1 mmol) or phenylhydrazine (1 mmol) was mixed in a reaction flask. The reaction mixture was refluxed for 3.5 h and reaction was observed by TLC. After completion the reaction, solvent was removed under reduced pressure and the residue was poured into ice-cold water (20 mL); the mixture was then extracted with ethylacetate (2 × 20 mL) followed by washing with water. The organic layer was dried over anhydrous Na_2SO_4, solvent was evaporated and the product obtained was purified by flash column chromatography using dichloromethane : ether (2 : 1) as eluent to afford the final corresponding 3-aminopyrazole derivatives (**VIIa–e**).

(8*S*)-8-(3-Amino-5-phenyl-1*H*-pyrazole-4-carbonyl)-3,3-dimethyl-12-(methylthio)-7-phenyl-3,4,6a,7,8,12-hexahydro-1*H*-benzo[4,5]thiazolo[2,3-*b*]quinazoline-1,9(2*H*)-dione (VIIa) was obtained as yellow crystals (1.6 g, 52.46%). Mp 173–175°C. IR (KBr pellets, cm^{-1}) ν_{max}, 3310, 3270 (2NH), 1745, 1622, 1683 (3C=O); ^{1}H NMR (400 MHz, DMSO-d_6); δ 1.08(s, 3H, $-CH_3$); 1.18 (s, 3H, $-CH_3$); 1.76 (s, 2H, $-CH_2-$); 2.06 (s, 2H, $-CH_2-$); 2.38 (s, 3H, $-SCH_3$); 3.40 (m, 1H, –CH–Cyclohexene); 3.52 (m, 1H, –CH–Cyclohexene); 3.61 (m, 1H, –CH–Cyclohexene); 4.80 (s, 1H, –CH–); 6.94 (s, 1H, –C=CH–); 8.12-8.40 (m, 10H, Ar); 8.25 (s, 2H, $-NH_2-D_2O$ exchangeable); 11.75 (s, 1H, $-NH-D_2O$ exchangeable); ^{13}C NMR (100 MHz, DMSO-d_6); δ 14.62, 23.15, 26.52, 30.12, 36.18, 42.46, 49.91, 58.21, 62.11, 98.08, 100.20, 123.14, 123.40, 125.30, 126.11, 126.32, 126.70, 128.15, 130.32, 132.16, 144.17, 152.25, 153.11, 156.08, 161.20, 192.41, 194.02, 196.34. Anal. calcd. for $C_{33}H_{31}N_5O_3S_2$: C, 65.00%; H, 5.12%, N, 11.49%. Found: C, 64.52%; H, 5.48%; N, 11.77%.

(8*S*)-8-(3-Amino-5-phenyl-1*H*-pyrazole-4-carbonyl)-7-(4-chlorophenyl)-3,3-dimethyl-12-(methylthio)-3,4,6a,7,8,12-hexahydro-1*H*-benzo[4,5]thiazolo-[2,3-*b*]quinazoline-1,9(2H)-dione (VIIb) was obtained as yellow crystals (2.2 g, 68.32%). Mp 155–156°C. IR (KBr pellets, cm^{-1}) ν_{max}, 3316, 3295 (2NH), 1760, 1722, 1713 (3C=O); ^{1}H NMR (400 MHz, DMSO-d_6); δ 1.14 (s, 3H, $-CH_3$); 1.23 (s, 3H, $-CH_3$); 1.68 (s, 2H, $-CH_2-$); 2.11 (s, 2H, $-CH_2-$); 2.42 (s, 3H, $-SCH_3$); 3.50 (m, 1H, –CH–Cyclohexene); 3.58 (m, 1H, –CH–Cyclohexene); 3.72 (m, 1H, –CH–Cyclohexene); 4.50 (s, 1H, –CH–); 7.11 (s, 1H, –C=CH–); 7.89 (s, 2H, $-NH_2-D_2O$ exchangeable); 8.14–8.45 (m, 9H, Ar); 12.25 (s, 1H, $-NH-D_2O$ exchangeable); ^{13}C NMR (100 MHz, DMSO-d_6); δ 11.12, 24.35, 28.41, 29.18, 41.07, 45.16, 53.11, 58.66, 60.91, 97.48, 103.30, 123.10, 126.35, 127.11, 128.21, 129.82, 130.24, 132.20, 134.15, 135.12, 143.34, 151.25, 154.31, 155.22, 161.20, 194.02, 196.11, 197.14. Anal. calcd. for $C_{33}H_{30}ClN_5O_3S_2$: C, 51.53%; H, 4.69%, N, 10.87%. Found: C, 50.98%; H, 4.40%; N, 10.23%.

(8*S*)-8-(3-Amino-5-phenyl-1*H*-pyrazole-4-carbonyl)-3,3-dimethyl-12-(methylthio)-7-(4-nitrophenyl)-3,4,6a,7,8,12-hexahydro-1*H*-benzo[4,5]thiazolo-[2,3-*b*]quinazoline-1,9(2*H*)-dione (VIIc) was obtained as yellow crystals (2.1 g, 64.22%). Mp 185–187°C. IR (KBr pellets, cm^{-1}) ν_{max}, 3330, 3254 (2NH), 1772, 1741, 1725 (3C=O); ^{1}H NMR (400 MHz, DMSO-d_6); δ 1.20 (s, 3H, $-CH_3$); 1.28 (s, 3H, $-CH_3$); 1.72 (s, 2H, $-CH_2-$); 2.10 (s, 2H, $-CH_2-$); 2.48 (s, 3H, $-SCH_3$); 3.46 (m, 1H, –CH–Cyclohexene); 3.51 (m, 1H, –CH–Cyclohexene); 3.64 (m, 1H, –CH–Cyclohexene); 4.53 (s, 1H, –CH–); 7.31 (s, 1H, –C=CH–); 7.97 (s, 2H, $-NH_2-D_2O$ exchangeable); 8.23–8.66 (m, 9H, Ar); 12.18 (s, 1H, $-NH-D_2O$ exchangeable); ^{13}C NMR (100 MHz, DMSO-d_6); δ 11.11, 24.28, 28.33, 29.30, 41.40, 45.40, 53.19, 58.58, 60.82, 97.36, 103.12, 123.16, 126.55, 127.32, 128.41, 129.62, 129.86, 132.50, 134.23, 135.35, 143.62, 151.30, 154.43, 155.31, 161.38, 194.42, 196.80, 197.56. Anal. calcd. for $C_{33}H_{30}N_6O_5S_2$:

C, 60.53%; H, 4.62%, N, 12.84%. Found: C, 60.10%; H, 4.08%; N, 12.35%.

(8*S*)-8-(3-Amino-5-phenyl-1*H*-pyrazole-4-carbonyl)-7-(5-chloro-2-methoxyphenyl)-3,3-dimethyl-12-(methylthio)-3,4,6a,7,8,12-hexahydro-1*H*-benzo[4,5]thiazolo[2,3-*b*]quinazoline-1,9(2*H*)-dione (VIId) was obtained white crystals (2 g, 59.35%). Mp 172–174°C. IR (KBr pellets, cm^{-1}) ν_{max}, 3338, 3260 (2NH), 1766, 1753, 1716 (3C=O); ^1H NMR (400 MHz, DMSO-d_6); δ 1.18 (s, 3H, $-CH_3$); 1.24 (s, 3H, $-CH_3$); 1.72 (s, 2H, $-CH_2-$); 2.23 (s, 2H, $-CH_2-$); 2.50 (s, 3H, $-SCH_3$); 3.26 (m, 1H, –CH–Cyclohexene); 3.48 (m, 1H, –CH–Cyclohexene); 3.65 (s, 3H, $-OCH_3$), 3.78 (m, 1H, –CH–Cyclohexene); 4.61 (s, 1H, –CH–); 7.23 (d, J = 7.20 Hz, 1H, Ar); 7.51 (s, 1H, –C=CH–); 7.62 (d, J = 7.20 Hz, 1H, Ar); 7.90 (s, 2H, $-NH_2-D_2O$ exchangeable); 8.40–8.82 (m, 6H, Ar); 12.12 (s, 1H, $-NH-D_2O$ exchangeable); ^{13}C NMR (100 MHz, DMSO-d_6); δ 10.22, 24.17, 27.23, 29.42, 43.20, 45.35, 54.29, 58.18, 61.42, 65.32, 95.16, 104.30, 112.30, 124.10, 125.15, 127.12, 127.40, 128.43, 128.80, 129.88, 131.20, 132.13, 135.42, 153.32, 154.83, 157.63, 158.61, 165.18, 193.11, 196.29, 198.16. Anal. calcd. for $C_{34}H_{32}ClN_5O_4S_2$: C, 60.57%; H, 4.78%, N, 10.39%. Found: C, 60.07%; H, 4.23%; N, 10.41%.

(8*S*)-8-(3-Amino-5-phenyl-1*H*-pyrazole-4-carbonyl)-7-(2,5-dimethylfuran-3-yl)-3,3-dimethyl-12-(methylthio)-3,4,6a,7,8,12-hexahydro-1*H*-benzo[4,5]-thiazolo[2,3-*b*]quinazoline-1,9(2*H*)-dione (VIIe) was obtained white crystals (2.4 g, 76.43%). Mp 162–164°C. IR (KBr pellets, cm^{-1}) ν_{max}, 3320, 3287 (2NH), 1752, 1713, 1703 (3C=O); ^1H NMR (400 MHz, DMSO-d_6); δ 1.13 (s, 3H, $-CH_3$); 1.34 (s, 3H, $-CH_3$); 1.68 (s, 2H, $-CH_2-$); 2.23 (s, 2H, $-CH_2-$); 2.50 (s, 3H, $-SCH_3$); 2.73 (s, 3H, $-CH_3$); 2.98 (s, 3H, $-CH_3$); 3.21 (m, 1H, –CH–Cyclohexene); 3.43 (m, 1H, –CH–Cyclohexene); 3.80 (m, 1H, –CH–Cyclohexene); 4.55 (s, 1H, –CH–); 6.85 (s, 1H, –C=CH–); 7.89–8.43 (m, 5H, Ar); 8.61 (s, 1H, –C=CH–); 8.82 (s, 2H, $-NH_2-D_2O$ exchangeable); 12.12 (s, 1H, $-NH-D_2O$ exchangeable); ^{13}C NMR (100 MHz, DMSO-d_6); δ 13.32, 14.71, 15.55, 20.19, 27.30, 30.52, 37.14, 48.22, 53.19, 57.32, 66.52, 94.36, 103.10, 105.55, 122.18, 126.15, 128.13, 128.61, 129.30, 130.33, 132.10, 135.26, 145.29, 148.46, 152.12, 157.23, 159.07, 161.44, 190.60, 193.18, 196.33. Anal. calcd. for $C_{33}H_{33}N_5O_4S_2$: C, 63.14%; H, 5.30%, N, 11.16%. Found: C, 62.69%; H, 5.27%; N, 10.82%.

General Procedure for the Synthesis of Compounds (VIIIa–e), (IXa–e), and (Xa–e)

An ethanolic solution of the appropriate acrylamide derivatives (**VIa–e**) (5 mmol) and the corresponding heterocyclic amine, viz. 3-methyl-5-amino pyrazole (0.49 g, 5 mmol), 3-amino-1,2,4-triazole (0.42 g, 5 mmol) and 2-aminobenzimidazole (0.67 g, 5 mmol) and few drops of piperidine (3 mL) was refluxed in EtOH for 6 h. The reaction was left to cool and the formed solid was filtered off, dried and finally purified by silica gel column chromatography using dichloromethan : methanol (6 : 1) as eluent to afford the corresponding (**VIIIa–e**), (**IXa–e**), and (**Xa–e**) derivatives, respectively.

(8*S*)-8-(5-Amino-7-phenylpyrazolo[1,5-*a*]pyrimidine-6-carbonyl)-3,3-dimethyl-12-(methylthio)-7-phenyl-3,4,6a,7,8,12-hexahydro-1*H*-benzo[4,5]thiazolo-[2,3-*b*]quinazoline-1,9(2*H*)-dione (VIIIa) was recrystallized from ethanolas yellow crystals (2.5 g, 75.76%). Mp 198–200°C. IR (KBr pellets, cm^{-1}) ν_{max}, 3364, 3211 (NH), 1750, 1724, 1616 (3C=O); ^1H NMR (400 MHz, DMSO-d_6); δ 1.13(s, 3H, $-CH_3$); 1.30 (s, 3H, $-CH_3$); 1.88 (s, 2H, $-CH_2-$); 2.16 (s, 2H, $-CH_2-$); 2.41 (s, 3H, $-SCH_3$); 3.28 (m, 1H, –CH–Cyclohexene); 3.41 (m, 1H, –CH–Cyclohexene); 3.74 (m, 1H, –CH–Cyclohexene); 4.61 (s, 1H, –CH–); 6.54 (s, 1H, –C=CH–); 6.92 (d, 1H, J = 4 Hz, –C=CH–); 7.06 (d, 1H, J = 4 Hz, –C=CH–); 8.10–8.52 (m, 10H, Ar); 8.85 (s, 2H, $-NH_2-D_2O$ exchangeable); ^{13}C NMR (100 MHz, DMSO-d_6); δ 13.12, 21.45, 25.11, 29.17, 34.48, 44.16, 50.82, 57.61, 60.91, 98.58, 104.33, 116.32, 125.34, 126.14, 126.48, 127.31, 128.55, 129.08, 131.12, 135.23, 143.26, 146.07, 148.11, 153.10, 155.66, 158.18, 160.72, 165.13, 190.62, 192.32, 195.14. Anal. calcd. for $C_{36}H_{32}N_6O_3S_2$: C, 65.43%; H, 4.88%, N, 12.72%. Found: C, 54.90%; H, 4.20%; N, 12.49%.

(8*S*)-8-(5-Amino-7-phenylpyrazolo[1,5-*a*]pyrimidine-6-carbonyl)-7-(4-chlorophenyl)-3,3-dimethyl-12-(methylthio)-3,4,6a,7,8,12-hexahydro-1*H*-benzo[4,5]-thiazolo[2,3-*b*]quinazoline-1,9(2*H*)-dione (VIIIb) was recrystallized from ethanol as pale orange crystals (2.1 g, 60.34%). Mp 211–213°C. IR (KBr pellets, cm^{-1}) ν_{max}, 3321, 3245 (NH), 1730, 1718, 1630 (3C=O); ^1H NMR (400 MHz, DMSO-d_6); δ 1.11(s, 3H, $-CH_3$); 1.28 (s, 3H, $-CH_3$); 1.80 (s, 2H, $-CH_2-$); 2.21 (s, 2H, $-CH_2-$); 2.56 (s, 3H, $-SCH_3$); 3.08 (m, 1H, –CH–Cyclohexene); 3.62 (m, 1H, –CH–Cyclohexene); 3.91 (m, 1H, –CH–Cyclohexene); 4.48 (s, 1H, –CH–); 6.57 (s, 1H, –C=CH–); 6.90 (d, 1H, J = 4 Hz, –C=CH–); 7.11 (d, 1H, J = 4 Hz, –C=CH–); 8.32–8.66 (m, 9H, Ar); 8.90 (s, 2H, $-NH_2-D_2O$ exchangeable); ^{13}C NMR (100 MHz, DMSO-d_6); δ 11.93, 22.15, 24.61, 28.54, 32.06, 41.90, 53.67, 56.40, 62.19, 97.08, 105.11, 115.21, 124.22, 125.32, 127.38, 128.24, 128.98, 130.22, 132.48, 135.16, 141.18, 145.32, 146.51, 152.40, 153.17, 156.43, 164.32, 168.21, 192.12, 194.51, 196.38. Anal. calcd. for $C_{36}H_{31}ClN_6O_3S_2$: C, 62.19%; H, 4.49%, N, 12.09%. Found: C, 61.98%; H, 4.03%; N, 11.87%.

(8*S*)-8-(5-Amino-7-phenylpyrazolo[1,5-*a*]pyrimidine-6-carbonyl)-3,3-dimethyl-12-(methylthio)-7-(4-nitrophenyl)-3,4,6a,7,8,12-hexahydro-1*H*-benzo[4,5]-thiazolo[2,3-*b*]quinazoline-1,9(2*H*)-dione (VIIIc) was

recrystallized from ethanol as orange crystals (2.6 g, 73.65%). Mp 185–187°C. IR (KBr pellets, cm^{-1}) ν_{max}, 3331, 3228 (NH), 1740, 1723, 1650 (3C=O); ^1H NMR (400 MHz, $CDCl_3$); δ 1.17(s, 3H, $-CH_3$); 1.23 (s, 3H, $-CH_3$); 1.65 (s, 2H, $-CH_2-$); 2.34 (s, 2H, $-CH_2-$); 2.60 (s, 3H, $-SCH_3$); 3.12 (m, 1H, –CH–Cyclohexene); 3.55 (m, 1H, –CH–Cyclohexene); 3.87 (m, 1H, –CH–Cyclohexene); 4.63 (s, 1H, –CH–); 6.50 (s, 1H, –C=CH–); 6.88 (d, 1H, J = 4 Hz, –C=CH–); 7.15 (d, 1H, J = 4 Hz, –C=CH–); 8.20–8.44 (m, 9H, Ar); 8.82 (s, 2H, $-NH_2-D_2O$ exchangeable); ^{13}C NMR (100 MHz, $CDCl_3$); δ 12.20, 23.22, 23.85, 27.11, 30.16, 40.02, 52.80, 56.56, 61.40, 98.22, 105.81, 116.06, 125.11, 125.43, 126.60, 128.14, 128.92, 130.42, 133.14, 140.53, 144.32, 146.60, 152.12, 154.43, 156.56, 160.11, 161.55, 164.24, 190.08, 193.22, 196.23. Anal. calcd. for $C_{36}H_{31}N_7O_5S_2$: C, 61.26%; H, 4.43%, N, 13.89%. Found: C, 61.04%; H, 4.10%; N, 14.27%.

(8*S*)-8-(5-Amino-7-phenylpyrazolo[1,5-*a*]pyrimidine-6-carbonyl)-7-(5-chloro-2-methoxyphenyl)-3,3-dimethyl-12-(methylthio)-3,4,6a,7,8,12-hexahydro-1*H*-benzo[4,5]thiazolo[2,3-*b*]quinazoline-1,9(2*H*)-dione (VIIId) was recrystallized from ethanol–benzene (1 : 2) as yellow crystals (1.8 g, 49.72%). Mp 212–214°C. IR (KBr pellets, cm^{-1}) ν_{max}, 3333, 3246 (NH), 1760, 1743, 1656 (3C=O); ^1H NMR (400 MHz, $CDCl_3$); δ 1.08 (s, 3H, $-CH_3$); 1.20 (s, 3H, $-CH_3$); 1.45 (s, 2H, $-CH_2-$); 2.40 (s, 2H, $-CH_2-$); 2.62 (s, 3H, $-SCH_3$); 3.02 (m, 1H, –CH–Cyclohexene); 3.30 (m, 1H, –CH–Cyclohexene); 3.60 (s, 3H, $-OCH_3$), 3.94 (m, 1H, –CH–Cyclohexene); 4.43 (s, 1H, –CH–); 6.52 (s, 1H, –C=CH–); 6.80 (d, 1H, J = 4 Hz, –C=CH–); 7.04 (d, 1H, J = 4 Hz, –C=CH–); 7.11 (d, J = 7.20 Hz, 1H, Ar); 7.24 (s, 1H, –C=CH–); 7.42 (d, J = 7.20 Hz, 1H, Ar); 7.84–8.24 (m, 6H, Ar); 8.82 (s, 2H, $-NH_2-D_2O$ exchangeable); ^{13}C NMR (100 MHz, $CDCl_3$); δ 10.40, 22.55, 23.15, 27.31, 29.46, 42.12, 51.70, 55.18, 57.32, 61.56, 97.46, 103.21, 113.32, 116.23, 125.13, 127.53, 128.10, 128.34, 128.62, 129.71, 120.11, 132.18, 139.23, 143.52, 147.13, 151.52, 154.28, 156.16, 159.21, 162.40, 170.34, 190.48, 192.52, 196.11. Anal. calcd. for $C_{37}H_{33}ClN_6O_4S_2$: C, 61.27%; H, 4.59%, N, 11.59%. Found: C, 60.78%; H, 4.91%; N, 11.42%.

(8*S*)-8-(5-Amino-7-phenylpyrazolo[1,5-*a*]pyrimidine-6-carbonyl)-7-(2,5-dimethylfuran-3-yl)-3,3-dimethyl-12-(methylthio)-3,4,6a,7,8,12-hexahydro-1*H*-benzo[4,5]thiazolo[2,3-*b*]quinazoline-1,9(2*H*)-dione (VIIIe) was recrystallized from ethanol as yellow crystals (2.8 g, 82.60%). Mp 218–220°C. IR (KBr pellets, cm^{-1}) ν_{max}, 3332, 3240 (NH), 1764, 1740, 1652 (3C=O); ^1H NMR (400 MHz, $CDCl_3$); δ 1.13 (s, 3H, $-CH_3$); 1.25 (s, 3H, $-CH_3$); 1.34 (s, 2H, $-CH_2-$); 2.14 (s, 2H, $-CH_2-$); 2.20 (s, 3H, $-SCH_3$); 2.65 (s, 3H, $-CH_3$); 2.80 (s, 3H, $-CH_3$); 3.12 (m, 1H, –CH–Cyclohexene); 3.31 (m, 1H, –CH–Cyclohexene); 3.80 (m, 1H, –CH–Cyclohexene); 4.41 (s, 1H, –CH–); 6.10 (s, 1H, –C=CH–); 6.60 (s, 1H, –C=CH–); 6.86 (d, 1H, J = 4 Hz, –C=CH–); 7.12 (d, 1H, J = 4 Hz, –C=CH–); 7.24 (s, 1H, –C=CH–); 7.86–8.24 (m, 5H, Ar); 8.83 (s, 2H, $-NH_2-D_2O$ exchangeable); ^{13}C NMR (100 MHz, $CDCl_3$); δ 9.80, 11.21, 16.25, 20.35, 25.48, 31.61, 41.62, 47.17, 52.30, 57.48, 67.11, 98.16, 103.41, 107.13, 116.10, 126.24, 127.43, 128.86, 129.62, 130.31, 132.18, 143.64, 146.53, 149.64, 150.18, 153.28, 156.41, 159.20, 161.17, 171.32, 190.20, 193.22, 196.35. Anal. calcd. for $C_{36}H_{34}N_6O_4S_2$: C, 63.70%; H, 5.05%, N, 12.38%. Found: C, 63.01%; H, 4.71%; N, 12.12%.

(8*S*)-8-(5-Amino-7-phenyl-[1,2,4]triazolo[1,5-*a*]-pyrimidine-6-carbonyl)-3,3-dimethyl-12-(methyl-thio)-7-phenyl-3,4,6a,7,8,12-hexahydro-1*H*-benzo[4,5]-thiazolo[2,3-*b*]quinazoline-1,9(2*H*)-dione (IXa) was recrystallized from ethanol–benzene (1 : 1) as yellow crystals (2.9 g, 87.61%). Mp 231–233°C. IR (KBr pellets, cm^{-1}) ν_{max}, 3322, 3240 (NH), 1755, 1742, 1668 (3C=O); ^1H NMR (400 MHz, $CDCl_3$); δ 1.07(s, 3H, $-CH_3$); 1.25 (s, 3H, $-CH_3$); 1.68 (s, 2H, $-CH_2-$); 2.20 (s, 2H, $-CH_2-$); 2.38 (s, 3H, $-SCH_3$); 3.14 (m, 1H, –CH–Cyclohexene); 3.31 (m, 1H, –CH–Cyclohexene); 3.60 (m, 1H, –CH–Cyclohexene); 4.55 (s, 1H, –CH–); 6.60 (s, 1H, –C=CH–); 7.68–8.40 (m, 10H, Ar); 8.65 (s, 2H, $-NH_2-D_2O$ exchangeable); 8.90 (s, 1H, –C=CH–); ^{13}C NMR (100 MHz, $CDCl_3$); δ 12.22, 22.50, 26.31, 29.41, 37.18, 43.36, 51.12, 57.40, 61.08, 102.17, 114.43, 125.14, 126.22, 127.51, 128.08, 128.64, 129.44, 131.42, 132.13, 148.50, 153.21, 155.30, 157.16, 159.20, 165.43, 172.19, 190.28, 192.62, 196.32. Anal. calcd. for $C_{35}H_{31}N_7O_3S_2$: C, 63.52%; H, 4.72%, N, 14.82%. Found: C, 63.15%; H, 4.37%; N, 14.93%.

(8*S*)-8-(5-Amino-7-phenyl-[1,2,4]triazolo[1,5-*a*]-pyrimidine-6-carbonyl)-7-(4-chlorophenyl)-3,3-dimethyl-12-(methylthio)-3,4,6a,7,8,12-hexahydro-1*H*-benzo[4,5]thiazolo[2,3-*b*]quinazoline-1,9(2H)-dione (IXb) was recrystallized from ethanol–hexane (1 : 1) as pale yellow crystals (1.3 g, 43.10%). Mp 231–233°C. IR (KBr pellets, cm^{-1}) ν_{max}, 3334, 3251 (NH), 1762, 1711, 1652 (3C=O); ^1H NMR (400 MHz, $CDCl_3$); δ 1.17(s, 3H, $-CH_3$); 1.28 (s, 3H, $-CH_3$); 1.66 (s, 2H, $-CH_2-$); 2.24 (s, 2H, $-CH_2-$); 2.31(s, 3H, $-SCH_3$); 3.24 (m, 1H, –CH–Cyclohexene); 3.36 (m, 1H, –CH–Cyclohexene); 3.64 (m, 1H, –CH–Cyclohexene); 4.48 (s, 1H, –CH–); 6.71 (s, 1H, –C=CH–); 7.88–8.54 (m, 9H, Ar); 8.80 (s, 2H, $-NH_2-D_2O$ exchangeable); 8.98 (s, 1H, –C=CH–); ^{13}C NMR (100 MHz, $CDCl_3$); δ 12.42, 23.12, 26.40, 29.35, 37.20, 43.46, 50.92, 56.30, 61.33, 102.84, 116.22, 125.43, 126.32, 127.65, 128.20, 128.68, 129.14, 130.10, 131.73, 148.30, 153.11, 154.20, 156.26, 158.17, 159.34, 161.80, 170.53, 191.60, 192.42, 196.15. Anal. calcd. for

$C_{35}H_{30}ClN_7O_3S_2$: C, 60.38%; H, 4.34%, N, 14.08%. Found: C, 59.95%; H, 4.17%; N, 13.81%.

(8*S*)-8-(5-Amino-7-phenyl-[1,2,4]triazolo[1,5-*a*]-pyrimidine-6-carbonyl)-3,3-dimethyl-12-(methyl-thio)-7-(4-nitrophenyl)-3,4,6a,7,8,12-hexahydro-1*H*-benzo-[4,5]thiazolo[2,3-*b*]quinazoline-1,9(2*H*)-dione (IXc) was recrystallized from ethanol as yellow crystals (2.1 g, 59.50%). Mp 211–213°C. IR (KBr pellets, cm^{-1}) ν_{max}, 3360, 3241 (NH), 1758, 1719, 1643 (3C=O); ^{1}H NMR (400 MHz, $CDCl_3$); δ 1.09 (s, 3H, $-CH_3$); 1.24 (s, 3H, $-CH_3$); 1.56 (s, 2H, $-CH_2-$); 2.26 (s, 2H, $-CH_2-$); 2.33 (s, 3H, $-SCH_3$); 3.20 (m, 1H, –CH–Cyclohexene); 3.38 (m, 1H, –CH–Cyclohexene); 3.71 (m, 1H, –CH–Cyclohexene); 4.55 (s, 1H, –CH–); 6.98 (s, 1H, –C=CH–); 7.81–8.62 (m, 9H, Ar); 8.80 (s, 2H, $-NH_2-D_2O$ exchangeable); 8.94 (s, 1H, –C=CH–); ^{13}C NMR (100 MHz, $CDCl_3$); δ 12.08, 23.17, 26.35, 29.81, 36.98, 44.08, 50.72, 56.47, 61.13, 104.55, 117.02, 124.32, 126.71, 127.14, 128.15, 129.13, 129.82, 131.20, 132.61, 148.42, 153.09, 154.33, 156.76, 158.68, 159.14, 164.50, 168.92, 190.20, 192.12, 195.37. Anal. calcd. for $C_{35}H_{30}N_8O_5S_2$: C, 59.48%; H, 4.28%, N, 15.85%. Found: C, 59.82%; H, 4.19%; N, 15.07%.

(8*S*)-8-(5-Amino-7-phenyl-[1,2,4]triazolo[1,5-*a*]-pyrimidine-6-carbonyl)-7-(5-chloro-2-methoxyphenyl)-3,3-dimethyl-12-(methylthio)-3,4,6a,7,8,12-hexa-hydro-1*H*-benzo[4,5]thiazolo[2,3-*b*]quinazoline-1,9-(2*H*)-dione (IXd) was recrystallized from ethanolas pale yallow powder (3.1 g, 85.40%). Mp 178–180°C. IR (KBr pellets, cm^{-1}) ν_{max}, 3355, 3230 (NH), 1750, 1706, 1635 (3C=O); ^{1}H NMR (400 MHz, DMSO-d_6); δ 1.13 (s, 3H, $-CH_3$); 1.32 (s, 3H, $-CH_3$); 1.80 (s, 2H, $-CH_2-$); 2.31 (s, 2H, $-CH_2-$); 2.38 (s, 3H, $-SCH_3$); 3.13 (m, 1H, –CH–Cyclohexene); 3.41 (m, 1H, –CH–Cyclohexene); 3.64 (s, 3H, $-OCH_3$), 3.95 (m, 1H, –CH–Cyclohexene); 4.60 (s, 1H, –CH–); 7.08 (d, J = 2 Hz, 1H, Ar); 7.20 (s, 1H, –C=CH–); 7.48 (d, J = 2 Hz, 1H, Ar); 7.85–8.36 (m, 5H, Ar); 8.73 (s, 2H, $-NH_2-D_2O$ exchangeable); 8.87 (s, 1H, –C=CH–); ^{13}C NMR (100 MHz, DMSO-d_6); δ 11.76, 24.53, 26.48, 29.77, 36.80, 44.16, 50.42, 54.60, 56.71, 61.40, 103.12, 110.22, 116.32, 124.22, 126.43, 128.40, 128.90, 129.34, 130.21, 131.13, 133.61, 139.23, 150.16, 151.73, 154.14, 156.15, 157.74, 159.80, 161.90, 167.84, 190.47, 191.53, 196.14.Anal.calcd. for $C_{36}H_{32}ClN_7O_4S_2$: C, 59.54%; H, 4.88%, N, 13.50%. Found: C, 59.03%; H, 4.38%; N, 13.87%.

(8*S*)-8-(5-Amino-7-phenyl-[1,2,4]triazolo[1,5-*a*]-pyrimidine-6-carbonyl)-7-(2,5-dimethylfuran-3-yl)-3,3-dimethyl-12-(methylthio)-3,4,6a,7,8,12-hexahy-dro-1*H*-benzo[4,5]thiazolo[2,3-*b*]quinazoline-1,9(2*H*)-dione (IXe) was recrystallized from ethanol-hexane (3.1) as white crystals (2.3 g, 67.65%). Mp 210–212°C. IR (KBr pellets, cm^{-1}) ν_{max}, 3357, 3223 (NH), 1761, 1716, 1656 (3C=O); ^{1}H NMR (400 MHz, $CDCl_3$); δ 1.08 (s, 3H, $-CH_3$); 1.42 (s, 3H, $-CH_3$); 1.89 (s, 2H, $-CH_2-$); 2.24 (s, 2H, $-CH_2-$); 2.46 (s, 3H, $-SCH_3$); 2.68 (s, 3H, $-CH_3$); 2.81 (s, 3H, $-CH_3$);3.08 (m, 1H, –CH–Cyclohexene); 3.40 (m, 1H, –CH–Cyclohexene); 3.87 (m, 1H, –CH–Cyclohexene); 4.65 (s, 1H, –CH–); 6.30 (s, 1H, –C=CH–); 6.85 (s, 1H, –C=CH–); 7.95–8.48 (m, 5H, Ar); 8.66 (s, 2H, $-NH_2-D_2O$ exchangeable); 8.92 (s, 1H, –C=CH–); ^{13}C NMR (100 MHz, $CDCl_3$); δ 11.20, 13.18, 15.30, 21.15, 28.20, 32.62, 40.80, 47.34, 51.62, 60.22, 69.11, 103.12, 107.46, 114.72, 125.62, 126.73, 128.60, 129.50, 131.28, 134.21, 143.17, 147.34, 151.23, 153.64, 155.35, 156.14, 159.20, 161.34, 170.15193.04, 195.41, 198.18. Anal. calcd. for $C_{35}H_{33}N_7O_4S_2$: C, 61.84%; H, 4.89%, N, 14.42%. Found: C, 51.93%; H, 4.53%; N, 14.71%.

(8*S*)-8-(2-Amino-4-phenylbenzo[4,5]imidazo[1,2-*a*]pyrimidine-3-carbonyl)-3,3-dimethyl-12-(methylthio)-7-phenyl-3,4,6a,7,8,12-hexahydro-1*H*-benzo[4,5]-thiazolo[2,3-*b*]quinazoline-1,9(2*H*)-dione (Xa) was recrystallized from ethanol (1.1) as white crystals (3.2 g, 90.14%). Mp 214–217°C. IR (KBr pellets, cm^{-1}) ν_{max}, 3340, 3223 (NH), 1746, 1713, 1690 (3C=O); ^{1}H NMR (400 MHz, $CDCl_3$); δ 1.10 (s, 3H, $-CH_3$); 1.32 (s, 3H, $-CH_3$); 1.73 (s, 2H, $-CH_2-$); 2.34 (s, 2H, $-CH_2-$); 2.52 (s, 3H, $-SCH_3$); 3.08 (m, 1H, –CH–Cyclohexene); 3.34 (m, 1H, –CH–Cyclohexene); 3.55 (m, 1H, –CH–Cyclohexene); 4.62 (s, 1H, –CH–); 6.82 (s, 1H, –C=CH–); 7.70–8.80 (m, 14H, Ar); 8.60 (s, 2H, $-NH_2-D_2O$ exchangeable); ^{13}C NMR (100 MHz, $CDCl_3$); δ 14.34, 23.18, 27.12, 32.53, 37.28, 41.60, 54.20, 57.12, 63.16, 104.22, 113.02, 115.81, 118.60, 122.31, 125.11, 126.34, 127.45, 128.12, 128.50, 129.32, 132.19, 133.28, 136.14, 144.29, 149.41, 152.16, 155.25, 156.24, 159.80, 165.08, 171.20, 190.18, 193.40, 196.14. Anal. calcd. for $C_{40}H_{34}N_6O_3S_2$: C, 67.58%; H, 4.82%, N, 11.82%. Found: C, 67.18%; H, 4.40%; N, 11.94%.

(8*S*)-8-(2-Amino-4-phenylbenzo[4,5]imidazo[1,2-*a*]pyrimidine-3-carbonyl)-7-(4-chlorophenyl)-3,3-dimethyl-12-(methylthio)-3,4,6a,7,8,12-hexahydro-1*H*-benzo[4,5]thiazolo[2,3-*b*]quinazoline-1,9(2*H*)-dione (Xb) was recrystallized from ethanolas pale yellow crystals (2.6 g, 69.71%). Mp 218–220°C. IR (KBr pellets, cm^{-1}) ν_{max}, 3341, 3257 (NH), 1751, 1753, 1713 (3C=O); ^{1}H NMR (400 MHz, $CDCl_3$); δ 1.13 (s, 3H, $-CH_3$); 1.38 (s, 3H, $-CH_3$); 1.66 (s, 2H, $-CH_2-$); 2.30 (s, 2H, $-CH_2-$); 2.59 (s, 3H, $-SCH_3$); 3.11 (m, 1H, –CH–Cyclohexene); 3.42 (m, 1H, –CH–Cyclohexene); 3.65 (m, 1H, –CH–Cyclohexene); 4.81 (s, 1H, –CH–); 6.90 (s, 1H, –C=CH–); 7.68–8.90 (m, 13H, Ar); 8.64 (s, 2H, $-NH_2-D_2O$ exchangeable); ^{13}C NMR (100 MHz, $CDCl_3$); δ 13.64, 23.20, 27.18, 32.60, 36.30, 41.55, 54.18, 57.45, 63.44, 103.80, 113.41, 115.66, 118.72, 122.48, 125.20, 126.28, 127.04, 128.31, 128.80, 131.12, 132.40, 133.57, 136.24, 144.31, 146.71, 152.33, 155.15, 156.36, 159.92, 165.16, 170.11, 191.28, 194.20, 195.29. Anal. calcd. for

$C_{40}H_{33}ClN_6O_3S_2$: C, 64.46%; H, 4.46%, N, 11.28%. Found: C, 63.98%; H, 4.16%; N, 11.53%.

(8*S*)-8-(2-Amino-4-phenylbenzo[4,5]imidazo-[1,2-*a*]pyrimidine-3-carbonyl)-3,3-dimethyl-12-(methylthio)-7-(4-nitrophenyl)-3,4,6a,7,8,12-hexahydro-1*H*-benzo[4, 5]thiazolo[2,3-*b*]quinazoline-1,9(2*H*)-dione (Xc) was recrystallized from ethanol-benzene (1.2) as yellow crystals (2.9 g, 76.72%). Mp 187–189°C. IR (KBr pellets, cm^{-1}) ν_{max}, 3323, 3269 (NH), 1760, 1745, 1720 (3C=O); ^{1}H NMR (400 MHz, DMSO-d_6); δ 1.16 (s, 3H, $-CH_3$); 1.27 (s, 3H, $-CH_3$); 1.60 (s, 2H, $-CH_2-$); 2.41 (s, 2H, $-CH_2-$); 2.64 (s, 3H, $-SCH_3$); 3.18 (m, 1H, –CH–Cyclohexene); 3.39 (m, 1H, –CH–Cyclohexene); 3.74 (m, 1H, –CH–Cyclohexene); 4.77 (s, 1H, –CH–); 6.96 (s, 1H, –C=CH–); 7.72–8.84 (m, 13H, Ar); 8.43 (s, 2H, $-NH_2-D_2O$ exchangeable); ^{13}C NMR (100 MHz, DMSO-d_6); δ 12.90, 23.24, 27.44, 32.62, 36.43, 41.60, 54.67, 57.29, 63.39, 103.61, 113.50, 116.40, 118.80, 122.61, 125.40, 126.11, 127.36, 128.42, 128.86, 131.24, 132.60, 133.11, 144.26, 145.16, 151.13, 153.08, 155.26, 156.17, 159.80, 164.16, 168.25, 191.16, 194.31, 195.47. Anal. calcd. for $C_{40}H_{33}N_7O_5S_2$: C, 63.56%; H, 4.40%, N, 12.97%. Found: C, 63.20%; H, 4.75%; N, 13.27%.

(8*S*)-8-(2-Amino-4-phenylbenzo[4,5]imidazo[1,2-*a*]pyrimidine-3-carbonyl)-7-(5-chloro-2-metho-xyphenyl)-3,3-dimethyl-12-(methylthio)-3,4,6a,7,8,12-hexahydro-1*H*-benzo[4,5]thiazolo[2,3-*b*]quinazoline-1,9-(2*H*)-dione (Xd) was recrystallized from ethanol as yellow powder (3.2 g, 82.47%). Mp 227–229°C. IR (KBr pellets, cm^{-1}) ν_{max}, 3333, 3237 (NH), 1768, 1717, 1686 (3C=O); ^{1}H NMR (400 MHz, $CDCl_3$); δ 1.13 (s, 3H, $-CH_3$); 1.24 (s, 3H, $-CH_3$); 1.66 (s, 2H, $-CH_2-$); 2.51 (s, 2H, $-CH_2-$); 2.80 (s, 3H, $-SCH_3$); 3.08 (m, 1H, –CH–Cyclohexene); 3.27 (m, 1H, –CH–Cyclohexene); 3.58 (m, 1H, –CH–Cyclohexene); 3.82 (s, 3H, $-OCH_3$),4.70 (s, 1H, –CH–); 6.92 (s, 1H, –C=CH–); 7.12 (d, J = 6 Hz, 1H, Ar); 7.32 (s, 1H, –C=CH–); 7.50 (d, J = 6 Hz, 1H, Ar); 7.92–8.44 (m, 10H, Ar); 8.80 (s, 2H, $-NH_2-D_2O$ exchangeable); ^{13}C NMR (100 MHz, $CDCl_3$); δ 10.10, 23.18, 27.64, 32.82, 35.20, 41.52, 54.35, 56.11, 57.21, 63.38, 104.14, 110.40, 114.12, 115.33, 120.55, 124.41, 125.17, 126.08, 127.42, 128.10, 128.55, 131.16, 132.25, 133.11, 138.23, 141.13, 151.14, 152.27, 154.21, 154.68, 159.11, 162.28, 167.19, 190.42, 193.23, 196.15. Anal. calcd. for $C_{41}H_{35}ClN_6O_4S_2$: C, 63.51%; H, 4.57%, N, 10.84%. Found: C, 63.21%; H, 4.09%; N, 10.37%.

(8*S*)-8-(2-Amino-4-phenylbenzo[4,5]imidazo[1,2-*a*]pyrimidine-3-carbonyl)-7-(2,5-dimethylfuran-3-yl)-3,3-dimethyl-12-(methylthio)-3,4,6a,7,8,12-hexahydro-1*H*-benzo[4,5]thiazolo[2,3-*b*]quinazoline-1,9(2*H*)-dione (Xe) was recrystallized from ethanol as white crystals (1.9 g, 52.20%). Mp 178–179°C. IR (KBr pellets, cm^{-1}) ν_{max}, 3412, 3250 (NH), 1750, 1727, 1710 (3C=O); ^{1}H NMR (400 MHz, $CDCl_3$); δ 1.10 (s, 3H, $-CH_3$); 1.20 (s, 3H, $-CH_3$); 1.52(s, 2H, $-CH_2-$); 2.40 (s, 2H, $-CH_2-$); 2.78 (s, 3H, $-SCH_3$); 2.84 (s, 3H, $-CH_3$); 2.96 (s, 3H, $-CH_3$); 3.28 (m, 1H, –CH–Cyclohexene); 3.42 (m, 1H, –CH–Cyclohexene); 3.58 (m, 1H, –CH–Cyclohexene); 4.70 (s, 1H, –CH–); 6.38 (s, 1H, –C=CH–); 7.45 (s, 1H, –C=CH–); 7.74–8.52 (m, 9H, Ar); 8.84 (s, 2H, $-NH_2-D_2O$ exchangeable); ^{13}C NMR (100 MHz, $CDCl_3$); δ 10.30, 12.22, 16.31, 20.25, 26.43, 30.82, 30.34, 44.58, 51.18, 61.08, 66.41, 102.20, 107.23, 110.34, 113.68, 120.48, 124.08, 126.46, 127.33, 127.86, 129.20, 131.31, 132.14, 136.23, 144.17, 146.60, 149.12, 151.30, 153.13, 154.32, 159.36, 162.19, 169.46, 191.16, 193.42, 195.20. Anal. calcd. for $C_{40}H_{36}N_6O_4S_2$: C, 65.91%; H, 4.98%, N, 11.53%. Found: C, 65.53%; H, 4.70%; N, 11.14%.

CONCLUSIONS

The novel thiazolo[2,3-*b*]quinazoloine **(IVa–e)**, **(VIa–e)**, **(VIIa–e)**, **(VIIIa–e)**, **(IXa–e)** and **(Xa–e)** derivatives were synthesized and their in vitro antifangal and antioxidant activity have been evaluated. Quinazoloine derivatives **(IXa–f)** and **(Xa–e)** having a triazolo[1,5-*a*]pyrimidine scaffold linked to thiazolo[2,3-*b*]quinazoline scaffold bearing 5-chloro-2-methoxy phenyl ring demonstrated potent antioxidant while target compounds **(VIIIa–e)**, **(IXa–e)**, and **(Xa–e)** having high electron density releated to existence of extra fused phenyl ring on imidazo[1,2-*a*]pyrimidin-2-amine scaffold and a chloro group at position 4 of the phenyl ring in thiazolo[2,3-*b*]quinazoline scaffold demonstrated potent anti-lipid peroxidation on the other hand the target compounds **(VIIa–e)**, **(VIIIa–e)** and **(IXa–e)** showed maximum antifangal activity in comparison with their corresponding standard drug. Further detailed studies are required to understand the mechanism of action of these compounds.

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COMPLIANCE WITH ETHICAL STANDARDS

This article does not contain any studies involving animals or human participants performed by any of the authors.

Conflict of Interests

The authors declare that they have no conflicts of interest.

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