Heterocyclic Letters
Vol. 11| No.1|63-72| Nov-Jan |2021
ISSN : (print) 2231–3087 / (online) 2230-9632
CODEN: HLEEAI
http://heteroletters.org

SYNTHESIS OF BIOLOGICALLY POTENT ALKOXYPHTHALIMIDO PLUGGED N-(2,4-DIOXO-1,4-DIHYDROQUINAZOLIN-3(2*H*)-YL)-4-OXO-4*H*-BENZO[4,5]THIAZOLO[3,2-A]PYRIMIDINE-3-CARBOXAMIDE *VIA* GOULD JACOBS REACTION

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Abstract. In the present study, convenient methods for the synthesis of new alkoxyphthalimidoquinazolinedione and their pyrimidobenzothiazole derivatives are elaborated. A series of substituted N-(2,4-dioxo-1,4-dihydroquinazolin-3(2*H*)-yl)-4-oxo-4*H*-benzo[4,5]thiazolo[3,2-a]pyrimidine-3-carboxamide**(3a-c)** and substituted N-(1-(2-((1,3-dioxoisoindolin-2-yl)oxy)ethyl)-2,4-dioxo-1,4-dihydroquinazolin-3(2*H*)-yl)-4-oxo-4*H*-benzo[4,5]thiazolo[3,2-a]pyrimidine-3-carboxamide **(4a-c)** have been prepared starting from substituted 2-aminobenzothiazoles *via* solvent free multi-component Gould–Jacobs reaction. Structures of newly synthesized compounds were established based on IR, ^{1}H-NMR, mass, analytical studies and fluorescence tests. Some of synthesized molecules **(3a-c, 4a-c)** have been assayed for their anti-malarial activity. IC_{50} values of anti-malarial activity of compounds were also determined.

Keywords: Multi-Component reaction, Benzothiazole, Quinazolinedione, Ethoxyphthalimide, Anti-malarial activity

Introduction

Multi-component reactions (MCRs) a powerful and target-oriented synthetic methodology, has extensively been used and applied for the fast construction of heterocyclic skeletons, and interest from various branches of science is growing continuously. Heterocyclic motifs bearing nitrogen, sulphur and thiazole moieties constitute the core structure of a number of biologically interesting compounds. Substituted aminobenzothiazoles have often received attention in connection with the synthesis of pyrimidobenzothiazoles by using MCRs[1]. 2-Aminobenzothiazole based Gould-Jacobs reaction was reported in 1994 to prepare substituted pyrimidobenzothiazoles[2]. Similarly, microwave assisted Gould-Jacobs reaction was reported for synthesis of others heterocycles by using MCRs[3]. Among various classes of heterocyclic

motifs, fused benzothiazole-containing molecules stand out as important molecules showing a various biological activities like- antitumour[4,5], antimicrobial[6-8], anti-inflammatory[9], antitubercular[10,11], anti-HIV[12], anti-malarial[13], anticonvulsant[14, 15], anthelmintic[16, 17], antioxidant[18] etc. Some important and clinically used drugs having benzothiazole ring in their structures are Riluzole, Thioflavin, Pittsburgh compound B, Ethoxzolamide, Pramipexole, Dimazole, Flutemetamol (Figure 1).Similarly, quinazolines are well known significant chemical for the synthesis of diverse physiological importance and biological utilized compounds[19].Quinazoline containing drugs like prazosin as adrenergic blockers for the treatment of high blood pressure, panic disorder and anxiety, alfuzocin as solid tumor and other analogues of quinazoline have been used as active ingredients in drugs like afatinib as antifungal, quinethazone as antihypertensive and proquazone as nonsteroidal anti-inflammatory agent (Figure 2). A series of 2, 4(1*H*,3*H*)-quinazolinediones were reported as an anticancer agents[20].A large number of alkoxyphthalimide derivatives of various heterocycles were reported to demonstrate a wide range of pharmacological activities like antimicrobial[21, 22], anti-inflmmatory[23], anti-malarial[24], antiviral[25] etc. The integration of structural features from diverse bioactive molecules in a single compound is very interesting. Consequently there have been recent efforts for the production of novel and hybrid compounds by using Gould-Jacobs reaction possessing bioactivity with the potential of being incorporated into the drug discovery process as drug candidates.

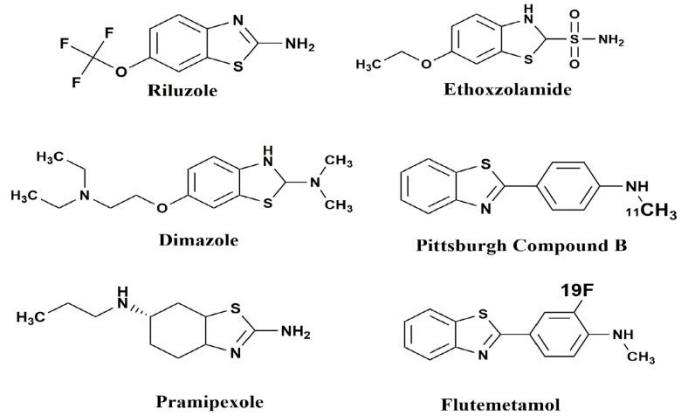


Figure 1. Benzothiazole based some medicinal agents

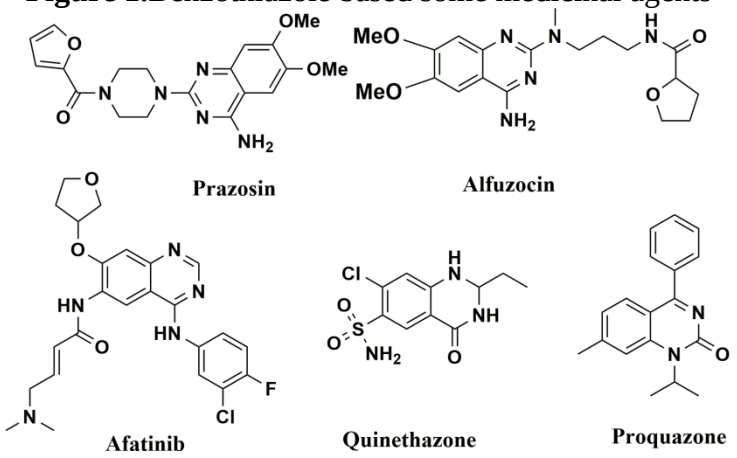
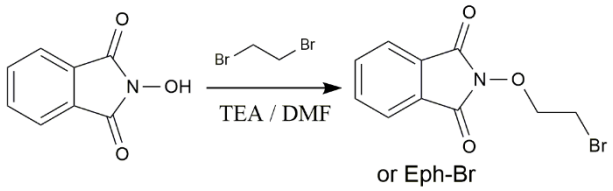


Figure 2. Quinazoline based some pharmaceutical agents

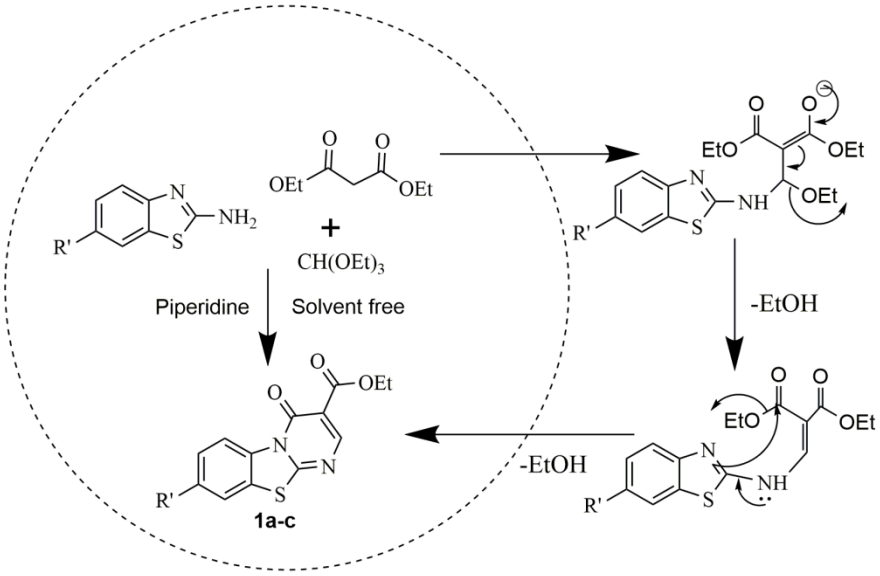
Results and Discussion

Chemistry. In continuation of our work, herein we presented the synthesis of 6 structural hybrid compounds of alkoxyphthalimide derivatives of quinazolinedione coupled to pyrimidobenzothiazles by using multi-component Gould-Jacobs reaction. The amide linkage serves as a connecting bridge fragment between hybrid molecules. Bromoethoxyphthalimide was prepared by literature methods. In this method, N-hydroxyphthalimide and 1,2 dibromoethane were kept overnight in dimethyl-formamide medium using triethylamine as base (Scheme1).



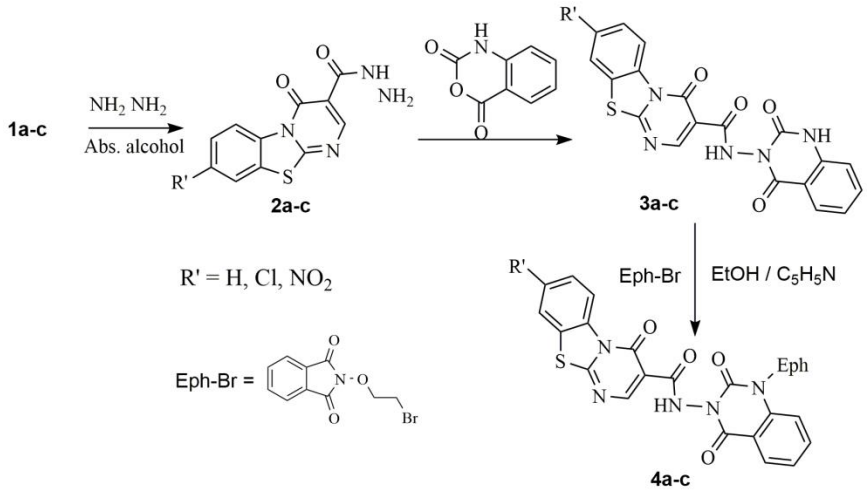
Scheme 1. Synthesis of Bromoethoxyphthalimide

Multi-component Gould-Jacobs reaction for the synthesis of 8-substituted-4-oxo-4*H*-pyrimido[2,1-b][1,3]benzothiazole-3-carboxylate derivatives**(1a-c)** using readily available diethyl propanedioate and triethyl orthoformate as staring materials in good yield (Scheme 2).



Scheme 2. Synthesis of Pyrimidobenzothiazoles via Gould-Jacobs reaction with mechanism.

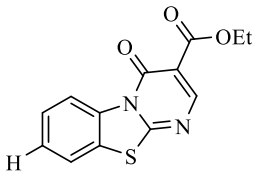
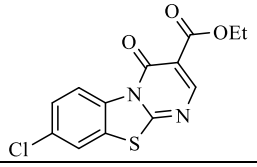
IR spectra of compound **1a** confirmed by disappearance of two absorption peaks of NH_2 group and appearance of absorption peaks at 1739 cm^{-1} corresponding to C=O group of fused pyrimidine ring. ^1H NMR spectra of compound **1a**methine (=CH) group of pyrimidine rings was observed at 6.85 δ as singlet peak. The synthesis of the target compounds was carried out as outlined in scheme 3.

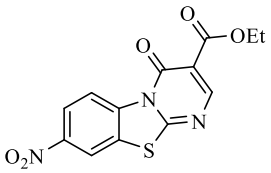
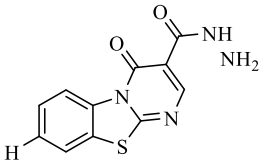
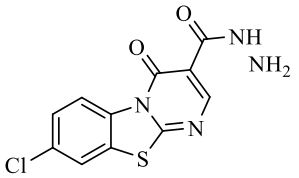
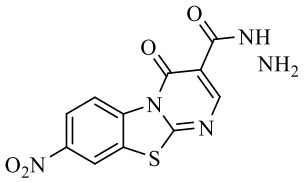
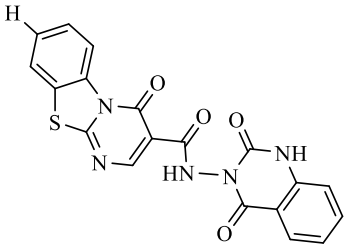
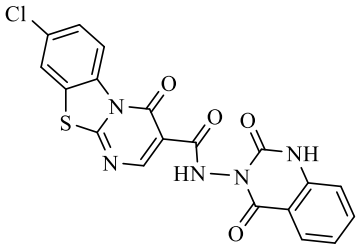
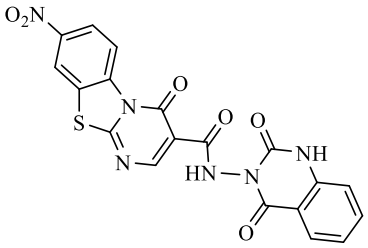
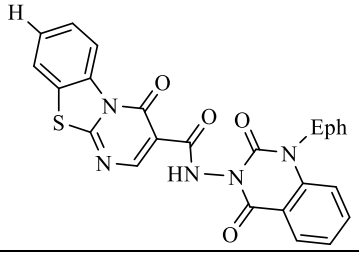


Scheme 3. Synthesis of ethoxyphthalimide linked quinazolinedione derivatives.

Treatment of **1a-c**with hydrazine hydrate in absolute alcohol furnished **2a-c.**Compound **2a** gave strong bands at 3305 cm^{-1} for –NH stretching and 1674 cm^{-1} due to CO str. of amide. Further treatment of compounds **2a-c**with isatoic anhydride in the presence of pyridine gave **3a-c** which was confirmed by a sharp peak at 1695 cm^{-1} of C=O stretching in IR region and disappearance of NH_2 signal in ^1H NMR spectrum . Subsequently, the NH proton of quinazoline ring was replaced by ethoxyphthalimide moiety to yielded final 8-substituted-N-(1-(2-((1,3-dioxoisoindolin-2-yl)oxy)ethyl)-2,4-dioxo-1,4-dihydroquinazolin-3(2*H*)-yl)-4-oxo-4*H*-benzo[4,5]thiazolo[3,2-a]pyrimidine-3-carboxamide(**4a-c)** Structure of compound **4a** was confirmed by presence of C-O and N-O stretching bands at 1085and 1376 cm^{-1} respectively, in IR spectrum and new signals in ^1H NMR spectrum for side chain protons. The mass spectrum also supports the proposed structure by viewing molecular ion peaks of final products. Further confirmation of phthalimidoxyl group attachment was achieved by usual chemical test including fluorescence formation. The observed physical properties presented in Table1. The synthesized compounds **3a-c** and **4a-c** tested for their anti-malarial activity Table 2.

Table 1.The physical properties of synthesized compounds **(1a-c** to **4a-c)**.

Compounds	Molecule structures	Mol. weight	Reflux time (hr)	m.p. (°C)	Yield (%)
1a		274.29	0.5	217-219	79
1b		308.74	1	225-227	76

1c		319.29	1	251-253	81
2a		260.27	5	205-207	68
2b		294.71	6	190-192	72
2c		305.27	4	210-212	73
3a		405.38	6	288-290	71
3b		439.83	8	265-267	65
3c		450.38	7	>300	72
4a		594.55	12	160-162	66

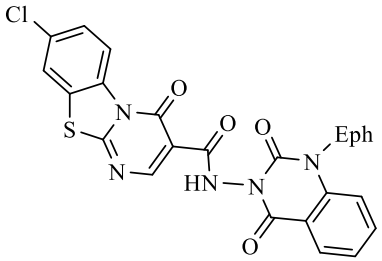
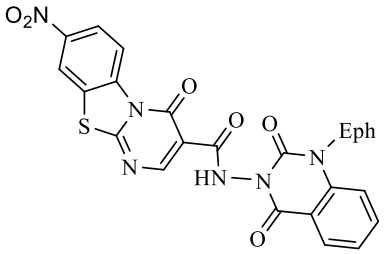
4b		628.99	15	172-174	68
4c		639.55	16	151-152	64

Table 2. Anti-malarial activity (MICs μg/mL) of synthesized compounds (**3a-c** and **4a-c**)

Compounds	R’	Mean IC_{50} values (μg/mL)
3a	H	1.92
3b	Cl	1.23
3c	NO_2	1.59
4a	H	1.07
4b	Cl	0.98
4c	NO_2	1.13
Quinine	-	0.268

Conclusion

In this paper, we have discussed the synthetic efficiency of multi-component Gould–Jacobs reaction of under solvent free conditions and also we have designed new synthetic route for the synthesis of ethoxyphthalimide plugged quinazolinedione and their pyrimidobenzothiazole derivatives. It was observed that ethoxyphthalimide containing derivatives are more active than the parent quinazolinedione analogues. It may be concluded that the addition of ethoxyphthalimide group in quinazolinedione part of molecule increases to anti-malarial activity. Finally, the several modifications and creations of bonds after the Gould Jacobs reaction promise a sustainable synthetic route towards the development of heterocyclic chemistry.

Experimental Section

General. All chemicals were commercially procured and were used without further purification.Melting points were determined in open capillary tube and are therefore uncorrected. Purity of synthesized compounds was checked by TLC using silica gel-G plates, n-hexane-ethyl acetate as developing solvent and the spots were exposed in an UV light chamber. FT-IR spectra were recorded with a Bruker spectrometer model alphaand NMR were recorded on a Bruker DRX-400 MHz spectrometer with dimethylsulfoxide DMSO-d_6/$CDCl_3$

as solvent using tetramethylsilane (TMS) as an internal standard. The mass spectra were recorded on water Q-TOF, Micromass (ES) model. Elemental analysis was done on "Heraeus Rapid Analyser".Structures of synthesized compounds were characterized by using IR, NMR, Mass and Elemental analysis. Bromoethoxyphthalimide was prepared by reported methods[26].

***Synthesis of compound* 1a.** A solution of compound substituted 2-amino benzothiazole (0.01mol) and an equivalent molar ratio of diethyl propanedioate in triethyl orthoformate (20 mL), in the presence of few drops of piperdine as a catalyst were heated under reflux for 30 min. The excess solvent was removed by distillation under reduced pressure and the residue was left to cool. The precipitated solid product was collected by filteration, washed with cold water and dried. Compounds **1b-c** were prepared in similar way with minor change in reflux time.

***Ethyl-4-oxo-4H-pyrimido[2,1-b][1,3]benzothiazole-3-carboxylate* (1a).** IR (ν_{max}, cm^{-1}): 3080 (Ar-H), 2899 (C-H str. CH_3), 1739 (C=O str.), 1614 (C=N str.), 1416 (C=C str. Ar), 1046(C-O str.); ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.38 (t, 3H, CH_3), 4.17 (q, 2H, OCH_2), 6.85 (s, 1H, CH), 7.02–7.18 (m, 4H, Ar-H) ; LCMS: m/z 274[M^+].

***Ethyl-8-chloro-4-oxo-4H-pyrimido[2,1-b][1,3]benzothiazole-3-carboxylate* (1b).**IR (ν_{max}, cm^{-1}): 3075 (Ar-H), 2895 (C-H str. CH_3), 1739 (C=O str.), 1620 (C=N str.), 1425 (C=C str. Ar), 1051 (C-O str.); ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.34 (t, 3H, CH_3), 4.08 (q, 2H, OCH_2), 6.95 (s, 1H, CH), 7.02–7.19 (m, 4H, Ar-H) ; LCMS: m/z 308 [M^+], 310 [M+2]$^+$.

***Ethyl-8-nitro-4-oxo-4H-pyrimido[2,1-b][1,3]benzothiazole-3-carboxylate* (1c).** IR (ν_{max}, cm^{-1}): 3078 (Ar-H), 2881 (C-H str. CH_3), 1735 (C=O str.), 1622 (C=N str.), 1441 (C=C str. Ar), 1048 (C-O str.); ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.33 (t, 3H, CH_3), 2.89 (s, 3H, OCH_3), 4.16 (q, 2H, OCH_2), 6.91 (s, 1H, CH), 7.02–7.18 (m, 4H, Ar-H) ; LCMS: m/z 319 [M^+].

***Synthesis of compounds* 2a .**Compound **1a** (0.01mol) and hydrazine hydrate (0.01mol) were dissolved in sufficient amount of absolute alcohol in 250 mL round bottom flask. The reaction mixture was refluxed on water bath for 5 hr. The reaction mixture was cooled at room temperature. Compound filtered and recrystallized with ethanol. Compounds **2b-c** were prepared in similar way with minor change in reflux time.

***4-Oxo-4H-pyrimido[2,1-b][1,3]benzothiazole-3-carbohydrazide* (2a).** IR (ν_{max}, cm^{-1}): 3455, 3332, 3189 (N-H str., NH_2), 3045 (Ar-H), 1676 (C=O str.), 1572 (C=N str.), 1425 (C=C str. Ar),; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.07–7.19 (m, 4H, Ar-H), 9.28 (s, 1H, CONH), 6.58 (s, 1H, CH), 4.48 (s, 2H, NH_2); LCMS: m/z 294 [M^+], 296 [M+2]$^+$.

***8-Chloro-4-oxo-4H-pyrimido[2,1-b][1,3]benzothiazole-3-carbohydrazide* (2b).** IR (ν_{max}, cm^{-1}): 3461, 3329, 3176 (N-H str., NH_2), 3042 (Ar-H), 1675 (C=O str.), 1572 (C=N str.), 1422 (C=C str. Ar); ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.06–7.18 (m, 3H, Ar-H), 9.19 (s, 1H, CONH), 6.59 (s, 1H, CH), 4.48 (s, 2H, NH_2); LCMS: m/z 260 [M^+];

***8-Nitro-4-oxo-4H-pyrimido[2,1-b][1,3]benzothiazole-3-carbohydrazide* (2c).** IR (ν_{max}, cm^{-1}): 34595, 3345, 3172 (N-H str., NH_2), 3022 (Ar-H), 2896 (C-H str. CH_3), 1678 (C=O str.), 1572 (C=N str.), 1419 (C=C str. Ar); ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.07–7.20 (m, 3H, Ar-H), 9.22 (s, 1H, CONH), 6.55 (s, 1H, CH), 4.49 (s, 2H, NH_2), 2.99 (s, 3H, OCH_3); LCMS: m/z 305 [M^+].

***Synthesis of compounds* 3a .** A mixture of compound **2a (**0.01 mol) and isatoic anhydride (0.01 mol) in ethanol was added to it with a catalytic amount of pyridine. Reaction mixture was refluxed for 6 hrs and poured on crushed ice. The solid obtained was filtered, and recrystallised from ethanol.Compounds **3b-c** were also prepared in similar way with minor changes in reflux time.

***N-(2,4-dioxo-1,4-dihydroquinazolin-3(2H)-yl)-4-oxo-4H-benzo[4,5]thiazolo[3,2-a]pyrimidine-3-carboxamide* (3a).** IR (ν_{max}, cm^{-1}): 3305 (N-H), 3032 (Ar-H), 1695 (C=O str.),

1585 (C=N), 1408 (C=C, Ar), 1221 (C-N), 676 (C-S-C); ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.52 (s, 1H,CONH ring),8.98 (s, 1H,CONH), 7.01-7.48 (m, 8H, Ar-H), 6.89 (s, 1H, CH) ; GCMS: m/z 405 [M^+]; Anal. calcd. for $C_{19}H_{11}N_5O_4S$: C, 56.29; H, 2.74; N, 17.28; Found: C, 56.42; H, 2.57; N, 17.51%.

***8-Chloro-N-(2,4-dioxo-1,4-dihydroquinazolin-3(2H)-yl)-4-oxo-4H-benzo[4,5]thiazolo[3,2-a]pyrimidine-3-carboxamide* (3b).** IR (ν_{max}, cm^{-1}): 3345 (N-H), 3038 (Ar-H), 1695 (C=O str.), 1578 (C=N), 1410 (C=C, Ar), 1224 (C-N), 679 (C-S-C); ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.56 (s, 1H,CONH ring),8.94 (s, 1H,CONH), 7.02-7.45 (m, 7H, Ar-H), 6.90 (s, 1H, CH) ; LCMS: m/z 439 [M^+], 441 [M+2]$^+$; Anal. calcd. for $C_{19}H_{10}ClN_5O_4S$: C, 51.88; H, 2.29; N, 15.92; Found: C, 51.68; H, 2.49; N, 15.98%.

***8-Nitro-N-(2,4-dioxo-1,4-dihydroquinazolin-3(2H)-yl)-4-oxo-4H-benzo[4,5]thiazolo[3,2-a]pyrimidine-3-carboxamide* (3c).**IR (ν_{max}, cm^{-1}): 3329 (N-H), 3032 (Ar-H), 2896 (C-H str. CH_3), 1694 (C=O str.), 1620 (C=N), 1408 (C=C, Ar), 1221 (C-N), 676 (C-S-C); ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.54 (s, 1H,CONH ring),8.98 (s, 1H,CONH), 6.99-7.52 (m, 7H, Ar-H), 6.92 (s, 1H, CH), 2.95 (s, 3H, OCH_3) ; LCMS: m/z 450 [M^+]; Anal. calcd. for $C_{19}H_{10}N_6O_6S$: C, 50.67; H, 2.24; N, 18.66; Found: C, 50.42; H, 2.45; N, 18.83%.

***Synthesis of compounds* 4a.** A mixture of compound **3a** (0.01 mol) and Bromoethoxyphthalimide (0.01 mol) in ethanol (25 mL) and pyridine (0.01 mol) was refluxed for 12 h in a round bottom flask. It was cooled to room temperature, and the mixture was slowly poured on to crushed ice with constant stirring. Solid obtained was filtered and washed twice with ice-cooled water. It was recrystallized from rectified spirit. Compounds **4b-c** were also synthesized by similar method with minor changes in reaction conditions.

***N-(1-(2-((1,3-dioxoisoindolin-2-yl)oxy)ethyl)-2,4-dioxo-1,4-dihydroquinazolin-3(2H)-yl)-4-oxo-4H-benzo[4,5]thiazolo[3,2-a]pyrimidine-3-carboxamide* (4a).** IR (ν_{max}, cm^{-1}): 3014 (Ar-H), 2905 (C-H str.), 1695 (C=O str.), 1682 (CO-N-CO), 1586 (C=N), 1410 (C=C, Ar), 1376 (N-O), 1225 (C-N), 1085 (C-O), 676 (C-S-C); ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.52 (s, 1H,CONH),7.01-8.32 (m, 13H, Ar-H), 6.86 (s, 1H, CH), 3.56 (t, 2H, OCH_2), 2.99 (t, 2H, NCH_2); LCMS: m/z 594 [M^+]; Anal. calcd. for $C_{29}H_{18}N_6O_7S$: C, 58.52; H, 3.05; N, 14.13; Found: C, 58.42; H, 3.39; N, 14.35%.

***8-Chloro-N-(1-(2-((1,3-dioxoisoindolin-2-yl)oxy)ethyl)-2,4-dioxo-1,4-dihydroquinazolin-3(2H)-yl)-4-oxo-4H-benzo[4,5]thiazolo[3,2-a]pyrimidine-3-carboxamide* (4b).** IR (ν_{max}, cm^{-1}): 3020 (Ar-H), 2902 (C-H str.), 1698 (C=O str.), 1684 (CO-N-CO), 1585 (C=N), 1415 (C=C, Ar), 1378 (N-O), 1227 (C-N), 1076 (C-O), 682 (C-S-C); ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.56 (s, 1H, CONH), 6.98-8.19 (m, 12H, Ar-H), 6.45 (s, 1H, CH), 3.45 (t, 2H, OCH_2), 2.98 (t, 2H, NCH_2); LCMS: m/z 628 [M^+], 630 [M+2]$^+$; Anal. calcd. for $C_{29}H_{17}ClN6_4O_7S$: C, 55.38; H, 2.72; N, 13.38; Found: C, 55.54; H, 2.99; N, 13.65%.

***8-Nitro-N-(1-(2-((1,3-dioxoisoindolin-2-yl)oxy)ethyl)-2,4-dioxo-1,4-dihydroquinazolin-3(2H)-yl)-4-oxo-4H-benzo[4,5]thiazolo[3,2-a]pyrimidine-3-carboxamide* (4c).** IR (ν_{max}, cm^{-1}): 3022 (Ar-H), 2899 (C-H str. CH_3), 1695 (C=O str.), 1682 (CO-N-CO), 1598 (C=N), 1422 (C=C, Ar), 1380 (N-O), 1220 (C-N), 1065 (C-O), 679 (C-S-C); ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.59 (s, 1H, CONH), 6.98-8.21 (m, 12H, Ar-H), 6.47 (s, 1H, CH), 3.49 (t, 2H, OCH_2), 2.99 (t, 2H, NCH_2), 2.76 (s, 3H, OCH_3); LCMS: m/z 639 [M^+]; Anal. calcd. for $C_{25}H_{20}N_4O_2S_2$: C, 54.46; H, 2.68; N, 15.33; Found: C, 54.49; H, 2.88; N, 15.71%.

Biologicalactivity

Material and Methods[28-31]

The *in-vitro* anti-malarial assay was carried out in 96 well microtitre plates according to the microassay protocol of Rieckmann and co-workers with minor modifications. The cultures (*P. falciparum* strain) were maintained in medium RPMI 1640 supplemented with 25 mM HEPES, 1% D-glucose, 0.23% sodium bicarbonate and 10% heat inactivated human serum. The asynchronous parasites of *P. falciparum* were synchronized after 5% D-sorbitol treatment to obtain only the ring stage parasitized cells. For carrying out the assay, an initial ring stage parasitaemia of 0.8 to 1.5% at 3% haematocrit in a total volume of 200 µl of medium RPMI-1640 was determined by Jaswant Singh Bhattacharya (JSB) staining to assess the percent parasitaemia (rings) and uniformally maintained with 50% RBCs (O+).

A stock solution of 5mg/mL of each of the test samples was prepared in DMSO and subsequent dilutions were prepared with culture medium. The diluted samples in 20 µL volume were added to the test wells so as to obtain final concentrations (at fivefold dilutions) ranging between 0.4 µg/ml to 100 µg/mL in duplicate well containing parasitized cell preparation. The culture plates were incubated at 37ºC in a candle jar. After 36 to 40 hrs incubation, thin blood smears from each well were prepared and stained with JSB stain. The slides were microscopically observed to record maturation of ring stage parasites into trophozoites and schizonts in presence of different concentrations of the test agents. The test concentration which inhibited the complete maturation into schizonts was recorded as the minimum inhibitory concentrations (MICs). Quinine was used as the reference drug. The results of anti-malarial activity are presented in Table 2. Out of six compounds screened three compounds i.e., **4a, 4b** and **4c** showed significant anti-malarial activity than the other compounds.

Acknowledgements

The authors are thankful to the Head, Department of Chemistry, M. L. Sukhadia University, Udaipur (Rajasthan) for providing laboratory facilities. I thankful to Microcare laboratory, Surat for pharmacological screening of compounds and NFDD, Rajkot for providing spectral data. I also thankful to chemistry staff members of the Mehesana Urban Institute of Sciences, Ganpat University, Gujarat for their support.

References

I. D. Gandhi, P. Kalal, P. Prajapat, D. K. Agarwal, S. Agarwal, *Comb Chem High T Scr.***2018,** 21, 236.

II. D.bartovic, O.Ilavsky Simo, L.Zalibera, A.Belicova and M. seman, *Collect. Czech. Chem. Commun.***1995**, 60.

III. A.U.Zaman, M.Khan, M.A.Munawar, M.M. Athar, M. Pervaiz, A.Pervaiz and A.Mahmood, *Asian J. Chem.* **2015**, 27, 2823.
R. M. Kumbhare, U. B. Kosurkar, M. J. Ramaiah, T. L.Dadmal, S. N. Pushpavalli, M. P. Bhadra,*Bioorg. Med. Chem. Lett*.**2012,** 22, 5424.

IV. H. Hiyoshi, N. Goto, M. Tsuchiya, K. Iida, Y. N. Nakajima, Hirata, Y. Kanda, K. Nagasawa, J. Yanagisawa,*Sci. Rep.***2014**, 4, 1.

V. N.B.Patel, F. M. Shaikh,*Saudi Pharm J.***2010**, 18, 129.

VI. N. H. Cano, M. S. Ballari, A. G. Lopez, A. N. Santiago,*J. Agri. Food .Chem.***2015** 63:3681.

VII. R. V. Patel, S. W. Park,*Res. Chem. Intermed.* **2015**, 41, 5599.

VIII. R. Mahtab, A. Srivastava, N. Gupta, S. K. Kushwaha, A.Tripathi,*J. Chem. Pharma. Sci.* **2014**, 7, 34.

IX. K. Hazra, L. V. G Nargund, P. Rashmi,J. N. S. Chandra, B. Nandha, M. S.

Harish,*Arch.Pharm. Chem. Life. Sci.* **2012**, 345, 137.
X. F. Mir, S. Shafi, M. S. Zaman, N. P. Kalia, V. S. Rajput, C. Mulakayala, N. Mulakayala, I. A. Khan, M. S. Alam,*Eur. J. Med. Chem.* **2014**,76, 274.
XI. Y. S. Xu, C. C. Zeng, Z. G. Jiao, L. M. Hu, R. G.Zhong,*Molecules.***2009**,14, 868.
XII. K. Takasu, H. Inoue, H. Kim, M. Suzuki, T. Shishido, Y. Wataya, M. Ihara,*J. Med. Chem.* **2002**, 45, 995.
XIII. N. Siddiqui, A. Rana, S. A. Khan, S. E. Haque, M. S. Alam, W. Ahsan, S. Ahmed,*J. Enz. Inhib. Med. Chem.***2009**, 24, 1344.
XIV. P. Yogeeswari, D. Sriram, S. Mehta, D. Nigam, M. M. Kumar, S. Murugesan, J. P. Stables,*IL Farmaco***2005**, 60,1.
XV. Munirajasekhar D, Himaja M, Malib SV. *J. Heterocyclic Chem.* **2014**, 51, 459.
XVI. S. Sarkar, J. Dwivedi, R. Chauhan,*J. pharm. Res.***2013**, 7, 439.
XVII. M. A.Gouda, H. F. Eldien, M. M. Girges, M. A. Berghot,*Med. Chem.* **2013**,3, 2228.
XVIII. E. Jafari, M.R.Khajouei,F. Hassanzadeh, G. H. Hakimelahi, & Khodarahmi, G.A. *Res. Pharm. Sci.***2016**, 11, 1.
XIX. H. Akgun, D. U. Yilmaz, R. C. Atalay, D, Gozen, *Lett. Drug Des. Discov.***2016**, 13, 64.
XX. P. Prajapat, M. Kumawat, B. Kherodiya, G. L. Talesara, *J. Indian Chem. Soc.*2**016**, 93, 539.
XXI. M. Kumawat, B. Kherodiya, P. Prajapat, G. L. Talesara, *Indian J. Chem.***2015**,54B, 117.
XXII. P Prajapat, G. L. Talesara, *J. Heterocyclic Chem.***2016,** 53, 1603.
XXIII. J. L.Jat, S.Ojha,D.B. N.Dhakar, G. L. Talesara, *J. Enzyme Inhib. Med. Chem.***2008**, 23, 882.
XXIV. N. Hussain, M. Ahmed, S. Khan,A. Joshi, P. Yogi, P. Prajapat, *J. Heterocyclic. Chem.***2017**, 54, 993.
XXV. L. Bauer, K. S. Suresh, *J. Org. Chem.***1963**, 28, 1604.
XXVI. K. H. Rieckmann, G. H. Campbell, L. J. Sax, J. E. Mrema,*Lancet***1978**, 1, 221,
XXVII. R. E. Desjardins,Germany *Springer Verlag.***1984**, 179.
W. Trager, J. B. Jensen, *Science* **1976**, 193, 673.
XXVIII. C. Lambros, J. P. Vanderberg,*J. Parasitol.***1979**, 65, 418.
XXIX. R. PanjarathinamText Book of Medical Parasitology. 2nd Ed *Orient Longman Pvt. Ltd. Chennai* **2007**, 329.

Received on August 21, 2021