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Synthesis and antiplasmodial evaluation of 1*H*-1,2,3-triazole grafted 4-aminoquinoline-benzoxaborole hybrids and benzoxaborole analogues

Anu Saini [a], Sumit Kumar [b], Raghu Raj [a,*], Shefali Chowdhary [b], Mathieu Gendrot [c,d,e], Joel Mosnier [c,d,e,f], Isabelle Fonta [c,d,e,f], Bruno Pradines [c,d,e,f], Vipan Kumar [b,*]

[a] *Department of Chemistry, DAV College, Amritsar, India*
[b] *Department of Chemistry, Guru Nanak Dev University, Amritsar, India*
[c] *Unité Parasitologie et Entomologie, Département Microbiologie et Maladies Infectieuses, Institut de Recherche Biomédicale des Armées, Marseille, France*
[d] *Aix Marseille Univ, IRD, SSA, AP-HM, VITROME, Marseille, France*
[e] *IHU Méditerranée Infection, Marseille, France*
[f] *Centre National de Référence du Paludisme, Marseille, France*

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ABSTRACT

A library of 1*H*-1,2,3-triazole-tethered 4-aminoquinoline-benzoxaborole hybrids as well as aryl substituted benzoxaborole analogues was synthesized and screened for their anti-plasmodial efficacy against both chloroquine-susceptibility 3D7 and chloroquine-resistant W2 strains of *P. falciparum*. The inclusion of quinoline core among the synthesized analogues resulted in substantial enhancement of anti-plasmodial activities. Further, the spacer of a flexible alkyl chain is marginally preferred over piperazyl-ethyl in inhibiting growth of *P. falciparum*. The most potent 4-aminoquinoline-benzoxaborole conjugate with ethyl as spacer exhibited IC_{50} values of 4.15 and 3.78 μM against 3D7 CQ-susceptible and W2 CQ-resistant strains of *P. falciparum* with lower cross resistance with Chloroquine. There was no difference in anti-plasmodial activities between the CQ-susceptible 3D7 and CQ-resistant W2 strains of *P. falciparum* for the benzoxaborole derivatives lacking a quinoline core.

1. Introduction

Malaria remains major health issue worldwide due to the lack of an effective vaccine and widespread resistance to the currently available drugs. Globally, ~228 million cases and 405,000 deaths occurred from malaria in 2018. Among these, 272,000 (67%) were children aged under the age of 5 years while 11 million pregnancies could have been exposed to malaria infection. The most virulent species of malarial protozoa, *Plasmodium falciparum* is responsible for 99.7% of malaria cases in the African region in 2018 [1]. Chloroquine (CQ) was an inexpensive and effective antimalarial drug used to combat the disease for decades and was considered as the Gold Standard. The emergence and spread of resistance to CQ and to the most antimalarial drugs used in monotherapy have paved the way for the development of new anti-malarial regimens [2,3]. World Health Organization (WHO) has currently recommended the combination of artemisinin and quinoline based drugs, popularly known as Artemisinin-based Combination Therapy (ACT) for treatment of *falciparum* malaria. However, the appearance of drug-resistance along with adverse effects such as hepatotoxicity and agranulocytosis associated with this therapy has hampered the efforts to eradicate this disease [4–7].

Structural re-engineering of 4-aminoquinolines along with its amalgamation with known bioactive pharmacophores, known as 4-aminoquinoline hybridization has emerged as one of the imperative strategies for accessing new frameworks with good anti-plasmodial activities and low incidence of resistance [8,9]. Numerous 4-aminoquinoline conjugates such as artemisinin-quinine, trioxaferroquines, clotrimazole-quinoline, 4-aminoquinoline-phthalimide (I), 4-aminoquinoline-naphthalimide (II), 4-aminoquinoline-pyrimidine (III), 4-aminoquinoline-purine (IV) (Fig. 1) etc. have revealed the success of this strategy by reversing the compound specific CQ-resistance [10–14].

Benzoxaborole has emerged as an important heterocycle for molecular recognition and biotechnology with varied therapeutic applications. The diverse potential of benzoxaborole was well exemplified by recent upsurge in its scientific literature including antifungal, antibacterial, antiviral, anti-inflammatory, anticancer and anti-parasitic

* Corresponding authors.
E-mail addresses: raghusharma4@gmail.com (R. Raj), vipan_org@yahoo.com (V. Kumar).

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activities [15,16]. The rationalization of literature revealed the recent emergence of benzoxaborole core as a promising motif with a potential to treat multi-drug resistant malaria. In one of such series, the compounds (**V** and **VI**) displayed *in vivo* efficacy against *P. berghei* infection with ED_{90} ranging from 7.4 to 16.2 mg/kg. The promising compounds exhibited a novel mechanism of action including the inhibition of *P. falciparum* LeuRS [17]. Another series of 7-methyl benzoxaborole pyrazine carboxamide was optimized to afford **VII** which has demonstrated longer half-life, higher bioavailability, and excellent *in vivo* efficacy against *P. Berghei* [18]. Peptidyl boronic acids have been identified as selective anti-plasmodium proteasome inhibitors with efficacy on both artemisinin-sensitive and -resistant parasites with one of the scaffold **VIII** being 56 folds more active than HepG2 [19].

Considering the novel anti-malarial targets of boron-containing benzoxaborole, it is considered worthwhile to explore the synthesis of their 7-chloroquinoline-based hybrids which could possibly act as a dual function anti-plasmodials. Thus in continuation of our endeavour for identifying new anti-plasmodials [20], the present communication describes the synthesis of a series of 1*H*-1,2,3-triazole linked phenyl/naphthyl/benzyl substituted benzoxaboroles having varied alkyl chain lengths for assaying their anti-plasmodial activities against both CQ-susceptible3D7 and CQ-resistant W2 strains of *P. falciparum*. The aryl core was then replaced with 4-aminoquinoiline, either directly linked to triazole core or through alkyl chains so as to determine its influence on the anti-plasmodial efficacy. 1*H*-1,2,3-triazole core was introduced as a linker because of its well established ability to participate in non-covalent interactions which can improve the pharmacokinetic properties along with binding with molecular targets [21].

2. Result and discussion

2.1. Synthetic chemistry

The first set of target scaffolds *viz.* 1*H*-1,2,3-triazole linked phenyl/naphthyl-benzoxaboroles was prepared by an initial base-promoted alkylation of phenol/1-naphthol **1** with varied di-bromoalkanes with subsequent treatment with sodium azide to yield *O*-alkylazido phenol/naphthol**2**. Cu-promoted azide-alkyne cycloaddition between **2** and *O*-propargylated-2-bromobenzaldehyde afforded the corresponding 1*H*-1,2,3-triazole tethered adduct**3** in excellent yields. Catalytic bornylation of **3** with (pinacolato)boronin the presence of $Pd(dppf)Cl_2$ as catalyst gave **4**. Sodium borohydride-promoted reduction of aldehydic group in **4** followed by acidification resulted in the formation of desired 1*H*-1,2,3-triazole linked phenyl/naphthyl-benzoxaboroles **5** (Scheme 1).

Similar sequence of synthetic steps, as described above, were employed to afford the second set of target scaffolds *viz.*1*H*-1,2,3-triazole-tethered benzyl-benzoxaboroles using benzyl-bromide **6** as the precursor (Scheme 2).

The synthesis of 4-aminoquinoline-benzoxaborole conjugates were synthesized *via* an initial treatment of 4,7-dichloroquinoline **11** with sodium azide at 60 °C to afford precursor **12**. The reaction of **12** with *O*-propargylated bromobenzaldehyde in presence of $CuSO_4$ and sodium ascorbate afforded **13**. Suzuki-miyaura borylation of **13** with Pin_2B_2 in the presence of $Pd(dppf)Cl_2$ generated the corresponding boronic ester **14**. The reduction of aldehydic group of **14** with sodium borohydride followed by acidification led to the formation of corresponding 4-aminoquinoline-benzoxaborole conjugates **15** (Scheme 3).

For the synthesis of 4-aminoquinoline-benzoxaborole conjugates having alkyl chain lengths between the two pharmacophores 19, the approach was initiated by reacting 4,7-dichloroquinoline with ethanol/propanol amine in presence of triethylamine followed by their mesylation and subsequent reaction with NaN_3 to afford click chemistry precursor **16**. Cu-promoted click chemistry between *O*-propargylated bromobenzaldehyde and **16** led to the synthesis of **17** which upon reaction with Pin_2B_2 in presence of $Pd(dppf)Cl_2$ and KOAc as base led to the formation of the corresponding boronic ester **18**. Sodium borohydride promoted reduction and subsequent acidification yielded 4-aminoquinoline-benzoxaborole conjugates **19** with alkyl chains as spacer, as depicted in Scheme 4.

Scheme 5 illustrated the methodology for the preparation of 4-aminoquinoline-benzoxaborole conjugate **24** linked *via* piperazinyl-ethyl core. Thus, the treatment of 11 with 2-piperazin-1-yl-ethanol gave 20 which upon a sequence of mesylation, azidation and click-chemistry with *O*-propargylated bromobenzaldehyde yielded **22**. Boronylation of **22** with subsequent aldehydic reduction and acidification generated the corresponding conjugate **24**.

The spectral features of conjugates were assigned on the basis of spectral data and analytical evidence. For example, the conjugate **19b**, exhibits a molecular ion peak [M+1] and [M+3] at 450.1413 and 452.1417 in its High Resolution Mass Spectrum (HRMS). In PMR spectrum, conjugate showed the presence of a singlet at δ 2.37 due to the presence of methyl group, two singlet at δ 4.57 and 5.18 due to presence of two methylene, and characteristic singlet at δ 8.22 corresponding to a triazole proton. Further, ^{13}C NMR spectrum exhibits appearances of characteristic signal at δ 157.9 due to carbonyl carbon along with the required number of carbons confirmed the assigned structure.

2.2. In vitro anti-plasmodial activity

The synthesized compounds were assayed for their anti-plasmodial potential against CQ-susceptibile 3D7 and CQ-resistant W2 strain of *P. falciparum*. A careful examination of Table 1 revealed that although

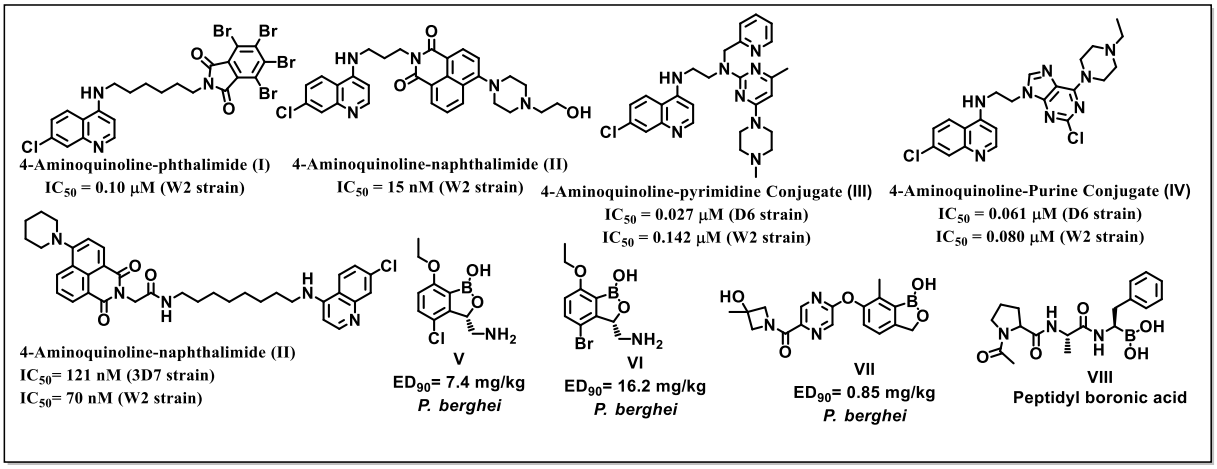
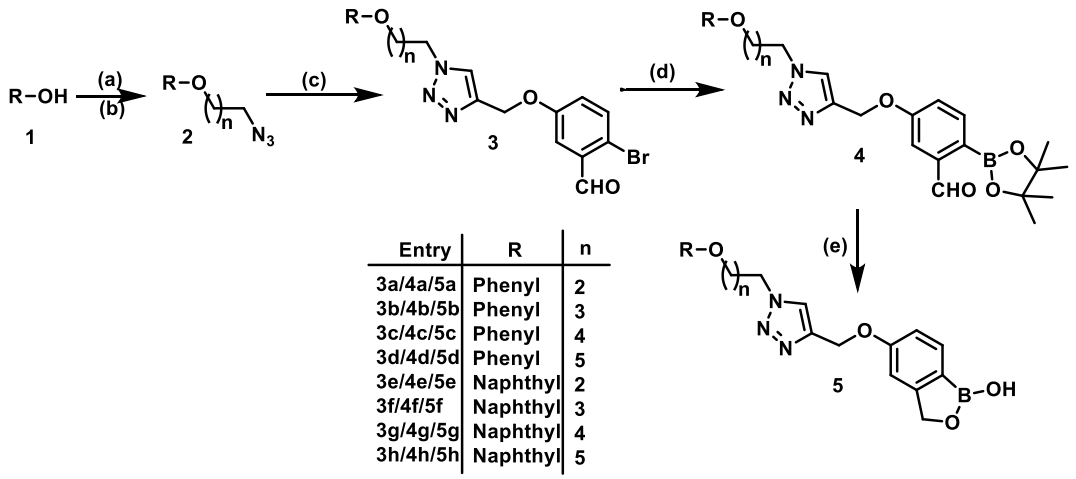
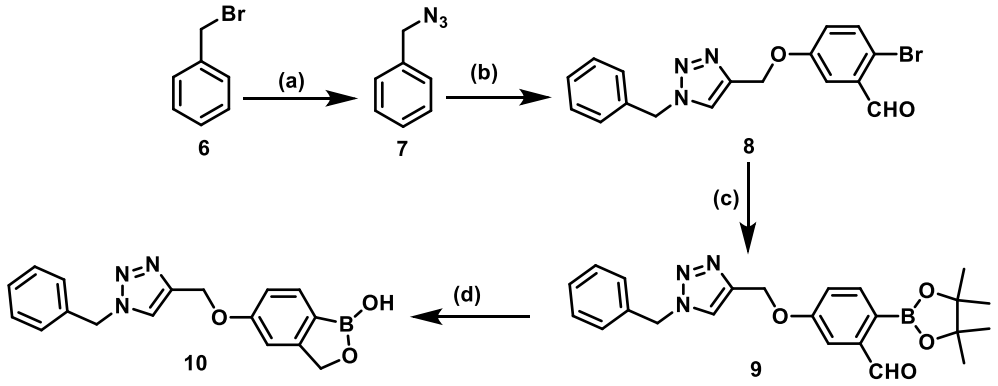


Fig. 1. Structures of few quinoline and benzoxaborole based antimalarials.

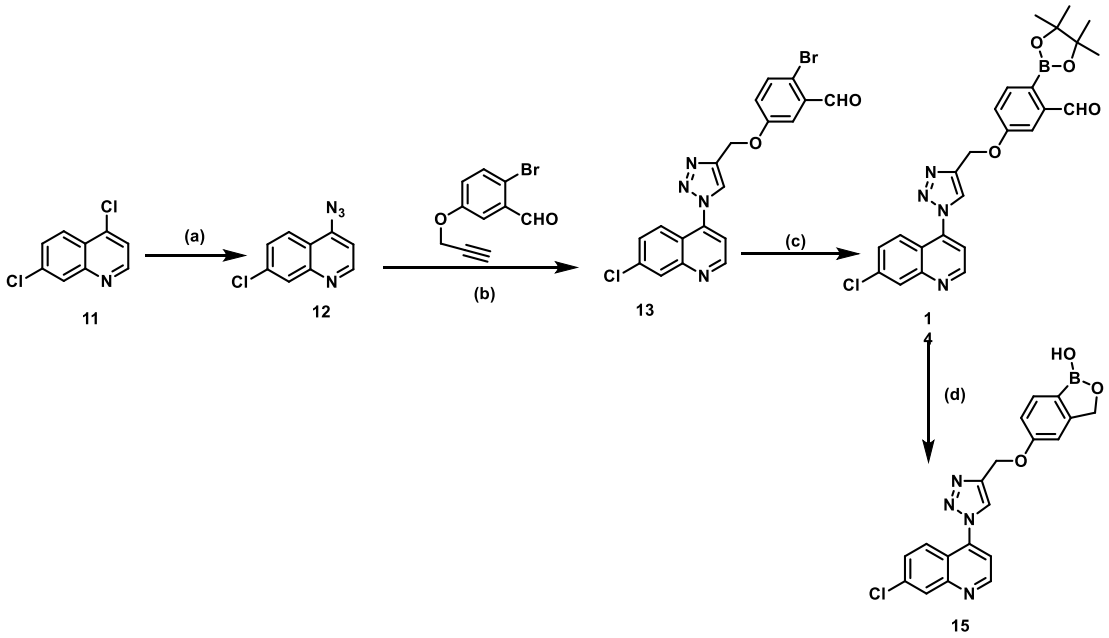


Entry	R	n
3a/4a/5a	Phenyl	2
3b/4b/5b	Phenyl	3
3c/4c/5c	Phenyl	4
3d/4d/5d	Phenyl	5
3e/4e/5e	Naphthyl	2
3f/4f/5f	Naphthyl	3
3g/4g/5g	Naphthyl	4
3h/4h/5h	Naphthyl	5

Scheme 1. Synthesis of 1*H*-1,2,3-triazole linked phenyl/naphthyl-benzoxaboroles **5.**

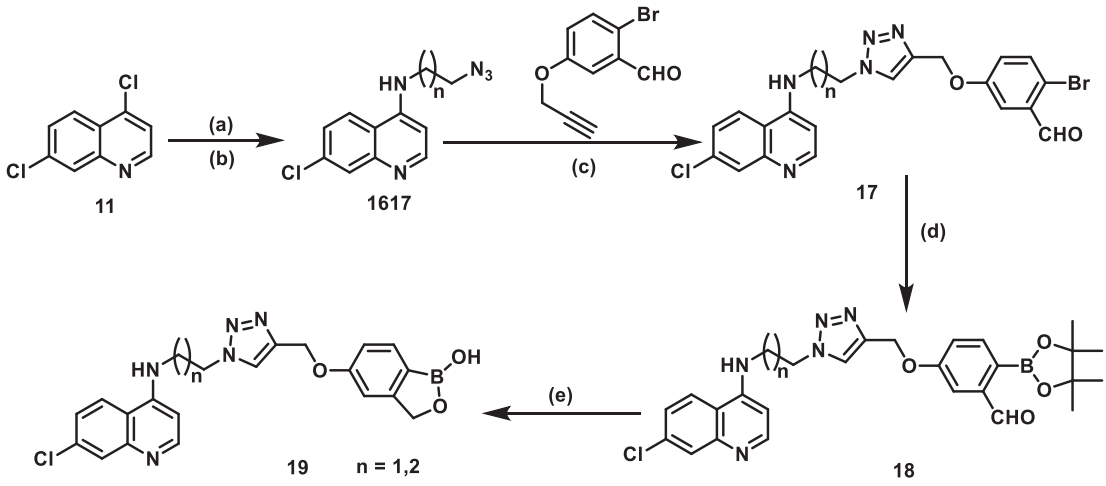


Scheme 2. Synthesis of 1*H*-1,2,3-triazole-tethered benzyl-benzoxaboroles **10.**

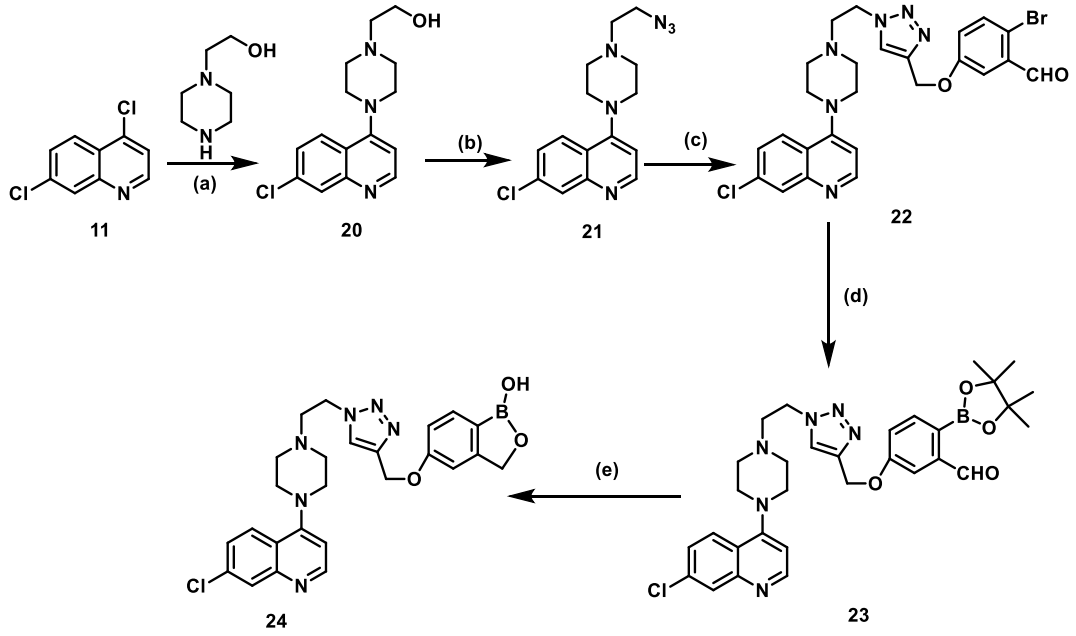


Scheme 3. Synthesis of 4-aminoquinoline-benzoxaborole conjugates **15.**

the synthesized compounds were not as active as the standard drug CQ, the compounds exhibited IC_{50s} in low micromolar range against both the tested strains and exhibited interesting Structure-Activity Relationship (SAR). Among the triazole-tethered precursors with phenyl-core **3a–d**, the compounds showed decent anti-plasmodial activities with IC_{50s} ranging from 5.55 to 7.46 and 4.83–7.56 μM against 3D7 and W2 strains,



Scheme 4. Synthesis of 4-aminoquinoline-benzoxaborole conjugates **19** with spacers.



Scheme 5. Synthesis of 4-aminoquinoline-benzoxaborole conjugate **24** linked *via* piperazinyl-ethyl core.

respectively. The conversion of **3** to corresponding boronate esters or oxaboroles did not improve the anti-plasmodial profiles as evident by **4a–d** and **5a–d**. The replacement of phenyl ring with naphthyl-core also had a little influence on the anti-plasmodial activities, especially in case of aldehydic precursors' **3e–h** and the corresponding boronate esters' **4e–h**. Slight improvement in anti-plasmodial activities, however has been observed in case of 1*H*-1,2,3-triazole-linked naphthyl-oxaboroles with the most potent compound among them, exhibiting IC_{50}s of 4.94 and 4.17 μM against 3D7 and W2-strains, respectively. The replacement of naphthyl with benzyl-core did not show any improvement in anti-plasmodial activities. Similar profiling of 4-aminoquinoline based precursor **13**, the corresponding boronate ester **14** and oxaborole **15** explicated an interesting SAR with activities improving considerably from the aldehydic precursor to oxaborole as evident by comparing **13** [(IC_{50} = 6.19 (3D7) and 7.39 μM (W2)] with **15** [(IC_{50} = 4.87 (3D7) and 5.22 μM (W2)]. Introducing alkyl chain length as spacer between the two pharmacophores substantially improved the anti-plasmodial activities with more influence being observed among 4-aminoquinoline-benzoxaboroles (**19a–b**) than the corresponding precursors (**17a–b**). The inclusion of a piperazyl-ethyl as spacer reduced the activities in the precursor **22** confirming the favourable influence of flexible chains on quinoline-core while the corresponding oxaborole **24** displayed moderate activities against both the strains. A graphical representation of the SAR of the synthesized compounds is depicted in Fig. 2. All synthesized compounds displayed reduced cross-resistance with chloroquine, with a resistance index (RI) factor, according to CQ susceptibility, in the range 0.64–1.30 as compared to 19.79 for standard drug, CQ. The most potent conjugate **19a** showed IC_{50} values of 4.15 and 3.78 μM against CQ-susceptibility (3D7) and CQ-resistant (W2) strain of *P. falciparum* with RI of 0.91 and thus considered to have a little cross-resistance with CQ [22]. Three of the most promising hybrids **19a**, **19b** and **24** were evaluated for their cytotoxicity against mammalian Vero kidney cell lines and the results are enlisted in Table 2. The hybrids were non-cytotoxic against Vero cells and exhibited selective indices SI in the range of 16.94–26.45.

The feeding of malarial parasites on hemoglobin for acquiring nutrition results in the release of huge amount of free heme which is itself toxic to the parasite's survival. The parasire has evolved a mechanism to detoxify the free heme by its conversion to a non-toxic insoluble material called hemozoin [23]. 4-Aminoquinolines are known to

Table 1
Antiplasmodial activities of synthesized compounds.

Compound	n	3D7 (CQ-S)[a] IC_{50} (μM)	W2 (CQ-R)[b] IC_{50} (μM)	RI[c]
3a	2	7.44	7.65	1.02
3b	3	7.46	4.83	0.64
3c	4	5.55	5.17	0.93
3d	5	7.42	6.80	0.91
3e	2	5.68	5.44	0.95
3f	3	6.03	7.28	1.20
3g	4	6.59	7.61	1.15
3h	5	6.12	5.77	0.94
4a	2	ND	ND	ND
4b	3	6.45	6.60	1.02
4c	4	ND	ND	ND
4d	5	6.05	6.98	1.15
4e	2	ND	ND	ND
4f	3	ND	ND	ND
4g	4	5.63	7.19	1.27
4h	5	ND	ND	ND
5a	2	5.66	5.18	0.91
5b	3	5.02	4.56	0.90
5c	4	5.24	6.80	1.29
5d	5	6.40	6.39	0.99
5e	2	4.94	4.17	0.84
5f	3	ND	ND	ND
5g	4	5.00	4.27	0.85
5h	5	5.00	5.37	1.07
8	–	5.20	6.77	1.30
9	–	5.59	7.74	1.38
10	–	5.18	5.22	1.00
13	–	6.19	7.39	1.19
14	–	6.49	6.19	0.95
15	–	4.87	5.22	1.07
17a	1	4.30	5.07	1.17
17b	2	6.29	7.09	1.12
18a	1	7.37	6.23	0.84
18b	2	5.18	4.64	0.89
19a	1	4.15	3.78	0.91
19b	2	4.13	3.91	0.94
22	–	8.34	8.26	0.99
23	–	ND	ND	ND
24	–	5.31	4.86	0.91
CQ		0.024	0.475	19.79

[a] CQ-S: Chloroquinesusceptible strain.
[b] CQ-R: Chloroquine resistant strain.
[c] Resistance index (RI): IC_{50}(W2)/IC_{50}(3D7) according to chloroquine susceptibility.

exert their anti-plasmodial activities *via* inhibiting heme to hemozoin conversion through formation of a complex between the porphyrin ring of free heme and quinoline core. CQ complexation with heme in aqueous medium therefore can be identified by changes in the UV–vis spectrum of aqueous hematin [24].

Thus, in order to decipher the primary mode of action of the synthesized hybrids, we conducted UV–vis spectrophotometry studies of the most potent compound, **19a**, with monomeric heme. A solution of hemin in 40% DMSO/water shows a band at 401 nm corresponding to monomeric heme, and a decrease in the intensity of this band after adding a drug is an indicator of drug-heme interactions. The titrations of **19a** with monomeric heme in aqueous DMSO solutions at pH 7.4 (0.02 M HEPES buffer, physiological pH, Fig. 3) and pH 5.6 (0.02 M MES buffer, parasites' DV, Fig. 4), respectively, showed a significant decrease in the intensity of the band representing monomeric heme. By analyzing the titration curves using HypSpec, a nonlinear least-square fitting program, the binding of compound **19a** with heme was determined *via* log K values at both tested pH conditions and the results are included in Table 3. To compare the values with those of the standard drug, CQ, the UV–vis experiment was conducted with CQ and monomeric heme under identical conditions. As evident, the binding of **19a** with heme was comparable to CQ at both physiological and acidic pH.

In conclusion, a series of 1*H*-1,2,3-triazole-tethered benzoxaborole-derivatives as well as 4-aminoquinoline-benzoxaborole conjugates were synthesized and evaluated for their anti-plasmodial activities against both CQ-sensitive as well as resistant strains of *P. falciparum*. SAR studies indicated the improvement in anti-plasmodial activities on replacing the aryl ring with quinoline core with a marginal preference of flexible alkyl chain as linker over piperazinering. Hybrids **19a**, **19b** and **24** with ethyl, propyl and piperazyl-ethyl as spacer along with 4-amino-quinoline core and oxaborole ring proved to be most promising among the series exhibiting IC_{50s} of 3.78, 3.91 and 4.86 μM on W2 strain, respectively.

3. Experimental section

^{1}H NMR spectra were recorded in deuterochloroform ($CDCl_3$) and DMSO-d_6 with Jeol 300 (300 MHz), Jeol 400 (400 MHz) and Bruker 500 (500 MHz) spectrometer using TMS as an internal standard. Chemical shift values are expressed as parts per million downfield from TMS and J values are in hertz. Splitting patterns are indicated as s: singlet, d: doublet, t: triplet, m: multiplet, dd: double doublet, ddd: doublet of a doublet of a doublet, and br: broad peak. ^{13}C NMR spectra were recorded on a Bruker 400 (100 MHz) and Bruker 500 (125 MHz) spectrometer in deuterochloroform ($CDCl_3$) and dimethylsulfoxide (DMSO-d_6) using TMS as internal standard. High resolution mass spectra were recorded on a Bruker-micrOTOF-Q II spectrometer.

Table 2
Cytotoxic activities of **19a**, **19b** and **24** on Vero cells.

Compounds	IC_{50} (μM) Vero Kidney Cell line	IC_{50} (μM) (W2 strain)	SI
19a	>100	3.78	26.45
19b	>100	3.91	25.57
24	82.36	4.86	16.94

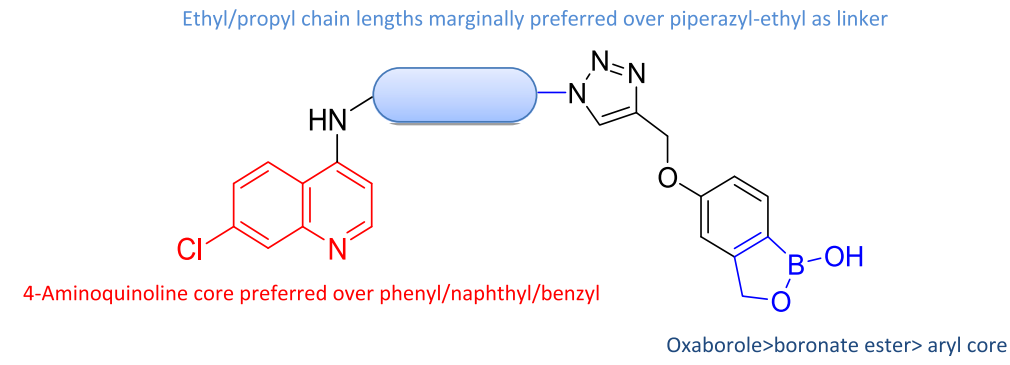


Fig. 2. General structure of lead compound and target hybrid compounds.

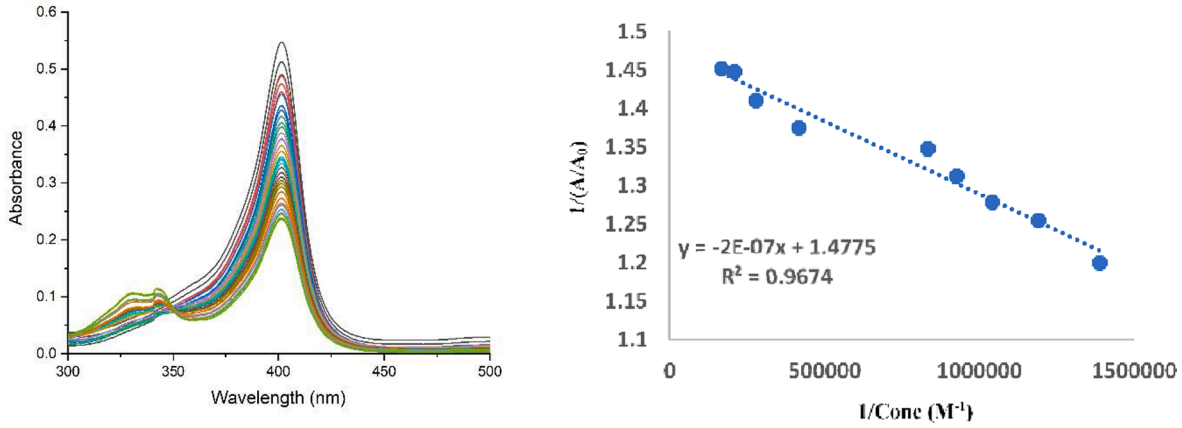


Fig. 3. Titration of monomeric heme (12 μM) at pH 7.4 (0.02 M HEPES buffer in aqueous DMSO solution) with increasing concentration of **19a** (0–18 μM) in 0.02 M HEPES buffer in aqueous DMSO solution and linear dependence of absorption at 401 nm on heme-**19a** complex concentration.

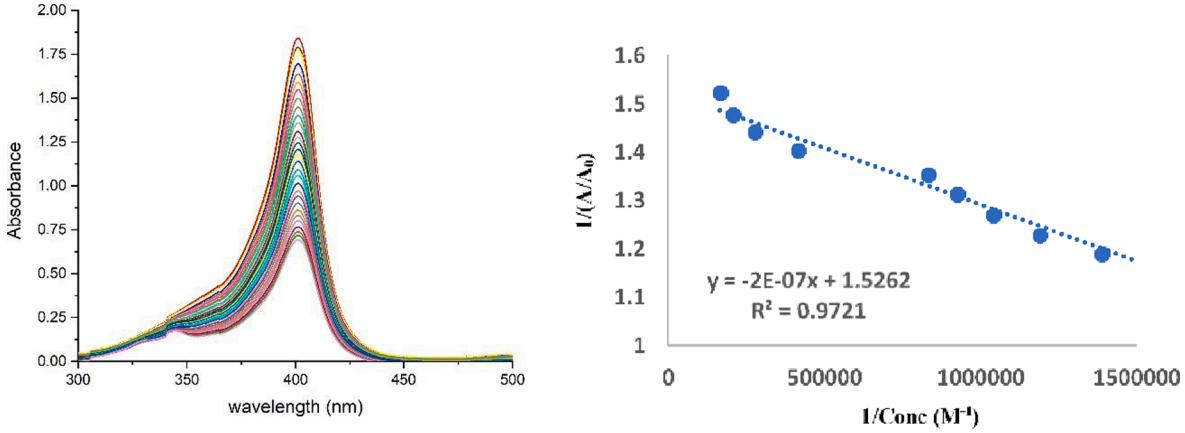


Fig. 4. Titration of monomeric heme (12 μM) at pH 5.6 (0.02 M MES buffer in aqueous DMSO solution) with increasing concentration of **19a** (0–16 μM) in 0.02 M MES buffer in aqueous DMSO solution and linear dependence of absorption at 401 nm on heme-**19a** complex concentration.

Table 3
Binding constant (log *K*) for 19a and CQ with monomeric heme.

Entry	pH 5.6 (MES Buffer)	pH 7.4 (HEPES Buffer)
19a	6.81	6.89
CQ	5.18	5.10

*3.1. General procedure for the synthesis of precursors **3/8/13/17/22***

To the stirred solution of azide based precursors **2/7/12/16/21** (1 mmol) and *O*-propargylated-2-bromobenzaldehyde (1 mmol) inEtOH: H_2O (90:10) mixture, was added $CuSO_4{\cdot}5H_2O$ (0.055 mmol) and sodium ascorbate (0.143 mmol). The reaction mixture was stirred at room temperature for 7–8 h and progress of reaction was monitored *via* TLC. After the usual workup in $CHCl_3$ and H_2O, organic layers were collected, combined, and dried over anhydrous sodium sulphate and evaporated to give crude product which was further purified through column chromatography.

*3.1.1. 2-bromo-5-((1-(3-phenoxypropyl)-1H-1,2,3-triazol-4-yl)methoxy) benzaldehyde (**3a**)*

White Solid; Yield: 90%; ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.41–2.44 (m, 2H, —CH_2—), 3.96–3.98 (m, 2H, —N—CH_2—), 4.61–4.64 (m, 2H, —O—CH_2—), 5.22 (s, 2H, —O—CH_2—), 6.87–6.88 (*d*, J = 8.0 Hz, 2H, ArH), 6.98 (t, J = 7.5 Hz, 1H, ArH), 7.11 (*dd*, J = 3.0, 8.5 Hz, 1H, ArH), 7.28 (d, J = 3.0 Hz, 1H, ArH), 7.30 (d, J = 8.0 Hz, 1H, ArH), 7.50–7.56 (m, 2H, ArH), 7.65 (s, 1H, triazole-H), 10.30 (s, 1H, —CHO); ^{13}C NMR (125 MHz, DMSO-d_6): δ ppm = 29.8, 47.2, 62.2, 63.8, 114.2, 114.4, 118.3, 121.2, 123.2, 123.5, 129.6, 134.0, 134.7, 143.0, 157.9, 158.3, 191.6. HRMS Calculated for $C_{19}H_{18}BrN_3O_3$ [M+1] 416.0532 and [M+3] 418.0532 found 416.0541 and 418.0524; Anal. Calcd. (%) for: C, 54.82; H, 4.36; N, 10.09; Found: C, 54.95; H, 4.46; N, 10.01.

*3.1.2. 2-bromo-5-((1-(4-phenoxybutyl)-1H-1,2,3-triazol-4-yl)methoxy) benzaldehyde (**3b**)*

White Solid; Yield: 88%; ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.81–1.87 (m, 2H, CH_2—), 2.02–2.09 (m, 2H, —CH_2—), 3.96–3.99 (m, 2H, —N—CH_2—), 4.51–4.54 (m, 2H,—O—CH_2—), 5.25 (s, 2H, —O—CH_2—), 6.88–6.90 (d, J = 8.0 Hz, 2H, ArH), 6.96 (t, J = 7.5 Hz, 1H, ArH), 7.20 (dd, J = 3.0, 8.5 Hz, 1H, ArH), 7.29 (d, J = 3.0 Hz, 1H, ArH), 7.32 (d, J = 8.0 Hz, 1H, ArH), 7.46–7.51 (m, 2H, ArH), 7.62 (s, 1H, triazole—H), 9.9 (s, 1H, —CHO); ^{13}C NMR (125 MHz, DMSO-d_6): δ ppm = 26.0, 27.1, 61.9, 63.0, 65.4, 114.0, 114.3, 118.4, 120.9, 122.8, 123.5, 129.1, 134.0, 134.5, 143.3, 158.1, 158.9, 191.2. HRMS Calculated for $C_{20}H_{20}BrN_3O_3$ [M+1] 430.0688 and [M+3] 432.0688 found 430.0674 and 432.0679; Anal. Calcd. (%) for: C, 55.83; H, 4.69; N, 9.77; Found: C, 55.91; H, 4.80; N, 9.94.

*3.1.3. 2-bromo-5-((1-(5-phenoxypentyl)-1H-1,2,3-triazol-4-yl)methoxy) benzaldehyde (**3c**)*

White Solid; Yield: 86%;^{1}H NMR (500 MHz, $CDCl_3$): δ 1.52–1.58 (m,

2H, —CH_2—), 1.82–1.87 (m, 2H, —CH_2—), 1.98–2.06 (m, 2H, —CH_2—), 3.95–3.98 (m, 2H, —N—CH_2—), 4.40–4.44 (m, 2H, —O—CH_2—), 5.24 (s, 2H, —O—CH_2—), 6.88 (d, J = 8.0 Hz,2H, ArH), 6.95 (t, J = 7.5 Hz, 1H, ArH), 7.14 (dd, J = 3.0, 8.5 Hz, 1H, ArH), 7.28–7.31 (m, 2H, ArH), 7.53–7.57 (m, 2H, ArH), 7.63 (s, 1H, triazole—H), 10.2 (s, 1H, —CHO); ^{13}C NMR (125 MHz, DMSO-d_6): δ ppm = 23.2, 28.6, 29.9, 50.3, 62.3, 67.1, 114.2, 114.4, 118.4, 120.7, 122.7, 123.3, 129.4, 134.0, 134.7, 143.0, 157.9, 158.8, 191.6. HRMS Calculated for $C_{21}H_{22}BrN_3O_3$ [M+1] 444.0845 and [M+3] 446.0845 found 444.0837 and 446.0856; Anal. Calcd. (%) for: C, 56.77; H, 4.99; N, 9.46; Found: C, 56.88; H, 4.91; N, 9.33.

3.1.4. 2-bromo-5-((1-(6-phenoxyhexyl)-1H-1,2,3-triazol-4-yl)methoxy) benzaldehyde (**3d**)

White Solid; Yield: 83%; ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.24–1.29 (m, 2H, —CH_2—), 1.51–1.58 (m, 2H, —CH_2—), 1.81–1.88 (m, 2H, —CH_2—), 2.06–2.10 (m, 2H, —CH_2—), 4.02–4.05 (m, 2H, —N—CH_2—), 4.54–4.57 (m, 2H, —O—CH_2—), 5.26 (s, 2H, —O—CH_2—), 6.84–6.87 (m, 2H, ArH), 7.00 (t, J = 7.5 Hz, 1H, ArH), 7.15 (dd, J = 3.0, 8.5 Hz, 1H, ArH), 7.25 (d, J = 3.0 Hz, 1H, ArH), 7.35 (d, J = 8.0 Hz, 1H, ArH), 7.45–7.49 (m, 2H, ArH), 7.56 (s, 1H, triazole—H), 10.3 (s, 1H, —CHO); ^{13}C NMR (125 MHz, DMSO-d_6): δ ppm = 25.5, 27.2, 28.5, 29.9, 50.1, 62.2, 68.0, 114.1, 114.5, 118.3, 121.2, 123.1, 123.5, 129.2, 134.2, 134.6, 143.0, 157.9, 158.6, 191.0. HRMS Calculated for $C_{22}H_{24}BrN_3O_3$ [M+1] 458.1001 and [M+3] 460.1001 found 458.1009 and 460.1015; Anal. Calcd. (%) for: C, 57.65; H, 5.28; N, 9.17; Found: C, 57.73; H, 5.11; N, 9.09.

3.1.5. 2-bromo-5-((1-(3-(naphthalen-1-yloxy)propyl)-1H-1,2,3-triazol-4-yl)methoxy)benzaldehyde (**3e**)

White Solid; Yield: 90%; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.43–2.49 (m, 2H, —CH_2—), 4.00–4.04 (m, 2H, —N—CH_2—), 4.58–4.63 (m, 2H, —O—CH_2—), 5.06 (s, 2H, —O—CH_2—), 6.63 (d, J = 7.8 Hz, 1H, ArH), 6.94 (dd, J = 3.0, 8.7 Hz, 1H, ArH), 7.24 (t, J = 8.1 Hz, 1H, ArH), 7.34–7.41 (m,5H, ArH), 7.52 (s, 1H, triazole—H), 7.71 (d, J = 8.1 Hz, 1H, ArH), 8.12 (d, J = 6.6 Hz, 1H, ArH); 10.17 (s, 1H, —CHO); ^{13}C NMR (125 MHz, DMSO-d_6): δ ppm = 28.5, 48.0, 62.4, 68.0, 105.2, 114.1, 114.9, 120.0, 121.4, 122.1, 123.1, 124.4, 125.3, 125.6, 126.1, 127.2, 128.6, 130.1, 137.1, 141.2, 155.9, 159.4, 191.2. HRMS Calculated for $C_{23}H_{20}BrN_3O_3$ [M+1] 466.0688 and [M+3] 468.0688 found 466.0672 and 468.0697; Anal. Calcd. (%) for: C, 59.24; H, 4.32; N, 9.01; Found: C, 59.33; H, 4.40; N, 9.15.

3.1.6. 2-bromo-5-((1-(4-(naphthalen-1-yloxy)butyl)-1H-1,2,3-triazol-4-yl)methoxy)benzaldehyde (**3f**)

White Solid; Yield: 88%; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.80–1.86 (m, 2H, —CH_2—), 2.10–2.15 (m, 2H, —CH_2—), 4.20–4.24 (m, 2H, —N—CH_2—), 4.60–4.64 (m, 2H, —O—CH_2—), 5.15 (s, 2H, —O—CH_2—), 6.61 (d, J = 7.8 Hz, 1H, ArH), 6.96 (dd, J = 2.7, 8.7 Hz, 1H, ArH), 7.23 (t, J = 8.1 Hz, 1H, ArH), 7.32–7.38 (m,5H, ArH), 7.55 (s, 1H, triazole—H), 7.69 (d, J = 8.1 Hz, 1H, ArH), 8.01 (d, J = 6.6 Hz, 1H, ArH); 10.20 (s, 1H, —CHO); ^{13}C NMR (125 MHz, DMSO-d_6): δ ppm = 26.2, 27.3, 47.8, 62.5, 67.6, 104.8, 113.8, 114.8, 120.1, 121.6, 122.0, 123.4, 124.3, 125.4, 125.6, 126.0, 127.5, 128.5,130.0, 136.9, 141.6, 155.4, 159.3, 191.1. HRMS Calculated for $C_{24}H_{22}BrN_3O_3$ [M+1] 480.0845 and [M+3] 482.0845 found 480.0853 and 480.0858; Anal. Calcd. (%) for: C, 60.01; H, 4.62; N, 8.75; Found: C, 59.92; H, 4.75; N, 8.86.

3.1.7. 2-bromo-5-((1-(5-(naphthalen-1-yloxy)pentyl)-1H-1,2,3-triazol-4-yl)methoxy)benzaldehyde (**3 g**)

White Solid; Yield: 91%; ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.52–1.57 (m, 2H, —CH_2—), 1.77–1.84 (m, 2H, —CH_2—), 2.05–2.11 (m, 2H, —CH_2—), 4.10–4.13 (m, 2H, —N—CH_2—), 4.55–4.59 (m, 2H, —O—CH_2—), 5.16 (s, 2H, —O—CH_2—), 6.71 (d, J = 8.0 Hz, 1H, ArH), 6.89 (dd, J = 3.0, 9.0 Hz, 1H, ArH), 7.29 (t, J = 8.0 Hz, 1H, ArH), 7.40–7.48 (m, 5H, ArH), 7.63 (s, 1H, triazole—H), 7.77 (d, J = 8.0 Hz, 1H, ArH), 8.09 (d, J = 6.5 Hz, 1H, ArH); 10.06 (s, 1H, —CHO); ^{13}C NMR (125 MHz, DMSO-d_6): δ ppm = 23.2, 28.6, 29.9, 48.1, 62.2, 67.9, 104.7, 114.2, 114.9, 120.2, 121.1, 122.5, 123.2, 124.3, 125.4, 125.6, 126.3, 127.0, 128.5, 130.0, 137.0, 142.0, 155.6, 159.0, 191.3. HRMS Calculated for $C_{25}H_{24}BrN_3O_3$ [M+1] 494.1001 and [M+3] 496.1001 found 494.1012 and 496.1009; Anal. Calcd. (%) for: C, 60.74; H, 4.89; N, 8.50; Found: C, 60.61; H, 4.97; N, 8.66.

3.1.8. 2-bromo-5-((1-(6-(naphthalene-1-yloxy)hexyl)-1H-1,2,3-triazol-4-yl)methoxy)benzaldehyde (**3 h**)

White Solid; Yield: 87%; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.25–1.28 (m, 2H, —CH_2—), 1.48–1.53 (m, 2H, —CH_2—), 1.81–1.85 (m, 2H, —CH_2—), 2.05–2.08 (m, 2H, —CH_2—), 3.99–4.02 (m, 2H, —N—CH_2—), 4.45–4.48 (m, 2H, —O—CH_2—), 5.14 (s, 2H, —O—CH_2—), 6.67 (d, J = 7.8 Hz, 1H, ArH), 6.91 (dd, J = 3.0, 8.7 Hz, 1H, ArH), 7.23 (t, J = 8.1 Hz, 1H, ArH), 7.35–7.40 (m, 5H, ArH), 7.64 (s, 1H, triazole—H), 7.77 (d, J = 8.1 Hz, 1H, ArH), 8.06 (d, J = 6.6 Hz, 1H, ArH); 10.11 (s, 1H, —CHO); ^{13}C NMR (125 MHz, DMSO-d_6): δ ppm = 25.6, 27.1, 28.6, 29.8, 47.8, 62.0, 68.0, 104.8, 114.2, 114.8, 120.3, 121.0, 122.3, 123.6, 124.6, 125.4, 125.7, 126.2, 127.4, 128.3, 130.2, 137.2, 141.5, 155.4, 159.1, 191.0. HRMS Calculated for $C_{26}H_{26}BrN_3O_3$ [M+1] 508.1158 and [M+3] 510.1158 found 508.1150 and 510.1170; Anal. Calcd. (%) for: C, 61.42; H, 5.15; N, 8.27; Found: C, 61.50; H, 5.26; N, 8.44.

3.1.9. 5-((1-benzyl-1H-1,2,3-triazol-4-yl)methoxy)-2-bromobenzaldehyde (**8**)

White Solid; Yield: 93%; ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.22 (s, 2H, —N—CH_2—), 5.42 (s, 2H, —O—CH_2—), 6.90–6.94 (m,2H, ArH), 7.22–7.27 (m, 2H, ArH), 7.42–7.45 (m, 3H, ArH), 7.65 (s, 1H, triazole—H), 7.75 (d, J = 8.0 Hz, 1H, ArH), 10.0 (s, 1H, —CHO); ^{13}C NMR (125 MHz, DMSO-d_6): δ ppm = 55.5, 70.1, 107.2, 114.8, 122.1, 128.3, 128.8, 129.2, 131.0, 134.5, 143.1, 145.2, 155.9, 159.8, 191.0. HRMS Calculated for $C_{17}H_{14}BrN_3O_2$ [M+1] 372.0269 and [M+3] 373.0269 found 372.0282 and 373.0259; Anal. Calcd. (%) for: C, 54.86; H, 3.79; N, 11.29; Found: C, 54.71; H, 3.91; N, 11.46.

3.1.10. 2-bromo-5-((1-(7-chloroquinolin-4-yl)-1H-1,2,3-triazol-4-yl) methoxy)benzaldehyde (**13**)

White Solid; Yield: 92%; ^{1}H NMR (300 MHz, DMSO-d_6): δ 5.25 (s, 2H, —O—CH_2—), 6.60 (d, J = 5.1 Hz, 1H, ArH), 7.18 (dd, J = 2.7, 8.7 Hz, 1H, ArH), 7.44–7.49 (m, 4H, —NH-exchangeable with D_2O + 3ArH), 7.82 (d, J = 3.0 Hz, 1H, ArH), 8.13 (d, J = 8.7 Hz, 1H, ArH), 8.31 (s, 1H, triazole—H), 8.34 (d, J = 5.1 Hz, 1H, ArH), 10.00 (s, 1H, —CHO); ^{13}C NMR (100 MHz, DMSO-d_6): δ ppm = 62.0,80.4, 113.1, 113.5, 118.1, 120.9, 125.5, 127.0, 128.5, 129.1, 131.0, 135.4, 141.1, 142.2, 144.7, 150.0, 152.7, 158.1, 190.0. HRMS Calculated for $C_{19}H_{12}BrClN_4O_2$ [M+1] 442.9832 and [M+3] 444.9832 found 442.9841 and 444.9821; Anal. Calcd. (%) for: C, 51.43; H, 2.73; N, 12.63; Found: C, 51.54; H, 2.59; N, 12.73.

3.1.11. 2-bromo-5-((1-(2-((7-chloroquinolin-4-yl)amino)ethyl)-1H-1,2,3-triazol-4-yl)methoxy)benzaldehyde (**17a**)

White Solid; Yield: 89%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.36–3.38 (m, 2H, —N—CH_2—), 4.63–4.65 (m, 2H, —N—CH_2—), 5.18 (s, 2H, —O—CH_2—), 6.51 (d, J = 5.2 Hz, 1H, ArH), 7.29 (dd, J = 2.8, 8.0 Hz,1H, ArH), 7.41–7.48 (m, 4H, —NH-exchangeable with D_2O + 3ArH), 7.76 (d, J = 3.2 Hz, 1H, ArH), 8.11 (d, J = 8.8 Hz, 1H, ArH), 8.25 (s, 1H, triazole—H), 8.36 (d, J = 5.2 Hz, 1H, ArH), 9.93 (s, 1H, —CHO); ^{13}C NMR (100 MHz, DMSO-d_6): δ ppm = 42.8, 48.4, 61.7,99.3, 112.8, 113.6, 117.6, 120.8, 125.8, 127.3, 128.6, 129.5, 131.0, 135.8, 140.8, 142.3, 144.3, 149.8, 152.8, 157.8, 190.5. HRMS Calculated for $C_{21}H_{17}BrClN_5O_2$ [M+1] 486.0254 and [M+3] 488.0254 found 486.0244 and 486.0269; Anal. Calcd. (%) for: C, 51.82; H, 3.52; N, 14.39; Found: C, 51.71; H, 3.66; N, 14.27.

*3.1.12. 2-bromo-5-((1-(3-((7-chloroquinolin-4-yl)amino)propyl)-1H-1,2,3-triazol-4-yl)methoxy)benzaldehyde **(17b)***

White Solid; Yield: 85%; ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.91–2.00 (m, 2H, —CH_2—), 3.32–3.36 (m, 2H, —N—CH_2—), 4.60–4.63 (m, 2H, —N—CH_2—), 5.11 (s, 2H, —O—CH_2—), 6.58 (d, J = 4.8 Hz, 1H, ArH), 7.30 (dd, J = 2.7, 9.0 Hz, 1H, ArH), 7.38–7.48 (m, 4H, —NH-exchangeable with D_2O + 3ArH), 7.76 (d, J = 3.0 Hz, 1H, ArH), 8.14 (d, J = 9.0 Hz, 1H, ArH), 8.23 (s, 1H, triazole—H), 8.37 (d, J = 4.8 Hz, 1H, ArH), 9.89 (s, 1H, —CHO); ^{13}C NMR (100 MHz, DMSO-d_6): δ ppm = 28.9, 42.7, 48.6, 62.0,99.5, 113.0, 113.6, 118.3, 121.0, 125.6, 127.2, 128.6, 129.4, 130.9, 135.5, 141.3, 142.4, 144.6, 150.2, 153.0, 157.9, 191.1. HRMS Calculated for $C_{22}H_{19}BrClN_5O_2$ [M+1] 500.0411 and [M+3] 502.0411 found 500.0401 and 502.0403; Anal. Calcd. (%) for: C, 52.77; H, 3.82; N, 13.99; Found: C, 52.87; H, 3.66; N, 13.90.

*3.1.13. 2-bromo-5-((1-(2-(4-(7-chloroquinolin-4-yl)piperazin-1-yl)ethyl)-1H-1,2,3-triazol-4-yl)methoxy)benzaldehyde **(22)***

White Solid; Yield: 85%; ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.12 (s, 4H, 2 × —N—CH_2—), 3.74 (s, 4H, 2 × —N—CH_2—), 4.17–4.28 (m, 4H, 2 × —N—CH_2—), 5.15 (s, 2H, —O—CH_2—), 6.65 (d, J = 5.1 Hz, 1H, ArH), 7.22 (dd, J = 2.4, 8.7 Hz,1H, ArH), 7.32–7.42 (m, 3H, ArH), 7.60 (d, J = 2.4 Hz, 1H, ArH), 8.04 (d, J = 9.0 Hz, 1H, ArH), 8.32 (s, 1H, triazole—H), 8.40 (d, J = 5.1 Hz, 1H, ArH), 10.01 (s, 1H, —CHO); ^{13}C NMR (100 MHz, DMSO-d_6): δ ppm = 49.0, 50.8, 52.7, 57.1, 70.2, 106.4, 112.7, 113.3, 119.2, 121.3, 125.1, 127.0, 128.9, 130.1, 132.2, 135.4, 142.0, 142.6, 145.3, 150.0, 152.8, 158.4, 190.6. HRMS Calculated for $C_{25}H_{24}ClBrN_6O_2$ [M+1] 555.0833 and [M+3] 557.0833 found 555.0849 and 557.0842; Anal. Calcd. (%) for: C, 54.02; H, 4.35; N, 15.12; Found: C, 54.11; H, 4.50; N, 15.04.

*3.2. General procedure for the synthesis of compounds **4/9/14/18/23***

Nitrogen was bubbled through the solution of **3/8/13/17/22**(1 mmol) in 1,4-dioxane for 15 min.. Potassium acetate (3 mmol), Pd(dppf)Cl_2 (0.1 mmol) and bis(pinacolato)diboron (1.5 mmol) were added and the reaction mixture was allowed to stir for 16–20 h at 100 °C under N_2. The reaction monitored by TLC and reaction mixture was evaporated under reduced pressure to dryness. The residue was purified *via* column chromatography using 60–120 silica gel to afford desired product as yellow waxy solid.

*3.2.1. 5-((1-(3-phenoxypropyl)-1H-1,2,3-triazol-4-yl)methoxy)-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzaldehyde **(4a)***

Yellow waxy Solid; Yield: 78%; ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.29 (s, 12H, 4 × —CH_3), 2.43–2.48 (m, 2H, —CH_2—), 3.98–4.02 (m, 2H, —N—CH_2—), 4.51–4.54 (m, 2H, —O—CH_2—), 5.24 (s, 2H, —O—CH_2—), 6.80 (d, J = 8.0 Hz, 2H, ArH), 6.90 (t, J = 7.5 Hz, 1H, ArH), 6.95 (d, J = 2.5 Hz, 1H, ArH), 7.28–7.39 (m, 3H, ArH),7.63 (s, 1H, triazole—H), 8.12 (d, J = 8.0 Hz, 1H, ArH), 9.88 (s, 1H, —CHO); ^{13}C NMR (125 MHz, DMSO-d_6): δ ppm = 22.8, 29.6, 51.0, 63.0, 69.2, 92.5, 113.7, 114.4, 120.0, 121.1, 128.4, 129.5, 132.0, 134.5, 137.6, 142.8, 158.7, 159.8, 191.4. HRMS Calculated for $C_{25}H_{30}BN_3O_5$ [M+1] 464.2279 found 464.2268; Anal. Calcd. (%) for: C, 64.81; H, 6.53; N, 9.07; Found: C, 64.73; H, 6.39; N, 8.95.

*3.2.2. 5-((1-(4-phenoxybutyl)-1H-1,2,3-triazol-4-yl)methoxy)-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzaldehyde **(4b)***

Yellow waxy Solid; Yield: 80%; ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.27 (s, 12H, 4 × —CH_3), 1.78–1.84 (m, 2H, —CH_2—), 2.07–2.14 (m, 2H, —CH_2—), 4.01–4.04 (m, 2H, —N—CH_2—), 4.46–4.49 (m, 2H, —O—CH_2—), 5.18 (s, 2H, —O—CH_2—), 6.76 (d, J = 8.0 Hz, 2H, ArH), 6.92–6.97 (m, 2H, ArH), 7.25–7.35 (m, 3H, ArH), 7.66 (s, 1H, triazole—H), 8.11 (d, J = 8.0 Hz, 1H, ArH), 9.80 (s, 1H, —CHO); ^{13}C NMR (125 MHz, DMSO-d_6): δ ppm = 23.0, 26.2, 27.0, 50.8, 62.9, 69.4, 92.3, 113.9, 114.5, 120.3, 121.0, 128.2, 129.5, 132.1, 134.3, 137.5, 143.0, 158.6, 160.2, 191.0. HRMS Calculated for $C_{26}H_{32}BN_3O_5$ [M+1] 478.2435 found 478.2448; Anal.Calcd. (%) for: C, 65.42; H, 6.76; N, 8.80; Found: C, 65.30; H, 6.69; N, 8.91.

*3.2.3. ((1-(5-phenoxypentyl)-1H-1,2,3-triazol-4-yl)methoxy)-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzaldehyde **(4c)***

Yellow waxy Solid; Yield: 71%; ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.33 (s, 12H, 4 × —CH_3), 1.55–1.64 (m, 2H, —CH_2—), 1.83–1.89 (m, 2H, —CH_2—), 2.14–2.19 (m, 2H, —CH_2—), 4.09–4.12 (m, 2H, —N—CH_2—), 4.52–4.55 (m, 2H, —O—CH_2—), 5.23 (s, 2H, —O—CH_2—), 6.82 (d, J = 8.0 Hz,2H, ArH), 6.95–6.99 (m, 2H, ArH), 7.26–7.35 (m, 3H, ArH), 7.60 (s, 1H, triazole—H), 8.19 (d, J = 8.0 Hz, 1H, ArH), 9.93 (s, 1H, —CHO); ^{13}C NMR (125 MHz, DMSO-d_6): δ ppm = 22.6, 23.5, 28.5, 29.6, 50.1, 62.8, 69.0, 92.1, 113.6, 114.2, 120.3, 121.1, 128.1, 129.6, 132.0, 133.9, 137.3, 143.1, 158.9, 160.0, 191.2. HRMS Calculated for $C_{27}H_{34}BN_3O_5$ [M+1] 492.2592 found 492.2584; Anal.Calcd. (%) for: C, 66.00; H, 6.97; N, 8.55; Found: C, 65.14; H, 7.07; N, 8.72.

*3.2.4. 5-((1-(6-phenoxyhexyl)-1H-1,2,3-triazol-4-yl)methoxy)-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzaldehyde **(4d)***

Yellow waxy Solid; Yield: 75%; ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.20 (s, 12H, 4 × —CH_3), 1.25–1.32 (m, 2H, —CH_2—), 1.60–1.68 (m, 2H, —CH_2—), 1.81–1.88 (m, 2H, —CH_2—), 2.02–2.10 (m, 2H, —CH_2—), 4.05–4.08 (m, 2H, —N—CH_2—), 4.55–4.58 (m, 2H, —O—CH_2—), 5.26 (s, 2H, —O—CH_2—), 6.77 (d, J = 8.0 Hz, 2H, ArH), 6.90–6.95 (m, 2H, ArH), 7.24–7.33 (m, 3H, ArH),7.62 (s, 1H, triazole—H), 8.13 (d, J = 8.0 Hz, 1H, ArH), 10.00 (s, 1H, —CHO); ^{13}C NMR (125 MHz, DMSO-d_6): δ ppm = 23.2, 25.0, 27.3, 28.8, 29.7, 51.0, 63.1, 69.5, 92.5, 113.8, 114.5, 120.6, 121.2, 128.0, 129.4, 132.1, 134.0, 137.3, 142.7, 158.8, 160.2, 190.9. HRMS Calculated for $C_{28}H_{36}BN_3O_5$ [M+1] 506.2748 found 506.2763; Anal.Calcd. (%) for: C, 66.54; H, 7.18; N, 8.31; Found: C, 66.60; H, 7.10; N, 8.18.

*3.2.5. 5-((1-(3-(naphthalen-1-yloxy)propyl)-1H-1,2,3-triazol-4-yl)methoxy)-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzaldehyde **(4e)***

Yellow waxy Solid; Yield: 79%; ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.25 (s, 12H, 4 × —CH_3), 2.32–2.37 (m, 2H, —CH_2—), 4.00–4.04 (m, 2H, —N—CH_2—), 4.52–4.55 (m, 2H, —O—CH_2—), 5.23 (s, 2H, —O—CH_2—), 6.71 (d, J = 8.0 Hz, 1H, ArH), 6.90 (d, J = 2.0 Hz, 1H, ArH), 7.29–7.45 (m, 6H, ArH), 7.60 (s, 1H, triazole—H), 7.79 (d, J = 6.0 Hz, 1H, ArH), 8.20 (d, J = 8.5 Hz, 1H, ArH); 9.78 (s, 1H, —CHO); ^{13}C NMR (125 MHz, DMSO-d_6): δ ppm = 22.7, 28.6, 48.9, 62.5, 69.0, 92.8, 106.0, 114.4, 120.0, 121.3, 123.2, 125.3, 125.9, 126.4, 127.5, 128.3, 131.0, 132.1, 133.9, 134.6, 137.1, 142.3, 155.0, 159.7, 191.3. HRMS Calculated for $C_{29}H_{32}BN_3O_5$ [M+1] 514.2435 found 514.2448; Anal. Calcd. (%) for: C, 67.85; H, 6.28; N, 8.18; Found: C, 67.96; H, 6.45; N, 8.31.

*3.2.6. 5-((1-(4-(naphthalen-1-yloxy)butyl)-1H-1,2,3-triazol-4-yl)methoxy)-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzaldehyde **(4f)***

Yellow waxy Solid; Yield: 74%; ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.22 (s, 12H, 4 × —CH_3), 1.82–1.88 (m, 2H, —CH_2—), 2.12–2.18 (m, 2H, —CH_2—), 4.06–4.09 (m, 2H, —N—CH_2—), 4.48–4.51 (m, 2H, —O—CH_2—), 5.19 (s, 2H, —O—CH_2—), 6.78 (d, J = 8.0 Hz, 1H, ArH), 6.95 (d, J = 2.0 Hz, 1H, ArH), 7.31–7.47 (m, 6H, ArH), 7.66 (s, 1H, triazole—H), 7.82 (d, J = 6.0 Hz, 1H, ArH), 8.12 (d, J = 8.0 Hz, 1H, ArH); 9.91 (s, 1H, —CHO); ^{13}C NMR (125 MHz, DMSO-d_6): δ ppm = 23.1, 26.3, 27.4,50.0, 62.6, 68.8, 92.7, 106.4, 114.2, 120.1, 121.4, 123.0, 125.2, 125.5, 126.6, 127.4, 128.3, 131.1, 132.3, 134.3, 134.9, 137.0, 142.3, 155.1, 159.6, 191.0. HRMS Calculated for $C_{30}H_{34}BN_3O_5$ [M+1] 528.2592 found 528.2582; Anal.Calcd. (%) for: C, 68.32; H, 6.50; N, 7.97; Found: C, 68.50; H, 6.41; N, 8.09.

*3.2.7. 5-((1-(5-(naphthalen-1-yloxy)pentyl)-1H-1,2,3-triazol-4-yl) methoxy)-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzaldehyde **(4 g)***

Yellow waxy Solid; Yield: 70%; ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.27 (s, 12H, 4 × —CH_3), 1.60–1.61 (m, 2H, —CH_2-), 2.00–2.09 (m, 4H, 2 × —CH_2—), 4.13–4.16 (m, 2H, —N—CH_2—), 4.42–4.45 (m, 2H, —O—CH_2—), 5.25 (s, 2H, —O—CH_2—), 6.80 (d, *J* = 8.0 Hz, 1H, ArH), 6.89 (d, *J* = 1.5 Hz, 1H, ArH), 7.36–7.48 (m, 6H, ArH), 7.62 (s, 1H, triazole—H), 7.80 (d, *J* = 6.0 Hz, 1H, ArH), 8.23 (d, *J* = 8.5 Hz, 1H, ArH); 9.98 (s, 1H, —CHO); ^{13}C NMR (125 MHz, DMSO-d_6): δ ppm = ^{13}C NMR (125 MHz, DMSO-d_6): δ ppm = 22.6, 23.5, 28.7, 29.8,50.2, 62.3, 69.2, 93.4, 106.5, 114.2, 120.5, 121.6, 123.1, 125.2, 125.8, 126.3, 127.4, 128.1, 131.1, 132.3, 133.9, 134.5, 137.2, 142.0, 154.8, 159.9, 190.7.HRMS Calculated for $C_{31}H_{36}BN_3O_5$ [M+1] 542.2748 found 542.2762; Anal.Calcd. (%) for: C, 68.77; H, 6.70; N, 7.76; Found: C, 68.61; H, 6.59; N, 7.90.

*3.2.8. 5-((1-(6-(naphthalen-1-yloxy)hexyl)-1H-1,2,3-triazol-4-yl) methoxy)-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzaldehyde **(4 h)***

Yellow waxy Solid; Yield: 72%; ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.22 (s, 12H, 4 × —CH_3), 1.52–1.60 (m, 2H, —CH_2—), 1.84–1.89 (m, 2H, —CH_2—), 2.10–2.16 (m, 2H, —CH_2—), 4.10–4.13 (m, 2H, —N—CH_2—), 4.55–4.58 (m, 2H, —O—CH_2—), 5.25 (s, 2H, —O—CH_2—), 6.75 (d, *J* = 8.0 Hz, 1H, ArH), 6.93 (d, *J* = 2.0 Hz, 1H, ArH), 7.35–7.49 (m, 6H, ArH), 7.61 (s, 1H, triazole—H), 7.83 (d, *J* = 6.0 Hz, 1H, ArH), 8.22 (d, *J* = 8.5 Hz, 1H, ArH); 9.99 (s, 1H, —CHO); ^{13}C NMR (125 MHz, DMSO-d_6): δ ppm = 23.1, 25.2, 27.6, 29.0, 30.1,51.0, 63.0, 68.7, 93.2, 106.3, 114.2, 120.1, 121.4, 123.1, 125.2, 125.6, 126.3, 127.6, 128.2, 131.2, 132.2, 133.8, 134.6, 137.0, 142.5, 155.4, 160.3, 191.5. HRMS Calculated for $C_{32}H_{38}BN_3O_5$ [M+1] 556.2905 found 556.2915; Anal.Calcd. (%) for: C, 69.19; H, 6.90; N, 7.56; Found: C, 69.30; H, 6.99; N, 7.38.

*3.2.9. 5-((1-benzyl-1H-1,2,3-triazol-4-yl)methoxy)-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzaldehyde **(9)***

Yellow waxy Solid; Yield: 69%; ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.24 (s, 12H, 4 × —CH_3), 5.25 (s, 2H, —N—CH_2—), 5.50 (s, 2H, —O—CH_2—), 6.90 (d, *J* = 8.0 Hz, 2H, ArH), 7.27–7.33 (m, 3H, ArH), 7.45–7.50 (m, 2H, ArH), 7.65 (s, 1H, triazole—H), 7.85 (d, *J* = 8.0 Hz, 1H, ArH), 10.2 (s, 1H, —CHO); ^{13}C NMR (125 MHz, DMSO-d_6): δ ppm = 23.3, 55.0, 70.0, 92.0, 114.5, 120.7, 122.2, 125.9, 127.8, 128.4, 129.4, 131.6, 134.2, 139.0, 143.7, 161.2, 191.6. HRMS Calculated for $C_{23}H_{26}BN_3O_4$ [M+1] 420.2016 found 420.2007; Anal.Calcd. (%) for: C, 65.89; H, 6.25; N, 10.02; Found: C, 65.70; H, 6.13; N, 10.19.

*3.2.10. 5-((1-(7-chloroquinolin-4-yl)-1H-1,2,3-triazol-4-yl)methoxy)-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzaldehyde **(14)***

Yellow waxy Solid; Yield: 72%; ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.21 (s, 12H, 4 × —CH_3), 5.30 (s, 2H, —O—CH_2—), 7.20–23 (m, 2H, ArH), 7.77 (dd, *J* = 2.5, 8.5 Hz, 1H, ArH), 7.88–7.92 (m, 2H, ArH), 8.09 (d, *J* = 9.0 Hz, 1H, ArH), 8.23 (d, *J* = 2.5 Hz, 1H, ArH), 8.88 (s, 1H, triazole—H), 9.11 (d, *J* = 5.0 Hz, 1H, ArH), 10.2 (s, 1H, —CHO); ^{13}C NMR (125 MHz, DMSO-d_6): δ ppm = 25.2, 68.8, 91.5, 99.4, 114.6, 117.9, 122.0, 123.1, 124.4, 124.9, 125.7, 128.0, 130.9, 134.0, 138.1, 142.7, 149.4, 150.2, 152.4, 159.0. HRMS Calculated for $C_{25}H_{24}BClN_4O_4$ [M+1] 491.1579 and [M+3] 493.1579 found 491.1590 and 493.1571; Anal. Calcd. (%) for: C, 61.19; H, 4.93; N, 11.42; Found: C, 61.33; H, 4.90; N, 11.52.

*3.2.11. 5-((1-(2-((7-chloroquinolin-4-yl)amino)ethyl)-1H-1,2,3-triazol-4-yl)methoxy)-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzaldehyde **(18a)***

Yellow waxy Solid; Yield: 69%; ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.24 (s, 12H, 4 × —CH_3), 3.34–3.37 (m, 2H, —N—CH_2—), 4.60–4.63 (m, 2H, —N—CH_2—), 5.20 (s, 2H, —O—CH_2—), 6.54 (d, *J* = 5.1 Hz, 1H, ArH), 7.29 (dd, *J* = 2.7, 8.4 Hz,1H, ArH), 7.36–7.42 (m, 4H, —NH-exchangeable with D_2O + 3ArH), 7.84 (d, *J* = 3.0 Hz, 1H, ArH), 8.09 (d, *J* = 8.7 Hz, 1H, ArH), 8.33 (s, 1H, triazole—H), 8.41 (d, *J* = 5.1 Hz, 1H, ArH), 9.90 (s, 1H, —CHO); ^{13}C NMR (100 MHz, DMSO-d_6): δ ppm = 25.4, 42.8, 48.4, 61.8, 92.2, 99.4, 114.6, 117.9, 122.0, 123.1, 124.4, 124.9, 125.9, 128.2, 130.7, 134.1, 138.2, 142.4, 149.2, 150.1, 152.0, 158.6. HRMS Calculated for $C_{27}H_{29}BClN_5O_4$ [M+1] 534.2001 and [M+3] 536.2001 found 534.2015 and 536.2018; Anal. Calcd. (%) for: C, 60.75; H, 5.48; N, 13.12; Found: C, 60.67; H, 5.35; N, 13.26.

*3.2.12. 5-((1-(3-((7-chloroquinolin-4-yl)amino)propyl)-1H-1,2,3-triazol-4-yl)methoxy)-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) benzaldehyde **(18b)***

Yellow waxy Solid; Yield: 74%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.28 (s, 12H, 4 × —CH_3), 3.40–3.45 (m, 2H, —N—CH_2—), 4.62–4.66 (m, 2H, —N—CH_2—), 5.22 (s, 2H, —O—CH_2—), 6.61 (d, *J* = 5.2 Hz, 1H, ArH), 7.24 (dd, *J* = 2.8, 8.8 Hz,1H, ArH), 7.39–7.46 (m, 4H, —NH-exchangeable with D_2O + 3ArH), 7.89 (d, *J* = 2.8 Hz, 1H, ArH), 8.13 (d, *J* = 8.8 Hz, 1H, ArH), 8.25 (s, 1H, triazole—H), 8.44 (d, *J* = 5.2 Hz, 1H, ArH), 9.97 (s, 1H, —CHO); ^{13}C NMR (100 MHz, DMSO-d_6): δ ppm = 25.4, 28.6, 43.1, 48.7, 62.0, 92.0, 98.9, 114.4, 117.8, 121.9, 123.1, 124.5, 125.2, 125.6, 128.1, 131.3, 134.2, 138.0, 142.8, 149.1, 150.4, 152.5, 158.8. HRMS Calculated for $C_{28}H_{31}BClN_5O_4$ [M+1] 548.2158 and [M+3] 550.2158 found 548.2172 and 550.2151; Anal. Calcd. (%) for: C, 61.39; H, 5.70; N, 12.78; Found: C, 61.30; H, 5.51; N, 12.62.

*3.2.13. 2-bromo-5-((1-(2-(4-(7-chloroquinolin-4-yl)piperazin-1-yl)ethyl)-1H-1,2,3-triazol-4-yl)methoxy)benzaldehyde **(23)***

Yellow waxy Solid; Yield: 65%; ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.10 (s, 4H, 2 × —N—CH_2—), 3.75 (s, 4H, 2 × —N—CH_2—), 4.10–4.18 (m, 4H, 2 × —N—CH_2—), 5.19 (s, 2H, —O—CH_2—), 6.66 (d, *J* = 5.1 Hz, 1H, ArH), 7.31 (dd, *J* = 2.7, 8.7 Hz,1H, ArH), 7.38–7.47 (m, 3H, ArH), 7.68 (d, *J* = 2.4 Hz, 1H, ArH), 8.10 (d, *J* = 9.0 Hz, 1H, ArH), 8.28 (s, 1H, triazole—H), 8.42 (d, *J* = 5.1 Hz, 1H, ArH), 10.12 (s, 1H, —CHO); ^{13}C NMR (100 MHz, DMSO-d_6): δ ppm = 25.1, 48.6, 51.1, 52.9, 57.0, 68.9, 92.1, 99.0, 114.5, 119.3, 123.9, 124.1, 124.5, 125.2, 125.9, 128.1, 131.0, 134.5, 137.7, 142.0, 148.6, 149.9, 152.1, 159.2, 191.3. HRMS Calculated for $C_{31}H_{36}ClBN_6O_4$ [M+1] 603.2580 and [M+3] 605.2580 found 603.2567 and 605.2571; Anal. Calcd. (%) for: C, 61.76; H, 6.02; N, 13.94; Found: C, 61.85; H, 6.18; N, 14.13.

*3.3. General procedure for the synthesis of compounds **5/10/15/19/24***

To the stirred solution of **4/9/14/18/23** (1 mmol) in methanol, add slowly $NaBH_4$ powder (1 mmol) at 0–10 °C. The reaction mixture was stirredfor1 h at rt. Then, reduce the volume of reaction mixture at low temperature under reduced pressure to one-third of methanol. The resulting mixture was further cooled to 0 °C and acidified with diluted HCl up to pH 3. Add 2-two-fold cold water to the acidified reaction mixture. The white precipitate was collected, wash firstly with H_2O and then with MeOH/water mixture, and finally dried to give pure product.

*3.3.1. 5-((1-(3-phenoxypropyl)-1H-1,2,3-triazol-4-yl)methoxy)benzo[c][1,2]oxaborol-1(3H)-ol **(5a)***

White Solid; Yield: 68%; ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.42–2.45 (m, 2H, —CH_2—), 3.97–3.98 (m, 2H, —N—CH_2—), 4.61–4.63 (m, 2H, —O—CH_2—), 5.00 (s, 2H, —O—CH_2—), 5.27 (s, 2H, —O—CH_2—), 5.34 (s, 1H, —OH exchangeable with D_2O), 6.87–6.89 (m, 2H, ArH), 6.95–6.98 (m, 3H, ArH), 7.28–7.31(m, 2H, ArH), 7.64–7.66 (m, 2H, ArH); ^{13}C NMR (125 MHz, DMSO-d_6): δ ppm = 29.8, 49.8, 62.3, 67.0, 70.3, 106.8, 114.2, 115.0, 120.9, 122.4, 129.6, 132.0, 138.7, 142.6, 144.1, 158.3, 160.8. HRMS Calculated for $C_{19}H_{20}BN_3O_4$ [M+1] 366.1547 found 366.1531; Anal.Calcd. (%) for: C, 62.49; H, 5.52; N, 11.51; Found: C, 62.35; H, 5.61; N, 11.40.

*3.3.2. 5-((1-(4-phenoxybutyl)-1H-1,2,3-triazol-4-yl)methoxy)benzo[c][1,2]oxaborol-1(3H)-ol (**5b**)*

White Solid; Yield: 70%; ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.87–1.93 (m,2H, —CH_2—), 2.10–2.15 (m, 2H, —CH_2—), 4.04–4.07 (m, 2H, —N—CH_2—), 4.51–4.54 (m, 2H, —O—CH_2—),5.02 (s, 2H, —O—CH_2—), 5.24 (s, 2H, —O—CH_2—), 5.39 (s, 1H, —OH exchangeable with D_2O), 6.90–6.93 (m, 2H, ArH), 7.01–7.05 (m, 3H, ArH), 7.24–7.29 (m, 2H, ArH), 7.63–7.67 (m, 2H, ArH); ^{13}C NMR (125 MHz, DMSO-d_6): δ ppm = 26.4, 27.3, 50.0, 62.0, 67.4, 70.1, 106.7, 114.1, 115.2, 120.8, 122.2, 129.3, 132.1, 138.8, 142.5, 144.2, 158.6, 160.9. HRMS Calculated for $C_{20}H_{22}BN_3O_4$ [M+1] 380.1703 found 380.1710; Anal.Calcd. (%) for: C, 63.35; H, 5.85; N, 11.08; Found: C, 63.45; H, 5.71; N, 11.20.

*3.3.3. 5-((1-(5-phenoxypentyl)-1H-1,2,3-triazol-4-yl)methoxy)benzo[c][1,2]oxaborol-1(3H)-ol (**5c**)*

White Solid; Yield: 63%; ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.55–1.59 (m, 2H, —CH_2—), 1.88–1.95 (m, 2H, —CH_2—), 2.02–2.09 (m, 2H, —CH_2—), 4.05–4.08 (m, 2H, —N—CH_2—), 4.51–4.54 (m, 2H, —O—CH_2—), 5.06 (s, 2H, —O—CH_2—), 5.27 (s, 2H, —O—CH_2—), 5.35 (s, 1H, —OH exchangeable with D_2O), 6.88–6.91 (m, 2H, ArH), 6.99–7.03 (m, 3H, ArH), 7.26–7.32(m, 2H, ArH), 7.60–7.64 (m, 2H, ArH); ^{13}C NMR (125 MHz, DMSO-d_6): δ ppm = 23.2, 28.6, 29.9, 50.3, 62.1, 67.1, 70.8, 106.6, 114.4, 115.1, 120.7, 122.5, 129.4, 131.8, 139.2, 142.7, 143.9, 158.8, 161.0. HRMS Calculated for $C_{21}H_{24}BN_3O_4$ [M+1] 394.1860 found 394.1845; Anal.Calcd. (%) for: C, 64.14; H, 6.15; N, 10.69; Found: C, 64.01; H, 6.06; N, 10.60.

*3.3.4. 5-((1-(6-phenoxyhexyl)-1H-1,2,3-triazol-4-yl)methoxy)benzo[c][1,2]oxaborol-1(3H)-ol (**5d**)*

White Solid; Yield: 65%; ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.22–1.28 (m, 2H, —CH_2—), 1.58–1.65 (m, 2H, —CH_2—), 1.83–1.89 (m, 2H, —CH_2—), 2.03–2.08 (m, 2H, —CH_2—), 3.97–4.00 (m, 2H, —N—CH_2—), 4.42–4.45 (m, 2H, —O—CH_2—), 5.05 (s, 2H, —O—CH_2—), 5.26 (s, 2H, —O—CH_2—), 5.34 (s, 1H, —OH exchangeable with D_2O), 6.85–6.89 (m, 2H, ArH), 6.94–6.98 (m, 3H, ArH), 7.29–7.93(m, 2H, ArH), 7.58–7.62 (m, 2H, ArH); ^{13}C NMR (125 MHz, DMSO-d_6): δ ppm = 25.8, 27.4, 28.9, 29.6, 49.9, 62.2, 67.0, 70.2, 106.4, 114.5, 115.0, 120.9, 122.0, 129.2, 132.0, 138.7, 142.3, 143.8, 158.9, 161.0. HRMS Calculated for $C_{22}H_{26}BN_3O_4$ [M+1] 408.2016 found 408.2024; Anal.Calcd. (%) for: C, 64.88; H, 6.43; N, 10.32; Found: C, 64.78; H, 6.29; N, 10.41.

*3.3.5. 5-((1-(3-(naphthalen-1-yloxy)propyl)-1H-1,2,3-triazol-4-yl)methoxy)benzo[c][1,2]oxaborol-1(3H)-ol (**5e**)*

White Solid; Yield: 65%; ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.54–2.58 (m, 2H, —CH_2—), 4.14–4.17 (m, 2H, —N—CH_2—),4.66 (s, 2H, —CH_2—O—), 4.69–4.72 (m, 2H, —O—CH_2—), 5.04 (s, 1H, —OH exchangeable with D_2O), 5.19 (s, 2H, —O—CH_2—), 6.76 (d, J = 7.5 Hz, 1H, ArH), 6.86–7.00 (m, 2H, ArH), 7.24 (t, J = 8.0 Hz, 1H, ArH), 7.36 (t, J = 8.0 Hz, 1H, ArH), 7.47 (d, J = 8.5 Hz,1H, ArH), 7.50–7.53 (m, 2H, ArH), 7.62 (s, 1H, triazole—H), 7.83 (d, J = 7.0 Hz, 1H, ArH), 8.23 (d, J = 7.0 Hz, 1H, ArH); ^{13}C NMR (125 MHz, DMSO-d_6): δ ppm = 29.9, 47.4, 61.9, 64.1, 65.0, 104.7, 113.1, 113.9, 119.6, 120.7, 121.6, 123.2, 125.40, 125.44, 125.8, 126.5, 127.6, 129.6, 134.5, 142.7, 144.2, 153.9, 158.4. HRMS Calculated for $C_{23}H_{22}BN_3O_4$ [M+1] 416.1703 found 416.1714; Anal.Calcd. (%) for: C, 66.53; H, 5.34; N, 10.12; Found: C, 66.60; H, 5.22; N, 10.05.

*3.3.6. 5-((1-(4-(naphthalen-1-yloxy)butyl)-1H-1,2,3-triazol-4-gyl)methoxy)benzo[c][1,2]oxaborol-1(3H)-ol (**5f**)*

White Solid; Yield: 67%; ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.77–1.84 (m, 2H, —CH_2—), 2.08–2.17 (m, 2H, —CH_2—), 3.95–3.98 (m, 2H, —N—CH_2—), 4.43–4.47 (m, 2H,—O—CH_2—), 5.02 (s, 2H, —O—CH_2—), 5.24 (s, 2H, —CH_2—O—), 5.36 (s, 1H, —OH exchangeable with D_2O), 6.84–6.89 (m, 2H, ArH), 6.91–6.98 (m, 3H, ArH), 7.24–7.28 (m, 4H, ArH), 7.62–7.64 (m, 2H, ArH); ^{13}C NMR (125 MHz, DMSO-d_6): δ ppm = 26.3, 27.6, 49.1, 61.5, 65.1, 66.4, 105.0, 112.9, 113.6, 119.5, 120.5, 121.5, 123.3, 125.3, 125.4, 125.9, 126.4, 127.8, 129.3, 134.4, 142.7, 144.6, 154.3, 159.0. HRMS Calculated for $C_{24}H_{24}BN_3O_4$ [M+1] 430.1860 found 430.1849; Anal.Calcd. (%) for: C, 67.15; H, 5.64; N, 9.79; Found: C, 67.03; H, 5.50; N, 9.95.

*3.3.7. 5-((1-(5-(naphthalen-1-yloxy)pentyl)-1H-1,2,3-triazol-4-yl)methoxy)benzo[c][1,2]oxaborol-1(3H)-ol (**5 g**)*

White Solid; Yield: 60%; ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.50–1.56 (m, 2H, —CH_2—), 1.84–1.89 (m, 2H, —CH_2—), 2.01–2.07 (m, 2H, —CH_2—), 3.96–3.99 (m, 2H, —N—CH_2—), 4.42–4.45 (m, 2H, —O—CH_2—), 5.02 (s, 2H, —O—CH_2—), 5.21(s, 2H, —O—CH_2—), 5.32 (s, 1H, —OH exchangeable with D_2O), 6.81–6.85 (m, 2H, ArH), 6.94–6.99 (m, 3H, ArH), 7.23–7.29 (m, 4H, ArH), 7.62–7.64 (m, 2H, ArH); ^{13}C NMR (125 MHz, DMSO-d_6): δ ppm = 23.1, 28.9, 29.6,48.5, 61.9, 65.0, 67.0, 104.6, 113.0, 113.8, 119.6, 120.3, 121.6, 123.8, 125.4, 125.6, 126.0, 126.5, 127.5, 129.1, 134.6, 142.4, 145.0, 154.0, 159.1. HRMS Calculated for $C_{25}H_{26}BN_3O_4$ [M+1] 444.2016 found 444.2019; Anal.Calcd. (%) for: C, 67.73; H, 5.91; N, 9.48; Found: C, 67.84; H, 5.83; N, 9.64.

*3.3.8. 5-((1-(6-(naphthalen-1-yloxy)hexyl)-1H-1,2,3-triazol-4-yl)methoxy)benzo[c][1,2]oxaborol-1(3H)-ol (**5 h**)*

White Solid; Yield: 61%; ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.22–1.27 (m, 2H, —CH_2—), 1.52–1.58 (m, 2H, —CH_2—), 1.89–1.95 (m, 2H, —CH_2—), 2.11–2.017 (m, 2H, —CH_2—), 3.95–3.98 (m, 2H, —N—CH_2—), 4.41–4.43 (m, 2H, —O—CH_2—), 5.01 (s, 2H, —O—CH_2—), 5.22 (s, 2H, —O—CH_2—), 5.30 (s, 1H, —OH exchangeable with D_2O), 6.70 (d, J = 7.5 Hz, 1H, ArH), 6.92–7.00 (m, 2H, ArH), 7.23 (t, J = 8.0 Hz, 1H, ArH), 7.35 (t, J = 8.0 Hz, 1H, ArH), 7.49 (d, J = 8.5 Hz,1H, ArH), 7.52–7.55 (m, 2H, ArH), 7.67 (s, 1H, triazole—H), 7.80 (d, J = 7.0 Hz, 1H, ArH), 8.13 (d, J = 7.0 Hz, 1H, ArH); ^{13}C NMR (125 MHz, DMSO-d_6): δ ppm = 25.8, 27.3, 28.8, 29.7, 48.6, 61.8, 65.9, 68.0, 104.4, 113.2, 113.9, 119.8, 120.9, 121.3, 123.6, 125.1, 125.4, 125.6, 126.9, 127.7, 129.5, 134.3, 142.8, 145.2, 153.9, 159.0. HRMS Calculated for $C_{26}H_{28}BN_3O_4$ [M+1] 458.2173 found 458.2160; Anal.Calcd. (%) for: C, 68.28; H, 6.17; N, 9.19; Found: C, 68.36; H, 6.07; N, 9.30.

*3.3.9. 5-((1-benzyl-1H-1,2,3-triazol-4-yl)methoxy)benzo[c][1,2]oxaborol-1(3H)-ol (**10**)*

White Solid; Yield: 72%; ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.04 (s, 2H, —N—CH_2—), 5.21 (s, 1H, —OH exchangeable with D_2O), 5.25 (s, 2H, —O—CH_2—), 5.55 (s, 2H, —O—CH_2—), 6.94–6.98 (m,2H, ArH), 7.28–7.30 (m, 2H, ArH), 7.38–7.40 (m, 3H, ArH), 7.55 (s, 1H, triazole—H), 7.65 (d, J = 8.0 Hz, 1H, ArH); ^{13}C NMR (125 MHz, DMSO-d_6): δ ppm = 54.3, 62.1, 70.9, 106.6, 115.1, 122.6, 128.1, 128.8, 129.1, 131.7, 134.3, 142.7, 144.3, 156.4, 161.0. HRMS Calculated for $C_{17}H_{16}BN_3O_3$ [M+1] 322.1285 found 322.1272; Anal.Calcd. (%) for: C, 63.58; H, 5.02; N, 13.08; Found: C, 63.65; H, 4.86; N, 13.19.

*3.3.10. 5-((1-(7-chloroquinolin-4-yl)-1H-1,2,3-triazol-4-yl)methoxy)benzo[c][1,2]oxaborol-1(3H)-ol (**15**)*

White Solid; Yield: 75%; ^{1}H NMR (500 MHz, DMSO-d_6): δ 4.16 (ddd, J = 5.0, 14.0, 19.0 Hz, 2H, —O—CH_2—), 5.06 (t, J = 5.5 Hz, 1H, —OH exchangeable with D_2O), 5.37 (s, 2H, —O—CH_2—), 7.02 (m, 2H, ArH), 7.27 (d, J = 2.0 Hz, 1H, ArH), 7.80 (dd, J = 2.0, 9.0 Hz, 1H, ArH), 7.90 (d, J = 5.0 Hz, 1H, ArH), 8.03 (d, J = 9.0 Hz, 1H, ArH), 8.30 (d, J = 3.0 Hz, 1H, ArH), 9.00 (s, 1H, triazole—H), 9.17 (d, J = 5.0 Hz, 1H, ArH); ^{13}C NMR (100 MHz, DMSO-d_6): δ ppm = 61.1, 61.3, 79.6, 112.8, 113.6, 117.6, 120.8, 125.8, 127.3, 128.6, 129.5, 131.0,135.8, 140.8, 142.3, 144.3, 149.8, 152.8, 157.8. HRMS Calculated for $C_{19}H_{14}BClN_4O_3$[M+1] 393.0847 and [M+3] 395.0847 found 393.0839 and 395.0858; Anal. Calcd. (%) for: C, 58.13; H, 3.59; N, 14.27; Found: C, 58.03; H, 3.73; N, 14.18.

*3.3.11. 5-((1-(2-((7-chloroquinolin-4-yl)amino)ethyl)-1H-1,2,3-triazol-4-yl)methoxy)benzo[c][1,2]oxaborol-1(3H)-ol (**19a**)*

White Solid; Yield: 73%; ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.80–3.82

(m, 2H, —N—CH_2—), 4.44 (s, 2H, —O—CH_2—), 4.66–4.69 (m, 2H, —N—CH_2—), 5.11 (s, 2H, —O—CH_2—), 5.31 (s, 1H, —OH exchangeable with D_2O), 6.57 (d, $J = 5.4$ Hz, 1H,ArH), 6.86 (d, $J = 7.5$ Hz,1H, ArH), 7.19 (s, 1H, ArH), 7.33 (br s, 1H, —NH-exchangeable with D_2O), 7.40–7.57 (m, 2H, ArH), 7.82 (s, 1H, ArH), 8.19 (d, $J = 8.7$ Hz, 1H, ArH), 8.26 (s, 1H, triazole—H), 8.40 (d, $J = 5.2$ Hz, 1H, ArH); ^{13}C NMR (100 MHz, DMSO-d_6): δ ppm = 42.9, 48.3, 61.8, 63.1, 99.4, 114.6, 117.9, 122.0, 123.1, 124.4, 124.9, 125.7, 128.0, 130.9, 134.0, 138.1, 142.7, 149.4, 150.2, 152.4, 159.0. HRMS Calculated for $C_{21}H_{19}BClN_5O_3$ [M+1] 436.1269 and [M+3] 438.1269 found 436.1278 and 438.1282; Anal. Calcd. (%) for: C, 57.89; H, 4.40; N, 16.08; Found: C, 57.75; H, 4.31; N, 15.97.

3.3.12. 5-((1-(3-((7-chloroquinolin-4-yl)amino)propyl)-1H-1,2,3-triazol-4-yl)methoxy)benzo[c][1,2] oxaborol-1(3H)-ol (**19b**)

White Solid; Yield: 68%; ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.94–2.02 (m, 2H, —CH_2—), 3.39–3.42 (m, 2H, —N—CH_2—), 4.57 (s, 2H, —O—CH_2—), 4.65–4.67 (m, 2H, —N—CH_2—), 5.18 (s, 2H, —O—CH_2—), 5.22 (s, 1H, —OH exchangeable with D_2O), 6.52 (d, $J =$ 4.8 Hz, 1H,ArH), 6.89 (dd, $J = 2.4$, 9.0 Hz,1H, ArH), 7.11 (d, $J = 2.4$ Hz,1H, ArH), 7.37–7.45 (m, 3H, —NH-exchangeable with D_2O + 2ArH), 7.85 (d, $J = 2.7$ Hz, 1H, ArH), 8.14 (d, $J = 9.0$ Hz, 1H, ArH), 8.22 (s, 1H, triazole—H), 8.33 (d, $J = 4.8$ Hz, 1H, ArH); ^{13}C NMR (100 MHz, DMSO-d_6): δ ppm = 28.6, 42.1, 48.9, 61.3, 62.1,99.5, 112.8, 113.5, 117.9, 120.6, 125.9, 127.4, 128.3, 129.6, 131.1, 135.8, 140.9, 142.5, 144.6, 149.9, 152.7, 157.9. HRMS Calculated for $C_{22}H_{21}BClN_5O_3$ [M+1] 450.1426 and [M+3] 452.1426 found 450.1413 and 452.1417; Anal. Calcd. (%) for: C, 58.76; H, 4.71; N, 15.57; Found: C, 58.85; H, 4.87; N, 15.40.

3.3.13. 5-((1-(2-(4-(7-chloroquinolin-4-yl)piperazin-1-yl)ethyl)-1H-1,2,3-triazol-4-yl)methoxy)benzo[c][1,2]oxaborol-1(3H)-ol (**24**)

White Solid; Yield: 58%; ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.20 (s, 4H, 2 × —N—CH_2—); 3.71 (s, 4H, 2 × —N—CH_2—); 4.22–4.31 (m, 4H, 2 × —N—CH_2—), 4.95 (s, 2H, —O—CH_2—), 5.21 (s, 2H, —O—CH_2—), 5.30 (s, 1H, —OH exchangeable with D_2O), 6.55 (d, $J = 5.4$ Hz, 1H, ArH), 7.28 (dd, $J = 2.4$, 9.0 Hz,1H, ArH), 7.38–7.47 (m, 3H, ArH), 7.80 (d, $J = 2.4$ Hz, 1H, ArH), 8.01 (d, $J = 9.0$ Hz, 1H, ArH), 8.28 (s, 1H, triazole—H), 8.35 (d, $J = 5.1$ Hz, 1H, ArH); ^{13}C NMR (100 MHz, DMSO-d_6): δ ppm = 49.2, 51.2, 52.6, 57.2, 69.9, 106.5, 112.9, 113.6, 118.4, 121.0, 125.5, 127.0, 128.2, 130.1, 132.0, 135.3, 141.5, 142.9, 145.0, 150.7, 152.8, 158.6. HRMS Calculated for $C_{25}H_{26}BClN_6O_3$ [M+1] 505.1848 and [M+3] 507.1848 found 505.1860 and 507.1839; Anal. Calcd. (%) for: C, 59.49; H, 5.19; N, 16.65; Found: C, 59.32; H, 5.31; N, 16.55.

3.4. Biological evaluation

3.4.1. In vitro antiplasmodial assay

The two *P. falciparum* strains, the chloroquine-susceptible 3D7 (isolated in West Africa; obtained from MR4, VA, USA), and the chloroquine-resistant strain W2 (isolated in Indochina; obtained from MR4, VA, USA), were maintained in culture in RPMI 1640 (Invitrogen, Paisley, UK), supplemented with 10% human serum (Abcys S.A. Paris, France) and buffered with 25 mM HEPES and 25 mM $NaHCO_3$. Parasites were grown in A-positive human blood (EtablissementFrançais du Sang, Marseille, France) under controlled atmospheric conditions that consisted of 10% O_2, 5% CO_2 and 85% N_2 at 37 °C with a humidity of 95%. The two *P. falciparums* trains 3D7 and W2, were synchronized twice with sorbitol before use [25]. The clonality of these strains was verified both in our laboratory and in an independent laboratory from the Worldwide Antimalarial Resistance Network (WWARN) by PCR genotyping of the polymorphic genetic markers *msp1* and *msp2* and microsatellite loci [26,27].

The compounds were re-suspended and then diluted RPMI- DMSO 5% (v/v) to obtain 11 final concentrations ranging from 0.78 nM to 10000 nM (final concentration of 0.5% of DMSO).Stock solution of chloroquine diphosphate (Sigma, Saint Louis, MO, USA) was prepared in water and then diluted in RPMI in order to have 11 final concentrations ranging from 5 nM to 3200 nM. Chloroquine was used for *P. falciparum* activity comparison. For the *in vitro* assay, 25 µl of each concentration of benzoxaborole derivatives or chloroquine were aliquoted with 200 µl of parasitized red blood cells (final parasitemia, 0.1%; final haematocrit, 1.5%) into 96-well plates. The plates were incubated for 72 hr at 37°Cin controlled atmospheric conditions 5% CO_2, 10% O_2 and 75% N_2.After thawing the plates, 50 µl of PBS 1x were added to haemolysed cultures and were homogenized by vortexing the plates. A volume of 50 µl of supernatant was added with 50 µl of lysis buffer containing SYBR Green I (final concentration 20x) (ThermoFisher Scientific, Paisley, UK) in flat bottom black plate (ThermoFisher Scientific, Kamstrupvej, Denmark) in a dark room. The plate was incubated at room temperature in the dark for 24 h. The fluorescence is read at 485 nm and 530 nm (excitation and emission wavelength bands, respectively) using a fluorescent plate reader (Tecan Infinite F200, Lyon, France).

The concentration at which the drugs were able to inhibit 50% of parasite growth (IC_{50}) was calculated with the inhibitory sigmoid E_{max} model, with estimation of the IC_{50} through non-linear regression using a standard function of the R software (IC Estimator version 1.2). The antiplasmodial *in vitro* assay was performed five times for each product. The IC_{50} values represented the mean value calculated from five experiments.

3.4.2. Cytotoxicity assay

Vero kidney epithelial cells (ATCC® CCL-81™) were cultured in RPMI 1640 cell culture medium (Life technologies) supplemented with 10% foetal calf serum and incubated at 37 °C with 5% CO2. Once the desired confluency was achieved, cells were detached from the flask surface using trypsin and centrifuged at 220 × *g* for 5 min at room temperature to pellet cells. The cell pellet was resuspended in 1 mL of culture medium and enumerated using a Malassez counting chamber. Cell density was adjusted to approximately 2×10^4 cells/well in 96-well plates and left to adhere overnight at 37 °C and 5% CO_2. To determine cytotoxicity of synthetic compounds, serial dilutions were performed ranging from 100 µg to 3.1 µg/mL. Cell cultures were placed back in the incubator at 37 °C and 5% CO_2 for 24 h. After incubation, 10% (vol/vol) resazurin was added to each well and left to incubate at 37 °C and 5% CO_2 prior to data acquisition using a fluorescent plate reader (excitation 540 nm, emission 590 nm). DMSO was included as a negative control, while 20% SDS was included as a positive control at the pre-designated concentrations. Data was analysed using Graphpad Prism 5 (Graphphad software). The half maximal inhibitory concentration (IC_{50}) was calculated using a non-linear regression dose response curve. Selectivity Index (SI) was calculated as a function of the IC50/MIC [12].

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bioorg.2021.104733.

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