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Original article

Synthesis and *in vitro* antimalarial activity of tetraoxane-amine/amide conjugates

Nitin Kumar [a], Shabana I. Khan [b,c], Himanshu Atheaya [a], Ritu Mamgain [a], Diwan S. Rawat [a,*]

[a] Department of Chemistry, University of Delhi, Delhi 110007, India
[b] National Centre for Natural Products Research, School of Pharmacy, University of Mississippi, MS 38677, USA
[c] Department of Pharmacognosy, School of Pharmacy, University of Mississippi, MS 38677, USA

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ABSTRACT

A series of tetraoxanes, tetraoxane-amine and tetraoxane-amide conjugates have been synthesized and screened for *in vitro* antimalarial activity against chloroquine-sensitive and chloroquine-resistant strains of *Plasmodium falciparum*. Most of the conjugates showed slightly better antimalarial activity than the parent tetraoxanes. Three of the conjugate compounds were potentially active with IC_{50} values in the range of 0.38–0.80 μM. Cytotoxicity of four selected compounds was also evaluated in a panel of four cancer (SK-MEL, KB, BT-549, SK-OV-3) and two non-cancer (Vero and LLC-PK_{11}) cell lines up to a concentration of 25 μM and none of the compounds was found toxic to any of the cells.

1. Introduction

Malaria is the third most deadly disease after tuberculosis and AIDS. It affects more than 225 million people with 781,000 deaths every year [1,2]. Amongst the four species of *Plasmodium* causing malaria in humans, *Plasmodium falciparum* is the most fatal and responsible for most of the malaria related deaths [3,4]. The problem has been complicated since *P. falciparum* has developed resistance against commonly used antimalarials and no new drug has been launched in last 30 years. Artemisinin and its semi-synthetic derivatives such as dihydroartemisinin, artemether, artether and artesunate are the only alternatives for the treatment of *P. falciparum* related infections [5–7]. However, clinical applications of these compounds have been limited due to their poor bioavailability, poor pharmacokinetic properties, and high cost [8]. Recent report of emergence of *P. falciparum* resistance to artemisinin further complicates the problem [9]. So there is an urgent need for the development of new drugs which can solve the problem of drug resistance and have higher efficacy for the treatment of malaria especially in the developing countries. In recent years, another class of cyclic peroxides namely 1,2,4,5-tetraoxanes has received considerable interest due to their artemisinin like antimalarial activity [10–12]. Some of these compounds have shown very promising activity and entered in the clinical trials [12]. These compounds exhibit antimalarial activity due to their ability to interact with heme or ferrous ions in the acidic food vacuole of the parasite which results in the generation of radical species [13–16]. In order to improve antimalarial activity of peroxide based antimalarials, several possibilities were explored and in one of the approach polar groups that can undergo protonation in the acidic food vacuole of the parasite were attached covalently to the endoperoxides [16–20]. It was hypothesized that this kind of chemical modification would enhance the cellular accumulation of the drug within the acidic food vacuole of the parasite by ion trapping and hence improve the antimalarial activity [21]. In continuation of our work on the development of novel antimalarials [22–26], we herein report the synthesis and antimalarial activity evaluation of tetraoxane and tetraoxane-imine, tetraoxane-amine or amide conjugates.

2. Chemistry

In order to incorporate polar functional groups in the tetraoxane pharmacophore, we explored the possibility of introducing a free CHO group in tetraoxanes, so that a library of compounds can be generated by chemical modification of CHO functionality. Keeping this in mind, we decided to synthesize tetraoxanes which have a free CHO group. Literature survey revealed that there are very few methods available for the synthesis of tetraoxanes. Among these, the acid-catalyzed cyclocondensation of hydrogen peroxides (30%, 50% and 70–90%) with ketones and aldehydes [27–30], ozonolysis of olefins [31], enol-ethers [32], *O*-ether oxime [33], and trimethyl silyltrifluoromethanesulphonate (TMSOTf) [34,35]

* Corresponding author. Tel.: +91 11 27667465; fax: +91 11 27667501.
E-mail address: dsrawat@chemistry.du.ac.in (D.S. Rawat).

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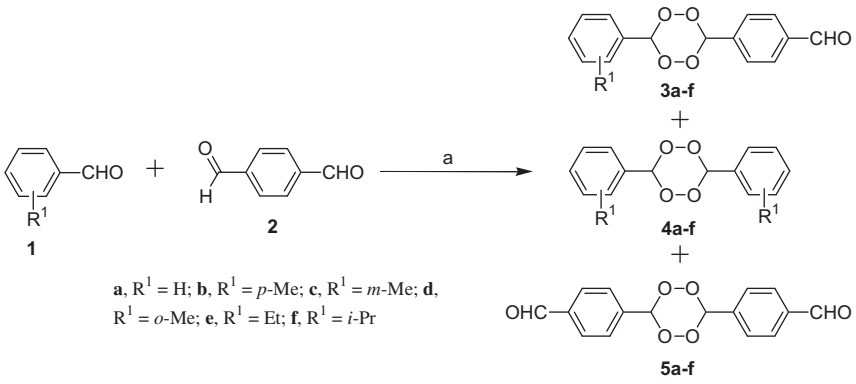


Scheme 1. Reagents and conditions: a) (i) MTO (0.001 equiv), TFE, H_2O_2 (2.0 equiv), 2 h, RT; (ii) **2** (2.0 equiv), $HBF_4{\cdot}Et_2O$ (1.0 equiv), 1 h, RT, 1 h, 32–45%.

catalyzed cyclocondensation of bis (trimethylsilyl) peroxides with carbonyl compounds are the most common methods. The non-symmetrical tetraoxanes have been synthesized by cyclocondensation of the carbonyl compounds with steroids gem-hydroperoxides (H_2SO_4, catalyst) [36], gem-bis(trimethylsillyldioxy) alkanes (TMSOTf catalyst [37]), alicyclic and aliphatic gem-hydroperoxide ($MeReO_3$–HBF_4 catalyst) [38] and cyclocondenstion of carbonyl compounds in the presence of I_2 as a catalyst [22]. Recently Dussault et al. have also reported Re_2O_7 calatyzed synthesis of tetraoxanes [39].

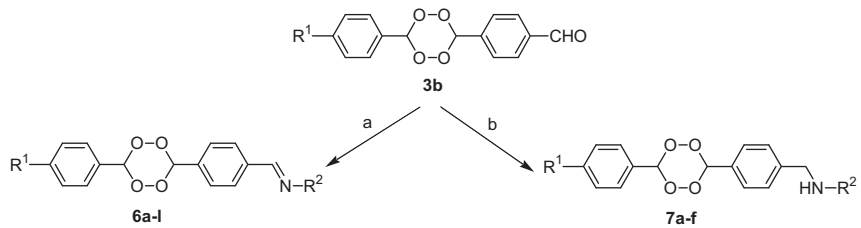
Over all 74 tetraoxanes, tetraoxane-amine and tetraoxane-amide conjugates have been synthesized by literature methods and synthetic route is shown in Schemes 1–4. The starting tetraoxanes (**3a**–**f**) were prepared by the acid-catalyzed peroxidation of substituted benzaldehydes by 30% H_2O_2 in fluorinated alcohol in the presence of MTO as a catalyst (Scheme 1). During the preparation of compounds **3a**–**f**, we noticed the formation of symmetrical tetraoxanes **4a**–**f** and **5a**–**f**. Compounds **3a**–**f** was isolated in 32–45% yield and compounds **4a**–**f** in 27–32% yield. Formation of compounds **5a**–**f** was noticed in LC–MS and all the efforts to isolate compounds **5a**–**f** were unsuccessful. The formation of symmetrical tetraoxanes during the preparation of non-symmetrical tetraoxanes has been reported earlier in low yield [25]. High yield of the symmetrical tetraoxanes (**4a**–**f**) may be due to the low reactivity of terephthalaldehyde under the given reaction conditions. Variations in the reaction conditions did not improve the yield of desired tetraoxanes (**3a**–**f**). The non-symmetrical tetraoxane (**3b**) was converted to corresponding imines as shown in Scheme 2 and amine counterpart of compound **3b** was prepared in moderate yield by the reductive amination as shown in Scheme 2 [40]. In both the cases yield of the desired product was moderate. So we decided to explore an alternative route for the synthesis of tetraoxane-amine conjugates and the synthesis is depicted in Scheme 3. Tetraoxanes (**3a**–**f**) which have a free CHO group were reduced to corresponding alcohols (**8a**–**f**) using $NaBH_4$ as a reducing agent and subsequently compounds **8b** and **8e** were converted to the mesylate derivatives (**9a**, **9b**). The nucleophilic substitution of mesylates (**9a**, **9b**) with substituted amines leads the desired products (**10a**–**w**) in quantitative yield.

Next, we explored the possibility of conversion of tetraoxanes to their amide counterparts. Jones oxidation of compounds **3b** and **3e** afforded the acid derivatives (**11a**, **11b**) in good yield (Scheme 4). The resulting acids were coupled with selected amines *via* a mixed anhydride method to give corresponding amides in good yield (Scheme 4).

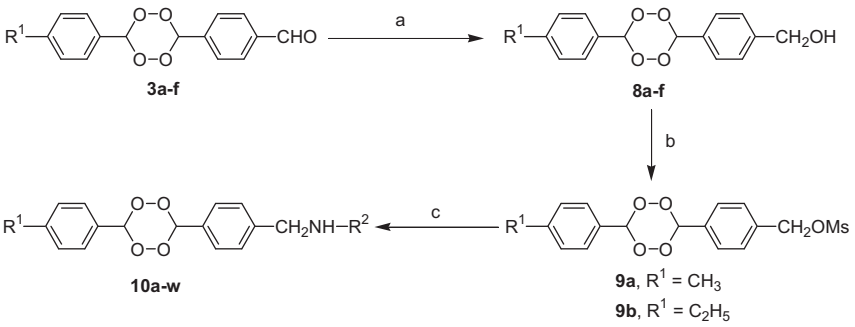
3. Results and discussion

3.1. Biological evaluations

All the synthesized compounds were screened for antimalarial activity against D6 (chloroquine-sensitive) and W2 (chloroquine-resistant) strains of *P. falciparum* and for cytotoxicity towards mammalian kidney cells (Vero cells) up to a highest concentration of 12.5 μM in an *in vitro* assay as described earlier [22,25]. Chloroquine and artemisinin were used as standard drugs for antimalarial activity and doxorubicin was used as standard drug for cytotoxicity. The *in vitro* antimalarial activity was determined on the basis of plasmodial LDH activity as an index of plasmodial growth [41] and expressed as IC_{50} values. Selectivity index (S.I.) of antimalarial activity was calculated based on the cytotoxicity to mammalian cells (S.I. = ratio of IC_{50} of cytotoxicity and IC_{50} of antimalarial activity). Antimalarial activity of all the tetraoxanes (**3a**–**f**, **8a**–**f**, **9a**, **9b**, **11a** and **11b**), tetraoxane-imines (**6a**–**l**), amine and amide conjugates (**6a**–**l**, **7a**–**f**, **10a**–**w**, **12a**–**q**) is shown in Tables 1 and 2. Compounds **3a**–**f**, **11a** and **11b** which contain electron withdrawing groups such as CHO and COOH at the *para* position of the phenyl ring of the tetraoxane were devoid of any activity with the exception of compounds **3a**, **3e**, **3f** and **11a**, which showed poor activity. This is in good agreement with our earlier observation that electron withdrawing CF_3 leads to devoid of antimalarial activity [25]. Interestingly, alcohol counterparts (**8a**–**f**) of compounds **3a**–**f** exhibited good antimalarial



Scheme 2. Reagents and conditions: a) R^2NH_2 (1.0 equiv), THF, RT, 18 h, 25–55%; b) R^2NH_2 (1.0 equiv), $NaBH(OAc)_3$ (1.5 equiv), THF, RT, 12 h, 20–52%.



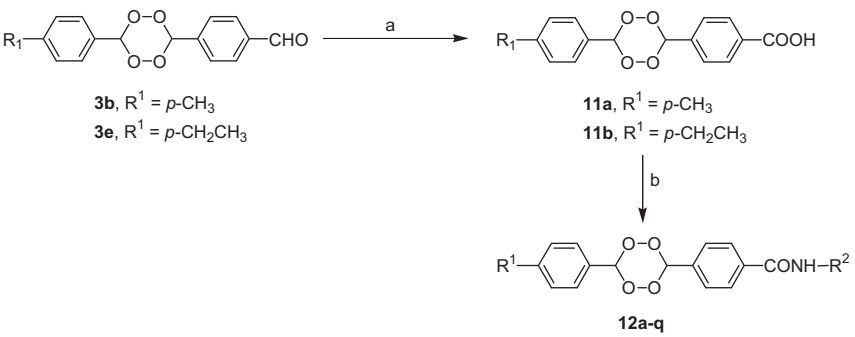
Scheme 3. Reagents and conditions: a) $NaBH_4$ (4.0 equiv), THF, RT, 4 h, 48–75%; b) MsCl (1.0 equiv), Et_3N (3.0 equiv), THF, 6 h, RT, 86–93%; c) R^2NH_2 (1.0 equiv), THF, RT, 18 h, 20–62%.

activity against both the strains of *P. falciparum* (Table 1) with IC_{50} values ranging from 1.28 to 3.09 μM against D6 clone and 1.09 to 2.42 μM against W2 clone. But activity dropped when alcohols were converted to mesylates (**9a**, **9b**). The amine analogues (**10a**–**w**) of compound **8a** exhibits almost similar kind of antimalarial activity pattern against both D6 and W2 strains of *P. falciparum* except compounds **10b**, **10d**, **10f**, and **10o** which were found to be totally inactive. Further derivatization of these alcohols is under progress and results will be published in due course of time. When compound **3b** was reacted with substituted amines, the resulting imines (**6a**–**l**) gained antimalarial activity against both the strains of *P. falciparum*. Compound **6a** (R2 = cyclohexyl) showed better activity [IC_{50} = 1.90 μM (D6), 1.85 μM (W2)] than **6b** [R^2 = phenyl, IC_{50} = 7.74 μM (D6), 5.53 μM (W2)]. There is a clear trend of improved activity in series of compounds **6b**–**d** when R^2 is Ph, CH_2Ph, CH_2CH_2Ph with IC_{50} values ranging between 7.74 μM (D6), 5.53 μM (W2); 4.80 μM (D6), 6.40 μM (W2) and 1.54 μM (D6), 1.49 μM (W2) respectively. The phenyl group with chloro at *para* position (**6e**) showed better antimalarial activity with IC_{50} values 1.46 μM against both D6 and W2 clones than its bromo counterpart (**6f**) with IC_{50} values 7.95 μM against D6 and 4.09 μM against W2 clone. Two compounds, **6h** and **6k**, were found to be the most active against both strains of *P. falciparum* with IC_{50} ranging from 0.47 to 0.75 μM (D6) and 0.57 to 0.80 μM (W2). The amine counterpart (**7d**, **7f**) of compounds **6h**, and **6k** showed IC_{50} values 0.38–2.64 μM (D6) and 0.57–1.62 μM (W2) clones respectively. In order to understand the role of basicity in the observed antimalarial activity of these compounds (**6h**, **6k**, **7d** and **7f**) we calculated pK_a values of compounds **6h**, **6k**, **7d** and **7f** and found no direct correlation of observed antimalarial activity with their basicity. Moving from imines (**6b**–**d**) to tetraoxane-amine conjugates (**10a**, **7a**, **7b**) trend of antimalarial activity was reversed. In case of imine compound **6d** ($R^2 = CH_2CH_2Ph$) was the most active compound while compound **6b** was the least, while in the amine derivative of the same compound (**10a**, R^2 = Ph) was the most active compound. The activity profile in case of imine was in the order of $R^2 = CH_2CH_2Ph > CH_2Ph >$ Ph, while in the case of amine derivatives the activity order was reversed ($R^2 = CH_2CH_2Ph < CH_2Ph <$ Ph). The imine of tetraoxane-aminoquinoline conjugate (**6k**) was more active than its reduced counterpart (**7f**). Two other compounds (**6h**, **7d**) were found to be very active against both the strains of *P. falciparum*. Among the tetraoxane-amine conjugates, compounds having fluoro or chloro group (**10k**–**p**) with phenyl ring attached with nitrogen have shown good activity compared to bromo derivative (**10r**). All the compounds in which OH, OMe, and NH_2 groups are at the *para* position of the phenyl ring were less active (**10s**–**w**). Other compounds in which methyl, ethyl and *iso*-propyl groups are at the *para* position of the phenyl ring showed varied activity pattern (**10h**–**j**). Among the amide series, the tetraoxane-aminoquinolines (**12k**–**m**) showed better antimalarial activity than other compounds of the series. Interestingly amide counterpart (**12a**) was found to be totally inactive, which could be due to less basicity of the amide.

Cytotoxicity of three potentially active compounds **6h**, **6k**, and **7d** along with compound **7f** (reduced counterpart of compound **6k**) was also evaluated in a panel of four cancer (SK-MEL, KB, BT-549, SK-OV-3) and two non-cancer (Vero and LLC-PK_{11}) cell lines up to a concentration of 25 μM and none of the compounds was found toxic to any of the cell lines (data not included).

4. Conclusion

We have successfully synthesized new series of substituted tetraoxanes using substituted benzaldehydes as a starting material and these compounds have been converted to imines, amines and amide derivatives. Electron withdrawing groups at *para* position of the phenyl ring have negative effect on the antimalarial activity.



Scheme 4. Reagents and conditions: a) $CrO_3/H_2SO_4/H_2O$ (1 g/1 mL/10 mL), acetone, RT, 4 h, 67–82%; b) Et_3N (3.0 equiv), $ClCO_2Et$ (1.0 equiv), R^2NH_2 (2.0 equiv), THF, RT, 2 h, 38–73%.

Table 1
In vitro antimalarial activity and cytotoxicity of tetraoxane-imine derivatives and tetraoxane-amine conjugates.

Entries	R^1	R^2	*P. falciparum* (D6) IC_{50} (μM)	S.I	*P. falciparum* (W2) IC_{50} (μM)	S.I	Cytotoxicity (vero cells)
3a	H		13.22	>1.3	>17.48	>1.0	NC
3b	*p*-CH_3		NA		NA		NC
3c	*m*-CH_3		NA		NA		NC
3d	*o*-CH_3		NA		NA		NC
3e	*p*-Et		10.9	>1.4	5.99	>2.6	NC
3f	*p*-*iso*-Pr		6.99	>2.2	3.11	>4.9	NC
6a	*p*-CH_3	C_6H_{11}	1.90	>6.8	1.85	>7.0	NC
6b	*p*-CH_3	C_6H_5	7.74	>1.7	5.53	>2.4	NC
6c	*p*-CH_3	$CH_2C_6H_5$	4.80	>2.6	6.4	>2.0	NC
6d	*p*-CH_3	$CH_2CH_2C_6H_5$	1.54	>7.9	1.49	>8.2	NC
6e	*p*-CH_3	4-ClC_6H_4	1.46	>8.2	1.46	>8.2	NC
6f	*p*-CH_3	4-BrC_6H_4	7.95	>1.4	4.09	>2.6	NC
6g	*p*-CH_3	2-SHC_6H_4	6.86	>1.8	5.08	>2.4	NC
6h	*p*-CH_3	3-Pyridine	0.75	>17.6	0.80	>16.4	NC
6i	*p*-CH_3	CH_2CH_2OH	2.82	>5.1	2.37	>6.1	NC
6j	*p*-CH_3	Adamantane	4.76	>2.4	5.24	>2.2	NC
6k	*p*-CH_3	CH_2CH_2NHCQ	0.47	>20.7	0.57	>17.0	NC
6l	*p*-CH_3	NH_2	2.59	>9.0	1.26	>9.0	NC
7a	*p*-CH_3	$CH_2C_6H_5$	3.44	>3.7	3.44	>3.7	NC
7b	*p*-CH_3	$CH_2CH_2C_6H_5$	7.67	>1.6	6.39	>1.9	NC
7c	*p*-CH_3	2-SHC_6H_4	2.19	>5.5	1.59	>7.6	NC
7d	*p*-CH_3	3-Pyridine	0.38	>34.0	0.57	>22.7	NC
7e	*p*-CH_3	Adamantane	6.64	>1.7	4.74	>2.4	NC
7f	*p*-CH_3	CH_2CH_2NHCQ	2.64	>3.7	1.62	>6.0	NC
8a	H		3.09	>5.6	1.82	>9.5	NC
8b	*p*-CH_3		1.83	>9.0	2.42	>6.8	NC
8c	*m*-CH_3		1.28	>12.9	1.38	>11.9	NC
8d	*o*-CH_3		2.15	>7.7	1.90	>8.7	NC
8e	*p*-Et		1.58	9.9	1.09	14.4	NC
8f	*p*-*iso*-Pr		2.02	>7.4	1.89	>7.9	NC
9a	*p*-CH_3		7.64	>1.7	8.18	>1.6	NC
9b	*p*-Et		4.99	>2.5	3.94	>3.2	NC
10a	*p*-CH_3	C_6H_5	1.84	>7.1	1.59	>8.2	NC
10b	*p*-CH_3	$C_{10}H_7$	NA		NA		NC
10c	*p*-CH_3	$NCH_3C_6H_4$	1.51	>8.4	2.11	>6.0	NC
10d	*p*-CH_3	4-$CH_3C_6H_4$	NA		NA		NC
10e	*p*-CH_3	3-$CH_3C_6H_4$	2.64	>4.8	2.38	>5.3	NC
10f	*p*-CH_3	2-$CH_3C_6H_4$	NA		NA		NC
10g	*p*-CH_3	2,6-$CH_3C_6H_3$	1.48	>8.2	1.45	>8.4	NC
10h	*p*-CH_3	4-EtC_6H_4	3.32	>3.7	2.35	>5.2	NC
10i	*p*-CH_3	4-*iso*-Pr-C_6H_4	2.39	>4.9	3.20	>3.7	NC
10j	*p*-CH_3	4-*n*-Pr-C_6H_4	5.67	>2.3	4.19	>2.8	NC
10k	*p*-CH_3	4-FC_6H_4	2.09	>6.0	2.35	>5.3	NC
10l	*p*-CH_3	3-FC_6H_4	2.46	>5.1	1.83	>6.8	NC
10m	*p*-CH_3	2-FC_6H_4	1.88	>6.6	1.83	>6.8	NC
10n	*p*-CH_3	4-ClC_6H_4	1.79	>6.8	1.70	>7.0	NC
10o	*p*-CH_3	3-ClC_6H_4	NA		NA		NC
10p	*p*-CH_3	2-ClC_6H_4	2.51	>4.8	2.76	>4.3	NC
10q	*p*-CH_3	2,4,5-ClC_6H_2	8.57	>1.2	6.42	>1.6	NC
10r	*p*-CH_3	4-BrC_6H_4	7.69	>1.4	4.97	>2.2	NC
10s	*p*-CH_3	4-$OCH_3C_6H_4$	8.13	>1.5	10.16	>1.2	NC
10t	*p*-CH_3	3,5-$OCH_3C_6H_3$	6.37	>1.8	9.20	>1.2	NC
10u	*p*-CH_3	4-OHC_6H_4	6.32	>1.8	7.11	>1.8	NC
10v	*p*-CH_3	3-OHC_6H_4	3.42	>3.7	3.95	>3.2	NC
10w	*p*-CH_3	4-$NH_2C_6H_4$	5.28	>2.4	7.39	>1.7	NC
Chloroquine			0.042	>300	0.42	>30	–
Artemisinin			0.03	>500	0.025	>670	–

Introduction of imine, amine, and amide functionalities in these inactive tetraoxanes leads to slightly better antimalarial activity of the resulting compounds. Some of the compounds have shown low micro molar *in vitro* antimalarial activity without showing any cytotoxicity. This study shows that basicity is not the main factor for the observed antimalarial activity of these compounds. This opens up the possibility of developing these new compounds (**6h**, **6k**, **7d** and **7f**) as potent, water soluble tetraoxane derivatives for malaria treatment. Further derivatization of the most active analogues is under progress and results will be published in due course.

5. Experimental section

All of the chemicals used in the syntheses were purchased from Sigma–Aldrich and were used as such. Thin layer chromatography was used to monitor the progress of the reaction. The compounds were purified by silica gel column. Melting points were determined on a melting point apparatus and are uncorrected. IR (KBr, film) spectra were recorded using Perkin–Elmer FT-IR spectrophotometer and the values are expressed as ν_{max} cm^{-1}. Mass spectral data were recorded in waters micro mass LCT Mass Spectrometer/Data system. The ^1H NMR spectra were recorded on Bruker 320

Table 2
In vitro antimalarial activity and cytotoxicity of the tetraoxane-amide conjugates.

Entries	R^1	R^2	*P. falciparum* (D6) IC_{50} (μM)	S.I	*P. falciparum* (W2) IC_{50} (μM)	S.I	Cytotoxicity (vero cells)
11a	CH_3		10.58	>1.5	9.26	>1.7	NC
11b	C_2H_5		NA		NA		NC
12a	CH_3	CH_2CH_2OH	NA		NA		NC
12b	C_2H_5	CH_2CH_2OH	6.67	>2.0	7.51	>1.8	NC
12c	CH_3	$CH_2(CH_2)_2OH$	NA		NA		NC
12d	C_2H_5	$CH_2(CH_2)_2OH$	4.82	>2.6	4.82	>2.6	NC
12e	CH_3	$CH_2(CH_2)_5OH$	NA		NA		NC
12f	C_2H_5	$CH_2(CH_2)_5OH$	3.36	>3.4	4.81	>2.4	NC
12g	CH_3	$(CH_2)_2CH_3$	8.73	>3.4	13.86	>1.0	NC
12h	CH_3	$(CH_2)_3CH_3$	NA		NA		NC
12i	C_2H_5	$(CH_2)_3CH_3$	6.73	>1.9	6.99	>1.8	NC
12j	C_2H_5	$(CH_2)_4CH_3$	NA		NA		NC
12k	CH_3	$(CH_2)_2NHCQ$	1.10	>8.5	1.5	>6.3	NC
12l	CH_3	$(CH_2)_3NHCQ$	1.19	>7.7	2.11	>4.3	NC
12m	C_2H_5	$(CH_2)_3NHCQ$	1.08	>8.2	2.43	>3.7	NC
12n	CH_3	$(CH_2)_2Ph$	2.71	>4.3	2.09	>5.6	NC
12o	CH_3	Ph piperazine	4.03	>2.6	7.16	>1.5	NC
12p	CH_3	Cyclohexyl	4.43	>2.8	2.86	>4.3	NC
12q	CH_3	$(CH_2)_7NH_2$	5.13	>2.2	4.66	>2.4	NC
Chloroquine			0.042	>300	0.42	>30	NC
Artemisinin			0.03	>500	0.025	>670	NC

Spectrospin spectrometer at 300 MHz and Jeol ECX spectospin at 400 MHz and ^{13}C NMR spectra recorded at 75.5 MHz and 100 MHz respectively, using TMS as an internal standard. The chemical shift values are recorded on the δ scale and the coupling constants (*J*) are in hertz. Elemental analyses were performed on a Carlo Erba Model EA-1108 elemental analyzer and the data of C, H and N are within ±0.4% of calculated values.

5.1. 4-(6-p-Tolyl[1,2,4,5]tetroxan-3-yl)benzaldehyde (**3b**)

A mixture of 4-methyl-benzaldehyde (5 g, 41.66 mmol), 30% H_2O_2 (9.43 mL, 83.33 mmol), and MTO (10 mg, 0.042 mmol) in 50 mL of 2,2,2-trifluoroethanol (TFE) was stirred for 2 h at room temperature and terephthalaldehyde (**2**) (11.15 g, 83.33 mmol) was added to the reaction mixture, followed by the addition of 54% ethereal solution of HBF_4 (5.68 mL, 41.66 mmol). The reaction mixture was stirred for an additional hour at room temperature. After the completion of reaction as evident by thin layer chromatography (TLC), chloroform was added to the reaction mixture and organic layer was washed with saturated $NaHSO_3$ solution followed by saturated solution of NaCl. Chloroform layer was then dried over Na_2SO_4 and solvent was evaporated under reduced pressure. The crude product was then purified over SiO_2 column chromatography using $CHCl_3$/hexane as an eluent to yield **3b** (4.76 g, 40%) as a white solid; mp 195 °C; IR (film, cm^{-1}): 2924, 2845, 1707, 1610, 1358, 1202, 1018, 1007, 911, 835, 797; ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 2.39 (s, 3H), 6.90 (s, 1H), 6.98 (s, 1H), 7.25 (d, 2H, $J = 7.8$ Hz), 7.40 (d, 2H, $J = 7.8$ Hz), 7.69 (d, 2H, $J = 7.8$ Hz), 7.95 (d, 2H, $J = 8.1$ Hz), 10.06 (s, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$): 21.52, 107.09, 108.53, 127.06, 127.80, 129.53, 129.90, 136.40, 138.13, 141.94, 191.47; ESI-MS: 287.30 ($M^+ + H$). Anal. calcd. for $C_{16}H_{14}O_5$: C, 67.13; H, 4.93. Found: C, 66.33;H, 4.90.

5.2. 4-(6-Phenyl[1,2,4,5]tetroxan-3-yl)benzaldehyde (**3a**)

Yield: 32%; mp 220 °C; IR (KBr, cm^{-1}): 2921, 2851, 1706, 1456, 1365, 1298, 1204, 1103, 1056, 1018, 1002, 914, 837, 806, 755, 696; ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 6.90 (s, 1H), 6.99 (s, 1H), 7.41–7.46 (m, 3H), 7.68–7.72 (m 3H), 7.79–8.22 (m, 3H), 10.08 (s, 1H); ESI-MS: 273.18 ($M^+ + H$). Anal. calcd. for $C_{15}H_{12}O_5$: C, 66.17; H, 4.44. Found: C, 66.12; H, 4.49.

5.3. 4-(6-m-Tolyl[1,2,4,5]tetroxan-3-yl)benzaldehyde (**3c**)

Yield: 36%; mp 185 °C; IR(KBr, cm^{-1}): 2922, 2850, 1708, 1610, 1354, 1203, 1018, 1007, 834, 786, 698; ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 2.39 (s, 3H), 6.90 (s, 1H), 6.99 (s, 1H), 7.26–7.32 (m, 3H), 7.59 (s, 1H), 7.69 (m, 2H), 7.96 (m, 2H), 10.07 (s, 1H); ESI-HRMS calcd. for $C_{16}H_{14}O_5$ 286.0841; found: 287.0842 ($M^+ + H$).

5.4. 4-(6-o-Tolyl[1,2,4,5]tetroxan-3-yl)benzaldehyde (**3d**)

Yield: 41%; mp 155 °C; IR (KBr, cm^{-1}): 2922, 2852, 1704, 1462, 1360, 1205, 1000, 913, 830, 753; ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 2.54 (s, 3H), 6.97 (s, 1H), 7.01 (s, 1H), 7.12 (s, 1H), 7.36–7.48 (m, 2H), 7.76–7.77 (m, 3H), 7.96–8.06 (m, 2H), 10.07 (s, 1H); ESI-HRMS calcd. for $C_{16}H_{14}O_5$ 286.0841; found: 287.0842 ($M^+ + H$).

5.5. 4-[6-(4-Ethyl-phenyl)[1,2,4,5]tetroxan-3-yl]benzaldehyde (**3e**)

Yield: 45%; mp 199 °C; IR (KBr, cm^{-1}): 2866, 1692, 1498, 1385, 1368, 1301, 1199, 1014, 910, 815, 772; ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 1.57 (t, 3H, $J = 5.3$ Hz), 2.65–2.72 (q, 2H), 6.91 (s, 1H), 6.94 (s, 1H), 7.26–7.29 (m, 2H), 7.42 (d, 2H, $J = 9.0$ Hz), 7.68 (m, 2H), 7.94–7.96 (d, 2H, $J = 6.5$ Hz), 9.98 (s, 1H); ESI-MS: 301.1 ($M^+ + H$). Anal. calcd. for $C_{17}H_{16}O_5$: C, 67.99; H, 5.37. Found: C, 67.43; H, 5.30.

5.6. 4-[6-(4-Isopropyl-phenyl)[1,2,4,5]tetroxan-3-yl]benzaldehyde (**3f**)

Yield: 40%; mp 170 °C; IR (KBr, cm^{-1}): 2963, 1706, 1639, 1423, 1364, 1298, 1066, 1017, 911, 841, 806; ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 1.24–1.26 (d, 6H, $J = 6.2$ Hz), 2.89–2.96 (m, 1H), 6.91 (s, 1H), 6.99 (s, 1H), 7.25–7.31 (m, 2H), 7.42–7.45 (m, 2H), 7.68–7.70 (m, 2H), 7.94–7.96 (m, 2H), 10.06 (s, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$): 23.76, 34.18, 107.11, 108.55, 126.99, 127.91, 128.00, 128.40, 129.91, 136.46, 138.16, 152.76, 191.46; ESI-MS: 315.1 ($M^+ + H$). Anal. calcd. for $C_{18}H_{18}O_5$: C, 68.78; H, 5.77. Found: C, 68.88; H, 5.94.

5.7. Benzyl[4-(6-p-tolyl-[1,2,4,5]tetroxan-3-yl)benzylidene]amine (**6c**)

Compound **3b** (100 mg, 0.35 mmol) was dissolved in dry THF (25 mL), benzylamine (37 mg, 0.35 mmol) was added to the above

solution and reaction mixture was stirred at room temperature for 18 h. After completion of reaction, the product was extracted with $CHCl_3$ and the solvent was removed under vaccum. The crude product was purified over silica gel column using EtOAc/hexane to yield **6c** (52 mg, 40%) as a white solid; mp 140 °C; IR (film, cm^{-1}): 2919, 2845, 1620, 1501, 1414, 1352, 1249, 1109, 938, 838, 797; ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 2.39 (s, 3H), 4.85 (s, 2H), 6.89 (s, 1H), 6.94 (s, 1H), 7.23–7.26 (m, 3H), 7.34–7.41 (m, 6H), 7.56 (d, 2H, $J = 7.8$ Hz), 7.85 (d, 2H, $J = 8.1$ Hz), 8.41 (s, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$): 21.48, 65.02, 107.61, 108.50, 127.08, 127.76, 128.03, 128.51, 129.46, 132.88, 138.67, 141.73, 160.85; ESI-MS calcd. for $C_{23}H_{21}NO_4$: 375.1; found: 376.1 ($M^+ + H$).

5.8. Phenethyl[4-(6-p-tolyl-[1,2,4,5]tetroxan-3-yl)benzylidene] amine (**6d**)

Yield: 48%; mp 188 °C; IR (film, cm^{-1}): 2921, 2845, 1358, 1259, 1201, 1019, 911, 832, 795; ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 2.34 (s, 3H), 2.90 (t, 2H, $J = 6.2$ Hz), 3.56 (t, 2H, $J = 6.3$ Hz), 6.81 (s, 1H), 6.84 (s, 1H), 7.16–7.19 (m, 2H), 7.32–7.38 (m, 6H), 7.43–7.45 (m, 3H), 7.80–7.98 (m, 2H), 8.41 (s, 1H); ESI-MS calcd. for $C_{24}H_{23}NO_4$ 389.1; found: 390.2 ($M^+ + H$).

5.9. N-(4-(6-p-Tolyl-1,2,4,5-tetraoxan-3-yl)benzylidene) cyclohexanamine (**6a**)

Yield: 48%; mp 121 °C; IR (film, cm^{-1}): 2924, 2853, 1638, 1610, 1450, 1360, 1176, 1108, 911, 831, 795; ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 1.25–1.60 (m, 5H), 1.65–1.86 (m, 4H), 2.38 (s, 3H), 3.22 (m, 2H), 6.87 (s, 1H), 6.88 (s, 1H), 7.15–7.22 (m, 2H), 7.38–7.41 (m, 2H), 7.53 (d, 2H, $J = 8.1$ Hz), 7.78 (d, 2H, $J = 8.1$ Hz), 8.32 (s, 1H); ESI-MS: 368.2 ($M^+ + H$). Anal. calcd. for $C_{22}H_{25}NO_4$: C, 71.91; H, 6.86; N, 3.81. Found: C, 71.63; H, 6.66; N, 3.83.

5.10. N-(4-(6-p-Tolyl-1,2,4,5-tetraoxan-3-yl)benzylidene)aniline (**6b**)

Yield: 42%; mp 166 °C; IR (KBr, cm^{-1}): 2919, 2845, 1620, 1501, 1414, 1352, 1249, 1109, 938, 838, 797; ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 2.32 (s, 3H), 6.84 (s, 1H), 6.89 (s, 1H), 7.18–7.33 (m, 9H), 7.56 (m, 2H), 7.89 (m, 2H), 8.41 (s, 1H); ESI-MS: 362.18 ($M^+ + H$). Anal. calcd. for $C_{22}H_{19}NO_4$: C, 73.12; H, 5.30; N, 3.88. Found: C, 73.43; H, 5.01; N, 3.86.

5.11. (4-Chloro-phenyl)[4-(6-p-tolyl-[1,2,4,5]tetroxan-3-yl) benzylidene]amine (**6e**)

Yield: 45%; mp 160 °C; IR (KBr, cm^{-1}): 2925, 2861, 1622, 1310, 1183, 1091, 1011, 911, 842, 795; ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 2.34 (s, 3H), 6.99 (s, 1H), 7.06 (s, 1H), 7.15–7.20 (m, 2H), 7.31–7.34 (m, 3H), 7.44–7.49 (m, 3H), 7.71–7.74 (m, 2H), 8.03–8.05 (m, 2H), 8.69 (s, 1H); ESI-MS: 396.1 ($M^+ + H$). Anal. calcd. for $C_{22}H_{18}ClNO_4$: C, 66.75; H, 4.85; N, 3.54. Found: C, 66.80; H, 4.61; N, 3.60.

5.12. (4-Bromo-phenyl)[4-(6-p-tolyl-[1,2,4,5]tetroxan-3-yl) benzylidene]-amine (**6f**)

Yield: 55%; mp 170 °C; IR (KBr, cm^{-1}): 2917, 2854, 1621, 1476, 1354, 1008, 913, 843, 828, 798; ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 2.41 (s, 3H), 7.14 (s, 1H), 7.16 (s, 1H), 7.30–7.35 (m, 2H), 7.44–7.46 (m, 2H), 7.64–7.66 (m, 2H), 7.83–7.89 (m, 2H), 8.04–8.20 (m, 4H), 8.88 (s, 1H); ESI-MS: 440.1 ($M^+ + H$). Anal. calcd. for $C_{22}H_{18}BrNO_4$: C, 60.01; H, 4.12; N, 3.18. Found: C, 59.80; H, 4.21; N, 3.28.

5.13. 2(4-(6-p-Tolyl-1,2,4,5-tetraoxan-3-yl)benzylideneamino) benzenethiol (6g)

Yield: 37%; mp 185 °C; IR (KBr, cm^{-1}): 2922, 2853, 1610, 1454, 1360, 1309, 1198, 1110, 1010, 911, 834, 798, 755; ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 2.39 (s, 3H), 4.35 (br s, 1H), 6.92 (s, 1H), 6.98 (s, 1H), 7.25–7.40 (m, 6H), 7.64–8.02 (m, 6H), 8.49 (s, 1H); ESI-HRMS calcd. for $C_{22}H_{19}NO_4S$: 393.1035; found: 394.1032 ($M^+ + H$).

5.14. N-(4-(6-p-Tolyl-1,2,4,5-tetraoxan-3-yl)benzylidene)pyridin-3-amine (**6h**)

Yield: 36%; mp 188 °C; IR (KBr, cm^{-1}): 2921, 2852, 1608, 1454, 1357, 1295, 1198, 1013, 908, 829, 792; ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 2.39 (s, 3H), 6.87 (m, 2H), 6.90 (s, 1H), 6.98 (s, 1H), 7.22–7.25 (m, 4H), 7.38–7.41 (m, 4H), 7.63–7.67 (m, 1H), 7.94 (s, 1H), 7.96 (s, 1H); ESI-MS: 363.2 ($M^+ + H$). Anal. calcd. for $C_{21}H_{18}N_2O_4$: C, 69.60; H, 5.01; N, 7.73. Found: C, 69.48; H, 5.23; N, 7.80.

5.15. 2-{[4-(6-p-Tolyl[1,2,4,5]tetroxan-3-yl)benzylidene]amino} ethanol (**6i**)

Yield: 32%; mp 143 °C; IR (KBr, cm^{-1}): 3310, 2920, 1645, 1611, 1360, 1307, 1260, 1199, 1055, 1022, 911, 873, 835, 796; ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 1.93 (br s, 1H), 2.58 (s, 3H), 3.98 (m, 2H), 4.11 (m, 2H), 7.09 (s, 1H), 7.13 (s, 1H), 7.43–7.45 (m, 2H), 7.58–7.61 (m, 2H), 7.74–7.77 (m, 2H), 7.98–8.01 (m, 2H), 8.56 (s, 1H); ESI-MS: 330.14 ($M^+ + H$). Anal. calcd. for $C_{18}H_{19}NO_5$: C, 65.64; H, 5.81; N, 4.25. Found: C, 65.81; H, 5.61; N, 4.23.

5.16. Adamantan-1-yl[4-(6-p-tolyl[1,2,4,5]tetraoxan-3-yl) benzylidene]amine (**6j**)

Yield: 35%; mp 161 °C; IR (KBr, cm^{-1}): 2915, 2851, 1629, 1529, 1381, 1007, 838, 801, 756; ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 1.74–2.17 (m, 15H), 2.38 (s, 3H), 6.89 (s, 1H), 6.92 (s, 1H), 7.25 (m, 2H), 7.39–7.41 (m, 2H), 7.55 (m, 2H), 7.82–7.96 (m, 2H), 8.27 (s, 1H); ESI-HRMS calcd. for $C_{26}H_{29}NO_4$: 419.2097; found: 420.2099 ($M^+ + H$).

5.17. N-(7-Chloro-quinolin-4-yl)-N′-[4-(6-p-tolyl[1,2,4,5]tetroxan-3-yl)benzylidene]ethane-1,2-diamine (**6k**)

Yield: 40%; mp 120 °C; IR (KBr, cm^{-1}): 3402, 3065, 2923, 2851, 1610, 1579, 1363, 1297, 1212, 1141, 1025, 1006, 912, 836, 800, 700; ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 2.32 (s, 3H), 3.60 (t, 2H, $J = 5.3$ Hz), 3.92 (t, 2H, $J = 5.2$ Hz), 5.61 (br s, 1H), 6.43 (d, 1H, $J = 5.1$ Hz), 6.82 (s, 1H), 6.87 (s, 1H), 7.17–7.21 (m, 2H), 7.29–7.34 (m, 3H), 7.49–7.52 (m, 2H), 7.64 (d, 1H, $J = 9.0$ Hz), 7.73(d, 2H, $J = 7.8$ Hz), 7.89 (s, 1H), 8.29 (s, 1H), 8.49 (d, 1H, $J = 5.2$ Hz); ESI-MS: 490.1 ($M^+ + H$). Anal. calcd. for $C_{27}H_{24}ClN_3O_4$: C, 66.19; H, 4.94; N, 8.58. Found: C, 66.39; H, 5.09; N, 8.78.

5.18. [4-(6-p-Tolyl[1,2,4,5]tetroxan-3-yl)benzylidene]hydrazine (**6l**)

Yield: 25%; mp 218 °C; IR (KBr, cm^{-1}): 3369, 2920, 2850, 1609, 1357, 1178, 1004, 910, 829, 792, 692; ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 2.38 (s, 3H), 4.74 (s, 2H), 6.88–6.95 (m, 2H), 7.23–7.60 (m, 8H), 7.73–7.75 (m, 1H); ESI-HRMS calcd. for $C_{16}H_{16}N_2O_4$: 300.1110; found: 301.1114 ($M^+ + H$).

*5.19. Phenethyl[4-(6-p-tolyl[1,2,4,5]tetroxan-3-yl)benzyl]amine (**7b**)*

Equimolar quantity of **3b** (150 mg, 0.52 mmol) and phenylethylamine (63 mg, 0.52 mmol) were stirred in THF (20 mL) and sodiumtriacetoxyborohydride (167 mg, 0.79 mmol) was added to the reaction mixture. The reaction mixture was stirred at room temperature for 12 h and progress of reaction was monitored by TLC. The solvent was evaporated under vaccum and product was extracted with chloroform. Organic layer was dried over anhydrous Na_2SO_4 and solvent was removed under vacuum. The crude product was purified over silica gel using EtOAc/hexane as eluent to give product **7b** (106 mg, 52%) as a white solid; mp 155 °C; IR (KBr, cm^{-1}): 3407, 3028, 2962, 2923, 2850, 1608, 1538, 1454, 1378, 1261, 1094, 1018, 912, 797, 773; ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 1.77 (br s, 1H), 2.31 (s, 3H), 2.77 (t, 2H, $J = 6.6$ Hz), 2.81 (t, 2H, $J = 6.6$ Hz), 3.76 (s, 2H), 6.80 (s, 1H), 6.82 (s, 1H), 7.11–7.15 (m, 5H), 7.18–7.22 (m, 3H), 7.26–731 (m, 2H), 7.34–7.37 (m, 3H); ESI-MS calcd. for $C_{24}H_{25}NO_4$: 391.1; found: 392.1 ($M^+ + H$), Anal. calcd. for $C_{24}H_{25}NO_4$: C, 73.64; H, 6.44, N, 3.58. Found: C, 73.81; H, 4.64, N, 3.88.

*5.20. Benzyl[4-(6-p-tolyl[1,2,4,5]tetroxan-3-yl)benzyl]amine (**7a**)*

Yield: 43%; mp 158 °C; IR (KBr, cm^{-1}): 3390, 2918, 2850, 1613, 1379, 1261, 1111, 1019, 827, 792, 697; ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 1.87 (br s, 1H), 2.38 (s, 3H), 3.80 (s, 2H), 3.84 (s, 2H), 6.87 (s, 1H), 6.88 (s, 1H), 7.23 (s, 2H), 7.33–7.39 (m, 4H), 7.41–7.46 (m, 5H), 7.47–7.59 (m, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$): 21.47, 52.37, 52.79, 108.10, 108.17, 126.95, 127.14, 127.75, 127.92, 128.21, 128.45, 128.53, 129.11, 139.50, 141.58, 141.63, 143.55; ESI-MS: 378.23 ($M^+ + H$). Anal. calcd. for $C_{23}H_{23}NO_4$: C, 73.19; H, 6.14; N, 3.71. Found: C, 73.32; H, 6.09; N, 3.58.

*5.21. 2-(4-(6-p-Tolyl-1,2,4,5-tetraoxan-3-yl)benzylamino) benzenethiol (**7c**)*

Yield: 46%; mp 198 °C; IR (KBr, cm^{-1}): 3394, 2919, 1592, 1494, 1458, 1417, 1311, 1008, 966, 913, 837, 801, 748; ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 1.17 (br s, 1H), 2.38 (s, 3H), 4.74 (s, 2H), 6.41–6.43 (m, 2H), 6.88 (s, 1H), 6.91 (s, 1H), 7.34–7.60 (m, 4H), 7.70–7.78 (m, 4H), 8.03–8.09 (m, 2H), 8.75 (br s, 1H); ESI-MS 396.2 ($M^+ + H$). Anal. calcd. for $C_{22}H_{21}NO_4S$ C, 66.82; H, 5.35; N, 3.54. Found: C, 66.51; H, 5.23; N, 3.71.

*5.22. N-(4-(6-p-Tolyl-1,2,4,5-tetraoxan-3-yl)benzyl)pyridin-3-amine (**7d**)*

Yield: 42%; mp 194 °C; IR (KBr, cm^{-1}): 3407, 3387, 1597, 1519, 1495, 1458, 1417, 1308, 1243, 1148, 1009, 876, 793, 744; ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 2.71 (br s, 1H), 2.36 (s, 3H), 4.68 (s, 2H), 6.81 (s, 1H), 6.84 (s, 1H), 7.16–7.19 (m, 5H), 7.34–7.48 (m, 6H), 7.90–7.93 (m, 1H); ESI-MS: 365.2 ($M^+ + H$). Anal. calcd. for $C_{21}H_{20}N_2O_4$: C, 69.22; H, 5.53; N, 7.69. Found: C, 68.96; H, 5.80; N, 7.53.

*5.23. Adamantan-1-yl[4-(6-p-tolyl-[1,2,4,5]tetraoxan-3-yl)benzyl] amine (**7e**)*

Yield: 20%; mp 178 °C; IR (KBr, cm^{-1}): 3395, 2908, 1593, 1494, 1416, 1310, 1174, 1085, 1006, 910, 834, 747; ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 0.81–2.21 (m, 15H), 2.34 (s, 3H), 3.5 (br s, 1H), 4.67 (s, 2H), 6.81 (s, 1H), 6.84 (s, 1H), 7.19 (m, 4H), 7.32–7.45 (m, 3H), 7.87–7.98 (m, 1H); ESI-HRMS calcd. for $C_{26}H_{31}NO_4$: 421.2253; found: 422.2258 ($M^+ + H$).

*5.24. N-(7-Chloro-quinolin-4-yl)-N′-[4-(6-p-tolyl[1,2,4,5]tetroxan-3-yl)benzyl]ethane-1,2-diamine (**7f**)*

Yield: 40%; mp 138 °C; IR (KBr, cm^{-1}): 3401, 3266, 2957, 2921, 2851, 1609, 1542, 1457, 1375, 1261, 1091, 1018, 897, 875, 805, 772; ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 2.32 (s, 3H), 2.98–2.99 (m, 2H), 3.28 (s, 2H), 3.82 (br s, 1H), 3.92 (s, 2H), 5.75 (br s, 1H), 6.31 (d, 1H, $J = 5.1$ Hz), 6.81 (s, 1H), 6.83 (s, 1H), 7.16–7.19 (m, 3H), 7.32–7.34 (m, 4H), 7.41–7.44 (m, 2H), 7.61 (d, 1H, $J = 9.0$ Hz), 7.89 (s, 1H), 8.50 (d, 1H, $J = 5.1$ Hz); ESI-MS: 492.2 ($M^+ + H$). Anal. calcd. for $C_{27}H_{26}ClN_3O_4$: C, 65.92; H, 5.33; N, 8.54. Found: C, 65.63; H, 5.60; N, 8.54.

*5.25. [4-(6-p-Tolyl[1,2,4,5]tetroxan-3-yl)phenyl]methanol (**8b**)*

The sodium borohrdride (106 mg, 2.80 mmol) was added to a solution of compound **3b** (200 mg, 0.70 mmol) in THF (20 mL) and the reaction mixture was stirred at room temperature for 4 h. The progress of reaction was monitored by TLC. After completion of reaction, the reaction mixture was extracted with $CHCl_3$ and water. The organic layer was dried over anhydrous Na_2SO_4 and solvent was removed under vacuum. The crude product thus obtained was purified over silica gel column using EtOAc/hexane as eluent to yield **8b** (167 mg, 83%); mp: 165 °C; IR (film, cm^{-1}): 3325, 2922, 1613, 1420, 1361, 1211, 1110, 1004, 912, 832, 792; ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 1.54 (br s, 1H), 2.31 (s, 3H), 4.67 (s, 2H), 6.81 (s, 1H), 6.84 (s, 1H), 7.16–7.19 (m, 2H), 7.32–7.38 (m, 4H), 7.43–7.45 (m, 2H); ESI-MS: 289.1 ($M^+ + H$). Anal. calcd. for $C_{16}H_{16}O_5$: C, 73.19; H, 6.14; N, 3.71. Found: C, 73.32; H, 6.09; N, 3.58.

*5.26. [4-(6-Phenyl[1,2,4,5]tetroxan-3-yl)phenyl]methanol (**8a**)*

Yield: 55%; mp 158 °C; IR (KBr, cm^{-1}): 3338, 2924, 2868, 1456, 1423, 1367, 1023, 999, 913, 842, 791, 753, 695; ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 3.76 (br s, 1H), 4.70 (s, 2H), 6.92 (s, 2H), 7.32–7.52 (m, 9H); ESI-MS: 275.1 ($M^+ + H$). Anal. calcd. for $C_{15}H_{14}O_5$: C, 65.69; H, 5.15. Found: C, 65.58; H, 5.20.

*5.27. [4-(6-m-Tolyl[1,2,4,5]tetroxan-3-yl)phenyl]methanol (**8c**)*

Yield: 75%; mp 145 °C; IR (KBr, cm^{-1}): 3354, 2921, 2847, 1612, 1422, 1356, 1199, 1008, 935, 905, 825, 783, 698; ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 1.61 (br s, 1H), 2.38 (s, 3H), 4.74 (s, 2H), 6.89 (s, 1H), 6.92 (s, 1H), 7.26–7.37 (m, 4H), 7.42–7.45 (m, 2H), 7.50–7.53 (m, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$): 20.29, 63.64, 106.95, 107.29, 123.92, 125.97, 127.03, 127.33, 127.67, 129.02, 129.67, 131.12, 137.67, 143.24; ESI-HRMS calcd. for $C_{16}H_{16}O_5$: 288.0997; found: 289.0994 ($M^+ + H$).

*5.28. [4-(6-o-Tolyl[1,2,4,5]tetroxan-3-yl)phenyl]methanol (**8d**)*

Yield: 55%; mp 136 °C; IR (KBr, cm^{-1}): 3428, 2921, 2851, 1613, 1454, 1423, 1357, 1017, 890, 827, 785, 699; ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 1.76 (br, 1H), 2.38 (s, 3H), 4.75 (s, 2H), 6.94 (s, 1H), 7.10 (s, 1H), 7.22–7.36 (m, 3H), 7.43–7.54 (m, 5H); ^{13}C NMR (75.5 MHz, $CDCl_3$): 19.23, 64.77, 106.25, 108.03, 126.23, 127.02, 127.67, 128.02, 129.28, 130.06, 130.90, 131.07, 137.42, 144.25; ESI-HRMS calcd. for $C_{16}H_{16}O_5$: 288.0997; found: 289.0992 ($M^+ + H$).

*5.29. {4-[6-(4-Ethyl-phenyl)[1,2,4,5]tetroxan-3-yl]phenyl} methanol (**8e**)*

Yield: 55%; mp 138 °C; IR (KBr, cm^{-1}): 3393, 2932, 1638, 1422, 1363, 1203, 1003, 948, 838, 794; ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 1.21 (t, 3H, $J = 9$ Hz), 1.80 (br s, 1H), 2.64–2.71 (m, 2H), 4.69 (s, 2H), 6.89 (s, 1H), 6.91 (s, 1H), 7.25–7.27 (m, 2H), 7.36–7.44 (m, 4H),

7.49–7.52 (m, 2H); ESI-MS: 303.3 ($M^+ + H$). Anal. calcd. for $C_{17}H_{18}O_5$: C, 67.54; H, 6.00. Found: C, 67.58; H, 6.01.

5.30. {4-[6-(4-Isopropyl-phenyl)[1,2,4,5]tetroxan-3-yl]phenyl} methanol (**8f**)

Yield: 48%; mp 131 °C; IR (KBr, cm^{-1}): 3306, 2961, 2863, 1613, 1424, 1363, 1261, 1203, 1005, 913, 839, 802; ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 1.24 (d, 6H), 1.72 (br s, 1H), 2.89–2.98 (m, 1H), 4.74 (s, 2H), 6.89 (s, 1H), 6.91 (s, 1H), 7.26–7.31 (m, 2H), 7.42–7.45 (m, 4H), 7.50–7.53 (m, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$): 23.77, 23.99, 34.14, 64.70, 107.89, 108.22, 126.63, 126.92, 126.98, 127.19, 127.89, 128.04, 128.25, 130.11, 144.21, 152.52; ESI-MS: 317.1 ($M^+ + H$). Anal. calcd. for $C_{18}H_{20}O_5$: C, 68.34; H, 6.37. Found: C, 68.58; H, 6.31.

5.31. Methanesulfonic acid 4-(6-p-tolyl[1,2,4,5]tetroxan-3-yl) benzyl ester (**9a**)

To a stirred solution of compound **8b** (245 mg, 0.85 mmol) in THF 20 mL, triethylamine (258 mg, 2.55 mmol) was added followed by the drop wise addition of methanesulfonyl chloride (97 mg, 0.85 mmol). The reaction mixture was stirred for 4 h at room temperature. The progress of reaction was monitored by TLC. After the completion of reaction, the reaction mixture was extracted with $CHCl_3$ and the organic layer was dried over anhydrous $MgSO_4$. The excess of solvent was removed under vacuum. The crude product was purified over silica gel column using EtOAc/hexane as eluent to give **9a** (290 mg, 93%) as white solid; mp 122 °C; IR (KBr, cm^{-1}): 2925, 2852, 1354, 1175, 1020, 953, 829, 796, 747, 695; ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 2.32 (s, 3H), 2.88 (s, 3H), 5.19 (s, 2H), 6.81 (s, 1H), 6.86 (s, 1H), 7.16–7.19 (d, 2H, $J = 7.5$ Hz), 7.31–7.34 (d, 2H, $J = 7.8$ Hz), 7.40–7.43 (d, 2H, $J = 7.8$ Hz), 7.48–7.50 (d, 2H, $J = 7.8$ Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$): 21.57, 38.47, 46.09, 70.25, 107.32, 108.32, 127.76, 128.31, 128.82, 129.48, 131.67, 136.58, 141.84; ESI-MS: 367.1 ($M^+ + H$). Anal. calcd. for $C_{17}H_{18}O_7S$: C, 55.73; H, 4.95. Found: C, 55.33; H, 5.04.

5.32. Methanesulfonic acid 4-[6-(4-ethyl-phenyl)[1,2,4,5]tetroxan-3-yl]benzyl ester (**9b**)

Yield: 86%; mp 139 °C; IR (film, cm^{-1}): 3033, 2962, 2919, 2868, 1424, 1346, 1253, 1173, 1005, 958, 919, 836, 801; ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 1.21–1.26 (t, 3H, $J = 7.5$ Hz), 2.64–2.72 (q, 2H), 2.96 (s, 3H), 5.26 (s, 2H), 6.89 (s, 1H), 6.93 (s, 1H), 7.26–7.28 (d, 2H, $J = 7.2$ Hz), 7.41–7.44 (d, 2H, $J = 8.1$ Hz), 7.47–7.50 (d, 2H, $J = 8.1$ Hz), 7.55–7.58 (d, 2H, $J = 8.1$ Hz); ESI-HRMS calcd. for $C_{18}H_{20}O_7S$: 380.0929; found: 381.0926 ($M^+ + H$).

5.33. Phenyl[4-(6-p-tolyl[1,2,4,5]tetroxan-3-yl)benzyl]amine (**10a**)

Compound **9a** (150 mg, 0.41 mmol) was stirred with aniline (38 mg, 0.41 mmol) for 18 h at room temperature in THF. The progress of the reaction was monitored by TLC. After usual workup the crude product was purified over SiO_2 column and the product was eluted in EtOAc/hexane to yield compound **10a** (77 mg, 52%) as a white solid; mp 128 °C; IR (film, cm^{-1}): 3392, 2924, 2845, 1733, 1600, 1506, 1460, 1362, 1311, 1253, 1181, 1019, 829, 793, 752; ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 2.39 (s, 3H), 4.38 (s, 2H), 6.60–6.76 (m, 3H), 6.88–6.90 (d, 2H, $J = 6.0$ Hz), 7.14–7.23 (m, 3H), 7.39–7.50 (m, 8H); ESI-MS: 364.1 ($M^+ + H$). Anal. calcd. for $C_{22}H_{21}NO_4$: C, 72.71; H, 5.82; N, 3.85. Found: C, 72.94; H, 5.80; N, 3.78.

5.34. Naphthalen-1-yl[4-(6-p-tolyl-[1,2,4,5]tetroxan-3-yl)benzyl] amine (**10b**)

Yield: 48%; mp 129 °C; IR (film, cm^{-1}): 3453, 2923, 1581, 1462, 1260, 1018, 913, 745; ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 2.32 (s, 3H), 4.55 (s, 2H), 6.52 (m, 1H), 6.81–6.84 (d, 2H, $J = 9.3$ Hz), 7.13 (m, 6H), 7.32–7.52 (m, 9H); ESI-MS: 414.2 ($M^+ + H$). Anal. calcd. for $C_{26}H_{23}NO_4$: C, 75.53; H, 5.61; N, 3.39. Found: C, 75.63; H, 5.58; N, 3.39.

5.35. Methyl-phenyl[4-(6-p-tolyl[1,2,4,5]tetroxan-3-yl)benzyl] amine (**10c**)

Yield: 38%; mp 137 °C; IR (film, cm^{-1}): 2924, 1599, 1426, 1506, 1360, 1278, 1212, 1120, 1022, 1003, 934, 909; ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 2.38 (s, 3H), 3.01 (s, 3H), 4.50 (s, 2H), 6.71–6.73 (m, 2H), 6.87–6.88 (m, 2H), 7.22–7.31 (m, 3H), 7.38–7.46 (m, 8H); ESI-HRMS calcd. for $C_{23}H_{23}NO_4$: 377.1627; found: 378.1625 ($M^+ + H$).

5.36. p-Tolyl[4-(6-p-tolyl[1,2,4,5]tetroxan-3-yl)benzyl]amine (**10d**)

Yield: 62%; mp 162 °C; IR (film, cm^{-1}): 3389, 2954, 2924, 1613, 1520, 1460, 1363, 1020, 911, 792, 772; ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 2.23 (s, 3H), 2.38 (s, 3H), 4.36 (s, 2H), 6.51–6.54 (d, 2H, $J = 8.4$ Hz), 6.88–6.90 (d, 2H, $J = 6.0$ Hz), 6.96–6.99 (d, 2H, $J = 8.1$ Hz), 7.23–7.26 (m, 3H), 7.39–7.49 (m, 6H); ESI-MS: 378.2 ($M^+ + H$). Anal. calcd. for $C_{23}H_{23}NO_4$: C, 73.19; H, 6.14; N, 3.71. Found: C, 73.52; H, 6.18; N, 3.69.

5.37. m-Tolyl[4-(6-p-tolyl[1,2,4,5]tetroxan-3-yl)benzyl]amine (**10e**)

Yield: 53%; mp 144 °C; IR (film, cm^{-1}): 3451, 3038, 2924, 2852, 1607, 1492, 1362, 1326, 1010, 908, 830, 793, 763, 611; ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 2.26 (s, 3H), 2.38 (s, 3H), 4.36 (s, 2H), 6.39–6.56 (m, 3H), 6.87–6.90 (d, 2H, $J = 6.6$ Hz), 7.02–7.07 (m, 2H), 7.22–7.25 (d, 2H, $J = 8.4$ Hz), 7.38–7.49 (m, 6H); ESI-MS 378.1 ($M^+ + H$), Anal. calcd. for $C_{23}H_{23}NO_4$: C, 73.19; H, 6.14; N, 3.71. Found: C, 73.41; H, 6.11; N, 3.71.

5.38. o-Tolyl[4-(6-p-tolyl[1,2,4,5]tetroxan-3-yl)benzyl]amine (**10f**)

Yield: 41%; mp 126 °C; IR (film, cm^{-1}): 3453, 3012, 2950, 2925, 2852, 1723, 1606, 1586, 1512, 1454, 1364, 1324, 1263, 1215, 1181, 1019, 1007, 911, 793, 764; ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 2.18 (s, 3H), 2.39 (s, 3H), 4.40 (s, 2H), 6.52–6.58 (m, 1H), 6.74 (m, 2H), 6.8–6.9 (m, 2H), 7.07 (m, 2H), 7.26–7.59 (m, 8H); ESI-HRMS calcd. for $C_{23}H_{23}NO_4$: 377.1627; found: 378.1690 ($M^+ + H$).

5.39. (2,6-Dimethyl-phenyl)[4-(6-p-tolyl-[1,2,4,5]tetroxan-3-yl) benzyl]amine (**10g**)

Yield: 55%; mp 148 °C; IR (film, cm^{-1}): 3392, 2950, 2923, 2853, 1733, 1612, 1362, 1216, 1003, 909, 793, 764; ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 2.25 (s, 6H), 2.38 (s, 3H), 4.18 (s, 2H), 6.88–6.95 (m, 3H), 6.99–7.02 (m, 2H), 7.22–7.25 (d, 2H, $J = 7.5$ Hz), 7.39–7.50 (m, 7H); ^{13}C NMR (75.5 MHz, $CDCl_3$): 18.53, 21.61, 52.49, 52.64, 108.03, 108.33, 127.88, 128.18, 128.35, 129.02, 129.39, 141.80, 143.92, 145.51, 162.32; ESI-HRMS calcd. for $C_{24}H_{25}NO_4$: 391.1783; found: 392.1784 ($M^+ + H$).

5.40. (4-Ethyl-phenyl)[4-(6-p-tolyl[1,2,4,5]tetroxan-3-yl)benzyl] amine (**10h**)

Yield: 52%; mp 140 °C; IR (film, cm^{-1}): 3401, 3033, 2956, 2924, 2854, 1614, 1518, 1459, 1362, 1311, 1016, 911, 827, 792, 696; ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 1.15–1.20 (t, 3H, $J = 7.8$ Hz), 2.38 (s, 3H),

2.49–2.57 (q, 2H), 4.35 (s, 2H), 6.53–6.56 (d, 2H, $J = 8.4$ Hz), 6.87–6.89 (d, 2H, $J = 6.0$ Hz), 6.98–7.01 (d, 2H, $J = 8.4$ Hz), 7.22–7.25 (d, 2H, $J = 8.1$ Hz), 7.38–7.49 (m, 7H); ^{13}C NMR (75.5 MHz, $CDCl_3$): 15.74, 16.03, 21.61, 28.02, 28.55, 48.39, 108.05, 108.32, 111.19, 121.06, 127.75, 127.89, 128.21, 128.71, 129.58, 141.79, 141.89, 143.46, 145.77, 158.37; ESI-MS: 392.2 ($M^+ + H$). Anal. calcd. for $C_{24}H_{25}NO_4$: C, 73.64; H, 6.44; N, 3.58. Found: C, 73.38; H, 6.48; N, 3.41.

*5.41. (4-Isopropyl-phenyl)[4-(6-p-tolyl[1,2,4,5]tetroxan-3-yl) benzyl]amine (**10i**)*

Yield: 42%; mp 142 °C; IR (film, cm^{-1}): 3393, 2956, 2922, 2852, 1615, 1518, 1662, 1362, 1008, 911, 827, 796, 695; ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 1.18–1.28 (d, 6H, $J = 6.9$ Hz), 2.38 (s, 3H), 2.77–2.82 (m, 1H), 4.35 (s, 2H), 6.54–6.57 (d, 2H, $J = 8.4$ Hz), 6.87–6.90 (d, 2H, $J = 6.6$ Hz), 7.02–7.05 (d, 2H, $J = 8.4$ Hz), 7.17–728 (m, 2H), 7.38–7.49 (m, 7H); ESI-MS: 406.1 ($M^+ + H$). Anal. calcd. for $C_{25}H_{27}NO_4$: C, 74.05; H, 6.71; N, 3.45. Found: C, 74.22; H, 6.81; N, 3.51.

*5.42. (4-Propyl-phenyl)[4-(6-p-tolyl-[1,2,4,5]tetroxan-3-yl)benzyl] amine (**10j**)*

Yield: 37%; mp 140 °C; IR (film, cm^{-1}): 3391, 3286, 2950, 2923, 2853, 1652, 1615, 1518, 1462, 1362, 1249, 1007, 911, 828, 796; ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 0.89–0.98 (m, 3H), 1.53–1.70 (m, 2H), 2.38 (s, 3H), 2.44–2.49 (t, 2H, $J = 7.2$ Hz), 4.35 (s, 2H), 6.52–6.55 (d, 2H, $J = 8.4$ Hz), 6.87–6.89 (d, 2H, $J = 6.3$ Hz), 6.96–6.99 (d, 2H, $J = 8.4$ Hz), 7.15–7.25 (m, 2H), 7.38–7.62 (m, 7H); ^{13}C NMR (75.5 MHz, $CDCl_3$): 13.82, 21.49, 24.83, 37.12, 48.22, 107.92, 108.18, 112.87, 120.83, 127.61, 127.77, 127.93, 128.09, 128.16, 128.90, 129.19, 129.45, 129.64, 132.10, 141.68, 143.39, 145.71; ESI-MS: 406.18 ($M + H^+$). Anal. calcd. for $C_{25}H_{27}NO_4$: C, 74.05; H, 6.71; N, 3.45. Found: C, 73.83; H, 6.79; N, 3.44.

*5.43. (4-Fluoro-phenyl)[4-(6-p-tolyl[1,2,4,5]tetroxan-3-yl)benzyl] amine (**10k**)*

Yield: 51%; mp 136 °C; IR (film, cm^{-1}): 3376, 2923, 2852, 1612, 1511, 1462, 1421, 1361, 1223, 1106, 1010, 911, 820, 792, 695; ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 2.38 (s, 3H), 4.33 (s, 2H), 6.50–6.55 (m, 4H), 6.84–6.90 (m, 2H), 7.20–7.30 (m, 2H), 7.38–7.49 (m, 7H); ^{13}C NMR (75.5 MHz, $CDCl_3$): 21.48, 48.47, 107.84, 108.20, 113.63, 113.69, 115.57, 115.79, 127.58, 127.76, 128.14, 129.45, 141.72, 142.89; ESI-HRMS calcd. for $C_{22}H_{20}FNO_4$: 381.1376; found: 382.1374 ($M^+ + H$).

*5.44. (3-Fluoro-phenyl)[4-(6-p-tolyl[1,2,4,5]tetroxan-3-yl)benzyl] amine (**10l**)*

Yield: 49%; mp 148 °C; IR (film, cm^{-1}): 3451, 3054, 2940, 2914, 2752, 1613, 1609, 1415, 1401, 1343, 1311, 1001, 843, 798, 730; ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 2.39 (s, 3H), 4.43 (s, 2H), 6.67–6.69 (m, 2H), 6.90–6.92 (d, 2H, $J = 6.0$ Hz), 6.95–7.04 (m, 2H), 7.24–7.27 (d, 2H, $J = 8.1$ Hz), 7.40–7.53 (m, 7H); ESI-HRMS calcd. for $C_{22}H_{20}FNO_4$: 381.1376; found: 382.1378 ($M^+ + H$).

*5.45. (2-Fluoro-phenyl)[4-(6-p-tolyl[1,2,4,5]tetroxan-3-yl)benzyl] amine (**10m**)*

Yield:47%; mp 160 °C; IR (film, cm^{-1}): 3453, 3064, 2950, 2924, 2852, 1653, 1619, 1515, 1451, 1363, 1335, 1010, 833, 795, 740; ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 2.38 (s, 3H), 4.41 (s, 2H), 6.65–6.67 (m, 2H), 6.88–6.90 (d, 2H, $J = 7.8$ Hz), 6.93–7.02 (m, 2H), 7.22–7.25 (d, 2H, $J = 8.7$ Hz), 7.38–7.51 (m, 7H); ^{13}C NMR (75.5 MHz, $CDCl_3$): 21.48, 47.39, 107.84, 108.19, 112.25, 112.28, 114.32, 114.51, 117.03, 117.10, 124.54, 124.58, 127.44, 127.76, 127.89, 128.18, 128.38, 129.45, 136.09, 136.20, 141.70, 142.80; ESI-MS 382.2 ($M^+ + H$). Anal. calcd. for $C_{22}H_{20}FNO_4$: C, 69.28; H, 5.29; N, 3.67. Found: C, 69.69; H, 5.29; N, 3.63.

*5.46. (4-Chloro-phenyl)[4-(6-p-tolyl-[1,2,4,5]tetroxan-3-yl)benzyl] amine (**10n**)*

Yield: 53%; mp 162 °C; IR (film, cm^{-1}): 3386, 3235, 2950, 2922, 2851, 1736, 1498, 1460, 1357, 1176, 1084, 1010, 824, 793; ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 2.38 (s, 3H), 4.35 (s, 2H), 6.50–6.52 (d, 2H, $J = 8.7$ Hz,), 6.87–6.90 (d, 2H, $J = 7.2$ Hz), 7.08–7.11 (d, 2H, $J = 9.0$ Hz), 7.15–7.25 (m, 2H), 7.35–7.50 (m, 7H); ESI-MS: 398.1 ($M^+ + H$). Anal. calcd. for $C_{22}H_{20}ClNO_4$: C, 66.42; H, 5.07; N, 3.52. Found: C, 66.01; H, 5.11; N, 3.57.

*5.47. (3-Chloro-phenyl)[4-(6-p-tolyl-[1,2,4,5]tetroxan-3-yl)benzyl] amine (**10o**)*

Yield: 46%; mp 132 °C; IR (film, cm^{-1}): 3449, 2953, 2925, 2854, 1735, 1597, 1499, 1482, 1377, 1363, 1325, 1007, 909, 830; ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 2.38 (s, 3H), 4.36 (s, 2H), 6.44–6.70 (m, 3H), 6.8–6.90 (m, 2H), 7.03–7.08 (m, 2H), 7.23–7.50 (m, 8H); ESI-MS: 398.2 ($M^+ + H$). Anal. calcd. for $C_{22}H_{20}ClNO_4$: C, 66.42; H, 5.07; N, 3.52. Found: C, 66.74; H, 5.01; N, 3.63.

*5.48. (2-Chloro-phenyl)[4-(6-p-tolyl[1,2,4,5]tetroxan-3-yl)benzyl] amine (**10p**)*

Yield: 33%; mp 188 °C; IR (film, cm^{-1}): 3443, 2921, 2852, 1597, 1509, 1459, 1423, 1365, 1325, 1288, 1007, 910, 835, 740; ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 2.38 (s,3H), 4.44–4.46 (d, 2H, $J = 5.7$ Hz), 6.52–6.54 (d, 2H, $J = 8.1$ Hz), 6.62–6.67 (m, 1H), 6.87–6.90 (d, 2H, $J = 7.8$ Hz), 7.04–7.09 (m, 1H), 7.22–7.28 (m, 2H), 7.38–7.50 (m, 7H); ESI-HRMS calcd. for $C_{22}H_{20}ClNO_4$: 397.1080; found: 398.1082 ($M^+ + H$).

*5.49. [4-(6-p-Tolyl[1,2,4,5]tetroxan-3-yl)benzyl](2,4,5-trichloro-phenyl)amine (**10q**)*

Yield: 31%; mp 180 °C; IR (film, cm^{-1}): 3384, 3235, 2955, 2921, 2851, 1755, 1498, 1460, 1357, 1176, 1084, 1001, 824, 791; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.32 (s, 3H), 4.33–4.34 (d, 2H, $J = 5.5$ Hz), 6.54 (s, 1H), 6.81 (s, 1H), 6.85 (s, 1H), 7.16–7.19 (m, 2H), 7.28 (s, 2H), 7.32–7.34 (d, 4H, $J = 8.2$ Hz), 7.44–7.46 (d, 2H, $J = 8.2$ Hz); ESI-HRMS calcd. for $C_{22}H_{18}Cl_3NO_4$: 465.0301; found: 466.0304 ($M^+ + H$).

*5.50. (4-Bromo-phenyl)[4-(6-p-tolyl[1,2,4,5]tetroxan-3-yl)benzyl] amine (**10r**)*

Yield: 34%; mp 149 °C; IR (film, cm^{-1}): 3411, 2997, 2950, 2927, 2850, 1613, 1512, 1460, 1362, 1174, 1204, 1152, 1010, 808, 757; ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 2.38 (s, 3H), 4.33 (s, 2H), 6.48–6.59 (m, 4H), 6.89–6.98 (m, 2H), 7.14–8.02 (m, 9H); ESI-MS: 442.1 ($M^+ + H$). Anal. calcd. for $C_{22}H_{20}BrNO_4$: C, 59.74; H, 4.56; N, 3.17. Found: C, 59.24; H, 4.55; N, 3.19.

*5.51. (4-Methoxy-phenyl)[4-(6-p-tolyl-[1,2,4,5]tetroxan-3-yl) benzyl]amine (**10s**)*

Yield: 39%; mp 146 °C; IR (film, cm^{-1}): 3390, 2925, 2852, 1702, 1611, 1513, 1460, 1363, 1247, 1112, 1008, 828, 794, 756; ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 2.39 (s, 3H), 3.79 (s, 3H), 4.38 (s, 2H), 6.62–6.79 (m, 4H), 6.87–6.93 (m, 2H), 7.23–7.46 (m, 9H); ESI-MS:

394.2 ($M^+ + H$). Anal. calcd. for $C_{23}H_{23}NO_5$: C, 70.21; H, 5.89; N, 3.56. Found: C, 66.93; H, 5.51; N, 3.53.

5.52. (3,5-Dimethoxy-phenyl)[4-(6-p-tolyl[1,2,4,5]tetroxan-3-yl) benzyl]amine (**10t**)

Yield: 48%; mp 125 °C; IR (film, cm^{-1}): 3447, 3374, 2924, 2852, 1610, 1460, 1421, 1361, 1204, 1152, 1008, 803, 677; ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 2.38 (s, 3H), 3.72 (s, 6H), 4.34 (s, 2H), 5.79–5.89 (m, 3H), 6.87–6.89 (d, 2H), 7.22–7.30 (m, 2H), 7.38–7.48 (m, 7H); ESI-MS 424.2 ($M^+ + H$). Anal. calcd. for $C_{24}H_{25}NO_6$: C, 68.07; H, 5.95; N, 3.31. Found: C, 68.51; H, 5.85; N, 3.33.

5.53. 4-[4-(6-p-Tolyl[1,2,4,5]tetroxan-3-yl)benzylamino]phenol (**10u**)

Yield: 45%; mp 117 °C; IR (film, cm^{-1}): 3449, 2950, 2922, 2847, 1701, 1363, 1207, 1007, 911, 829, 793; ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 2.39 (m, 3H), 4.32 (s, 2H), 4.75 (br s, 1H), 6.50–6.53 (d, 2H, $J = 8.1$ Hz), 6.68–6.70 (d, 2H, $J = 8.7$ Hz), 6.88–6.91 (m, 2H), 7.23–7.53 (m, 9H); ESI-HRMS: 380.1438 ($M^+ + H$). Anal. calcd. for $C_{22}H_{21}NO_5$: C, 69.64; H, 5.58; N, 3.69. Found: C, 69.42; H, 5.57; N, 3.61.

5.54. 3-[4-(6-p-Tolyl[1,2,4,5]tetroxan-3-yl)benzylamino]phenol (**10v**)

Yield: 43%; mp 150 °C; IR (film, cm^{-1}): 3425, 2955, 2925, 1615, 1458, 1363, 1208, 1008, 793, 760; ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 2.38 (s, 3H), 4.36 (s, 2H), 4.74 (br s, 1H), 6.28 (m, 2H), 6.88–6.91 (m, 2H), 7.23–7.30 (m, 2H), 7.38–7.52 (m, 9H); ESI-HRMS calcd. for $C_{22}H_{21}NO_5$: 379.1419; found: 380.1413 ($M^+ + H$).

5.55. N1-(4-(6-p-Tolyl-1,2,4,5-tetraoxan-3-yl)benzyl)benzene-1,4-diamine (**10w**)

Yield: 20%; mp 138 °C; IR (film, cm^{-1}): 3386, 2924, 2854, 1597, 1509, 1363, 1009, 912, 827, 794, 739; ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 0.78–0.80 (br s, 2H), 2.31 (s, 3H), 4.27 (s, 2H), 5.86–6.03 (m, 4H), 6.80–6.90 (m, 2H), 7.15–7.18 (m, 2H), 7.31–7.42 (m, 7H); ESI-HRMS calcd. for $C_{22}H_{22}N_2O_4$: 378.1579; found: 379.1576 ($M^+ + H$).

5.56. 4-(6-p-Tolyl[1,2,4,5]tetroxan-3-yl)benzoic acid (**11a**)

Compound **3b** (400 mg, 1.40 mmol) was dissolved in acetone (80 mL), and a solution of $CrO_3/H_2SO_4/H_2O$ (1 g/1 mL/10 mL) was added drop wise to the above solution at the interval of 2 h. The progress of the reaction was monitored by TLC. After usual workup the crude product was purified over silica gel column using EtOAc/hexane as eluent to obtain compound **11a** (346 mg, 82%) as a white solid; mp 247 °C; IR (Nujol, cm^{-1}): 2924, 2854, 1720, 1695, 1460, 1377, 1292, 1034, 1003, 915,765; ^1H NMR (300 MHz, DMSO-d_6): δ (ppm) 2.26 (s, 3H), 6.98 (s, 1H), 7.09 (s, 1H), 7.22–7.24 (d, 2H, $J = 7.5$ Hz), 7.38–7.41 (d, 2H, $J = 7.5$ Hz), 7.61–7.64 (d, 2H, $J = 7.8$ Hz), 7.95–7.98 (d, 2H, $J = 7.8$ Hz), 13.17 (br s, 1H); ^{13}C NMR (75.5 MHz, DMSO-d_6): 21.04, 106.53, 107.53, 127.77, 127.96, 128.16, 129.47, 129.76, 133.50, 134.62, 141.65, 166.56; ESI-MS: 303.1 ($M^+ + H$). Anal. calcd. for $C_{16}H_{14}O_6$: C, 63.57; H, 4.67. Found: C, 63.65; H, 4.63.

5.57. 4-[6-(4-Ethyl-phenyl)[1,2,4,5]tetroxan-3-yl]benzoic acid (**11b**)

Yield: 67%; mp 248–250 °C; IR (Nujol, cm^{-1}): 2924, 2854, 2669, 1695, 1612, 1463, 1316, 1285, 1031, 1001, 914, 767; ^1H NMR (300 MHz, DMSO-d_6): δ (ppm) 1.21–1.26 (t, 3H), 2.69–2.71 (m, 2H), 7.13 (s, 1H), 7.23 (s, 1H), 7.38–7.41 (d, 2H, $J = 7.2$ Hz), 7.55–7.57 (d, 2H, $J = 7.2$ Hz), 7.76–7.78 (d, 2H, $J = 7.5$ Hz), 8.09–8.12 (d, 2H, $J = 7.2$ Hz), 13.33 (br s, 1H); ESI-MS: 317.1 ($M^+ + H$). Anal. calcd. for $C_{17}H_{16}O_6$: C, 64.55 H, 5.10. Found: C, 64.94; H, 5.07.

5.58. General procedure for the synthesis of amides

The acid **11a** or **11b** was dissolved in THF and triethylamine was added to the solution. After 15 min ethylchloroformate was added to the reaction mixture. The reaction mixture was stirred for 30 min and amine was added to the reaction mixture. Reaction mixture was stirred for 2 h and progress of the reaction was monitored by TLC. The reaction mixture was extracted with $CHCl_3$ and organic layer was dried over anhydrous Na_2SO_4. Excess of the solvent was removed under vacuum. The crude product was purified over silica gel column using EtOAc/hexane as eluent.

5.58.1. N-(2-Hydroxy-ethyl)-4-(6-p-tolyl[1,2,4,5]tetroxan-3-yl) benzamide (**12a**)

Yield: 53%; mp 190 °C; IR (Nujol, cm^{-1}): 3286, 2924, 2854, 1638, 1551, 1458, 1377, 1120, 852, 804; ^1H NMR (300 MHz, DMSO-d_6): δ (ppm) 2.26 (s, 3H), 3.39–3.43 (t, 2H, $J = 5.7$ Hz), 4.63–4.67 (t, 2H, $J = 5.7$ Hz), 6.97 (s, 1H), 7.05 (s, 1H), 7.21–7.24 (d, 2H, $J = 7.8$ Hz), 7.37–7.40 (d, 2H, $J = 8.1$ Hz), 7.57–7.59 (d, 2H, $J = 8.1$ Hz), 7.84–7.87 (d, 2H, $J = 8.1$ Hz), 8.49 (br s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): 21.07, 42.27, 59.63, 106.72, 107.50, 127.77, 127.91, 127.98, 129.51, 133.03, 137.38, 141.67, 165.58; ESI-MS: 346.12 ($M^+ + H$). Anal. calcd. for $C_{18}H_{19}NO_6$: C, 62.60; H, 5.55; N, 4.06. Found: C, 62.91; H, 5.47; N, 4.16.

5.58.2. 4-[6-(4-Ethyl-phenyl)[1,2,4,5]tetroxan-3-yl]-N-(2-hydroxy-ethyl)benzamide (**12b**)

Yield: 68%; mp 197 °C; IR (film, cm^{-1}): 3286, 2918, 2850, 1718, 1638, 1621, 1543, 1461, 1418, 1286, 1178, 1062, 1021, 996, 914, 852; ^1H NMR (300 MHz, DMSO-d_6): δ (ppm) 1.16–1.21 (t, 3H, $J = 7.2$ Hz), 2.62–2.66 (q, 2H), 3.38–3.52 (m, 4H), 4.56 (br s, 1H), 7.07 (s, 1H), 7.14 (s, 1H), 7.34–7.36 (d, 2H, $J = 7.5$ Hz), 7.49–7.52 (d, 2H, $J = 7.2$ Hz), 7.66–7.69 (d, 2H, $J = 7.5$ Hz), 7.94–7.96 (d, 2H, $J = 7.5$ Hz), 8.57 (br s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): 15.34, 28.10, 41.08, 59.62, 106.71, 107.50, 127.75, 127.89, 128.05, 128.19, 128.34, 133.01, 137.37, 147.78, 165.54; ESI-MS: 360.1 ($M^+ + H$). Anal. calcd. for $C_{19}H_{21}NO_6$: C, 63.50; H, 5.89; N, 3.90. Found: C, 63.11; H, 5.79; N, 3.89.

5.58.3. N-(3-Hydroxy-propyl)-4-(6-p-tolyl-[1,2,4,5]tetroxan-3-yl) benzamide (**12c**)

Yield: 72%; mp 170 °C; IR (film, cm^{-1}): 3390, 3297, 2950, 2852, 2918, 1637, 1540, 1018, 997, 852, 803; ^1H NMR (300 MHz, DMSO-d_6): δ (ppm) 1.66–1.72 (m, 2H), 2.35 (s, 3H), 3.45–3.47 (m, 2H), 4.48 (m, 3H), 7.06 (s, 1H), 7.14 (s, 1H), 7.30–7.33 (d, 2H, $J = 7.8$ Hz), 7.47–7.49 (d, 2H, $J = 7.8$ Hz), 7.66–7.68 (d, 2H, $J = 8.1$ Hz), 7.91–7.94 (d, 2H, $J = 7.8$ Hz), 8.57–8.59 (br s, 1H); ^{13}C NMR (75.5 MHz, DMSO-d_6): 21.02, 32.30, 36.67, 58.55, 56.25, 106.69, 107.46, 127.64, 127.87, 127.92, 129.45, 136.95, 137.45, 141.60, 165.43; ESI-MS: 360.1 ($M^+ + H$). Anal. calcd. for $C_{19}H_{21}NO_6$: C, 63.50; H, 5.89; N, 3.90. Found: C, 63.59; H, 5.47; N, 3.84.

5.58.4. 4-[6-(4-Ethyl-phenyl)[1,2,4,5]tetroxan-3-yl]-N-(3-hydroxy-propyl)benzamide (**12d**)

Yield: 73%; mp 162 °C; IR (film, cm^{-1}): 3297, 2919, 2850, 1695, 1635, 1538, 1259, 1017, 993, 851, 810, 766; ^1H NMR (300 MHz, DMSO-d_6): δ (ppm) 1.16–1.21 (t, 3H, $J = 7.5$ Hz), 1.64–1.73 (m, 2H), 2.62–2.71 (q, 2H), 3.30–3.49 (m, 5H), 7.07 (s, 1H), 7.14 (s, 1H), 7.34–7.36 (d, 2H, $J = 7.8$ Hz), 7.49–7.52 (d, 2H, $J = 7.8$ Hz), 7.66–7.69 (d, 2H, $J = 8.1$ Hz), 7.92–7.95 (d, 2H, $J = 7.8$ Hz), 8.57–8.58 (br s, 1H);

^{13}C NMR (100 MHz, DMSO-d_6): 15.35, 28.87, 32.08, 46.23, 58.55, 106.72, 107.51, 127.69, 127.93, 128.06, 128.35, 132.99, 137.46, 147.79, 165.46; ESI-MS: 374.2 ($M^+ + H$). Anal. calcd. for $C_{20}H_{23}NO_6$: C, 64.33; H, 6.21; N, 3.75. Found: C, 64.42; H, 6.30; N, 3.69.

*5.58.5. N-(6-Hydroxy-hexyl)-4-(6-p-tolyl[1,2,4,5]tetroxan-3-yl) benzamide (**12e**)*

Yield: 69%; mp 175 °C; IR (film, cm^{-1}): 3298, 2927, 2857, 1804, 1701, 1637, 1534, 1458, 1255, 1198, 1148, 1121, 1078, 1007, 873, 760; ^{1}H NMR (300 MHz, DMSO-d_6): δ (ppm) 1.03–1.52 (m, 6H), 2.35 (s, 3H), 3.25–3.45 (m, 4H), 3.92–3.99 (m, 3H), 7.03–7.18 (m, 2H), 7.30–7.33 (d, 2H, $J = 7.5$ Hz), 7.47–7.57 (m, 2H), 7.66–7.83 (m, 2H), 7.89–8.16 (m, 2H), 8.57 (br s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): 21.06, 25.25, 26.20, 29.52, 32.51, 56.04, 59.45, 60.67, 106.57, 107.62, 127.99, 128.20, 129.50, 132.92, 133.52, 135.98, 137.52, 141.66, 143.02, 156.30, 166.60; ESI-MS 402.2 ($M^+ + H$). Anal. calcd. for $C_{22}H_{27}NO_6$: C, 65.82; H, 6.78; N, 3.49. Found C, 65.49; H, 6.69; N, 3.51.

*5.58.6. 4-[6-(4-Ethyl-phenyl)[1,2,4,5]tetroxan-3-yl]-N-(6-hydroxy-hexyl)benzamide (**12f**)*

Yield: 64%; mp 202 °C; IR (film, cm^{-1}): 3308, 2929, 2859, 1696, 1638, 1537, 1506, 1362, 1016, 1003, 843; ^{1}H NMR (300 MHz, DMSO-d_6): δ (ppm) 1.06–1.53 (m, 11H), 2.64–2.67 (m, 2H), 3.28–3.39 (m, 5H), 7.05 (s, 1H), 7.12–7.14 (m, 1H), 7.33–7.35 (d, 2H, $J = 7.2$ Hz), 7.49–7.51 (d, 2H, $J = 7.5$ Hz), 7.65–7.72 (m, 2H), 7.92–7.94 (d, 2H, $J = 6$ Hz), 8.48 (br s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): 14.70, 15.32, 25.28, 26.42, 28.14, 29.08, 32.52, 60.65, 106.70, 107.51, 127.68, 127.91, 128.06, 128.35, 129.43, 132.96, 137.52, 147.80, 165.31; ESI-HRMS calcd. for $C_{23}H_{29}NO_6$: 415.1994; found: 416.1998 ($M^+ + H$).

*5.58.7. N-Propyl-4-(6-p-tolyl[1,2,4,5]tetroxan-3-yl)benzamide (**12g**)*

Yield: 48%; mp 209 °C; IR (film, cm^{-1}): 3293, 2922, 1806, 1698, 1638, 1540, 1421, 1364, 1288, 1200, 1018, 914, 852, 709; ^{1}H NMR (300 MHz, DMSO-d_6): δ (ppm) 0.87–0.92 (t, 3H), 1.51–1.58 (m, 2H), 2.36 (s, 3H), 3.20–3.26 (m, 2H), 7.07 (s, 1H), 7.16 (s, 1H), 7.31–7.33 (d, 2H, $J = 7.5$ Hz), 7.47–7.50 (d, 2H, $J = 7.8$ Hz), 7.66–7.69 (d, 2H, $J = 8.1$ Hz), 7.92–7.95 (d, 2H, $J = 7.8$ Hz), 8.58 (br s, 1H,); ^{13}C NMR (100 MHz, DMSO-d_6): 11.46, 15.33, 22.31, 39.50, 41.05, 106.72, 107.49, 127.68, 127.90, 128.05, 128.34, 165.37; ESI-MS: 344.2 ($M^+ + H$). Anal. calcd. for $C_{19}H_{21}NO_5$: C, 66.46; H, 6.16; N, 4.08. Found: C, 66.77; H, 6.05; N, 4.04.

*5.58.8. N-Butyl-4-(6-p-tolyl[1,2,4,5]tetroxan-3-yl)benzamide (**12h**)*

Yield: 53%; mp 180 °C; IR (film, cm^{-1}): 3305, 2924, 2854, 1637, 1539, 1463, 1377; ^{1}H NMR (300 MHz, DMSO-d_6): δ (ppm) 0.87–0.92 (t, 3H), 1.29–1.36 (m, 2H), 1.48–1.53 (m, 2H), 2.35 (s, 3H), 3.25–3.34 (m, 2H), 7.06 (s, 1H), 7.14 (s, 1H), 7.31–7.33 (d, 2H, $J = 7.5$ Hz), 7.47–7.49 (d, 2H, $J = 7.8$ Hz), 7.65–7.68 (d, 2H, $J = 7.8$ Hz), 7.91–7.94 (d, 2H, $J = 7.8$ Hz), 8.57 (br s, 1H); ^{13}C NMR (75.5 MHz, DMSO-d_6): 13.70, 19.64, 20.13, 31.13, 106, 107, 127.66, 127.86, 127.93, 129.46, 129.58, 129.72; ESI-MS: 358.2 ($M^+ + H$). Anal. calcd. for $C_{20}H_{23}NO_5$: C, 67.21; H, 6.49; N, 3.92. Found: C, 67.42; H, 6.43; N, 3.91.

*5.58.9. N-Butyl-4-[6-(4-ethyl-phenyl)[1,2,4,5]tetroxan-3-yl] benzamide (**12i**)*

Yield: 58%; mp 198 °C; IR (film, cm^{-1}): 3302, 2950, 2921, 2850, 1635, 1542, 1458, 1364, 1292, 1017, 994, 852; ^{1}H NMR (300 MHz, DMSO-d_6): δ (ppm) 0.88–0.92 (t, 3H, $J = 7.2$ Hz), 1.16–1.21 (t, 3H, $J = 7.5$ Hz), 1.27–1.39 (m, 2H), 1.46–1.56 (m, 2H), 2.61–2.69 (q, 2H), 3.23–3.33 (m, 2H), 7.07 (s, 1H), 7.16 (s, 1H), 7.33–7.36 (d, 2H, $J = 7.8$ Hz),7.49–7.52 (d, 2H, $J = 7.8$ Hz), 7.65–7.69 (m, 2H), 7.89–7.94 (m, 2H), 8.53–8.58 (br s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): 14.30, 15.90, 20.19, 28.69, 31.74, 107.30, 108.06, 127.62, 128.24, 128.47, 128.62, 128.91, 133.52, 137.44, 138.10, 148.33, 165.90; ESI-HRMS: 372.1740 ($M^+ + H$). Anal. calcd. for $C_{21}H_{25}NO_5$: C, 67.91; H, 6.78; N, 3.77. Found: C, 68.11; H, 6.68; N, 3.77.

*5.58.10. 4-[6-(4-Ethyl-phenyl)[1,2,4,5]tetroxan-3-yl]-N-pentyl-benzamide (**12j**)*

Yield: 65%; mp 190 °C; IR (film, cm^{-1}): 3300, 2950, 2924, 2853, 1696, 1636, 1539, 1256, 1020, 999, 853, 803, 769; ^{1}H NMR (300 MHz, DMSO-d_6): δ (ppm) 0.83–0.87 (m, 3H), 1.06–1.53 (m, 9H), 2.91–2.98 (m, 2H), 3.18–3.34 (m, 2H), 7.07 (s, 1H), 7.17 (s, 1H), 7.30–7.33 (d, 2H, $J = 7.8$ Hz), 7.47–7.50 (d, 2H, $J = 7.8$ Hz), 7.66–7.69 (d, 2H, $J = 8.1$ Hz), 7.93–7.95 (d, 2H, $J = 7.8$ Hz), 8.57 (br s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): 13.92, 14.70, 21.04, 21.84, 28.45, 28.71, 29.13, 59.36, 106.72, 107.49, 127.67, 127.89, 127.96, 128.17, 129.77, 132.95, 141.62, 156.23, 165.29; ESI-MS: 386.2 ($M^+ + H$). Anal. calcd. for $C_{22}H_{27}NO_5$: C, 68.55; H, 7.06; N, 3.63. Found: C, 68.92; H, 7.12; N, 3.69.

*5.58.11. N-[2-(7-Chloro-quinolin-4-ylamino)ethyl]-4-(6-p-tolyl [1,2,4,5]tetroxan-3-yl)benzamide (**12k**)*

Yield: 45%; mp 128 °C; IR (film, cm^{-1}): 3278, 2931, 1701, 1611, 1582, 1543, 1369, 1264, 1140, 1036, 805; ^{1}H NMR (300 MHz, DMSO-d_6): δ (ppm) 2.36 (s, 3H), 3.24–3.66 (m, 4H), 6.57–6.68 (m, 2H), 7.28–7.30 (m, 2H), 7.40–7.55 (m, 2H), 7.70–7.84 (m, 2H), 7.92–8.12 (m, 3H), 8.24–8.32 (m, 3H), 8.37–8.50 (m, 2H), 8.89–8.95 (br s, 1H); ESI-MS: 506.2 ($M^+ + H$). Anal. calcd. for $C_{27}H_{24}ClN_3O_5$: C, 64.10; H, 4.78; N, 8.31. Found: C, 64.52; H, 4.91; N, 8.29.

*5.58.12. N-[3-(7-Chloro-quinolin-4-ylamino)propyl]-4-(6-p-tolyl [1,2,4,5]tetroxan-3-yl)benzamide (**12l**)*

Yield: 38%; mp 118 °C; IR (film, cm^{-1}): 3210, 2923, 2852, 1702, 1610, 1463, 1377, 722; ^{1}H NMR (300 MHz, DMSO-d_6): δ (ppm) 1.74–1.96 (m, 2H), 2.36 (s, 3H), 3.07–3.13 (m, 2H), 3.28–3.42 (m, 2H), 6.51–6.56 (m, 2H), 7.06 (s, 1H), 7.14–7.18 (m, 1H), 7.28–7.69 (m, 6H), 7.80–8.04 (m, 4H), 8.27–8.42 (m, 2H), 8.71–8.73 (br s, 1H); ESI-MS: 520.1 ($M^+ + H$). Anal. calcd. for $C_{28}H_{26}ClN_3O_5$: C, 64.68; H, 5.04; N, 8.08. Found: C, 64.89; H, 5.17; N, 8.11.

*5.58.13. N-[3-(7-Chloro-quinolin-4-ylamino)propyl]-4-[6-(4-ethyl-phenyl)[1,2,4,5]tetroxan-3-yl]benzamide (**12m**)*

Yield: 42%; mp 138 °C; IR (film, cm^{-1}): 3390, 2929, 2857, 1702, 1582, 1541, 1370, 1273, 1043, 804; ^{1}H NMR (300 MHz, DMSO-d_6): δ (ppm) 1.11–1.22 (m, 3H), 1.76–1.83 (m, 2H), 2.65–2.71 (m, 2H), 3.06–3.13 (m, 2H), 3.25–3.45 (m, 2H), 6.47–6.51 (m, 2H), 7.17 (m, 2H), 7.31–7.47 (m, 4H), 7.78–8.11 (m, 4H), 8.24–8.40 (m, 4H), 8.75 (br s, 1H); ESI-HRMS calcd. for $C_{29}H_{28}ClN_3O_5$: 533.1717; found: 534.1758 ($M^+ + H$).

*5.58.14. N-Phenethyl-4-(6-p-tolyl[1,2,4,5]tetroxan-3-yl)benzamide (**12n**)*

Yield: 39%; mp 146 °C; IR (film, cm^{-1}): 3312, 2921, 2852, 1695, 1634, 1534, 1255, 1181, 1004, 909, 849, 798, 744, 696; ^{1}H NMR (300 MHz, DMSO-d_6): δ (ppm) 2.33 (s, 3H), 2.81–2.86 (t, 2H, $J = 7.2$ Hz), 3.47–3.51 (t, 2H, $J = 6.3$ Hz), 6.99 (s, 1H), 7.12–7.31 (m, 8H), 7.45–7.48 (d, 2H, $J = 7.8$ Hz), 7.64–7.67 (d, 2H, $J = 7.8$ Hz), 7.88–7.91 (d, 2H, $J = 8.1$ Hz), 8.69 (br s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): 14.62, 21.05, 35.06, 106.61, 107.49, 126.00, 127.97, 128.36, 128.67, 129.48, 139.42, 165.37; ESI-HRMS calcd. for $C_{24}H_{23}NO_5$: 405.1576; found: 406.1573 ($M^+ + H$).

*5.58.15. (4-Phenyl-piperazin-1-yl)[4-(6-p-tolyl[1,2,4,5]tetroxan-3-yl)phenyl]methanone (**12o**)*

Yield: 42%; mp 204 °C; IR (film, cm^{-1}): 3018, 2925, 1635, 1540, 1311, 1018, 945, 914, 852, 834, 812, 767, 668; ^{1}H NMR (300 MHz, DMSO-d_6): δ (ppm) 2.38 (s, 3H), 3.34–3.60 (m, 8H), 6.26 (m, 1H), 6.85 (m, 2H), 7.03–7.19 (m, 2H), 7.28–7.53 (m, 4H), 7.63–7.81 (m,

2H), 7.98–8.13 (m, 4H); ESI-MS: 447.2 ($M^+ + H$). Anal. calcd. for $C_{26}H_{26}N_2O_5$: C, 69.94; H, 5.87; N, 6.27. Found: C, 69.64; H, 5.77; N, 6.31.

*5.58.16. N-Cyclohexyl-4-(6-p-tolyl-1,2,4,5-tetraoxan-3-yl) benzamide (**12p**)*

Yield: 43%; mp 220 °C; IR (film, cm^{-1}): 3440, 3307, 2928, 2854, 1805, 1705, 1630, 1537, 1450, 1368, 1253, 1215, 1172, 1058, 1005, 804, 759; ^1H NMR (300 MHz, DMSO-d_6): δ (ppm) 1.14–1.82 (m, 10H), 2.36 (s, 3H), 3.77 (m, 1H,), 7.06 (s, 1H), 7.13 (s, 1H), 7.31–7.33 (d, 2H, $J = 6.9$ Hz), 7.46–7.49 (d, 2H, $J = 7.2$ Hz), 7.64–7.67 (d, 2H, $J = 7.8$ Hz), 7.91–7.94 (d, 2H, $J = 7.5$ Hz), 8.31 (br s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): 20.98, 24.88, 25.24, 32.33, 48.46, 106.38, 107.40, 127.76, 127.81, 127.94, 128.05, 129.43, 132.86, 137.66, 141.69, 164.62; ESI-MS: 384.1 ($M^+ + H$). Anal. calcd. for $C_{22}H_{25}NO_5$: C, 68.91; H, 6.57; N, 3.65. Found: C, 69.42;, 6.36; N, 3.61.

*5.58.17. N-(7-Aminoheptyl)-4-(6-p-tolyl-1,2,4,5-tetraoxan-3-yl) benzamide (**12q**)*

Yield: 50%; mp 178 °C; IR (film, cm^{-1}): 3310, 2927, 2852, 1804, 1688, 1636, 1540, 1463, 1367, 1264, 1200, 1006, 853, 804, 759; ^1H NMR (300 MHz, DMSO-d_6): δ (ppm) 1.03–1.52 (m, 8H), 2.35 (s, 3H), 2.92–2.94 (m, 2H), 3.25–3.44 (m, 4H), 3.88–3.96 (m, 2H), 7.07–7.21 (m, 2H), 7.31–7.33 (d, 2H, $J = 6$ Hz), 7.47–7.49 (d, 2H, $J = 6$ Hz), 7.65–7.73 (m, 2H), 7.79–7.94 (m, 2H), 8.56 (br s, 1H); ESI-HRMS calcd. for $C_{23}H_{30}N_2O_5$: 414.2154; found: 415.2152 ($M^+ + H$).

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