ISSN: 2249 –4820

Chemistry & Biology Interface, 2012, 2, 6, 373-393

Chemistry & Biology Interface

An official Journal of ISCB, Journal homepage; www.cbijournal.com

Research Paper

Syntheses of low molecular weight hydroxamates as potent antiprotozoal and antifungal agents

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*Received 11July 2012; Accepted 29*August *2012*

Keywords: Malaria, *Plasmodium falciparum*, *Trypanosoma*, Human African trypanosomiasis, Hydroxamic acid, Antifungal.

Abstract: Syntheses of a small library of hydroxamates by reacting esters of different carboxylic acids with hydroxyl amine hydrochloride has been achieved. All the synthesized compounds were screened in *vitro* against *Trypanosoma brucei brucei S427* and *Plasmodium falciparum 3D7* strain. The IC_{50} values of potent anti-trypanosomal agents ranged between 0.025-5.69 µg/mL, while these values varied in the range of 0.78 - 40.89 µg/mL against *P. falciparum*. Five compounds with very good SI values were active against both the protozoans. Some compounds have also shown strong antifungal activities with MIC as low as 0.19 µg/mL. These simple low molecular weight hydroxamates with triple activities and high degree of SI values revealed a new strategy in malaria/HAT and fungal chemotherapy.

Introduction

Human African trypanosomiasis (HAT) and Malaria are vector-borne parasitic diseases caused by protozoans *Trypanosoma brucei brucei* (*T.b.b*) and *Plasmodium falciparum* (*P. falciparum*) respectively. Both the diseases are responsible for major public health and economic problems in rural population of sub-Saharan Africa and other tropical and sub tropical countries. Even though advancement in fighting malaria worldwide, this disease kills nearly 700,000 people annually [1].

On the other hand *Trypanosoma brucei,* the causative agent of sleeping sickness infects about 10,000 people per year [2]. Major reason for this devastating situation is the emergence of drug resistance, differing susceptibility to classical and affordable drugs besides producing undesirable side effects. In absence of suitable and effective vaccines against HAT and malaria, it is very difficult to fight against these diseases.

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ISSN: 2249 –4820

Chemistry & Biology Interface, 2012, 2, 6, 373-393

Furthermore, to combat the problem of drug resistance it is necessary to add new weapons of chemotherapeutic agents in the existing arsenal of drugs directed against new, selective and unexploited parasite enzyme targets [3].

The hydroxamates, identified as key structural motif in many naturally occurring biomolecules such as siderophores, pseudobactin, desferrioxamines, ferrichromes etc [4]. The hydroxamates have recently emerged as a key pharmacophore to develop various chemotherapeutic agents. They inhibit various enzymes including the peroxidases, matrix metalloproteinase, TNF-α–converting enzyme and ureases [5-8]. These molecules have attracted the attention of scientific community in drug development arena to develop chemotherapeutic agents against several human ailments. They also hold potential as anti-inflammatory, antiasthmatic, antimetastatic, antibacterial, psychotropic, insecticidal, acaricidal and nematocidal agents [9-16]. The versatile biological activities in hydroxamic acid derivatives is due to their strong metal ion chelating [17], their ability to form salt linkages (in ionized form) in their complexes with proteins [18], or when unionized to engage in key hydrogen bonding interactions [19], and to provide sites for acylation [20, 21]. Keeping these views in mind we have reported the synthesis of glycosyl hydroxamic acids as possible malarial PDF inhibitors and few of the compounds displayed interesting antimalarial activities *in vitro* [22]. Recently it has been reported that compounds with hydroxamic acid functionality can inhibit histone decyclase enzyme of the malaria parasite and found to have strong antimalarial as well as anti-trypanosomal activity [23-26].

The hydroxamates have been synthesized from carboxylic acids or their esters by reaction with hydroxyl amine hydrochlorides or their equivalents under different acid group activating experimental conditions [27] using solid or solution phase syntheses [27-34]. However, the solid phase methods suffer an inherent limitation for the syntheses of low molecular weight hydroxamic acids their preparation on a multi-milligram scale requires large quantities of the solid support. In view of above facts we have reported one pot eco-friendly and economic syntheses of low molecular weight hydroxamic acids and evaluated their anti-trypanosomal, antimalarial and antifungal potential. The compounds were synthesized by reaction of the methyl carboxylates of the carboxylic acids with hydroxyl amine hydrochloride in the presence of KOH. In continuation of this programme we have synthesized a small library of hydroxamates and screened them for their anti-trypanosomal, antimalarial and antifungal activity.

Results and discussion

Chemistry:

Syntheses of these low molecular hydroxamtes are very simple and economical starting with small aliphatic and aromatic carboxylic acids. Three different prototypes of hydraxamtes were prepared. Prototypes **A** were prepared by reaction of the carboxylic acid (**1a-d)** with 20% mol sulphuric acid in methanol separately to lead the respective methyl carboxylates (**2a-d)** [34-42] in quantitative yields. These methyl carboxylates (1.0 eq.) were treated separately with hydroxyl amine hydrochloride salt (10.0 eq.) in methanol followed by addition of potassium hydroxide (20.0 eq.) at 0°C followed by stirring at ambient temperature to gave the

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respective hydroxamic acids (**3-6)** (**Scheme 1)**.

The structures of all the above hydroxyamides (**3-6)** were established on the basis of their spectroscopic data and microanalyses. The IR spectra of the compounds, in general, exhibited the absorption band at around 3260 cm^{-1} and 1659 cm^{-1} for the -OH and carbonyl of N-C=O of hydroxamic acid moiety respectively. The ESMS (mass spectra) of the compounds showed $(M+H)^+$ peaks corresponding to their molecular formulae. The NMR spectra (^1H and ^{13}C) are consistent with the proposed structures. The ^1H NMR spectrum of a prototype of these hydroxyamides (compound **3**), the methyl group was observed as singlet at δ 0.84. One of the CH_2 group was observed as multiplet at δ 2.05 ppm whereas the remaining CH_2 are observed as broad singlet at δ 1.22 ppm. In ^{13}C NMR spectrum C=O of amide linkage was observed at δ 172.2 Ppm. The methyl group was observed at δ 13.6 ppm whereas the methylene carbons are appeared at δ 33.6, 31.6, 29.3, 29.2, 29.0, 28.9, 25.2, and 22.3 ppm respectively.. Almost similar patterns were observed in ^1H NMR and ^{13}C NMR spectra of other compounds **4-6** of the series.

Similarly prototype B, salicylic acid based hydroxamates were prepared from salicylic acid (**7**), which on esterification with methanol in presence of 20 mol% of concentrated sulphuric acid gave methyl salicylate (**8**) (43) in good yield. The latter was alkylated with different alkyl halides viz. 3-chlorobenzyl bromide, pentyl bromide, 3,4-dichlorobenzyl bromide, *N*-ethyl piperidine bromide, hexyl bromide, allyl bromide, and benzyl bromide in THF in presence of anhydrous K_2CO_3 and catalytic amount of TBAB under reflux to give the respective 2-*O*-alkyl methyl salicylate (**9-15**) in good yields. The reaction of these alkylmethyl salicylates separately with hydroxyl amine hydrochloride in presence of methanolic KOH as above led to the formation of respective hydroxamides (**16-22**) in moderate to good yields. (**Scheme 2**) The structures of all the products were established on the basis of their spectroscopic data and microanalyses.

The ^1H NMR spectrum of compound **9** showed the methylene protons of OCH_2 as a singlet at δ 4.21 while three methyl protons of OCH_3 were observed as singlet in at δ 3.81. The aromatic protons were visible as double doublet at δ 7.15 with coupling constant J = 7.7 Hz, and as multiplets at the range of δ 6.54-6.26 and δ 6.15-6.02. In the ^{13}C NMR spectrum of compound **9**, methylene (OCH_2) carbon was observed at δ 72.1, while CH_3 carbons of OCH_3 were visible at δ 52.3 and aromatic carbons were observed at their usual chemical shifts. Similar patterns were observed for ^1H NMR and ^{13}C NMR spectra of other compounds **10-15** of the series**.**

The structures of all the above salicylic based hydroxamates (**16-22**) were established on the basis of their spectroscopic data and microanalyses. The IR spectra of the compounds, in general, exhibited the absorption band at around 3448 cm^{-1} and 3021 cm^{-1} for the -OH and carbonyl of NH group respectively. The ESMS (mass spectra) of the compounds showed $(M+H)^+$ peaks corresponding to their molecular formulae. ^1H NMR spectrum of compound **16** was similar to the compound **9** with absence of signal for methoxy group protons. In the ^{13}C NMR spectrum of compound **16**, carbon of amide linkage was observed at δ 166.6, while other carbons were visible at their usual chemical shifts. Almost similar patterns were

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observed in ^{1}H NMR and ^{13}C NMR spectra of other compounds **17-22** of the series.

Lastly, hydroxamic acids based on naphthoic acid, prototype C, were prepared from 1-hydroxy- 2-napthoic acid (**23)**, which on esterification with methanol in the presence of 20% mol conc. H_2SO_4 gave 1-hydroxy-2-naphthoate (**24)** in good yield. The latter on alkylation with different alkyl halides in THF in presence of anhydrous K_2CO_3 and catalytic amount of TBAB under reflux as above resulted in the formation of respective methyl 1-O-alkyl-2-naphthoates (**25-30**) in good yields. The latter were reacted with hydroxyl amine hydrochloride in presence of methanolic KOH separately to give the respective N-hydroxy-1-(alkyloxy)-2-naphthamides (**31-36**) in good yields (**Scheme.3)**.

The structures of all the above compounds (**25-30)** were established on the basis of their spectroscopic data and microanalyses. The IR spectra of the compounds, in general, exhibited the absorption band at around 1721 cm^{-1} indicated the presence of COOMe group. The ESMS (mass spectra) of the compounds showed $(M+H)^+$ peaks corresponding to their molecular formulae. The ^{1}H NMR spectrum of a prototype compound **25** showed the methylene protons of pentyl chain as multiplets at δ 1.98-1.90 and at δ 1.59-1.44, while protons of OCH_2 group were observed as triplet 4.11 with coupling constant J = 6.6Hz. The protons of the OCH_3 group and three methyl protons were observed as singlet at δ 3.93 and triplet at δ 1.00 (J = 6.8 Hz) respectively. The aromatic protons were visible as multiplets around δ 8.26-7.48. In the ^{13}C NMR spectrum of compound **25** the methylene of pentyl chain were observed at δ 23.0, 28.6, 30.56 and OCH_2 carbon was observed at δ 74.8. The CH_3 and OCH_3 carbons were visible at δ 14.3 and at δ 52.3. The aromatic carbons were observed at their usual chemical shifts. Similar patterns were observed for the other compounds **26-30** of the series.

The structures of above hydroxamates were established on the basis of their spectroscopic data and microanalyses. The IR spectra of the compounds, in general, exhibited the absorption band at around 3295 cm^{-1} and 2932 cm^{-1} for the existence of the NH and OH groups the -OH and carbonyl of NH group respectively. The ESMS (mass spectra) of the compounds showed $(M+H)^+$ peaks corresponding to their molecular formulae. The ^{1}H NMR spectrum of prototype compound **31** showed the methylene protons of pentyl chain as multiplets at δ 2.01-1.93 and at δ 1.58-1.25, while protons of OCH_2 were observed as triplet 4.07 with coupling constant J = 6.7 Hz. Methyl protons of the alkyl chain appeared as multiple at δ 1.00-0.93. The aromatic protons were visible as multiplets in the range of δ 8.10-7.49. In the ^{13}C NMR the carbonyl carbon of the amide functionality appeared at δ 164.9. Methylene carbons of pentyl chain were observed at δ 30.3, 28.4, 22.9, and OCH_2 carbon was observed at δ 77.2 while CH_3 carbon was visible at δ 14.4, and aromatic carbons were observed at their usual chemical shifts. Similar patterns were observed for the other compounds **32-36** of the series.

Biology

Antimalarial Activity

All the synthesized hydroxamic acids were evaluated for their antimalarial activity against *P. falciparum 3D7 in vitro* and the results are depicted in **Table-1**. Their IC_{50} values varied in range of 0.78-40.89 μg/mL. Among all the compounds screened, five compounds **4**, **16, 17, 19** and **21** are potent

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antimalarials with IC_{50} <2 μg/mL. Compound **21** had shown the best activity with IC_{50} of 0.78 μg/mL. The IC_{50} of standard drug chloroquine was found to be 5.6ng/mL.

Anti-trypanosomal activity

Almost all the hydroxamates screened showed good anti-trypanosomal activity. Compounds **4, 5, 6, 16, 17, 18, 19, 21, 35** exhibited IC_{50} values <2 μg/mL. Compounds **5**, **16**, and **17** were found to be the most potent compounds of the series against *T. b.b.* with low IC_{50} values i.e. 0.25, 0.2 and 0.025 μg/ml respectively. The IC_{50} of standard drug pentamidine was 1.8 ng/mL (**Table 1)**. Moreover these five compounds namely **4**, **16, 17, 19**, and **21** which showed both antimalarials as well as anti-trypanosomal activity with IC_{50} of <2μg/ml.

Cytotoxicity

All the compounds showed high values of CC_{50} having low cytotoxic effect against the Vero cells. Their CC_{50} values ranged from 20.76 to 3063μg/ml (data not shown). Based on IC_{50} and CC_{50} values selective indices (CC_{50}/IC_{50}) of these compounds were calculated and compounds **3, 4, 5**, **6**, **16**, **17**, **18**, **19**, **21**, **22**, **33**, **36** showed good safety margin for antimalarial activity and compounds **3-6**, **16-22**, **31, 33**, **35 and 36** for anti-trypanosomal activity (**Table 1)**.

In the screening of a large number of newly synthesized hydroxamic acids, they showed moderate to high activity against both the parasitic protozoans. The compounds **4**, **5**, **6**, **16**, **17**, **18**, **19**, **21** and **35** were found to be very effective against *T.b.b* and, compounds **4**, **16**, **17**, **19** and **21** showed good antimalarial activity against *P. falciparum.* Fifty percent inhibitory conc. (IC_{50}) of these compounds were <2μg/ml. Among all screened compounds, compound **17** was the most active against trypanosomes and had the highest degree of selective index i.e. **3422**. Rest of the active compounds had also shown high degree of selective index **(15-1967)**. Compound **21** was the most effective against malaria parasite. Remaining five active antimalarial compounds had shown a high degree of selective indices (**28.2-186.19)**. Furthermore, antimalarial as well as anti-trypanosomal activity of some newly synthesized compounds were compared with their acid counter parts and they possess more effective antimalarial as well as anti-trypanosomal activity than later which favors the role of hydroxamic acid moiety for the activity (data not shown). Our results showed that some of the compounds have good antimalarial as well as anti-trypanosomal activity with high degree of selective safety index which may overcome the problems of cytotoxicity.

Looking in to SAR it is evident from **Table.1** that among the aliphatic hydroxamic acids (**3**, **4)**, pentadecanoic acid hydroxamate with C-15 chain was the best one (**4**). Among aromatic hydroxamic acids those derived from salicylic acid posses the best antimalarial activity. Substitution of aromatic hydroxy group in salicylic acid with chlorobenzyl or benzyl substituent resulted potent compound (**16**, **21)**. Substitution of 2-OH with hexyloxy unit also gave an active compound (**17**) and decrease in carbon (pentyloxy) chain resulted low activity (**18**). Replacement with 3,4 dichlorobenzyl substituent (**20**) resulted in loss of antimalarial activity.

In general replacement of benzene ring with naphthalene ring in aromatic hydroxamic acids did not provide better compounds rather activity was reduced (**31-36**).

A similar observation of SAR was noticed for anti-trypanosomal activity with few

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exceptions. However the best active compound in the series was found to be a salicylic acid derived hydroxamate having hexyl substituent (**17**). Benzoic acid derived hydroxamic acids with electron withdrawing or donating substituent generally show good anti-trypanosomal activity (**16-22**). Replacement of benzene ring with naphthalene ring resulted in the loss of activity.

Antibacterial and Antifungal activity

Few of the compounds were evaluated *in vitro* against different strains of bacteria and fungi. Main strains of fungi used in study were *Candida albicans, Candida neoformans, Sporothrix schenckii, Trichophyton mentagrophytes, Aspergillus fumigatus, Candida parapsilosis* (ATCC 22019). The antibacterial activity was evaluated against *Escherichia coli* (ATCC 9637), *Pseudomonas aeruginosa* (ATCC-BAA 427), Gram-negative bacteria *Klebsiella pneumoniae* (ATCC 27736) and *staphylococcus aureus.* All these results are shown in the Table 2.

From the above results we found that none of the compound shows good antibacterial activity. However, some of the compounds show significant antifungal activity. Two compounds of the series *viz.* **3 and 4** showed strong antifungal activities against different strains of fungi. A closer look into SAR indicates that aliphatic hydroxamates are better antifungals as compared to the aromatic hydroxamates. Among aromatic hydroxamic acids, in general, naphthoic acid derived hydroxamic acids (**31-36**) are better than those of simple aromatic or salicylic acid based hydroxamates except compound **4**. Antifungal compounds namely **3,** and **4** have shown high CC_{50} conc. i.e. 296.05, and 3063.6 µg/mL respectively. Out of these all the screened compounds, comp. no. **4** is having all the three activities *viz* anti fungal, antimalarial and anti-trypanosomal activities. Additionally, this compound has very high CC_{50} indicating its safety value. Therefore we can select this compound (**4**) for further development.

Experimental

Commercially available reagent grade chemicals were used as received. All reactions were followed by TLC on E. Merck Kieselgel 60 F_{254}, with detection by UV light, spraying a 20% $KMnO_4$ aq solution. Column chromatography was performed on silica gel (100-200 mesh E. Merck). IR spectra were recorded as thin films or in KBr solution with a Perkin Elmer Spectrum RX-1 (4000-450 cm^{-1}) spectrophotometer. ^1H and ^{13}C NMR spectra were recorded on a Brucker DRX-200 in $CDCl_3$ and $CDCl_3$+CCl_4. Chemical shift values are reported in ppm relative to TMS (tetramethylsilane) as internal reference, unless otherwise stated; s (singlet), d (doublet), m (multiplet); *J* in hertz. ESI mass spectra were performed using Quattro II (Micromass). Elemental analyses were performed on a Perkin–Elmer 2400 II elemental analyzer.

Typical Experimental Procedure for the synthesis of compounds (3-6):

To a magnetically stirred solution of carboxylic acids (**1c**, **1d**, 5.3 mmol) in methanol, concentrated sulphuric acid (0.2 mmol) was added and mixture was refluxed for 1h to get the corresponding methyl ester but in case of aliphatic carboxylic acids compounds (**1a**, **1b,** 4.1mmol) stirred in methanol were treated with thionyl chloride (4.1mmol) and refluxed for 2-2.5 h to get the respective desired compounds. To a magnetically stirred solution of methyl esters, (1.0g, 5.1mmol), in dry methanol

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hydroxylamine hydrochloride (3.5g, 51.0mmol) was added, followed by addition of potassium hydroxide (5.7g, 102mmol) at 0 ºC to -5 ºC and reaction mixture was stirred for 30-45 minute at room temperature. After completion of reaction, 10% citric acid solution was added till pH is 7.0. The solution was extracted with ethyl acetate and water, ethyl acetate layer was separated and dried over sodium sulphate. The ethyl acetate layer was evaporated under reduced pressure to get crude mass, which was purified by column chromatography performed over silica-gel (60-120 mesh) and methanol/chloroform as eluant (2% MeOH/$CHCl_3$) to get the simple hydroxamic acid (**3-6**).

Hexadecanoic acid hydroxyamide (3): It was obtained by reaction of correspoding methyl ester (1.0g, 3.9mmol) with the hydroxyl amine hydrochloride salt (2.73g, 39.3mmol) and poatassium hydroxide (4.4g, 78.7mmol) in methanol as white solid (0.87g, 87%); R_f = 0.49 (Ethyl acetate/hexane; 3:7); mp = 98-99 ^oC; IR(KBr): ν_{max} in cm^{-1} 3260, 2580, 2367, 1659, 1564, 1469, 1118; ^1H NMR (200 MHz, $CDCl_3$): δ = 2.05-2.02 (m, 2H, CH_2), 1.22 (bs, 26H, CH_2) 0.84 (m, 3H, CH_3); ^{13}CNMR (50MHz,$CDCl_3$): δ = 172.2 (CONH), 33.6 (CH_2), 31.6 (CH_2), 29.3 (CH_2), 29.2 (CH_2), 29.0 (CH_2), 28.9 (CH_2), 25.2 (CH_2), 22.3 (CH_2), 13.6 (CH_3); ESMS: *m/z*: 272$(M+H)^+$; Calculated elemental analysis for $C_{16}H_{33}NO_2$: C, 46.59; H, 8.80; N, 13.58, Elemental analysis found: C, 46.56; H, 8.79; N, 13.61.

Pentadecanoic acid hydroxyamide (4): It was obtained by reaction of correspoding methyl ester (0.8g, 3.3mmol) with the hydroxyl amine hydrochloride salt (2.31g, 33.3mmol) and poatassium hydroxide (3.73g, 66.6mmol) in methanol as white solid (0.64g, 80%); R_f = 0.5 (Ethyl acetate/hexane; 3:7), mp = 99-101 ^oC; IR(KBr): ν_{max} in cm^{-1} 3257, 3059, 2849, 1662, 1623, 1423, 1119 ^1H NMR (200 MHz, $CDCl_3$): δ = 2.91 (m, 2H, CH_2), 2.01 (m, 2H, CH_2), 1.61 (m, 2H, CH_2), 1.19 (bs, 20H, CH_2), 0.82 (m, 3H, CH_3),^{13}C NMR (50MHz,$CDCl_3$): δ = 171.2 (CONH), 42.5 (CH_2), 32.5 (CH_2), 29.4 (CH_2), 29.2 (CH_2), 29.0 (CH_2), 28.9 (CH_2), 25.3 (CH_2), 22.4 (CH_2), 13.7(CH_3); ESMS: *m/z*: 258 $(M+H)^+$; Calculated elemental analysis for $C_{15}H_{31}NO_2$: C, 69.99; H, 12.14; N, 5.44, Elemental Analysis found: C, 69.96; H, 12.15; N, 5.43.

4.1.1.3 ***N-Hydroxy-2,6-dimethyl-benzamide (5):*** It was obtained by reaction of correspoding methyl ester (0.4g, 2.4mmol) with the hydroxyl amine hydrochloride salt (1.69g, 24.3mmol) and poatassium hydroxide (2.73g, 48.7mmol) in methanol as white solid (0.28g, 70%); R_f = 0.51 (Ethyl acetate/hexane; 3:7), mp =131-133 ^oC; IR(KBr): ν_{max} in cm^{-1} 3225, 3060, 1630, 1441, 1282; ^1H NMR (200 MHz, $CDCl_3$+CD_3OD): δ = 7.13-7.02 (m, 3H, Ar-H), 4.81 (bs, 1H, NH), 2.36-2.32 (Ar-CH_3); ^{13}C NMR (50MHz,$CDCl_3$+CD_3OD): δ = 171.1 (CONH), 146.6 (Ar-C), 139.0 (Ar-C), 134.8 (Ar-CH), 134.5 (Ar-CH), 134.1 (Ar-CH); ESMS: *m/z*: 166 $(M+H)^+$; Calculated elemental analysis for $C_9H_{11}NO_2$: C, 65.44; H, 6.71; N, 8.48, Elemental analysis found: C, 65.48; H, 6.79; N, 8.42.

N-Hydroxy-3-phenoxy-benzamide (6): It was obtained by reaction of correspoding methyl ester (0.4g, 2.35mmol) with the hydroxyl amine hydrochloride salt (1.63g, 23.5mmol) and poatassium hydroxide (2.63g, 47.0mmol) in methanol as white solid (0.32g, 80%); R_f = 0.47 (Ethyl acetate/hexane; 3:7), mp = 120-122 ^oC; IR(KBr): ν_{max} in cm^{-1} 3420, 3021, 2362, 1622, 1216; ^1H NMR (200 MHz, $CDCl_3$): δ = 10.28 (bs, 1H, NH), 8.24-8.20 (m, 1H, Ar-

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H), 7.41-6.77 (m, 8H, Ar-H); ^{13}C NMR (50MHz, $CDCl_3$): δ = 163.5 (CONH), 156.3 (Ar-C), 154.9 (Ar-C), 133.4 (Ar-CH), 132.3 (Ar-CH), 130.6 (Ar-CH), 125.7 (Ar-CH), 123.6 (Ar-CH), 120.8 (Ar-CH), 117.3 (=CH_2); ESMS: *m/z*: 230 $(M+H)^+$; Calculated elemental analysis for $C_{13}H_{11}NO_3$: C, 68.11; H, 4.84; N, 6.11, Elemental analysis found: C, 68.09; H, 4.82; N, 6.09.

Typical Experimental Procedure for the synthesis of alkylated hydroxamic acids (16-22 and 31-36):

To a magnetically stirred solution of salicylic acid (1.0 eq.) or 1-hydroxy napthoic acid (1.0 eq.) in methanol concentrated sulphuric acid (20% mol) was added and mixture was refluxed for 1h to get the corresponding methyl ester (**8**, **24)**. To a magnetically stirred solution of methyl esters (**8** or **24**, 1.2g, 7.8mmol or 1.7g, 8.41mmol), in dry THF (10.0 mL) potassium carbonate (1.08g, 7.8mmol/1.16g, 8.41mmol) was added followed by addition of alkyl halides (1.01ml, 7.8mmol/1.05ml, 8.41mmol) and tetra butyl ammonium bromide (0.50g, 1.5mmol/0.54g, 1.61mmol) the reaction mixture was refluxed for 2-4 hours to get corresponding alkylated ester **9** or **25** (1.52g, 70%, or 1.92g, 84%). Compounds **9** (1.0g, 3.6mmol) or **25**(1.3g, 4.7mmol) was dissolved in methanol and hydroxylamine hydrochloride (2.5g, 36.2mmol/3.32g, 47.7mmol) was added, followed by addition of potassium hydroxide (4.05g, 72.4mmol/5.35g, 95.5mmol) at 0°C to -5°C and reaction mixture was stirred for 30-45 minute at room temperature. After completion of reaction, 10% citric acid solution was added till Ph is 7.0. The solution was extracted with ethyl acetate and water, ethyl acetate layer was separated and dried over sodium sulphate. The ethyl acetate layer was evaporated under reduced pressure to get crude mass, which was purified by column chromatography performed over silica-gel (60-120 mesh) and methanol/chloroform as eluent (2% MeOH/$CHCl_3$) to get the corresponding alkylated hydroxamic acids **16** or **31.**

***Methyl 2-(3-chlorobenzyloxy)benzoate (9)*:** It was obtained, by reaction of methyl salicylate (1.2g, 7.8mmol) with 3-chloro benzyl bromide (1.01mL, 7.8mmol) in the presence of potassium carbonate (1.08g, 7.8mmol) and tetrabutyl ammonium bromide (0.50g, 1.5mmol) in THF, as Colourless syrup (1.52g, 70%); R_f = 0.54 (Ethyl acetate/hexane; 1:9); IR (neat): ν_{max} in cm^{-1} 3380, 3021, 2361, 1717, 1216; ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.15 (dd, *J* = 7.7 Hz, 1H, Ar-H), 6.56-6.26 (m, 5H, Ar-H), 6.15-6.02, (m, 2H, Ar-H), 4.23 (s, 2H, OCH_2), 3.81 (s, 3H, OCH_3); ^{13}C NMR (50 MHz, $CDCl_3$): δ = 171.6 (COOMe), 159.2 (Ar-C), 148.5(Ar-C), 134.4 (Ar-CH), 132.1(Ar-CH), 122.7 (Ar-CH), 121.8 (Ar-CH), 120.5 (Ar-CH), 115.6 (Ar-C), 71.6 (-OCH_2), 52.0 (-OCH_3); ESMS: *m/z*: 277 $(M+H)^+$; Calculated elemental analysis for $C_{15}H_{13}ClO_3$: C, 65.11; H, 4.74, Elemental analysis found, C, 65.07; H, 4.69.

***Methyl 2-(hexyloxy)benzoate (10)*:**It was obtained, by reaction of methyl salicylate (1.1g, 7.2mmol) with 1-bromohexane (1.02mL, 7.2mmol) in the presence of potassium carbonate (0.99g, 7.2mmol) and tetrabutyl ammonium bromide (0.46g, 1.0mmol) in THF, as Colourless syrup (1.2g, 80%); R_f = 0.53 (Ethyl acetate/hexane; 1:9); IR (neat): ν_{max} in cm^{-1} 3350, 3178, 2923, 2262, 1719, 1239; ^{1}H NMR (200 MHz, $CDCl_3$): δ = 8.15-8.10 (m, 1H, Ar-H), 7.42-7.31 (m, 1H, Ar-H), 7.01-6.89 (m, 2H, Ar-H), 4.21-4.00 (t, *J* = 6.7Hz, 2H, OCH_2), 3.87 (s, 3H, OCH_3), 1.98-1.85 (m, 2H, CH_2), 1.54-1.23 (m, 6H, CH_2), 0.93-0.88 (t, *J* =

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6.8Hz, 3H, CH_3); ^{13}C NMR (50MHz,$CDCl_3$): δ = 166.0 (CONH), 157.9 (Ar-C), 134.1 (Ar-C), 133.5 (Ar-CH), 132.2 (Ar-CH), 121.6 (Ar-CH), 112.4 (Ar-CH), 69.7 (-OCH_2), 52.9 (s, 3H, OCH_3), 30.8 (CH_2), 29.2 (CH_2), 22.8 (CH_2), 14.2 (CH_3); ESMS: *m/z*: 237 $(M+H)^+$; Calculated elemental analysis for $C_{14}H_{20}O_3$: C, 71.16; H, 8.53, Elemental analysis found: C, 71.10; H, 8.49.

***Methyl 2-(pentyloxy)benzoate (11)*:** It was obtained, by reaction of methyl salicylate (2.1g, 13.8mmol) with 1-bromopentane (1.72 mL, 13.8mmol) in the presence of potassium carbonate (1.90g, 13.8mmol) and tetrabutyl ammonium bromide (0.88g, 2.7mmol) in THF, as Colourless syrup (1.17g, 85%); R_f = 0.54 (Ethyl acetate/hexane; 1:9), mp = 85-88 ^oC; IR (neat): ν_{max} in cm^{-1} 3221, 2948, 2860, 1725, 1244; ^1H NMR (200 MHz, $CDCl_3$): δ = 8.16-7.12 (m, 1H, Ar-H), 7.41-7.32 (m, 1H, Ar-H), 7.04-6.91 (m, 2H, Ar-H), 4.15-4.08, (t, *J* = 6.7Hz, 2H, OCH_2), 3.91 (OCH_3), 1.98-1.84 (m, 2H, CH_2), 1.54-1.45 (m, 4H, CH_2), 0.99-0.92 (t, *J* = 6.7Hz, 3H, CH_3); ^{13}C NMR (50MHz, $CDCl_3$): δ = 164.3 (COOMe), 157.0 (Ar-C), 133.4 (Ar-C), 132.2 (Ar-CH), 121.6 (Ar-CH), 118.9 (Ar-C), 112.4 (Ar-CH), 70.7 (-OCH_2), 53.1 (OCH_3), 29.2(CH_2), 28.4 (CH_2), 22.8 (CH_2), 14.4 (CH_3); ESMS: *m/z*: 223 $(M+H)^+$; Calculated elemental analysis for $C_{13}H_{18}O_3$: C, 70.24; H, 8.16, Elemental analysis found: C, 70.21; H, 8.14.

***Methyl 2-(allyloxy)benzoate (12)*:** It was obtained, by reaction of methyl salicylate (1.0g, 6.5mmol) with allyl bromide (0.5mL 6.51mmol) in the presence of potassium carbonate (0.92g, 6.57mmol) and tetrabutyl ammonium bromide (0.42g, 1.31mmol) in THF, as Colourless syrup (0.96g, 80%); R_f= 0.52 (Ethyl acetate/hexane; 1:9), IR (neat): ν_{max} in cm^{-1} 3204, 2912, 1724, 1267; ^1H NMR (200 MHz, $CDCl_3$): δ = 8.07-8.03 (m, 1H, Ar-H), 7.45-7.34 (m, 1H, Ar-H), 7.10-6.90 (m, 2H, Ar-H), 6.11-6.01 (m, 1H, -CH), 5.42-5.32 (m, 2H, =CH_2), 4.71-4.67 (d, *J* = 5.4Hz, 2H, OCH_2), 3.91 (s, 3H, OCH_3); ^{13}C NMR (50MHz,$CDCl_3$): δ = 168.5 (COOMe), 156.3 (Ar-C), 133.5 (Ar-C), 133.0 (Ar-CH), 131.2 (Ar-CH), 131.0 (Ar-CH), 121.3 (Ar-CH), 119.2 (=CH_2), 112.8 (-CH=), 72.1 (-OCH_2), 52.1 (OCH_3); ESMS: *m/z*: 193 $(M+H)^+$; Calculated elemental analysis for $C_{11}H_{12}O_3$: C, 68.74; H, 6.29, Elemental Analysis found: C, 68.72; H, 6.24.

***Methyl 2-(3,4-dichlorobenzyloxy)benzoate (13)*:** It was obtained, by reaction of methyl salicylate (1.4g, 9.2mmol) with 3,4-dichloro benzyl bromide (2.2g, 9.2mmol) in the presence of potassium carbonate (1.27g, 9.2mmol) and tetrabutyl ammonium bromide (0.59g, 1.8mmol) in THF, as Colourless syrup (2.37g, 83%); R_f = 0.49 (Ethyl acetate/hexane; 1:9); IR (neat): ν_{max} in cm^{-1} 3180, 3120, 2332, 1724, 1234; ^1H NMR (200 MHz, $CDCl_3$): δ 7.94-7.91 (m, 1H, Ar-H), 7.10-6.97 (m, 2H, Ar-H), 7.61-7.34(m, 4H, Ar-H), 5.19 (bs, 2H, OCH_2), 3.92 (s, 3H, OCH_3); ^{13}C NMR (50MHz,$CDCl_3$): δ = 169.9 (COOMe), 157.9 (Ar-C), 139.4 (Ar-C), 136.2 (Ar-CH) 133.3 (Ar-CH), 133.0 (Ar-CH), 132.3 (Ar-CH), 129.4 (Ar-CH), 124.6 (Ar-CH), 123.4 (Ar-C)116.3 (Ar-CH), 71.7 (-OCH_2), 53.0 (s, 3H, OCH_3); ESMS: *m/z*: 312 $(M+H)^+$; Calculated elemental analysis for $C_{15}H_{12}Cl_2O_3$: C, 57.90; H, 3.89, Elemental analysis found: C, 57.88; H, 3.87.

***Methyl 2-(benzyloxy)benzoate (14)*:** It was obtained, by reaction of methyl salicylate (0.8g, 5.2mmol) with benzyl bromide (0.9mL, 5.2mmol) in the presence of potassium carbonate (0.72g, 5.2mmol) and tetrabutyl ammonium bromide (0.33g, 1.0mmol) in THF, as Colourless syrup

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(1.01g, 80%); R_f = 0.61 (Ethyl acetate/hexane; 1:9); IR (neat): ν_{max} in cm^{-1} 3261, 3061, 1724, 1599, 1429; ^1H NMR (200 MHz, $CDCl_3$): δ = 8.12-8.05 (m, 1H, Ar-H), 7.43-7.31 (m, 5H, Ar-H), 7.11-6.98 (m, 3H, Ar-H), 4.91 (s, 2H, OCH_2), 3.83 (s, 3H, OCH_3); ^{13}C NMR (50MHz,$CDCl_3$): δ = 168.2 (COOMe), 156.6 (Ar-C), 135.7 (Ar-C), 134.5 (Ar-CH), 133.4 (Ar-CH), 132.1 (Ar-CH), 129.3 (Ar-CH), 129.2 (Ar-CH), 128.0 (Ar-CH), 127.8 (Ar-CH), 122.8 (Ar-CH), 114.0 (Ar-CH), 70.4 (-OCH_2), 52.7 (OCH_3); ESMS: *m/z*: 243 $(M+H)^+$ Calculated elemental analysis for $C_{15}H_{14}O_3$: C, 74.36; H, 5.82, Elemental analysis found: C, 74.31; H, 5.81.

***Methyl 2-(2-piperidin-1-yl-ethoxy)benzoate (15)*:** It was obtained, by reaction of methyl salicylate (1.8g, 11.8mmol) with 2-chloroethyl piperidine hydrochloride salt (1.33g, 11.8mmol) in the presence of potassium carbonate (1.63g, 11.8mmol) and tetrabutyl ammonium bromide (0.76g, 2.3mmol) in THF, as Colourless syrup (2.46g, 79%); R_f = 0.41 (Ethyl acetate/hexane; 1:9); IR (neat): ν_{max} in cm^{-1} 3235, 3020, 1727, 1215; ^1H NMR (200 MHz, $CDCl_3$): δ = 8.17-8.04 (m, 1H, Ar-H), 7.85-7.81 (m, 1H, Ar-H), 7.66-7.45 (m, 2H, Ar-H), 4.19 (s, 2H, OCH_2), 3.79 (s, 3H, OCH_3), 2.81 (bs, 2H, NCH_2), 2.62 (bs, 4H, NCH_2), 1.79 (bs, 4H, CH_2), 1.50 (bs, 2H, CH_2); ^{13}C NMR (50MHz,$CDCl_3$); δ = 169.5 (COOMe), 153.2 (Ar-C), 135.9 (Ar-C), 128.4 (Ar-CH), 127.0 (Ar-CH), 126.4 (Ar-CH), 124.5 (Ar-CH), 119.7 (-NCH_2), 73.0 (-OCH_2), 58.9 (CH_2), 55.6 (CH_2), 52.4 (OCH_3) 30.1 (CH_2), 25.2 (CH_2), 24.4 (CH_2); ESMS: *m/z*: 264 $(M+H)^+$; Calculated elemental analysis for $C_{15}H_{21}NO_3$: C, 68.42; H, 8.04; N, 5.32, Elemental analysis found: C, 68.42; H, 8.04; N, 5.32.

***2-(3-Chloro-benzyloxy)-N-hydroxy-benzamide* (16):** It was obtained by reaction of correspoding methyl ester (1.0g, 3.6mmol) with the hydroxyl amine hydrochloride salt (2.5g, 36.2mmol) and poatassium hydroxide (4.05g, 72.4mmol) in methanol as white solid (0.87g, 87%); R_f = 0.52 (Ethyl acetate/hexane; 3:7), mp = 92-95 ^oC; IR (KBr): ν_{max} in cm^{-1} 3448, 3021, 2361, 1645, 1216; ^1H NMR (200 MHz, $CDCl_3$): δ = 7.15 (dd, *J* = 7.7 Hz, 1H, Ar-H), 6.56-6.26 (m, 5H, Ar-H), 6.15-6.02, (m, 2H, Ar-H), 4.23 (s, 2H, OCH_2); ^{13}C NMR (50 MHz, $CDCl_3$): δ = 166.6 (CONH), 159.2 (Ar-C), 148.5(Ar-C),134.4 (Ar-CH), 132.1(Ar-CH), 122.7 (Ar-CH), 121.8 (Ar-CH), 120.5 (Ar-CH),115.6 (Ar-C), 71.6 (-OCH_2); ESMS: *m/z* : 278 $(M + H)^+$ Calculated elemental analysis for $C_{14}H_{12}ClNO_3$: C, 60.55; H, 4.36; N, 5.04, Elemental analysis found: C, 60.51; H, 4.32; N, 5.14.

***2-(Hexyloxy)-N-hydroxybenzamide (17)*:** It was obtained by reaction of correspoding methyl ester (0.8g, 3.38mmol) with the hydroxyl amine hydrochloride salt (2.35g, 33.8mmol) and poatassium hydroxide (3.79g, 67.7mmol) in methanol as white solid (0.64g, 80%); R_f = 0.56 (Ethyl acetate/hexane; 3:7), mp = 82-85 ^oC; IR(KBr): ν_{max} in cm^{-1} 3450, 3278, 2926, 2362, 1625, 1239; ^1H NMR (200 MHz, $CDCl_3$): δ = 10.37 (bs, NH), 8.19-8.12(m, 1H, Ar-H), 7.45-7.37 (m, 1H, Ar-H), 7.08-6.91 (m, 2H, Ar-H), 4.24-4.08 (t, *J* = 6.6Hz, 2H, OCH_2), 1.97-1.83 (m, 2H, CH_2), 1.53-1.25 (m, 6H, CH_2), 0.95-0.89 (t, *J* = 6.6Hz, 3H, CH_3), ^{13}C NMR (50MHz,$CDCl_3$): δ = 166.0 (CONH), 157.9 (Ar-C), 134.1 (Ar-C), 133.5 (Ar-CH), 132.2 (Ar-CH), 121.6 (Ar-CH), 112.4 (Ar-CH), 69.7 (-OCH_2), 31.8 (CH_2), 29.4 (CH_2), 22.9 (CH_2), 14.3 (CH_3); ESMS: *m/z*: 238 $(M+H)^+$; Calculated elemental analysis for $C_{13}H_{19}NO_3$: C, 65.80; H, 8.07; N, 5.90, Elemental analysis found: C, 65.78; H, 8.01; N, 5.89.

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***N-Hydroxy-2-(pentyloxy)benzamide (18)*:** It was obtained by reaction of correspoding methyl ester (0.85g, 4.06mmol) with the hydroxyl amine hydrochloride salt (2.81g, 40.4mmol) and poatassium hydroxide (4.5g, 80.9mmol) in methanol as white solid (0.69g, 82%); R_f = 0.51 (Ethyl acetate/hexane; 3:7), mp = 85-88 ^oC; IR (KBr): ν_{max} in cm^{-1} 3311, 2951, 2868, 1605, 1244; ^1H NMR (200 MHz, $CDCl_3$): δ = 10.37 (bs, NH), 8.18-7.14(m, 1H, Ar-H), 7.45-7.36 (m, 1H, Ar-H), 7.07-6.90 (m, 2H, Ar-H), 4.14-4.07, (t, J = 6.6Hz, 2H, OCH_2), 1.96-1.83 (m, 2H, CH_2), 1.53-1.43 (m, 4H, CH_2), 0.99-0.92 (t, J = 6.7Hz, 3H, CH_3); ^{13}C NMR (50MHz,$CDCl_3$): δ = 164.3 (CONH), 157.0 (Ar-C), 133.4 (Ar-C), 132.2 (Ar-CH), 121.6 (Ar-CH), 118.9 (Ar-C), 112.4 (Ar-CH), 69.7 (-OCH_2), 29.1 (CH_2), 28.5 (CH_2), 22.7 (CH_2), 14.3 (CH_3); ESMS: *m/z*: 224 $(M+H)^+$; Calculated elemental analysis for $C_{12}H_{17}NO_3$: C, 64.55; H, 7.67; N, 6.27, Elemental analysis found: C, 64.49; H, 7.61; N, 6.24.

***2-Allyloxy-N-hydroxy-benzamide (19)*:** It was obtained by reaction of correspoding methyl ester (0.90g, 4.68mmol) with the hydroxyl amine hydrochloride salt (3.25g, 46.8mmol) and poatassium hydroxide (5.25g, 93.7mmol) in methanol as white solid (0.63g, 70%); R_f = 0.51 (Ethyl acetate/hexane; 3:7), mp = 120-122 ^oC; IR(KBr): ν_{max} in cm^{-1} 3300, 2904, 1625, 1600, 1267; ^1H NMR (200 MHz, $CDCl_3$): δ = 8.09-8.04 (m, 1H, Ar-H), 7.47-7.38 (m, 1H, Ar-H), 7.10-6.95 (m, 2H, Ar-H), 6.16-6.02 (m, 1H, -CH), 5.49-5.34 (m, 2H, =CH_2), 4.71-4.69 (d, J = 5.4Hz, 2H, OCH_2) ; ^{13}C NMR (50MHz,$CDCl_3$): δ = 164.5 (CONH), 156.4 (Ar-C), 134.5 (Ar-C), 133.3 (Ar-CH), 132.2 (Ar-CH), 131.8 (Ar-CH), 121.8 (Ar-CH), 119.4 (=CH_2), 112.9 (-CH=), 70.1 (-OCH_2), ESMS: *m/z*: 194.2 $(M+H)^+$; Calculated elemental analysis for $C_{10}H_{11}NO_3$: C, 62.17; H, 5.74; N, 7.25, Elemental analysis found: C, 62.12; H, 5.73; N, 7.21.

***2-(3,4-Dichloro-benzyloxy)-N-hydroxy-benzamide (20)*:** It was obtained by reaction of correspoding methyl ester (1.2g, 3.85mmol) with the hydroxyl amine hydrochloride salt (2.68g, 38.5mmol) and poatassium hydroxide (4.32g, 77.1mmol) in methanol as white solid (1.10g, 92%); R_f = 0.49 (Ethyl acetate/hexane; 3:7); mp = 138-140^oC; IR(KBr): ν_{max} in cm^{-1} 3387, 3120, 2362, 1645, 1234; ^1H NMR (200 MHz, $CDCl_3$+CD_3OD): δ = 7.95-7.92 (m, 1H, Ar-H), 7.12-6.99 (m, 2H, Ar-H), 7.65-7.31 (m, 4H, Ar-H), 5.19 (bs, 2H, OCH_2); ^{13}C NMR (50MHz,$CDCl_3$+ CD_3OD): δ = 167.7 (CONH), 158.9 (Ar-C), 139.5 (Ar-C), 136.0 (Ar-CH) 134.2 (Ar-CH), 133.9 (Ar-CH), 132.4 (Ar-CH), 129.8 (Ar-CH), 124.8 (Ar-CH), 123.6 (Ar-C)116.1 (Ar-CH), 72.7 (-OCH_2); ESMS: *m/z*: 313 $(M+H)^+$; Calculated elemental analysis for $C_{14}H_{11}Cl_2NO_3$: C, 53.87; H, 3.55; N, 4.49, Elemental analysis found: C, 53.84; H, 3.52; N, 4.46.

***2-Benzyloxy-N-hydroxy-benzamide (21)*:** It was obtained by reaction of correspoding methyl ester (0.58g, 2.06mmol) with the hydroxyl amine hydrochloride salt (1.43g, 20.6mmol) and poatassium hydroxide (2.31g, 41.3mmol) in methanol as white solid (0.43g, 86%); R_f = 0.49 (Ethyl acetate/hexane; 3:7); mp = 148-150 ^oC; IR(KBr): ν_{max} in cm^{-1} 3367, 3161, 1648, 1599, 1429; ^1H NMR (200 MHz, $CDCl_3$ +CD_3OD): δ = 8.14-8.09 (m, 1H, Ar-H), 7.45-7.30 (m, H, 5Ar-H), 7.10-6.99 (m, 3H, Ar-H), 5.19 (s, 2H, OCH_2); ^{13}C NMR (50MHz,$CDCl_3$+CD_3OD): δ = 164.2 (CONH), 156.7 (Ar-C), 135.7 (Ar-C), 134.5 (Ar-CH), 133.4 (Ar-CH), 132.1 (Ar-CH), 129.3 (Ar-CH), 129.2 (Ar-CH), 129.0 (Ar-CH), 127.9 (Ar-CH), 122.0 (Ar-CH), 113.0 (Ar-CH), 71.7 (-OCH_2); ESMS: *m/z*: 244

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$(M+H)^+$; Calculated elemental analysis for $C_{14}H_{13}NO_3$: C, 69.12; H, 5.39; N, 5.76, Elemental analysis found: C, 69.09; H, 5.37; N, 5.71.

***N-Hydroxy-2-(2-piperidin-1-yl-ethoxy)-benzamide (22)*:** It was obtained by reaction of correspoding methyl ester (0.7g, 2.65mmol) with the hydroxyl amine hydrochloride salt (1.84g, 26.5mmol) and poatassium hydroxide (2.96g, 53.0mmol) in methanol as white solid (0.49g, 70%), R_f = 0.52 (Ethyl acetate/hexane; 3:7); mp = 132-135^{o}C; IR (KBr) ν_{max} in cm^{-1} 3425, 3020, 1632, 1460, 1215; ^{1}H NMR (200 MHz, $CDCl_3$ +CD_3OD): δ = 9.69 (bs, 1H), 8.15-8.02 (m, 1H, Ar-H), 7.84-7.80 (m, 1H, Ar-H), 7.65-7.48 (m, 2H, Ar-H), 4.21 (s, 2H, OCH_2), 2.81 bs, 2H, NCH_2), 2.62 (bs, 4H, NCH_2), 1.79 (bs, 4H, CH_2), 1.50 (bs, 2H, CH_2); ^{13}C NMR (50MHz,$CDCl_3$+ CD_3OD): δ = 162.5 (CONH), 154.2 (Ar-C), 136.9 (Ar-C), 128.6 (Ar-CH), 127.0 (Ar-CH), 126.6 (Ar-CH), 124.8 (Ar-CH), 119.5 (-NCH_2), 71.7 (-OCH_2), 58.9 (CH_2), 55.6 (CH_2), 30.1 (CH_2), 25.2 (CH_2), 24.4 (CH_2); ESMS: *m/z*: 265 $(M+H)^+$; Calculated elemental analysis for $C_{14}H_{20}N_2O_3$: C, 63.62; H, 7.63; N, 10.60, Elemental analysis found: C, 63.59; H, 7.61; N, 10.55.

***Methyl 1-(pentyloxy)-2-naphthoate (25)*:** It was obtained, by reaction of methyl 1-hydroxy-2-napthoate (1.7g, 8.41mmol) with 1-bromopentane (1.05mL, 8.41mmol) in the presence of potassium carbonate (1.16g, 8.41mmol) and tetrabutyl ammonium bromide (0.54g, 1.61mmol) in THF, as Colourless syrup (1.92g, 84%); R_f = 0.52 (Ethyl acetate/hexane; 1:9); IR (neat): ν_{max} in cm^{-1} 3180, 2922, 2286, 1721, 1202; ^{1}H NMR (200 MHz, $CDCl_3$): δ = 8.26-8.22 (m, 2H, Ar-H), 7.83-7.75 (m, 1H, Ar-H), 7.55-7.48 (m, 3H, Ar-H), 4.11, (t, *J* = 6.7Hz, 2H, OCH_2), 3.93 (s, 3H, OCH_3), 1.98-1.90 (m, 2H, CH_2), 1.59-1.37 (m, 4H, CH_2), 1.00-0.93 (m, 3H, CH_3); ^{13}C NMR ($CDCl_3$): δ = 166.9 (COOMe), 157.6 (Ar-C), 136.7 (Ar-C), 128.4 (Ar-CH), 128.3 (Ar-CH), 126.3 (Ar-CH), 126.2 (Ar-CH), 124.5 (Ar-CH), 123.5 (Ar-CH), 119.4 (Ar-C), 74.4 (-OCH_2), 52.3 (OCH_3), 29.6 (CH_2), 28.6 (CH_2), 22.8 (CH_2), 14.3 (CH_3), ESMS: *m/z*: 273 $(M+H)^+$; Calculated elemental analysis for $C_{17}H_{20}O_3$: C, 74.97; H, 7.40, Elemental analysis found: C, 74.91; H, 7.37.

***Methyl 1-(hexyloxy)-2-naphthoate (26)*:** It was obtained, by reaction of methyl 1-hydroxy-2-napthoate (1.4g, 6.93mmol) with 1-bromohexane (0.97mL, 6.93mmol) in the presence of potassium carbonate (0.95g, 6.93mmol) and tetrabutyl ammonium bromide (0.44g, 1.3mmol) in THF, as Colourless syrup (1.60g, 81%); R_f = 0.49 (Ethyl acetate/hexane; 1:9); IR(neat): ν_{max} in cm^{-1} 3222, 3021, 2350, 1715, 1216; ^{1}H NMR (200 MHz, $CDCl_3$): δ = 8.03-7.78 (m, 2H, Ar-H), 7.81-7.76 (m, 1H, Ar-H), 7.54-7.51 (m, 3H, Ar-H), 4.08-4.00, (t, *J* = 6.7Hz, 2H, OCH_2), 3.79 (s, 3H, OCH_3), 1.99-1.89 (m, 2H, CH_2), 1.51-1.21 (m, 6H, CH_2), 0.93-0.89 (m, 3H, CH_3); ^{13}C NMR (50 MHz,$CDCl_3$): δ = 167.9 (COOMe), 153.8 (Ar-C), 137.0 (Ar-C), 129.1 (Ar-C), 128.4 (Ar-CH), 128.3 (Ar-CH), 127.2 (Ar-CH), 125.8 (Ar-CH), 125.3 (Ar-CH), 122.3 (Ar-CH), 74.3 (-OCH_2), 52.4 (OCH_3), 29.6 (CH_2), 29.4 (CH_2), 29.3 (CH_2), 26.0 (CH_2), 22.8 (CH_2), 14.4 (CH_3); ESMS: *m/z*: 287 $(M+H)^+$, Calculated elemental analysis for $C_{18}H_{22}O_3$: C, 75.50; H, 7.74, Elemental analysis: C, 75.47; H, 7.71.

***Methyl 1-(allyloxy)-2-naphthoate (27)*:** It was obtained, by reaction of methyl 1-hydroxy-2-napthoate (1.7g, 8.41mmol) with allyl bromide (0.72mL, 8.41mmol) in the presence of potassium carbonate (1.16g, 8.41mmol) and tetrabutyl ammonium bromide (0.54g, 1.6mmol) in THF, as Colourless syrup (1.75g, 86%); R_f = 0.55

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(Ethyl acetate/hexane; 1:9); IR (neat): ν_{max} in cm^{-1} 3226, 3021, 2351, 1719, 1216; ^1H NMR (200 MHz, $CDCl_3$): δ = 8.09-7.95 (m, 2H, Ar-H), 7.83-7.77 (m, 1H, Ar-H), 7.64-7.45 (m, 3H, Ar-H), 6.21-6.12 (m, 1H, -CH=), 5.55-5.34 (m, 2H, $=CH_2$), 4.55 (m, 2H, OCH_2), 3.91 (s, 3H, OCH_3); ^{13}C NMR (50 MHz, $CDCl_3$): δ = 167.8 (COOMe), 154.1 (Ar-C), 137.6 (Ar-C), 132.5 (Ar-CH), 126.1 (Ar-CH), 125.3 (Ar-CH), 125.0 (Ar-CH), 123.1 (Ar-CH), 116.3 (=CH2), 75.1 (-OCH_2), 52.6 (OCH_3), ESMS: *m/z*: 243 ($(M+H)^+$; Calculated elemental analysis for $C_{15}H_{14}O_3$: C, 74.36; H, 5.82, Elemental analysis found: C, 74.26; H, 5.72.

***Methyl 1-(3,4-dichlorobenzyloxy)-2-naphthoate (28)*:** It was obtained, by reaction of methyl 1-hydroxy-2-napthoate (0.7g, 3.46mmol) with 3,4-dichloro benzyl bromide (0.82g, 3.46mmol) in the presence of potassium carbonate (0.47g, 3.46mmol) and tetrabutyl ammonium bromide (0.22g, 0.61mmol) in THF, as Colourless syrup (0.98g, 79%); R_f = 0.54 (Ethyl acetate/hexane; 1:9); IR (neat): ν_{max} in cm^{-1} 3115, 3041, 1723, 1355; ^1H NMR (200 MHz, $CDCl_3$): δ = 8.09-7.37 (m, 9H, Ar-H), 4.98 (s, 2H, OCH_2), 3.94 (s, 3H, OCH_3); ^{13}C NMR (50MHz, $CDCl_3$): δ = 171.4 (COOMe), 157.2 (Ar-C), 140.4 (Ar-C), 140.4 (Ar-C), 135.2 (Ar-CH), 134.4 (Ar-CH), 134.4 (Ar-CH), 134.2 (Ar-CH), 132.3 (Ar-CH), 128.8 (Ar-CH), 127.3 (Ar-CH), 125.8 (Ar-CH), 78.1 (-OCH_2), 52.7(OCH_3); ESMS: *m/z*: 361 $(M+H)^+$; Calculated elemental analysis for $C_{19}H_{14}Cl_2O_3$: C, 63.18; H, 3.91, Elemental analysis found: C, 63.10; H, 3.87.

***Methyl 1-(3-chlorobenzyloxy)-2-naphthoate (29)*:** It was obtained, by reaction of methyl 1-hydroxy-2-napthoate (0.9g, 4.41mmol) with 3-chloro benzyl bromide (0.61mL, 4.42mmol) in the presence of potassium carbonate (0.61g, 4.45mmol) and tetrabutyl ammonium bromide (0.28g, 0.80mmol) in THF, as Colourless syrup (1.29g, 89%); R_f = 0.45 (Ethyl acetate/hexane; 1:9), IR(neat): ν_{max} in cm^{-1} 3034, 2850, 1720, 1610, 1215; ^1H NMR (200 MHz, $CDCl_3$): δ = 8.0-7.99 (d, *J* = 5.4 Hz, 1H, Ar-H), 7.82-7.78 (m, 2H, Ar-H), 7.54-7.47, (m, 4H, Ar-H), 7.40-7.17, (m, 3H, Ar-H), 4.88 (s, 2H, OCH_2), 3.88 (s, 3H, OCH_3); ^{13}C NMR (50MHz,$CDCl_3$): δ = 169.5 (COOMe), 152.7 (Ar-C), 130.6 (Ar-CH), 130.6 (Ar-CH), 128.9 (Ar-CH), 128.7 (Ar-CH), 128.3 (Ar-CH), 127.0 (Ar-CH), 126.3 (Ar-CH), 126.1 (Ar-CH), 125.2 (Ar-CH), 123.0(Ar-CH),119.4 (Ar-C), 74.3 (-OCH_2), 52.0 (OCH_3); ESMS: *m/z*: 327 $(M+H)^+$; Calculated elemental analysis for $C_{19}H_{15}ClO_3$: C, 69.84; H, 4.63, Elemental analysis found: C, 69.78; H, 4.54.

***Methyl 1-(benzyloxy)-2-naphthoate (30)*:** It was obtained, by reaction of methyl 1-hydroxy-2-napthoate (0.9g, 4.45mmol) with benzyl bromide (0.52mL, 4.45mmol) in the presence of potassium carbonate (0.61g, 4.45mmol) and tetrabutyl ammonium bromide (0.28g, 0.81mmol) in THF, as Colourless syrup (1.06g, 82%); R_f = 0.52 (Ethyl acetate/hexane; 1:9), mp =133-135 ^oC; IR (neat): ν_{max} in cm^{-1} 3240, 2931, 1716, 1218; ^1H NMR (200 MHz, $CDCl_3$): δ = 8.14-8.11 (m, 1H, Ar-H), 7.96-7.91 (m, 1H, Ar-H), 7.61-7.56 (m, 1H, Ar-H), 7.51-7.42 (m, 8H, Ar-H),4.9 (s, 2H, OCH_2), 3.9 (OCH_3); ^{13}C NMR (50MHz,$CDCl_3$): δ = 167.9 (COOMe), 153.0 (Ar-C), 136.0 (Ar-C), 134.8 (Ar-C), 129.1 (Ar-CH), 128.4 (Ar-CH), 128.1 (Ar-CH), 127.0 (Ar-CH), 126.1 (Ar-CH), 125.0 (Ar-CH), 122.8 (Ar-CH), 74.7 (-OCH_2), 52.5 (OCH_3), ESMS: *m/z*: 293 $(M+H)^+$; Calculated elemental analysis for $C_{19}H_{16}O_3$: C, 78.06; H, 5.52, Elemental analysis found: C, 78.0; H, 5.67.

***N-Hydroxy-1-(pentyloxy)-2-naphthamide (31)*:** It was obtained by reaction of

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correspoding methyl ester (1.3g, 4.7mmol) with the hydroxyl amine hydrochloride salt (3.32g, 47.7mmol) and poatassium hydroxide (5.35g, 95.5mmol) in methanol as white solid (1.13g, 87%); R_f = 0.54 (Ethyl acetate/hexane; 3:7); mp =104-106 ^oC; IR(KBr): ν_{max} in cm^{-1} 3295, 2932, 2865, 1727, 1608, 1202; ^1H NMR (200 MHz, $CDCl_3$): δ = 8.10-7.97 (m, 2H, Ar-H), 7.82-7.77 (m, 1H, Ar-H), 7.54-7.49 (m, 3H, Ar-H), 4.07, (t, *J* = 6.7Hz, 2H, OCH_2), 2.01-1.93 (m, 2H, CH_2), 1.58-1.25 (m, 4H, CH_2), 1.00-0.93 (m, 3H, CH_3); ^{13}C NMR ($CDCl_3$): δ = 164.9 (CONH), 154.8 (Ar-C), 137.0 (Ar-C), 128.5 (Ar-CH), 128.4 (Ar-CH), 126.9 (Ar-CH), 126.4 (Ar-CH), 124.9 (Ar-CH), 123.3 (Ar-CH), 119.7 (Ar-C), 77.2 (-OCH_2), 30.3 (CH_2), 28.4 (CH_2), 22.9 (CH_2), 14.4 (CH_3); ESMS: *m/z*: 274 $(M+H)^+$; Calculated elemental analysis for $C_{16}H_{19}NO_3$: C, 70.31; H, 7.01; N, 5.12, Elemental Analysis found: C, 70.30; H, 6.91; N, 5.09.

***1-(Hexyloxy)-N-hydroxy-2-naphthamide (32)*:** It was obtained by reaction of correspoding methyl ester (1.1g, 3.8mmol) with the hydroxyl amine hydrochloride salt (2.66g, 38.3mmol) and poatassium hydroxide (4.29g, 76.6mmol) in methanol as white solid (0.93g, 85%); R_f = 0.56 (Ethyl acetate/hexane; 3:7); mp =104-106 ^oC ; IR (KBr): ν_{max} in cm^{-1} 3422, 3021, 2361, 1648, 1216; ^1H NMR (200 MHz, $CDCl_3$): δ = 8.10-7.79 (m, 2H, Ar-H), 7.82-7.78 (m, 1H, Ar-H), 7.58-7.50 (m, 3H, Ar-H), 4.08-4.01, (t, *J* = 6.6Hz, 2H, OCH_2), 2.03-1.89 (m, 2H, CH_2), 1.55-1.25 (m, 6H, CH_2), 0.95-0.89 (m, 3H, CH_3); ^{13}C NMR (50 MHz,$CDCl_3$): δ = 164.9 (CONH), 154.8 (Ar-C), 137.0 (Ar-C), 129.0 (Ar-C), 128.5 (Ar-CH), 128.4 (Ar-CH), 127.0 (Ar-CH), 126.3 (Ar-CH), 125.0 (Ar-CH), 123.3 (Ar-CH), 77.2 (-OCH_2), 32.0 (CH_2), 30.6 (CH_2), 30.1 (CH_2), 26.0 (CH_2), 23.0 (CH_2), 14.4 (CH_3); ESMS: *m/z*: 288 $(M+H)^+$; Calculated elemental analysis for $C_{17}H_{21}NO_3$: C, 71.06; H, 7.37; N, 4.87, Elemental analysis found: C, 71.0; H, 7.31; N, 4.82.

***1-(Allyloxy)-N-hydroxy-2-naphthamide (33)*:** It was obtained by reaction of correspoding methyl ester (0.7g, 2.89mmol) with the hydroxyl amine hydrochloride salt (2.01g, 28.9mmol) and poatassium hydroxide (3.23g, 57.8mmol) in methanol as white solid (0.54g, 78%); R_f = 0.53 (Ethyl acetate/hexane; 3:7); mp =139-141^oC; IR (KBr): ν max in cm^{-1} 3446, 3021, 2361, 1634, 1216; ^1H NMR (200 MHz, $CDCl_3$): δ = 8.10-7.97 (m, 2H, Ar-H), 7.81-7.76 (m, 1H, Ar-H), 7.62-7.47 (m, 3H, Ar-H), 6.21-6.12 (m, 1H, -CH=), 5.55-5.34 (m, 2H, =CH2), 4.55 (m, 2H, OCH_2); ^{13}C NMR (50 MHz, $CDCl_3$): δ = 164.8 (CONH), 154.1 (Ar-C), 137.1 (Ar-C), 132.6 (Ar-CH), 126.3 (Ar-CH), 125.7 (Ar-CH), 125.2 (Ar-CH), 123.3 (Ar-CH), 116.7 (=CH_2), 77.1 (-OCH_2); ESMS: *m/z*: 244 $(M+H)^+$; Calculated elemental analysis for $C_{14}H_{13}NO_3$: C, 69.12; H, 5.39; N, 5.76, Elemental analysis found: C, 69.19; H, 5.59; N, 5.66.

***1-(3,4-Dichlorobenzyloxy)-N-hydroxy-2-naphthamide (34)*:** It was obtained by reaction of correspoding methyl ester (0.5g, 1.38mmol) with the hydroxyl amine hydrochloride salt (0.96g, 13.8mmol) and poatassium hydroxide (1.5g, 27.7mmol) in methanol as white solid (0.46g, 93%); R_f = 0.47 (Ethyl acetate/hexane; 3:7); mp =149-152 ^oC; IR(KBr): ν_{max} in cm^{-1} 3215, 3061, 1633, 1355; ^1H NMR (200 MHz, $CDCl_3$ +CD_3OD): δ = 8.12-7.39 (m, 9H, Ar-H), 5.03 (s, 2H, OCH_2); ^{13}C NMR (50MHz,$CDCl_3$+ CD_3OD): δ = 169.4 (CONH), 157.3 (Ar-C), 140.7 (Ar-C), 140.6 (Ar-C), 135.0 (Ar-CH), 134.7 (Ar-CH), 134.4 (Ar-CH), 134.3 (Ar-CH), 132.4 (Ar-CH), 129.8 (Ar-CH), 127.5 (Ar-CH), 126.8 (Ar-CH), 80.1 (-OCH_2); ESMS: *m/z*: 363 ($(M+H)^+$; Calculated elemental analysis for

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$C_{18}H_{13}Cl_2NO_3$: C, 59.69; H, 3.62; N, 3.87, Elemental analysis found: C, 59.64; H, 3.59; N, 3.81.

***1-(3-Chlorobenzyloxy)-N-hydroxy-2-naphthamide (35)*:** It was obtained by reaction of correspoding methyl ester (0.8g, 2.41mmol) with the hydroxyl amine hydrochloride salt (1.70g, 24.5mmol) and poatassium hydroxide (2.74g, 49.0mmol) in methanol as white solid (0.69g, 87%); R_f = 0.51 (Ethyl acetate/hexane; 3:7); mp =99-101 ^oC; IR(KBr): ν_{max} in cm^{-1} 3380, 3020, 2360, 1655, 1215; ^1H NMR (200 MHz, $CDCl_3$): δ = 8.10 (d, *J* = 5.2 Hz, 1H, Ar-H), 7.88-7.78 (m, 2H, Ar-H), 7.64-7.47, (m, 4H, Ar-H), 7.41-7.17, (m, 3H, Ar-H), 4.98 (s, 2H, OCH_2); ^{13}C NMR (50MHz, $CDCl_3$): δ = 164.5 (CONH), 153.7 (Ar-C), 130.6 (Ar-CH), 130.6(Ar-CH), 129.3 (Ar-CH), 128.7 (Ar-CH), 128.6 (Ar-CH), 127.3 (Ar-CH), 126.8 (Ar-CH), 126.2 (Ar-CH), 125.5 (Ar-CH), 123.0(Ar-CH),119.7 (Ar-C), 76.2 (-OCH_2); ESMS: *m/z*: 328 $(M+H)^+$; Calculated elemental analysis for $C_{18}H_{14}ClNO_3$: C, 65.96; H, 4.31; N, 4.27, Elemental analysis found: C, 65.89; H, 4.21; N, 4.19.

***1-(Benzyloxy)-N-hydroxy-2-naphthamide (36)*:** It was obtained by reaction of correspoding methyl ester (0.6g, 2.06mmol) with the hydroxyl amine hydrochloride salt (1.43g, 20.6mmol) and poatassium hydroxide (2.30g, 41.2mmol) in methanol as white solid (0.45g, 75%), R_f = 0.57 (Ethyl acetate/hexane; 3:7), mp = 133-135 ^oC; IR(KBr): ν_{max} in cm^{-1} 3373, 2921, 1598, 1350; ^1H NMR (200 MHz, $CDCl_3$ +CD_3OD): δ = 8.19-8.14 (m, 1H, Ar-H), 7.97-7.93 (m, 1H, Ar-H), 7.63-7.59 (m, 1H, Ar-H), 7.56-7.40 (m, 8H, Ar-H), 5.03 (s, 2H, OCH_2); ^{13}C NMR (50MHz,$CDCl_3$+ CD_3OD): δ = 164.9 (CONH), 154.0 (Ar-C), 137.0 (Ar-C), 135.8 (Ar-C), 129.1 (Ar-CH), 128.6 (Ar-CH), 128.5 (Ar-CH), 127.2 (Ar-CH), 126.3 (Ar-CH), 125.3 (Ar-CH), 123.3 (Ar-CH), 78.7 (-OCH_2); ESMS: *m/z*: 294 $(M+H)^+$; Calculated elemental analysis for $C_{18}H_{15}NO_3$: C, 73.71; H, 5.15; N, 4.78; Elemental analysis: found C, 73.67; H, 5.12; N, 4.68.

Biology

Antimalarial assay

3D7 clone of *P. falciparum* was maintained *in-vitro* in RPMI-1640 (HEPES modification) medium supplemented with 0.5% AlbuMaxII, 0.2% glucose,0.2% $NaHCO_3$ and additionally 15 µM hypoxanthine, incubated at 37^0C with 5% CO_2 and medium was changed every day. The parasite growth rate and stage was determined by the examination of giemsa's stained smears of the parasitized RBCs. The parasite culture with ~0.5% initial parasitaemia at 1-1.5% hematocrit was used for antimalarial assay in 96 well microtiter plates.

Stock solutions of compounds were prepared at 10mg/ml in DMSO and stored at 0^0C until use. Two fold serial dilutions of the newly synthesized hydroxamates as well as standard drug chloroquine were prepared and 200µL asynchronous culture of *P. falciparum* 3D7 was added to each well. Plates were incubated in CO_2 incubator maintained at 37°C with 5% $CO_2$for 24 h, radiolabelled hypoxanthine solution (25 µL) containing 0.5 µ Ci radioactivity was added to each well. Plates were further incubated for additional 48 h and red blood cells were harvested on Whattmann filter papers, dried overnight,10 ml scintillation cocktail was added to the harvested cells. Radioactivity was counted under scintillation counter [43], IC_{50} values of compounds were calculated on the basis of uptake of radiolabelled hypoxanthine by the parasite at the

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corresponding drug dilutions compared with control using MS EXEL.

Anti-trypanosomal assay

Test was carried out in 96 well microtiter plates against *Trypanosoma brucei brucei* S427 a rodent laboratory strain [44]. Briefly, parasites were cultivated in HMI-18 medium in a 24-well plate at 37^0C in 5% CO_2 and sub-passaged on alternate day. A visually log phase growth of trypanosomes were selected and diluted to $2x10^5$ parasite/ml by counting the parasite density using a Neubaur chamber.

Three fold dilutions of compounds (50µl) were prepared in triplicates. Same amount of parasites ($2x10^5$ /ml) was added in these wells. Plates were incubated at 37 ºC in 5% CO_2 for 72 h and 10µl resazurin solution (12.5mg/100ml in PBS) was added in each well. Plates were further incubated in the same environment for additional 4 hours and read under synergy fluorescence reader (Biotek) with excitation wavelength 430±25nm and emission wavelength 490 ±25nm. Fifty percent conc. (IC_{50}) were calculated on the basis of fluorescence reading of samples relative to control wells with the help of MS excel. Pentamidine was used as standard anti-trypanosomal drug.

Cytotoxicity assay

Cytotoxic assay was carried out against monkey kidney cell line C1008 (Vero cells). Cells were cultivated in $25cm^2$ tissue culture flask supplemented with MEM-medium (9.7g MEM, 2.2g/l $NaHCO_3$,6g HEPES, Gentamycine sulphate 50 mg, amphotericin B 2.5 mg,TDW-1000ml)+15%FBS provided with 5% CO_2 at 37^0C. The culture medium was changed on alternate days**.** For the cytotoxicity assay cells were washed with PBS, trypsinized with 0.25% trypsin and a cell suspension was made in culture medium and counted in Neubaur chamber to make appropriate dilution ($1x10^5$ cells/ml). Vero cell suspension (100µL) was added to the microtiter plates and allowed to adhere overnight. Serial dilutions of test compounds were prepared in these plates and incubated for 72 hours. Resazurin solution (10%) was added in each well and after 4 h, plates were read under florescence reader (Biotek) [45]. Cytotoxic concentration (CC_{50}) was determined using MS-EXEL.

Antifungal and antibacterial activities

Minimum inhibitory concentration of compounds for their antifungal and antibacterial activity was tested according to the standard microbroth dilution technique as per NCCLS guidelines in flat bottom 96-well tissue culture plates (CELLSTAR_ Greiner bio-one GmbH, Germany) in RPMI 1640 medium buffered with MOPS (3-(N-morpholino)propanesulfonicacid) (Sigma Chem. Co., MO, USA) for fungal strains and in Muller Hinton Broth (Titan Biotech Ltd, India) for bacterial strains [46-48]. The concentration ranges for the tested compounds were 0.36-50 and 0.0028-32 µg/mL for standard compounds. Plates were incubated at 35°C in a moist chamber (24 hrs. for all the bacterial strains, 48 hrs. for *C. albicans* and *C. parapsilosis*, 72 hrs. for *A. fumigatus*, *S. schenckii* and *C. neoformans*, and 96 hrs. for *T. mentagrophytes*). MICs were determined as 90% inhibition of growth with respect to the growth in control spectrophotometrically.

Conclusion

In conclusion, the present study suggests that hydroxamic acids may be exploited as a safe, broad spectrum promising antiprotozoals for further development. These active compounds having good safety

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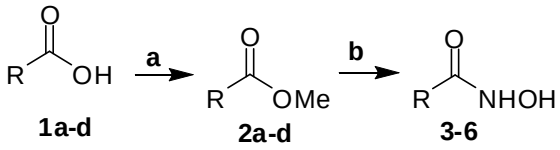
index, would be further explored alone or in combination for their *in-vivo* anti parasitic response. Furthermore, these compounds also show better antifungal activities, which may be further explored in future.

Acknowledgments

Authors thank, CSIR and DRDO New Delhi for financial assistance. S.K. Pandey, M. Mishra, Hemlata and Anindra are thankful to CSIR New Delhi for SRF. We are also thankful to SAIF Division, CDRI for providing the spectral data and microanalyses. SKP is thankful to Prof. Shakir Ali, Dept. of Biochemistry, Jamia Hamdard for his valuable suggestions. This is CDRI communication no 7742.

Schemes

Prototype A



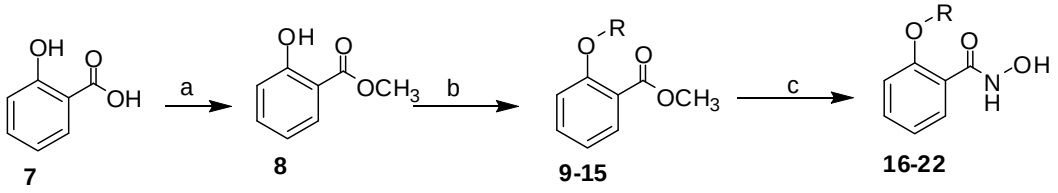
1a-d **2a-d** **3-6**

1a, **2a**, **3** = R= tetradecyl, **1b, 2b, 4** = R= 2,6-dimethyl phenyl,
1c, 2c, 5 = R=Phenoxymethyl, **1d, 2d, 6** = R= p-Phenoxyphenyl.

Reagents: a = 20% H_2SO_4, MeOH, Reflux; b = $NH_2OH.HCl$, KOH, RT

Scheme 1. Synthesis of hydroxamic acids.

Prototype B



7 **8** **9-15** **16-22**

9, **16** = R= 3-chlorobenzyl, **10**, **17** = R= Hexyl,
11, 18 = R= Pentyl, **12**, **19** = R= Allyl,
13, **20** = R= 3,4-dichlorobenzyl, **14**, **21**= R= Benzyl,
15, 22 = R=N-ethyl piperidine

Reagents: a = 20% H_2SO_4, MeOH, Reflux, **b** = R-Br, K_2CO_3, TBAB, THF,RT, **c** = $NH_2OH.HCl$, KOH, RT

Scheme 2. Synthesis of salicylic acid based alkylated hydroxamic acids

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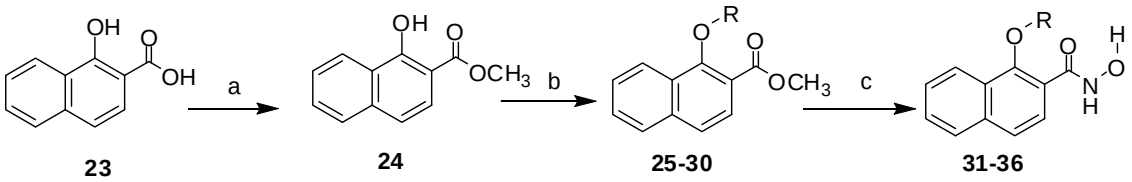
Prototype C



25, 31= R= Pentyl, **26, 32 =**R= Hexyl,
27, 33 = R= Allyl, **28, 34**= R= 3,4-dichlorobenzyl,
29, 35 = R= 3-chlorobenzyl, **30, 36** = R= Benzyl,

Reagents: a = 20% H_2SO_4, MeOH, Reflux, **b** = R-Br, K_2CO_3, TBAB, THF,RT, **c** = $NH_2OH.HCl$, KOH, RT

Scheme 3. Synthesis of naphthoic acid derived alkylated hydroxamic acids.

Tables

Table 1. Antimalarial and anti-trypanosomal activities of low molecular weight hydroxamates.

S. No.	Compound	*P. falciparum*		*T. b.b* .	
		IC_{50} (µg/ml)	Selective Index	IC_{50} (µg/ml)	Selective Index
1	**3**	8.61	355.81	4.44	690
2	**4**	1.59	186.19	1.28	231.28
3	**5**	14.2	34.63	0.25	1967.16
4	**6**	9.48	33	1.2	260.51
5	**16**	1.28	147.73	0.2	945.5
6	**17**	1.13	75.7	0.025	3422.4
7	**18**	3.75	20.77	1.81	43.03
8	**19**	1.33	56.23	1.67	44.78
9	**20**	40.89	4.16	4.05	42.06
10	**21**	0.78	28.2	1.05	20.95
11	**22**	9.95	14.98	2.06	72.36
12	**31**	8.36	9.1	5.69	13.37
13	**32**	8.19	5.01	5.8	7.08
14	**33**	8.99	12.42	4.34	25.72
15	**34**	8.39	2.47	3.9	5.32
16	**35**	5.71	4.26	1.58	15.4
17	**36**	27.31	18.21	3.1	160.42
18	**Chloroquine**	0.0056	ND	NA€	NA€
19	**Pentamidine**	NA€	NA€	0.0018	ND

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Table 2. *In vitro* antimicrobial activities of low molecular weight hydroxamates on different strains of bacteria and fungi.

S. no.	Comp. No.	Minimum inhibitory conc. (MIC) in μg/ml against									
		BACTERIA				FUNGI					
		1	2	3	4	5	6	7	8	9	10
1	**3**	>50	50	25	>50	**0.39**	**0.39**	**1.25**	50	>50	**0.78**
2	**4**	>50	>50	25	>50	**0.19**	**0.19**	**6.25**	25	>50	**0.39**
3	**5**	>50	>50	>50	>50	>50	>50	>50	>50	>50	>50
4	**16**	>50	>50	>50	>50	50	25	25	50	>50	50
5	**17**	>50	>50	>50	>50	25	25	25	50	>50	50
6	**18**	>50	>50	>50	>50	25	25	25	25	>50	50
7	**19**	>50	>50	>50	>50	12.5	12.5	12.5	25	>50	12.5
8	**20**	>50	>50	>50	>50	50	25	50	50	>50	50
9	**21**	>50	>50	>50	>50	50	50	>50	>50	>50	50
10	**31**	50	>50	>50	>50	6.25	6.25	6.25	6.25	25	6.25
11	**32**	50	>50	>50	>50	12.5	12.5	12.5	12.5	>50	12.5
12	**33**	50	>50	>50	>50	12.5	12.5	12.5	25	>50	12.5
13	**34**	>50	>50	>50	>50	25	25	25	50	>50	50
14	**35**	50	>50	>50	>50	6.25	6.25	3.12	6.25	12.5	6.25
15	**36**	50	50	>50	>50	6.25	6.25	6.25	6.25	25	6.25
16	**Amphotericine B**	-	-	-	-	**0.016**	**0.125**	**0.16**	**0.125**	**0.125**	**0.031**
17	**Fluconazole**					**4.00**	**0.50**	**2.00**	**16.0**	**>6.4**	**2.00**

1. E. coli (ATCC 9637) *2*. Pseudomonas aeruginosa (ATCC BAA-427), 3. Staphyloccus aerus (ATCC 25923), 4. Klebsiella pneumoniae (ATCC 27736). 5. *Candida albicans* 6. *Cryptococcus neoformans* 7. *Sporothrix schenckii, 8*. *Trichophyton mentagrophytes, 9*. *Aspergillus fumigatus* 10. *Candida parapsilosis* (ATCC-22019).

Captions

Scheme 1. Synthesis of hydroxamic acids.
Scheme 2. Synthesis of salicylic acid based alkylated hydroxamic acids.
Scheme 3. Synthesis of naphthoic acid derived alkylated hydroxamic acids.

Table 1. Antimalarial and anti-trypanosomal activities of low molecular weight hydroxamates.

Table 2. *In vitro* antimicrobial activities of low molecular weight hydroxamates on different strains of bacteria and fungi.

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