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SYNTHESIS OF PHARMACOLOGICALLY IMPORTANT ANALOGUES OF NATURAL TRYPTANTHRINS

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Abstract- The work included in present paper describes a synthetic strategy for series of new Tryptanthrin aminoalkyl analogues of pharmacological importance.The synthesis of tryptanthrin aminoalkyl derivatives have been achieved via multistep synthesis involving firstly creation of oxime functionality in the parent tryptanthrin structure and then alkylation of oxime functionality of by various alkyl amino pharmacophoric groups. Pharmacohoric cyclic amines were legated using potassium carbonate as base. 15 membered small library of Trytanthrin aminoalkyl analogues were synthesized with variation in both parent natural alkaloid and also in amino alkyl side chains. Synthesized compounds were fully characterized with ^{1}H and ^{13}C NMR, IR spectroscopy.

Keywords: Antimalarial, Tryptanthrin, Natural product, Animo alkyl chains, Oximes, Natural product Inspired

Introduction

Billions of people die due to various health ailments like pathothogenic or lifestyle diseases every year worldwide. The development of resistance and multidrug resistances in pathogen make this situation more critical and crucial. So the Scientists and Chemists involved in drug discovery research and Medicinal Chemistry programme have tremendous burden of developing new therapeutics to combat this situation. As a result a number of new synthetic molecules are being synthesized everyday in order to obtain molecules of better biological property. Synthesis of hybrid molecules containing one or more pharmacophore and one molecule of therapeutic importance is among one of the important tool in the field of medicinal chemistry.[I-V] If one of the therapeutically important molecules is natural molecule then this synthesis is known as natural product inspired synthesis. In the present work we followed the same path of natural product inspired synthesis by using the beneficial properties of tryptanthrin nucleus.[VI-X]Tryptanthrin is a natural alkaloid having (quinazoline 6, 12-dione) nucleus present in a number of plant species.[XI-XII] It is active most important component of a traditional Japanese herbal remedy for fungal infections. Indolo[2,1-b]-quinazoline-6,12-dione (tryptanthrin) is a compound with a long history and is well documented to possess

antibacterial activityagainst variety of pathogenic bacteria, particularly the causative agent of tuberculosis.[XIII-XVII] Tryptanthrin and its analogues are also reported as potential anticancer agents against MCF-7, NCI-H460 and SF-268 human cancer cell lines.[XIX-XXII] Tryptanthrin have quinazolines and indole moieties in their core structure. The quinazoline core is a building block for approximately 150 naturally occurring alkaloids isolated from a number of families of plant kingdom.[XXIII-XXVII] We are working for in the field of natural product inspired synthesis and synthesis of small molecules of therapeutic interest[XXIX-XXXII]. In continuation of this we have earlier reported the first green synthesis of Tryptanthrins.[XXXIII-XXXVI] These pharmacological properties associated with tryptanthrin and importance of quinazoline nucleus in medicinal chemistry prompted us to synthesize tryptanthrin derivatives as therapeutic agents. In this report we hypothesized to synthesize Tryptanthrin nucleus and ligate them with different pharmacophoric aminoalky groups in order to evaluate their antimalarial potential. Figure 1 demostrates few representative structures of biologically active naturally occuring molecules.

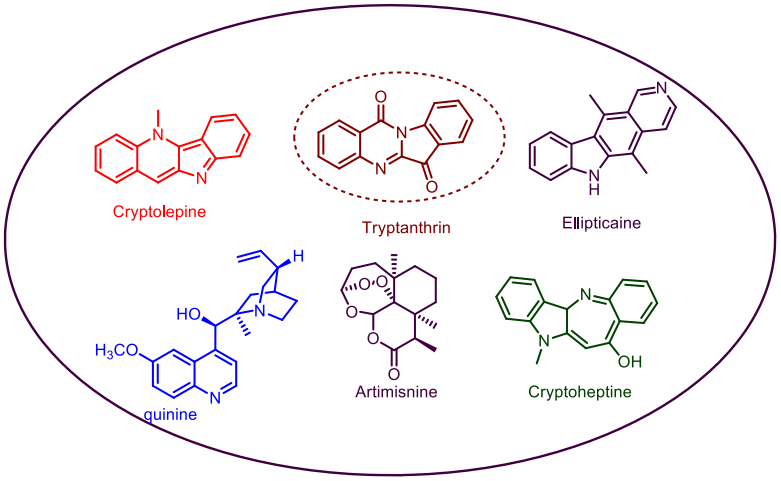


Figure 1: Some biologically active naturally occuring molecules containing qunazoline nucleus

4. Experimental

All the reactions were carried out at room temperature that is 28-32^{0}C. Unless otherwise specified, all the reagents were purchased from Sigma-Aldrich Chemical Co, Lancaster and were used directly without further any purification. NMR spectra were obtained using the Brucker DRX 300MHz spectrometer. Chemical shifts (δ) are given in ppm relative to TMS, coupling constants (*J*) in Hz. IR spectra were taken on VARIAN FT-IR spectrometer as KBr pellets (when solid). Elemental analysis was performed using a Perkin Elmer Autosystem XL Analyzer. Melting points were measured using a COMPLAB melting- point apparatus. Reactions were monitored by thin-layer chromatography (TLC) carried out on 0.25 mm silica gel plates visualized with UV light.

Synthesis of Oxime analogues (4a-c): Tryptanthrin derivatives (3a-c) 1Mol Eq. , Hydroxylamine hydrochloride 1.1 Mol Eq. and Sodium hydroxide pallets 1.5 Mol Eq. were reacted in 10Vol of Toluene under reluxing condition. Progress of reaction was monitored by Silica TLC. After completion toluene was evaporated under reduced pressure and reaction mixture was extracted with ethyl acetate and water. Organic layer was dried over sodium sulfate and purified by silica coloumn chromatography. Corresponding oxime derivative was isolated as light green solid in excellent yield.

Synthesis of Aminoalkyl Derivatives (5a-o): Oxime derivative of tryptanthrin (1 mmol) was taken in 100ml RB flsk and dissolve in dry acetone. Dry potassium carbonate (10 mmol) was added over it. Then aminoalkyl chain (1.2 mmol) was added in form of their hydrochloride salts. Reaction mixture was allowed to reflux on water bath upto completion of reaction. After completion solvent was evaporated under reduced pressure. Solid residue was poured in water and extracted with ethyl acetate. Organic layer was dried over sodium sulphate and concentrated in rotavapour. Solid residue was further purified with column chromatography.

indolo[2,1-b]quinazoline-6,12-dione (3a) Green solid; mp= >200^{0}C; ^{1}H NMR (300 MHz $CDCl_3$)δ= 8.61 (d, 1H, *J*= 3.4 Hz), 8.44 (d, 1H, *J*= 1.17 Hz), 8.06 (d, 1H, *J*= 8.01 Hz), 7.94-7.80 (m, 3H), 7.69 (t, 1H, *J*= 7.08 Hz), 7.28 (t, 1H, *J* = 7.44 Hz); ^{13}C NMR (75 MHz $CDCl_3$) δ=117.5, 120.6, 125.4, 126.3, 127.1, 129.7, 130.0, 133.2, 134.6, 145.3, 146.6, 160.4, 183.8; ESMS (*m*/*z*): 249 $(M+H)^+$; Anal. Calcd for $C_{15}H_8N_2O_2$: C, 72.58; H, 3.25; N, 11.28. Found: C, 72.55; H, 3.21; N, 11.31.

8-chloroindolo[2,1-b]quinazoline-6,12-dione (3b) Green solid; mp= >200^{0}C; ^{1}H NMR (300 MHz $CDCl_3$)δ= 8.62 (d, 1H, *J*= 6.8 Hz), 8.44 (d, 1H, *J*= 5.8 Hz), 8.06 (d, 1H, *J*= 7.15 Hz), 7.90-7.88 (m, 2H), 7.76-7.68 (m, 2H); ^{13}C NMR (75 MHz $CDCl_3$) δ= 116.5, 121.8, 123.5, 127.6, 127.9, 128.3, 130.0, 133.9, 134.4, 141.3, 146.5, 148.6, 152.7, 161.6, 188.4; ESMS (*m*/*z*): 283 $(M+H)^+$; Anal. Calcd for $C_{15}H_7ClN_2O_2$: C, 63.73; H, 2.50; N, 9.91. Found: C, 63.70; H, 2.46; N, 9.94.

8-nitroindolo[2,1-b]quinazoline-6,12-dione (3c) Green solid; mp= >200^{0}C; ^{1}H NMR (300 MHz $CDCl_3$)δ=8.74-8.72 (m, 2H), 8.54(s, 1H), 8.39 (d, 1H, *J*= 6.0), 7.79 (d, 2H, *J*= 3.14 Hz), 7.77-7.74 (m, 1H); ^{13}C NMR (75 MHz $CDCl_3$) δ=115.0, 120.0, 120.8, 123.8, 126.6, 127.3, 133.4, 145.5, 147.1, 153.9, 160.6, 186.4; ESMS (*m*/*z*): 294 $(M+H)^+$; Anal. Calcd for $C_{15}H_7N_3O_4$: C, 61.44; H, 2.41; N, 14.33. Found: C, 61.41; H, 2.37; N, 14.36.

(E)-6-(hydroxyimino)indolo[2,1-b]quinazolin-12(6H)-one (4a) Green solid; mp= >200^{0}C; ^{1}H NMR (300 MHz $CDCl_3$)δ= 8.59 (d, 1H, *J*= 4.4 Hz), 8.42-8.29 (m, 2H), 7.89-7.80(m, 2H), 7.68-7.48(m, 2H), 7.43 (t, 1H, *J*= 7.00Hz), 2.50(s, 1H); ^{13}C NMR (75 MHz $CDCl_3$) δ=117.2, 120.6, 124.3, 126.3, 127.1, 129.7, 130.0, 133.2, 134.6, 145.3, 146.6, 158.6, 183.8; ESMS (*m*/*z*): 384 $(M+H)^+$; Anal. Calcd for $C_{19}H_{15}ClN_2O_2$: C, 67.36; H, 4.46; N, 8.27. Found: C, 67.31; H, 4.42; N, 8.29.

(E)-8-chloro-6-(hydroxyimino)indolo[2,1-b]quinazolin-12(6H)-one (4b) Green solid; mp= >200^{0}C; ^{1}H NMR (300 MHz $CDCl_3$)δ= 8.60 (d, 1H, *J*= 7.2Hz), 8.46 (d, 1H, *J*= 6.4 Hz), 8.10 (d, 1H, *J*= 7.1 Hz), 7.94-7.85 (m, 2H), 7.74-7.69 (m, 2H), 2.54(s, 1H); ^{13}C NMR (75 MHz $CDCl_3$) δ= 117.0, 121.6, 124.1, 124.4, 127.2, 127.3, 128.1, 130.3, 133.4, 133.2, 140.6, 144.3, 146.2, 152.4, 160.2, 188.2; ESMS (*m*/*z*): 298 $(M+H)^+$; Anal. Calcd for $C_{15}H_8ClN_3O_2$: C, 60.52; H, 2.71; N, 14.12. Found: C, 60.48; H, 2.68; N, 14.16.

(E)-6-(hydroxyimino)-8-nitroindolo[2,1-b]quinazolin-12(6H)-one (4c) Green solid; mp= >200^{0}C; ^{1}H NMR (300 MHz $CDCl_3$)δ=8.72-8.70 (m, 2H), 8.51(s, 1H), 8.34 (d, 1H, *J*= 7.2), 7.79 (d, 2H, *J*= 3.1 Hz), 7.76-7.71 (m, 1H), 2.58(s, 1H); ^{13}C NMR (75 MHz $CDCl_3$) δ=116.2, 120.1, 120.8, 123.6, 126.6, 132.2, 133.4, 145.5, 147.4, 153.9, 158.8, 186.4; ESMS (*m*/*z*): 309 $(M+H)^+$; Anal. Calcd for $C_{15}H_8N_4O_4$: C, 58.45; H, 2.62; N, 18.18 Found: C, 58.42; H, 2.58; N, 18.21

(E)-6-(2-(piperidin-1-yl)ethoxyimino)indolo[2,1-b]quinazolin-12(6H)-one (5a) Pale yellow viscous oil, ^{1}H NMR (300 MHz, $CDCl_3$) 8.68 (1 H, d, J = 8.0 Hz), 8.44 (1H, d, J = 7.9 Hz), 8.35 (1H, d, J = 7.5 Hz), 7.98 (1H, d, J = 8.0 Hz), 7.88-7.75 (1 H, m), 7.64-7.52 (2 H, m), 7.38 (1 H, t, J = 7.58 Hz), 4.76 (2 H, t, J = 7.6 Hz), 2.89 (2 H, t, J = 5.8 Hz), 2.53 (4H, t, J = 5.4 Hz), 1.75-1.56 (m, 4H), 1.46-1.44 (2H, m); ^{13}C NMR (75 MH_Z $CDCl_3$) δ= 28.6, 41.3, 64.8, 117.4, 121.1, 124.6, 127.2, 127.1, 129.5, 130.8, 133.8, 135.7, 144.1, 146.2, 157.9, 183.6; ESMS (*m*/*z*): 375 $(M+H)^+$; Anal. Calcd for $C_{22}H_{22}N_4O_2$: C, 70.57; H, 5.92; N, 14.96. Found: C, 70.53; H, 5.88; N, 14.97.

(E)-6-(2-(pyrrolidin-1-yl)ethoxyimino)indolo[2,1-b]quinazolin-12(6H)-one (5b) Viscous oil; ^{1}H NMR (300 MHz, $CDCl_3$) 8.67 (1 H, d, J = 8.4 Hz), 8.46 (1H, d, J = 7.9 Hz), 8.45 (1H, d, J = 7.5 Hz), 7.99 (1H, d, J = 8.07 Hz), 7.84-7.79 (1 H, m), 7.65-7.56 (2 H, m), 7.41 (1 H, t, J = 7.6 Hz), 4.84 (2 H, t, J = 5.7 Hz), 3.13 (2 H, t, J = 5.7 Hz), 2.70-2.76 (4 H, m), 1.88-1.70 (4 H, m); ^{13}C NMR (75 MH_Z $CDCl_3$) δ= 23.4, 54.6, 56.2, 67.8, 117.4, 121.0, 124.6, 126.2, 127.4, 129.4, 131.1, 133.4, 134.6, 146.1, 146.6, 157.6, 183.8; ESMS (*m*/*z*): 361 $(M+H)^+$; Anal. Calcd for $C_{21}H_{20}N_4O_2$: C, 69.98; H, 5.59; N, 15.55. Found: C, 69.94; H, 5.54; N, 15.58.

(E)-6-((3-chloropropoxy)methylene)indolo[2,1-b]quinazolin-12(6H)-one (5c) Faint white solid; mp= 188^0C; ^{1}H NMR (300 MHz, $CDCl_3$) 8.68 (1 H, d, J = 8.3 Hz), 8.48 (1H, d, J = 7.4 Hz), 8.27 (1H, d, J = 7.6 Hz) 7.99 (1H, d, J = 8.0 Hz), 7.84-7.78 (1 H, m), 7.76-7.56 (2 H, m), 7.40(t, 1H, J= 7.7 Hz), 4.80 (2 H, t, J = 6.0 Hz), 3.75 (2 H, t, J = 6.4 Hz), 2.42-2.38 (2H, m); ^{13}C NMR (75 MH_Z $CDCl_3$) δ= 29.2, 41.4, 65.1, 117.1, 121.0, 124.6, 127.4, 127.1, 140.5, 130.8, 133.8, 135.7, 144.1, 146.2, 157.9, 183.6; ESMS (*m*/*z*): 339 $(M+H)^+$; Anal. Calcd for $C_{19}H_{15}ClN_2O_2$: C, 67.36; H, 4.46; N, 8.27. Found: C, 67.31; H, 4.42; N, 8.29.

(E)-6-(2-(diisopropylamino)ethoxyimino)indolo[2,1-b]quinazolin-12(6H)-one (5d) viscous oil; ^{1}H NMR (300 MHz, $CDCl_3$) 8.61 (1 H, d, J = 8.0 Hz), 8.48 (1H, d, J = 7.9 Hz), 8.37 (1H, d, J = 7.5Hz), 7.98 (1H, d, J = 7.86 Hz), 7.86-7.75 (1H, t, J = 6.8 Hz), 7.60 (2H, q, J = 7.4 Hz), 7.41 (1 H, t, J = 7.5 Hz), 4.60 (2 H, t, J = 6.7 Hz), 3.12-3.67(2 H, m), 2.96 (2H, t, J = 6.6 Hz), 1.07(s, 1H), 1.05(s, 1H); ^{13}C NMR (75 MH_Z $CDCl_3$) δ= 21.8, 41.6, 52.1, 64.8, 117.4, 121.1, 124.6, 127.2, 127.1, 129.5, 130.8, 133.8, 135.7, 144.1, 146.2, 157.9, 183.6; ESMS (*m*/*z*): 391 $(M+H)^+$; Anal. Calcd for $C_{23}H_{26}N_4O_2$: C, 70.75; H, 6.71; N, 14.35. Found: C, 70.71; H, 6.68; N, 14.38.

(E)-6-(2-(dimethylamino)ethoxyimino)indolo[2,1-b]quinazolin-12(6H)-one (5e) viscous oil; ^{1}H NMR (300 MHz, $CDCl_3$) 8.71 (1 H, d, J = 8.3 Hz), 8.62 (1H, d, J = 8.0 Hz), 8.33 (1H, d, J = 7.6 Hz), 8.00 (1H, d, J = 7.1 Hz), 7.84-7.61 (1 H, m), 7.61-7.56 (2 H, m), 7.40 (1 H, t, J = 6.9 Hz), 4.76 (2 H, t, J = 5.8 Hz), 2.89 (2 H, t, J = 5.7 Hz), 2.41(6H, s); ^{13}C NMR (75 MH_Z $CDCl_3$) δ= 44.2, 56.2, 68.8, 117.3, 121.0, 124.6, 126.9, 127.1, 129.5, 130.6, 133.8, 134.7, 144.1, 146.2, 157.1, 183.4; ESMS (*m*/*z*): 335 $(M+H)^+$; Anal. Calcd for $C_{19}H_{18}N_4O_2$: C, 68.25; H, 5.43; N, 16.76. Found: C, 68.21; H, 5.40; N, 16.79.

(E)-8-chloro-6-(2-(piperidin-1-yl)ethoxyimino)indolo[2,1-b]quinazolin-12(6H)-one (5f) viscous oil; ^{1}H NMR (300 MHz, $CDCl_3$) 8.62 (1 H, d, J = 7.4 Hz), 8.46 (1H, d, J = 7.8 Hz), 8.33 (1H, s), 7.96 (1H, d, J = 8.0 Hz), 7.62-7.56 (2 H, m), 7.37 (1 H, t, J = 7.58 Hz), 4.75 (2 H, t, J = 7.6 Hz), 2.90 (2 H, t, J = 5.8 Hz), 2.53 (4H, t, J = 5.4 Hz), 1.77-1.54 (m, 4H), 1.44-1.46 (2H, m); ^{13}C NMR (75 MH_Z $CDCl_3$) δ= 23.2, 26.4, 54.3, 56.8, 68.6, 116.8, 121.7, 124.2, 124.4, 127.2, 127.6, 128.1, 130.4, 133.2, 133.6, 140.9, 146.4, 148.2, 152.6, 151.2, 188.4; ESMS (*m*/*z*):

409 $(M+H)^+$; Anal. Calcd for $C_{22}H_{21}ClN_4O_2$: C, 64.62; H, 5.18; N, 13.70. Found: C, 64.58; H, 5.14; N, 13.73.

(E)-8-chloro-6-(2-(pyrrolidin-1-yl)ethoxyimino)indolo[2,1-b]quinazolin-12(6H)-one (5g) viscous oil; ^{1}H NMR (300 MHz, $CDCl_3$) 8.52 (1 H, d, J = 8.1 Hz), 8.48 (1H, d, J = 7.4 Hz), 8.09 (1H, d, J = 7.3 Hz), 7.96-7.84 (2H, m), 7.81-7.75 (2H, m), 4.83 (2 H, t, J = 5.6 Hz), 3.15 (2 H, t, J = 5.4 Hz), 2.71-2.75 (4 H, m), 1.86-1.70 (4 H, m); ^{13}C NMR (75 MH_Z $CDCl_3$) δ= 25.3, 55.6, 58.2, 68.4, 116.2, 121.6, 124.2, 124.3, 127.2, 127.4, 128.1, 130.3, 133.2, 133.4, 140.9, 146.3, 148.2, 152.5, 151.2, 188.5; ESMS (*m*/*z*): 395 $(M+H)^+$; Anal. Calcd for $C_{21}H_{19}ClN_4O_2$: C, 63.88; H, 4.85; N, 14.19. Found: C, 63.84; H, 4.81; N, 14.22.

(E)-8-chloro-6-((3-chloropropoxy)methylene)indolo[2,1-b]quinazolin-12(6H)-one (5h) White solid; mp= 179^{0}C; ^{1}H NMR (300 MHz, $CDCl_3$) 8.63 (1 H, d, J = 8.3 Hz), 8.48 (1H, d, J = 7.4 Hz), 8.27 (1H, d, J = 7.6 Hz) 7.99 (1H, d, J = 8.0 Hz), 7.84-7.78 (1 H, m), 7.76-7.56 (2 H, m), 4.81 (2 H, t, J = 6.0 Hz), 3.75 (2 H, t, J = 6.4 Hz), 2.41-2.38 (2H, m); ^{13}C NMR (75 MH_Z $CDCl_3$) δ= 29.4, 40.2, 64.6, 116.5, 121.8, 123.5, 124.9, 127.6, 127.9, 128.3, 130.0, 133.9, 134.4, 141.3, 146.5, 148.6, 152.7, 151.6, 188.4; ESMS (*m*/*z*): 373 $(M+H)^+$; Anal. Calcd for $C_{19}H_{14}Cl_2N_2O_2$: C, 61.14; H, 3.78; N, 7.51. Found: C, 61.10; H, 3.75; N, 7.55.

(E)-8-chloro-6-(2-(diisopropylamino)ethoxyimino)indolo[2,1-b]quinazolin-12(6H)-one (5i) viscous oil; ^{1}H NMR (300 MHz, $CDCl_3$) 8.63 (1 H, d, J = 7.8 Hz), 8.51 (1H, d, J = 7.9 Hz), 8.17 (1H, d, J = 7.6Hz), 7.90-7.77 (2H, m), 7.60-7.41 (2H, m), 4.61 (2 H, t, J = 6.7 Hz), 3.13-3.67(2 H, m), 2.96 (2H, t, J = 6.6 Hz), 1.07(s, 1H), 1.05(s, 1H). ^{13}C NMR (75 MH_Z $CDCl_3$) δ= 21.4, 40.2, 50.3, 64.4, 116.8, 122.1, 124.0, 124.5, 127.2, 127.8, 128.1, 130.2, 133.6, 134.1, 141.2, 146.4, 148.6, 152.4, 151.2, 188.2; ESMS (*m*/*z*): 425 $(M+H)^+$; Anal. Calcd for $C_{23}H_{25}ClN_4O_2$: C, 65.01; H, 5.93; N, 13.19. Found: C, 65.00; H, 5.89; N, 13.22

(E)-8-chloro-6-(2-(dimethylamino)ethoxyimino)indolo[2,1-b]quinazolin-12(6H)-one (5j) viscous oil; ^{1}H NMR (300 MHz, $CDCl_3$) 8.68 (1 H, d, J = 8.3 Hz), 8.54 (1H, d, J = 8.0 Hz), 8.21 (1H, d, J = 7.6 Hz), 7.90-7.77 (2H, m), 7.81-7.76 (2 H, m), 4.74 (2 H, t, J = 5.8 Hz), 2.84 (2 H, t, J = 5.7 Hz), 2.40(6H, s). ^{13}C NMR (75 MH_Z $CDCl_3$) δ= 44.2, 58.4, 66.6, 116.6, 121.8, 124.1, 124.3, 127.0, 127.8, 128.1, 130.4, 133.2, 133.8, 140.9, 146.8, 148.6, 152.4, 151.2, 188.6; ESMS (*m*/*z*): 369 $(M+H)^+$; Anal. Calcd for $C_{19}H_{17}ClN_4O_2$: C, 61.87; H, 4.65; N, 15.19. Found: C, 61.84; H, 4.61; N, 15.22.

(E)-8-nitro-6-(2-(piperidin-1-yl)ethoxyimino)indolo[2,1-b]quinazolin-12(6H)-one (5k) viscous oil; ^{1}H NMR (300 MHz, $CDCl_3$) 8.64-8.58 (2 H, m), 8.54 (1H, s), 8.38 (1H, d, J = 7.3 Hz), 7.82 (1H, d, J = 7.1 Hz), 7.74-7.69 (1 H, m), 7.64-7.52 (2 H, m), 7.38 (1 H, t, J = 7.58 Hz), 4.74 (2 H, t, J = 7.6 Hz), 2.86(2 H, t, J = 5.8 Hz), 2.55-2.48 (4H, m), 1.75-1.56 (m, 4H), 1.46-1.44 (2H, m); ^{13}C NMR (75 MH_Z $CDCl_3$) δ= 24.1, 25.8, 54.5, 56.9, 68.4, 116.5, 121.2, 120.8, 124.1, 126.4, 132.3, 133.4, 146.4, 147.1, 154.3, 160.6, 186.4; ESMS (*m*/*z*): 420 $(M+H)^+$; Anal. Calcd for $C_{22}H_{21}ClN_5O_4$: C, 63.00; H, 5.05; N, 16.70. Found: C, 62.96; H, 5.01; N, 16.73.

(E)-8-nitro-6-(2-(pyrrolidin-1-yl)ethoxyimino)indolo[2,1-b]quinazolin-12(6H)-one (5l) viscous oil; ^{1}H NMR (300 MHz, $CDCl_3$) 8.29-8.23 (2H, m), 8.10 (1H, s), 7.81 (1H, d, J = 7.5 Hz), 7.53-7.41 (2H, m), 7.34-7.21 (1 H, m), 4.84 (2 H, t, J = 5.7 Hz), 3.12 (2 H, t, J = 5.7 Hz), 2.71-2.75 (4 H, m), 1.88-1.71(4 H, m); ^{13}C NMR (75 MH_Z $CDCl_3$) δ= 24.7, 55.2, 56.2, 68.2, 115.8, 121.3, 120.8, 124.1, 126.3, 132.3, 133.4, 146.5, 147.1, 154.1, 160.6, 186.2; ESMS (*m*/*z*):

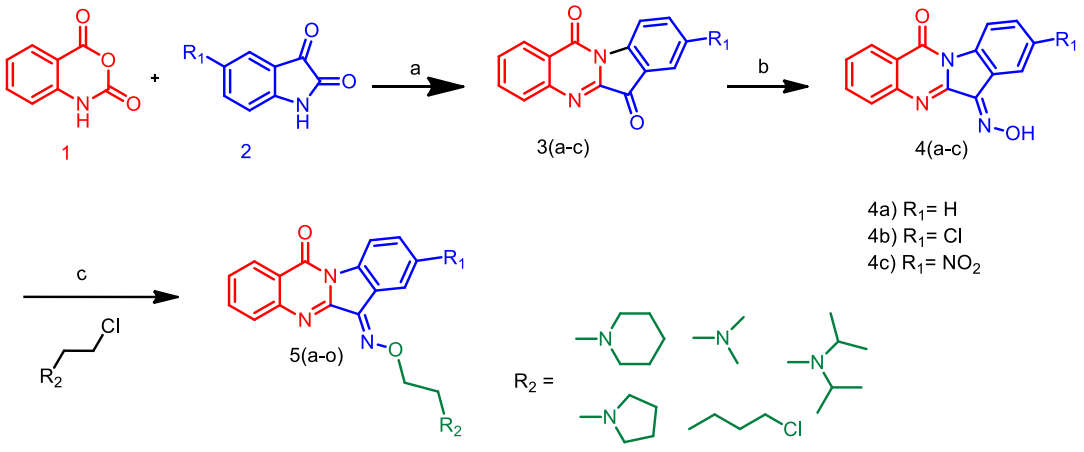
406 $(M+H)^+$; Anal. Calcd for $C_{21}H_{19}N_5O_4$: C, 62.22; H, 4.72; N, 17.27. Found: C, 62.18; H, 4.69; N, 17.30.

(E)-6-(2-(dimethylamino)ethoxyimino)-8-nitroindolo[2,1-b]quinazolin-12(6H)-one (5n) viscous oil; ^{1}H NMR (300 MHz, $CDCl_3$) 8.35-8.29 (2H, m), 8.18 (1H, s), 8.02 (1H, d, J = 7.4 Hz), 7.63-7.51 (2H, m), 7.44-7.36 (2 H, m), 4.75 (2 H, t, J = 5.8 Hz), 2.85 (2 H, t, J = 5.7 Hz), 2.41(6H, s); ^{13}C NMR (75 MH_Z $CDCl_3$) δ= 43.6, 58.2, 68.6, 116.1, 120.5, 121.8, 124.4, 126.4, 132.2, 133.8, 146.4, 147.2, 154.3, 160.4, 186.1; ESMS (*m/z*): 380 $(M+H)^+$; Anal. Calcd for $C_{19}H_{17}N_5O_4$: C, 60.15; H, 4.52; N, 18.46. Found: C, 60.11; H, 4.47; N, 18.49.

(E)-6-(2-(diisopropylamino)ethoxyimino)-8-nitroindolo[2,1-b]quinazolin-12(6H)-one (5o) viscous oil; ^{1}H NMR (300 MHz, $CDCl_3$) 8.56-8.47 (2 H, m), 8.24 (1H, s), 7.81-7.74 (2H, m), 7.60-7.48 (2H, m), 4.61 (2 H, t, J = 6.7 Hz), 3.13-3.67(2 H, m), 2.96 (2H, t, J = 6.6 Hz), 1.07(s, 1H), 1.05(s, 1H); ^{13}C NMR (75 MH_Z $CDCl_3$) δ= 21.8, 41.6, 51.8, 64.6, 116.8, 120.2, 121.6, 124.4, 127.4, 132.4, 133.8, 145.4, 146.2, 154.3, 161.4, 186.3; ESMS (*m/z*): 436 $(M+H)^+$; Anal. Calcd for $C_{23}H_{25}N_5O_4$: C, 63.44; H, 5.79; N, 16.08. Found: C, 63.40; H, 5.74; N, 16.11.

Result and discussion

Our research interest in area of Natural Product Inspired synthesis motivated us to work to develop pharmacologically active analogues of Tryptanthrins. Earlier we reported the first green synthesis of Tryptanthrin derivatives from Isatoic Anhydride and Isatins. The Starting point of our work was to synthesizethree substituted Tryptanthrin analogues (3a-c). Tryptanthrins (3a-c) were synthesized by our earlier reported procedure, using commercially available substituted isatins and isatoic anhydride in water. β-cyclodextrin was employed as catalyst in aqueous medium. Tryptanthrins (3a-c) were isolated in excellent yields (up to 90%) and negligible chromatographic purification was required at this stage. Then we tried to convert the ketonic group of tryptanthrin in oxime functionality and achieved this reacting Tryptanthrins with hydroxylamine hydrochloride using KOH pallets as base in (scheme 1).



Scheme 1: Synthesis of tryptanthrin derivatives. *Reagent and condition*: a) β-cyclodextrin, water, stirring, RT. b) toluene, hydroxylamine hydrochloride, refluxing, 12 hrs. c) dry acetone, K_2CO_3, aminoalkyl chain, refluxing.

Corresponding oxime derivatives were isolated in excellent yield (4a-c upto 92%). Formation of oxime analogue was confirmed by IR, ^{1}H and ^{13}C NMR spectroscopy. Tryptanthrin oxime

derivatives were precipitated in reaction medium and separated by filteration and purified by washing with water and ethanol. No chromatographic purification was required at this stage.

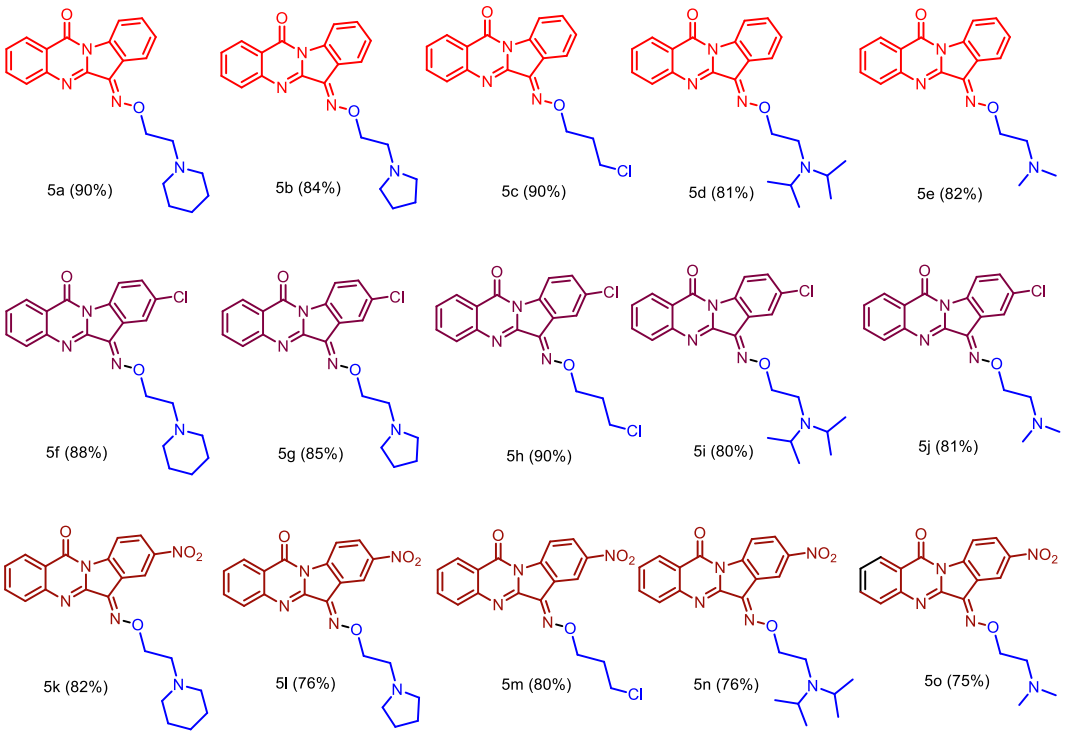


Figure 1. Synthesized Tryptanthrin Aminoalkyl Derivatives.

Next strategy was to attach pharmacophoric aminoalkyl side chains in selected natural product scaffold. To achieve this hydroxyl group of oxime derivative was alkylated with various aminoalkyl chains using a strong base as sodium hydride in DMF. Thin Layer Chromatography in silica was used to check the progress of reaction. Surprisingly we observed that derivative with nitro substitution on Tryptanthrin nucleus having poor solubity and probably due to this reason the isolated yields of products (5k-l) were low. The alkylated Tryptanthrin derivatives were isolated as oily products. Compounds (5a-o) were formed in good to excellent yields and all the synthesized aminoalkyl derivatives were characterized by IR, ^{1}H and ^{13}C NMR spectroscopy, mass spectroscopy and elemental analysis. These aminoalkyl derivatives were further evaluated for their pharmacological activity.

Conclusion

In conclusion, we have synthesized a series of aminoalkylchain substituted analogues of natural product tryptanthrin in excellent yields. These compounds were evaluated against P. Falciparum in both sensitive 3D7 and resistant pf k1 strain. Most of the compounds among compounds synthesized showed significant antimalarial at low nanomolar level. Our results reveal that our synthesized natural product derived analogues are more potent antimalarial agents than the parent natural product scaffold. Thus our findings open up new doors towards the antimalarial chemotherapy which can be helpful for the discovery of new therapeutics against malaria in near future. We have also shown cytotoxicity as well as selectivity of synthesized compounds which shows that our stnthesized compounds are more selective and very low toxic. Further in vivo exploration of this study is currently underway.

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Conflict of Interest
Authors declare no conflict of interest

References

I. C. E. Schiaffo, M. Rottman, S. Wittlin, and P. H. Dussault, 3-Alkoxy-1,2-Dioxolanes: Synthesis and Evaluation as Potential Antimalarial Agents. *ACS Med. Chem. Lett.* 2011, 2, 316–319.
II. V. Kumar, A. Mahajan, K. Chibale, Synthetic medicinal chemistry of selected antimalarial natural products Bioorganic & Medicinal Chemistry 17 (2009) 2236–2275.
III. D. G. Cabrera, F. Douelle, T.-S. Feng, A. T. Nchinda, Y. Younis, K. L. White, Q. Wu, E. Ryan, J. N. Burrows, D. Waterson, M. J. Witty, S. Wittlin, S. A. Charman, K. Chibale, Novel Orally Active Antimalarial Thiazoles J. Med. Chem. XXXX, XXX, 000–000 dx.doi.org/10.1021/jm201108k |
IV. S. Zhu, Q. Zhang, C. Gudise, L. Wei, E. Smith, Y. Zeng, Synthesis and biological evaluation of febrifugine analogues as potential antimalarial agents Bioorganic & Medicinal Chemistry 17 (2009) 4496–4502.
V. E. F. Álvaro, G. L. Nixon, F. Calderón, Antimalarial Chemotherapy: Natural Product Inspired Development of Preclinical and Clinical Candidates with Diverse Mechanisms of Action *J. Med. Chem*. 2016, 59, 12, 5587-5603.
VI. World Malaria Report. World Health Organization 2018.
VII. Price, R. N.; Nosten, F. Single-Dose Radical Cure of Plasmodium Vivax : A Step Closer. The Lancet. 2014, 383, 1020–1021.
VIII. Roy, K. K. Targeting the Active Sites of Malarial Proteases for Antimalarial Drug Discovery: Approaches, Progress and Challenges. *Int. J. Antimicrob. Agents*. 2017, 50, 287–302.
IX. Bobrovs, R.; Jaudzems, K.; Jirgensons, A. Exploiting Structural Dynamics To Design Open-Flap Inhibitors of Malarial Aspartic Proteases. J. Med. Chem. 2019, 62, 8931-8950.
X. Banerjee, R.; Liu, J.; Beatty, W.; Pelosof, L.; Klemba, M.; Goldberg, D. E. Four Plasmepsins Are Active in the Plasmodium Falciparum Food Vacuole, Including a Protease with an Active-Site Histidine. Proc. Natl. Acad. Sci. 2002, 99, 990–995.
XI. Uhlemann, A.-C., Fidock, D. A. Loss of malarial susceptibility to Artemisinin in Thailand. Lancet 2012, 379 (9830), 1928−1930.
XII. Sofowora, A. Medicinal Plants and Traditional Medicine in Africa. 1st ed.; John Wiley and Sons: Chichester, UK, 1982; pp 221-223.
XIII. Cimanga, K. Pieters, L. Claeys, M. Vanden Berghe, D. Vlietinck, A. J. Planta Med. 1991, 57, A98.
XIV. Newman, D. J. Cragg, G. M. Natural products as sources of new drugs over the last 25 years J. Nat. Prod. 2007, 70, 461.
XV. Lee, K. H. J. Nat. Discovery and Development of Natural Product-Derived Chemotherapeutic Agents Based on a Medicinal Chemistry Approach J. Nat. Prod Prod. 2010, 73, 500.
XVI. White, N. J. Qinghaosu (artemisinin): the price of success. Science 2008, 320, 330.
XVII. J. Achan, A. O. Talisuna, A. Erhart, A. Yeka, J. K. Tibenderana, F. N. Baliraine, P. J.

Rosenthal, and U. D'Alessandro, Quinine, an old anti-malarial drug in a modern world: role in the treatment of malaria Malar J. 2011; 10: 144.

XVIII. Kumar A., Katiyar S. B., Agarwal A., Chauhan P. M., Perspective in antimalarial chemotherapy. Curr Med Chem. 2003, 10(13):1137-50.

XIX. Noedl, H.; Se, Y.; Schaecher, K.; Smith, B. L.; Socheat, D.; Fukuda, M. M. Evidence of artemisinin-resistant malaria in western Cambodia. N. Engl. J. Med. 2008, 359, 2619–2620.

XX. Tang, Y. Dong, Y. Vennerstrom, J. L. Synthetic peroxides as antimalarials. Med. Res. Rev. 2004, 24, 425–448.

XXI. Lin, J. A. Klayman, D. L. Milhous, W. K. J. Med. Chem. 1987, 30, 447.

XXII. V. W.-W. Yam, Molecular Design of Transition Metal Alkynyl Complexes as Building Blocks for Luminescent Metal-Based Materials: Structural and Photophysical Aspects Acc. Chem. Res. 2002, 35, 7, 555-563.

XXIII. Posner, G. H., C. H. Wang, D. Gerena, L. Milhous, W. K. Meshnick, S. R. Asawamadhasadka, W. Mechanism- Based Design, Synthesis, and in vitro Antimalarial Testing of New 4-Methylated Trioxanes Structurally Related to Artemisinin. J. Med. Chem. 1994, 37, 1256–1258.

XXIV. C. M. Martínez-Viturro, D. Domínguez, Synthesis of the antitumoural agent batracylin and related isoindolo[1,2-b]quinazolin-12(10H)-ones Volume 48, Issue 6, 5 February 2007, Pages 1023-1026.

XXV. K. Dzierzbicka, P. Trzonkowski, P. Sewerynek, A. Myśliwski, Synthesis and Cytotoxic Activity of Conjugates of Muramyl and Normuramyl Dipeptides with Batracylin Derivatives J. Med. Chem. 2003, 46, 6, 978-986.

XXVI. Yu, S.-T. Chen, T.-M. Teng, S.-Y. Chen, Y.-H. Synthesis of visible-light mediated tryptanthrin derivatives from isatin and isatoic anhydride under transition metal-free conditions Biochem. Biophys. Res. Commun. 2007, 358, 79-84.

XXVII. Scovill, J. Blank, E. Konnick, M. Nenortas, E. Shapiro, T. Antitrypanosomal Activities
of TryptanthrinsAntimicrob. Agents Chemotherapy., 2002, 46, 882.

XXVIII. Dzierzbicka, K. Trzonkowski, P. Sewerynek, P. L. Mysliwski, Rapid synthesis of novel isoindolo[1,2-a]quinazoline on ionic liquid support under microwave irradiation A. J. Med. Chem. 2003, 46, 978-986.

XXIX. Bhattacharjee, A. K. Skanchy, D. J. Jennings, B. T. Hudson, H. Brendle, J. J. Werbovetz, K. A. Role of in silico stereoelectronic properties and pharmacophores in aid of discovery of novel antimalarials, antileishmanials, and insect repellents. Bioorg. Med. Chem. 2002, 10, 1979–1989.

XXX. Danz, H. Stoyanova, S. Thomet, O. A. R. Simon H.-U. Dannhardt, G. Ulbrich H. Hamburger, M. Inhibitory Activity of Tryptanthrin on Prostaglandin and Leukotriene Synthesis Planta Med., 2002, 68, 875.

XXXI. Bowman, W. R. Elsegood, M. R. J. Stein, T. Weaver, G. W. Radical reactions with 3H-quinazolin-4-ones: synthesis of deoxyvasicinone, mackinazolinone, luotonin A, rutaecarpine and tryptanthrin Org. Biomol. Chem., 2007, 5, 103-113.

XXXII. Tripathi V. D. and Shukla A. K. Design and Synthesis of Novel Heterocyclic Curcumin Analogues as Anticancer Agents and Filarial Topoisomerase II Inhibitors Asian J. of Org. and Med. Chem. 2018, 3(4), 164-170.

XXXIII. Tripathi V. D. and Saxena N. Synthesis and Antifungal Activity of New Dihydropyrazoles of Designed Curcumin Analogues. Asian J. of Org. and Med. Chem. 2019, 4(2), 94-100.

XXXIV. Tripathi V. D. Ultrasound Assisted Regioselective Synthesis of Polyhydrospiro

[Indoline-3,3'-pyrrolizine]-2-one Library via Multicomponent Cycloaddition Reaction. J. Bio. Chem. Chron. 2019, 5(1), 52-60.

XXXV. Tripathi V. D. Synthesis of New Dihydropyrazoles of Designed Curcumin Analogues. Asian J. of Chem. 2019, 31(9), 1889-1894.

XXXVI. Kumar A. Tripathi V. D. Kumar P. β-cyclodextrin catalysed synthesis of Tryptanthrin in Water. Green Chem. 2011, 13, 51-54.

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