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Synthesis, antimicrobial and antimalarial activity of novel carbazole derivatives

Piyush Sharma & Tirth H Thaker*

Department of Chemical Science, Parul Institute of Applied Science, Parul University, Vadodara 391 760, Gujarat, India

E-mail: tirth6582@gmail.com

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1-((9*H*-Carbazol-4-yl)oxy)-3-(piperazine-1-yl) propane-2-ol **3** has been synthesized by condensing epoxy carbazole **1** and piperazine **2**. 2-(4-(3-((9*H*-Carbazol-4-yl)oxy)-2-hydroxypropyl)piperazin-1-yl)-1-phenylpropan-1-one **5a-c** derivatives have been synthesized by using 1-((9*H*-carbazol-4-yl)oxy)-3-(piperazin-1-yl)propan-2-ol **3** and different derivatives of 2-bromo-1-phenylpropan-1-one **4a-c**. IR, ^{1}H and ^{13}C NMR, mass spectroscopy and CHN analysis have been used to elucidate the structures of the compounds. The title compounds have been explored for antimalarial and antibacterial activity and have shown promising results.

Keywords: Epoxy carbazole, Carbazole-piperazine derivatives, Antimicrobial screening, Antimalarial activity

Carbazole analogues have attracted both medicinal chemists and biologists due to their ever-growing pharmacological activities[1-3]. Thus, carbazole has become a beneficial scaffold to access natural and unnatural biologically active molecules[4]. Due to their adaptability in functionalization and chemical stability, carbazole compounds are of wide interest[5]. Strychnos alkaloids are structurally composed of carbazole derivatives and a tetracyclic azocino[4,3-b]indole and possess a wide range of pharmacological activities, such as antibacterial, antifungal, antiviral, antihypertensive and anti-Alzheimer[6-12]. The biological features of piperazine and its hybrid compounds with carbazoles, make them more relevant in medicine, especially in antibacterial, antiallergenic, and antioxidants[13,14]. The carbazole moiety is present in several important commercially available drug molecules such as ellipticine, alectinib, midostaurin, carvedilol, carazolol, carprofen, and frovatriptan. Carvedilol was approved in 1995 to treat high blood pressure and congestive heart failure[15,16]. Carazolol is a truncated analogue of carvedilol and was approved to treat cardiovascular disorders in non-human mammals. The 5-hydroxytryptamine (5-HT) receptor agonist, frovatriptan has been approved for the acute treatment of moderate to severe migraines in humans[17]. Looking towards pharmaceutical aspects of carbazoles, the present research is focused on the synthesis, antimicrobial and antimalarial activity of novel carbazole analogues.

Experimental Section

Materials and Methods

All chemicals were purchased from commercial sources (LOBA chem, Spectrochem, Merck, and Sigma-Aldrich). Melting points were determined using the equiptronics model EQ-730 instrument. TLC was carried out using Merck silica gel 60 F254 plates. Visualization of the plates was done using a UV lamp (λmax = 254 or 365 nm). ^{1}H NMR spectra were recorded using Bruker 400MHz NMR spectrometer in DMSO-d_6 solution and TMS as internal standard. IR spectra were recorded using the Bruker alpha FTIR spectrometer. Mass spectral data were recorded using a Shimadzu LC2010 mass analyser and C, H, N analysis using Perkin Elmer PE 2400.

Synthesis of 1-((9*H*-carbazol-4-yl)oxy)-3-(piperazin-1-yl)propan-2-ol, 3

Epoxy carbazole **1** (25 g, 0.104 mole) was added in small portions over the mixture of piperazine **2** (90 g, 1.04 mole) and methanol (250 mL) at 15-20° C. Reaction mass was added to water (500 mL) and stirred for half an hour to get precipitate, which on filtration gives a crude solid 15 g. This crude was purified *via* column chromatography using silica gel as a stationary phase and Dichloromethane: Methanol (9:1) as eluent to afford 10 g compound.

Characterization data of synthesized Compound 3

1-((9*H*-Carbazol-4-yl)oxy)-3-(piperazin-1-yl)propan-2-ol, 3: Yield 30%. m.p.182-187°C. IR (KBr): 2984 (N-H), 3136 (C-H), 3294 (O-H) cm^{-1};

^{1}H NMR (400 MHz, DMSO-d_6): δ 2.44-2.73 (m, 2H of N-CH_2 and 8H of CH_2 of piperazine ring), 4.14-4.23 (m, 3H of O-CH_2, 1H of O-CH), 6.69-6.71 (1H, d, *J*= 8Hz, ArH), 7.11-7.13 (1H, d, 8Hz, ArH), 7.16-7.20 (1H, t, 7.2 Hz, 6.8Hz, ArH), 7.29-7.39 (2H, m, ArH), 7.48-7.50 (1H, d, *J*= 8Hz, ArH), 8.30-8.32 (1H, d, *J*= 8Hz, ArH), 11.35 (bs, NH of Piperazine ring); MS (ESI): *m/z* Calcd for $C_{19}H_{23}N_3O_2$: $[M+H]^+$: 326.18. Found 326.20. Anal. Calcd for $C_{19}H_{23}N_3O_2$: C, 70.13; H, 7.12; N, 12.91; O, 9.83. Found: C, 70.43; H, 6.88; N, 12.75%.

Synthesis of 2-(4-(3-((9*H*-carbazol-4-yl)oxy)-2-hydroxypropyl)piperazin-1-yl)-1-phenylpropan-1-one derivatives, 5a-c

Compound **3** (3 mmol) was taken in 10 mL DMF and added potassium carbonate (0.848 g, 6 mmol). The resulting mass was stirred at 25°C for 30 minutes with α-bromo acetophenones (3 mmol) (**4a-c**). Water (100 mL) was added and the resulting mass was extracted with MTBE (2×50 mL). MTBE layer was washed with water (50 mL) and dried over anhydrous sodium sulfate. MTBE layer was concentrated to leave a minimum to ppt out the solid which was collected by filtration to get pure compounds **5a-c**.

Characterization of potent compounds

2-(4-(3-((9*H*-Carbazol-4-yl)oxy)-2-hydroxypropyl)piperazin-1-yl)-1-phenylpropan-1-one, 5a: Yield 60%. m.p.70-75°C. IR (KBr): 1339 (CH_3), 1681 (C=0), 3000 (N-H), 3400 (b, O-H), cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.13 (3H, d, *J* = 6.4 Hz 4 Hz, -CH_3), 2.43-2.57 (m, 8H of N-CH_2, 2H of N-CH_2), 4.10-4.16 (m, 2H of O-CH_2, 1H of O-CH), 4.27 (1H, m, N-CH), 4.92-4.93 (1H, bs, OH), 6.65-6.67 (d, 1H, 8 Hz, ArH), 7.05-7.12 (m, 2H, ArH), 7.25-7.27 (1H, d, 6.8Hz, ArH), 7.29-7.33 (2H, m, ArH), 7.42-7.48 (1H, d, 8 Hz, ArH), 7.5 (1H, t, 8 Hz), 7.59-7.61 (1H, d, 7.2 Hz, ArH), 8.04 (2H, m, ArH), 8.05-8.06 (1H, d, 7.2 Hz, ArH), 11.27 (1H, bs, NH of carbazole ring); ^{13}C NMR: δ 155.46, 141.55, 139.35, 136.66, 133.39, 129.10, 128.89, 126.93, 124.96, 122.97, 122.19, 118.97, 112.04, 110.07, 104.25, 100.90, 71.24, 67.17, 63.05, 61.76, 54.43, 49.01, 10.45; MS (ESI): *m/z* Calcd for $C_{28}H_{31}N_3O_3$: $[M+H]^+$: 458.24. Found 458.3. Anal. Calcd for $C_{28}H_{31}N_3O_3$: C, 73.50; H, 6.83; N, 9.18. Found C, 73.18, H, 6.98, N, 9.34%.

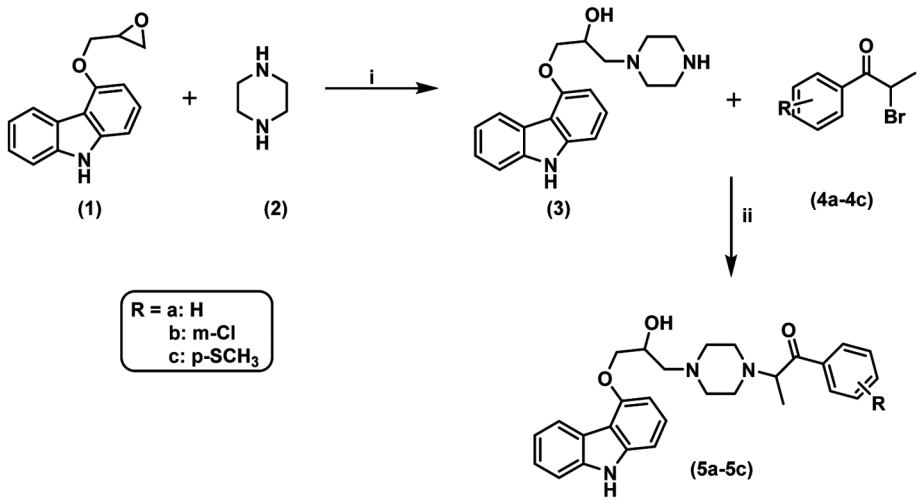
2-(4-(3-((9*H*-Carbazol-4-yl)oxy)-2-hydroxypropyl) piperazin-1-yl)-1-(3-chlorophenyl)propan-1-one, 5b: Yield 50%. m.p.62-67°C. IR (KBr): 1332 (CH_3), 1686 (C=O), 2934 (N-H), 3400 (b, O-H), cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.10 (3H, d, *J* = 4.0 Hz, -CH_3), 2.44-2.56 (m, 8H of N-CH_2, 2H of N-CH_2), 4.10-4.15 (m, 2H of O-CH_2, 1H of O-CH, 1H of N-CH), 5.0 (1H, bs, OH), 6.60-6.68 (d, 1H, 8 Hz, ArH), 7.06-7.13 (m, 3H, ArH), 7.26-7.30 (2H, m, ArH), 7.33-7.34 (1H, m, ArH), 7.44-7.46 (1H, m, ArH), 7.51-7.66 (1H, m, 8 Hz), 7.98-8.05 (2H, d, 7.2 Hz, ArH), 11.24 (1H, bs, NH of carbazole ring); ^{13}C NMR: δ 199.34, 155.48, 141.58, 139.38, 138.45, 133.73, 133.03, 130.83, 128.81, 126.92, 124.96, 123.00, 122.23, 118.97, 112.08, 110.79, 104.27, 100.90, 72.51, 71.23, 67.17, 63.36, 61.76, 54.43, 49.18, 9.7; MS (ESI): *m/z* Calcd for $C_{28}H_{30}ClN_3O_3$: $[M+H]^+$: 492.20. Found 492.3. Anal. Calcd for $C_{28}H_{30}ClN_3O_3$: C, 68.35; H, 6.15; N, 8.54. Found: C, 68.52, H, 6.12, N, 8.22%.

2- (4-(3-((9*H*-Carbazol-4-yl) oxy) -2-hydroxypropyl) piperazin-1-yl)-1-(4-(methylthio) phenyl) ethan-1 –one, 5c: Yield 55%. m.p. 90-95°C. IR (KBr): 1354 (CH_3), 1595 (C=O), 2973 (N-H) cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.21 (3H, s, CH_3), 2.55-2.97 (m, 10H of N-CH_2, 2H of N-CH_2), 3.81 (s, 2H, CH2), 4.25-4.34 (m 3H, 2H of O-CH_2, 1H of O-CH), 6.69-6.71 (d, 1H, *J* =8 Hz, ArH), 7.07-7.09 (m, 1H, ArH), 7.25-7.43 (3H, m, ArH), 7.51-7.56 (2H, m, ArH), 7.95-7.96 (4H, m, ArH), 8.11-8.30 (2H, m ArH); ^{13}C NMR: δ 195.43, 146.20, 140.81, 138.60, 132.29, 128.60, 126.66, 125.01, 124.94, 122.97, 122.53, 119.68, 109.95, 103.76, 101.20, 70.31, 65.68, 64.33, 60.96, 53.58, 26.98, 14.76; MS (ESI): *m/z* Calcd for $C_{28}H_{31}N_3O_3S$: $[M+H]^+$: 490.21. Found 490.4. Anal. Calcd for $C_{28}H_{31}N_3O_3S$: C, 68.69; H, 6.38; N, 8.58; S, 6.55. Found: C, 68.42, H, 6.25, N, 8.43, S, 6.76%.

Results and Discussion

Chemistry

The synthesis of carbazole derivatives (**5a-c**) were carried out by condensing 1-((9*H*-carbazol-4-yl)oxy)-3-(piperazin-1-yl)propan-2-ol (3) with α-bromo acetophenones (**4a-c**) in DMF and K_2CO_3 (Scheme 1). All the derivatives have been confirmed by ^{1}H NMR, IR and Mass analyses. As shown in ^{1}H NMR and IR data of 2-(4-(3-((9*H*-carbazol-4-yl)oxy)-2-hydroxy propyl)piperazin-1-yl)-1-phenylpropan-1-one (**5a**) which showed that 1.1 ppm, 3H for CH_3 group and 1345 Cm-1 (CH_3 bending) in IR data, similarly C=O stretching is observed at 1681 Cm-1. Disappearance



Reagents & Conditions: (i) MeOH, 15-20°C, Stir. (ii) K_2CO_3 (2 ME), DMF (10 V), 20-30°C

Scheme 1 — Reaction scheme for synthesis of carbazole derivatives

Table 1 — Antimicrobial screening of carbazole derivatives, inhibition zone in mm

Sr. No.	Name of bacteria	Gram ±	Compd				Standard (Streptomycin)
			3	**5a**	**5b**	**5c**	
1	*Escherichia coli*	–	12±2	13±2	14±2	17±2	12±2
2	*Pseudomonas aeruginosa*	–	12±2	14±2	15±2	16±2	12±2
3	*Staphylococcus aureus*	+	14±2	14±2	17±2	18±2	13±2
4	*Bacillus cereus*	+	14±2	14±2	18±2	18±2	13±2

of 11.35 ppm, ^{1}H for NH proton of piperazine from precursor 1-((9*H*-carbazol-4-yl)oxy)-3-(piperazin-1-yl)propan-2-ol (3) and additional phenyl ring protons in compound **5a** confirms the synthesis. Hence from the IR and ^{1}H NMR data compound confirmation of 2-(4-(3-((9*H*-carbazol-4-yl)oxy)-2-hydroxypropyl) piperazin-1-yl)-1-phenylpropan-1-one **5a** was done and from mass data molecular weight 491.2 of the compound was confirmed. Similarly, all the compounds were confirmed.

Antimicrobial assay

Microorganisms used to test synthesized compounds for their antibacterial properties included Gram-negative *Escherichia coli, Pseudomonas aeruginosa,* and Gram-positive *Bacillus cereus, Staphylococcus aureus*. Streptomycin was used as a reference antibiotic in the bacterial culture, and the test was conducted using the Kirby-Bauer disk diffusion susceptibility test method[18]. Use a sterile spreader to create a bacterial lawn. Use the antibiotic disc dispenser to apply the antimicrobial disc. All plates should be incubated at 37°C for 48 hrs with the lids taped to the bottom. Each inhibitory zone is measured in millimetres. The size of the inhibitory zone created by the different chemicals on the microorganisms was assessed, and the activity was graded according to its size. We also find that intermediate 3 exhibits equal potency as the standard (Streptomycin), both have 12±2 values. It is shown from the data in Table 1 that compound **5a** (13+2) exhibits the highest antimicrobial activity against the E. coli standard, with an activity of 14+2 against Pseudomonas aeruginosa, Staphylococcus aureus, and *Bacillus cereus*. Compound **5a** and Intermediate **3** is most potent in candidates for antibacterial drugs.

Antimalarial activity

The *In-vitro* antimalarial assay[19] was carried out in 96 well microtiter plates according to the microassay protocol of Rieckmann and co-workers with minor modifications. The cultures of *Plasmodium falciparum* 3D7 strain were maintained in medium RPMI 1640 supplemented with 25 mM HEPES, 1% D-glucose, 0.23% sodium bicarbonate and 10% heat-inactivated human serum. The asynchronous parasites of *Plasmodium falciparum* were synchronized after 5% D-sorbitol treatment to obtain only the ring-stage

Table 2 — Antimalarial Mean IC_{50} of Carbazole Derivatives

Sr. No.	Compd	Mean IC_{50} value (µg/mL)
1	**3**	0.73
2	**5a**	0.76
3	**5b**	0.62
4	**5c**	0.68
5	Chloroquine	0.020
6	Quinine	0.268

Standard: Chloroquine: IC_{50} 0.020 µg/mL, Quinine: IC_{50} 0.268 µg/mL

parasitized cells. For carrying out the assay, an initial ring stage parasitemia of 0.8 to 1.5% at 3% haematocrit in a total volume of 200 µL of medium RPMI-1640 was determined by JSB stain to assess the percent parasitemia (rings) and uniformly maintained with 50% RBCs (O +). A stock solution of 5mg/mL of each of the test samples was prepared in DMSO and subsequent dilutions were prepared with culture medium. The diluted samples in 20 µL volume were added to the test wells to obtain final concentrations (at fivefold dilutions) ranging between 0.4 µg/mL to 100 µg/mL in duplicate well containing parasitized cell preparation. The culture plates were incubated at 37°C in a candle jar. After 36 to 40 h incubation, thin blood smears from each well were prepared and stained with JSB stain. The slides were microscopically observed to record the maturation of ring-stage parasites into trophozoites and schizonts in the presence of different concentrations of the test agents. The test concentration which inhibited the complete maturation into schizonts was recorded as the minimum inhibitory concentration (MIC) [20].

As a conclusion, compound **5b** showed the highest antimalarial activity against all of the synthesized compounds. Greater effectiveness against the parasite is indicated by lower IC50 values. For example, compound **5b** showed the highest potency with an IC 50 value of 0.62 µg/mL, followed by compound **5c** (0.68 µg/mL) and compound **5a** (0.76 µg/mL). Compounds **5a** and **5c** showed slightly lower potency with an IC 50 value. In the Table 2, we used chloroquine and quinine as standard drugs.

Molecular docking of carbazole derivatives

Our SAR analysis revealed that compounds with similar PfHsp90 binding affinities can exhibit very distinct antimalarial potency. We also found that the removal of halogens is detrimental to the growth inhibitory activity but does not always reduce

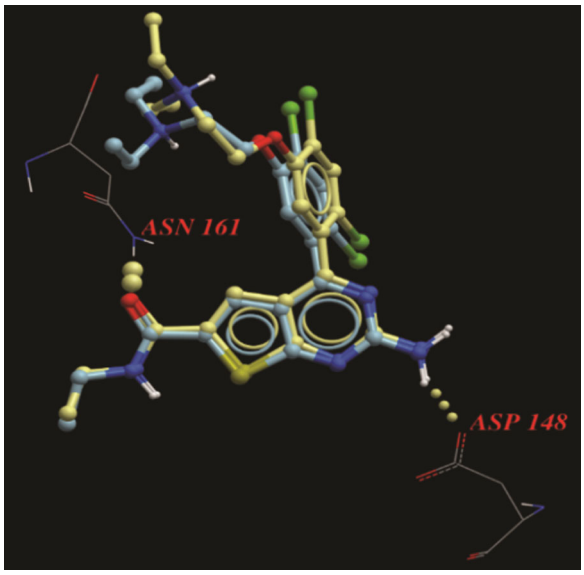


Fig. 1 — Docking pose of thienopyrimidine (yellow) superposed with Reference molecule (blue) in the binding site of HSP90 from *Plasmodium falciparum* (PDB id: 3PEH) (Score: -32.19, RTCNN Score:34.46)

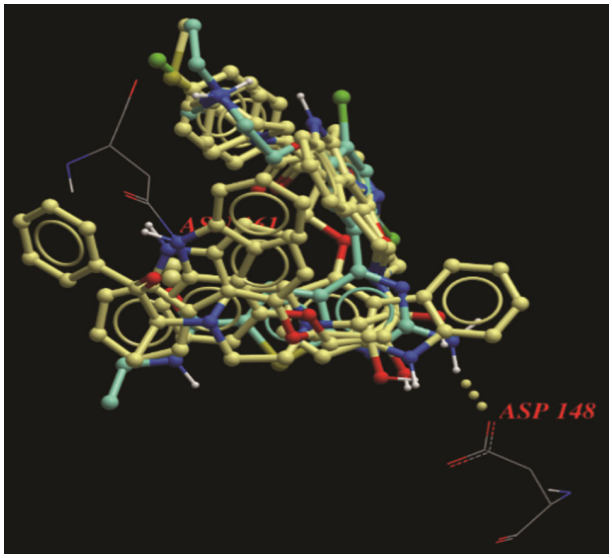


Fig. 2 — Docking pose of NCEs (yellow) superposed with Reference molecule (blue) in the binding site of HSP90 from *Plasmodium falciparum* (PDB id: 3PEH) (Score: -32.19, RTCNN Score: 34.46)

binding to PfHsp90. Previous studies had indicated that strong inhibition of PfHsp90 alone is sufficient for effective antimalarial activity. In the case of compound **5b**, a good representative of our set of active compounds, this supports the speculation that compounds such as **5b** are growth inhibitory for PfHsp90 and other critical target proteins that have yet to be identified (Fig. 1-6, Table 3). In any case, our studies support the speculation that high affinity

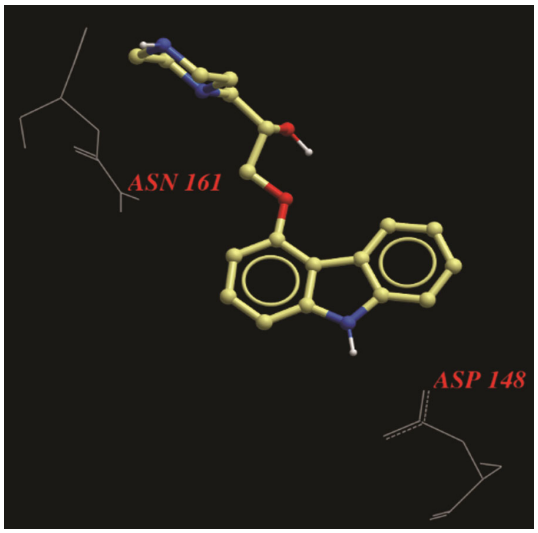


Fig. 3 — Docking pose of Intermediate 3 (yellow) in the binding site of *Plasmodium falciparum* HSP90 (PDB id: 3PEH) (Score: -14.64, RTCNN Score: -:14.64)

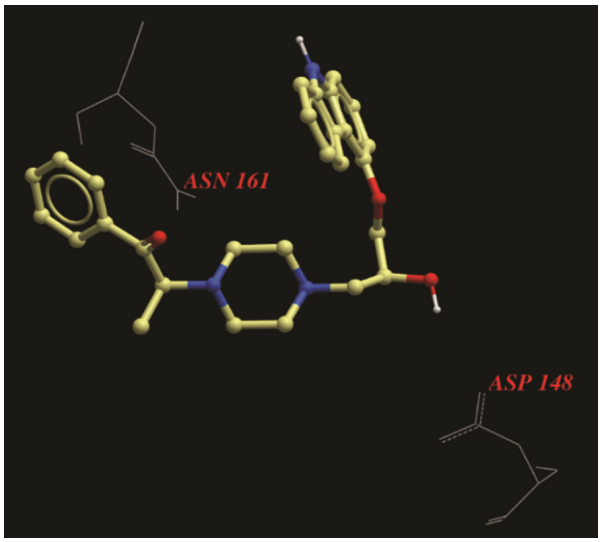


Fig. 5 — Docking pose of Compound **5a** (yellow) in the binding site of *Plasmodium falciparum* HSP90 (PDB id: 3PEH) (Score: -10.29, RTCNN Score: -: -13.48)

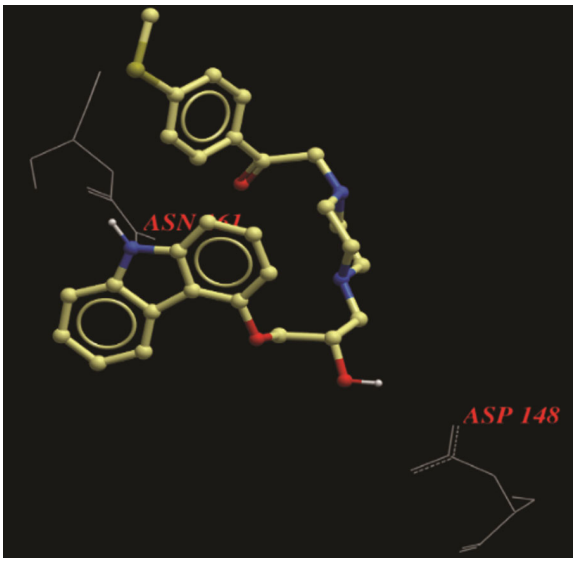


Fig. 4 — Docking pose of Compound **5c** (yellow) in the binding site of *Plasmodium falciparum* HSP90 (PDB id: 3PEH) (Score: -12.67, RTCNN Score: -: -13.59)

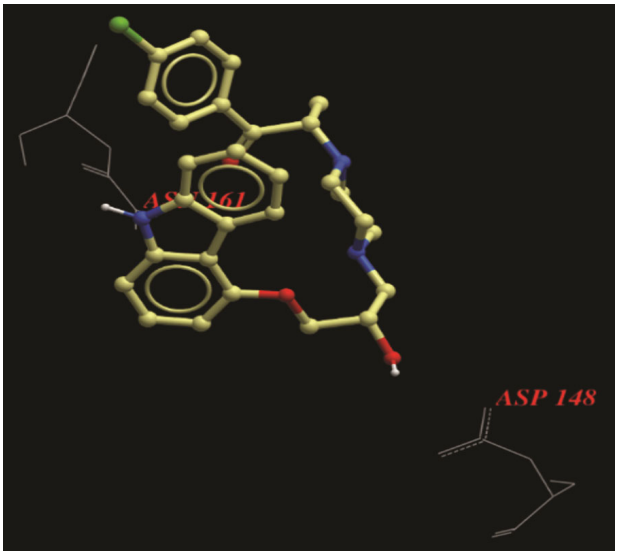


Fig. 6 — Docking pose of Compound **5b** in the binding site of *Plasmodium falciparum* HSP90 (PDB id: 3PEH) (Score: -16.27, RTCNN Score: -: -13.17

Table 3 — Docking in Hsp 90 *Plasmodium falciparum*

Docking in Hsp 90 *Plasmodium falciparum*	Score	RTCNN
Docking pose of thienopyrimidine (yellow) superposed with Reference molecule (blue) in the binding site of HSP90 from *Plasmodium falciparum* (PDB id: 3PEH)	–32.19	–34.46
Docking pose of NCEs (yellow) superposed with Reference molecule (blue) in the binding site of HSP90 from *Plasmodium falciparum* (PDB id: 3PEH)	–32.19	–34.46
Docking pose of 3 (yellow) in the binding site of *Plasmodium falciparum* HSP90 (PDB id: 3PEH)	–14.64	–14.64
Docking pose of **5a** (yellow) in the binding site of *Plasmodium falciparum* HSP90 (PDB id: 3PEH)	–10.29	–13.48
Docking pose of **5b** (yellow) in the binding site of *Plasmodium falciparum* HSP90 (PDB id: 3PEH)	–16.27	–13.17
Docking pose of **5c** (yellow) in the binding site of *Plasmodium falciparum* HSP90 (PDB id: 3PEH)	–12.67	–13.59

inhibitors of PfHsp90 are more likely to be effective antimalarials.

Conclusion

Novel carbazole derivatives have been synthesized by condensing epoxy carbazole with piperazine followed by reaction with α-halo ketones. Carbazole derivatives explored to molecular docking and superposed with Reference molecule in the binding site of HSP90 from *Plasmodium falciparum* (PDB id: 3PEH). All of the compounds give moderated binding energy to the respected HSP90 inhibitor. Title compounds showed good potency against *Plasmodium falciparum* and can exhibit as an antimalarial. Carbazole derivatives inhibit moderate potency against *Escherichia coli, Pseudomonas aeruginosa, Bacillus cereus, and Staphylococcus aureus strains* and intermediate 3 equally potent as such antimicrobial standard. Title compounds exhibit excellent antimalarial activity based on the antimalarial mean IC_{50} values compared to standard chloroquine and quinine. This research assists scientists in finding a better derivative for antimalarial activity based on the results.

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