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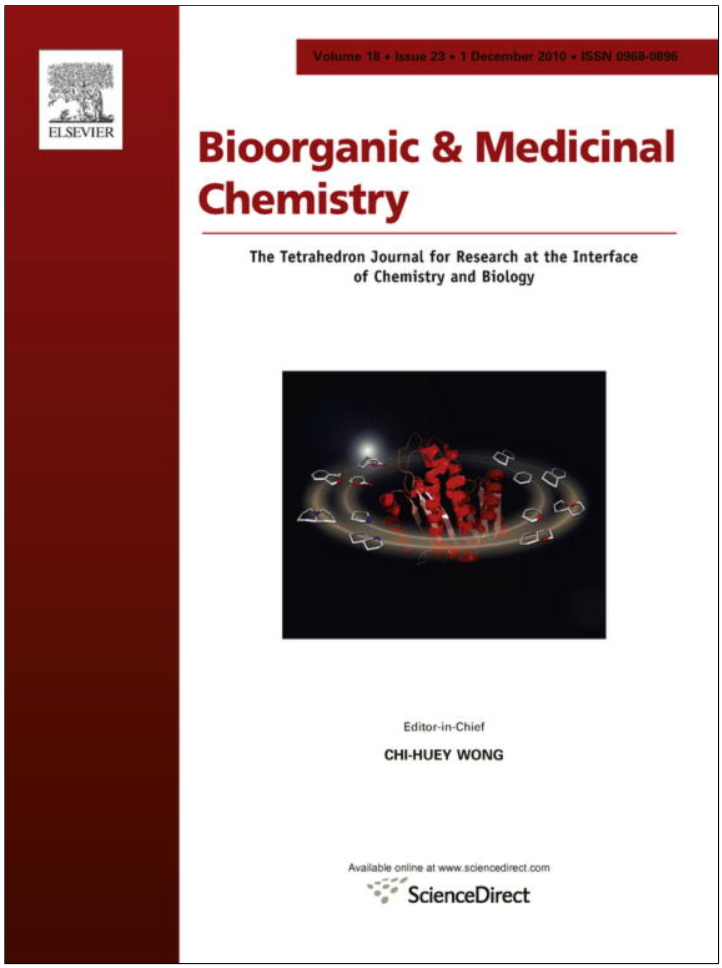

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ABSTRACT

A series of 4-alkylaminoaryl phenyl cyclopropyl methanones (**6a**–**6u** and **8a**–**8c**) were synthesized from 4-fluorochalcones (**3a** and **3b**) by cyclopropanation of double bond followed by nucleophilic substitution of F with different amines. The compounds were screened for their antitubercular and antimalarial activities against *Mycobacterium tuberculosis* H37Rv and *Plasmodium falciparum* 3D7 strains in vitro respectively. Several compounds (**6a**, **6d**–**6h**, **6p**, **6q** and **8a**–**8c**) exhibited good in vitro antitubercular activities with MIC values 3.12–12.5 μg/mL and preferentially inhibited the growth of *P. falciparum* in vitro (**4a**, **4c**, **6a**–**6d**, **6f**, **6s**, **8a** and **8c**) with IC_{50} as low as 0.080 and 0.035 μg/mL and SI values 4975 and 6948, respectively. Molecular docking studies and in vitro evaluation against FAS-II enzymes using reporter gene assays were carried out to elucidate the mode of action of these molecules. Two compounds **4a** and **6g** showed significant inhibition at 25 μM concentration of the compound.

1. Introduction

The current arsenal of antiinfective agents in our hand for the treatment of tuberculosis and malaria is insufficient to protect us over the long term. With more than 1.6 million deaths and 9.2 million new cases being reported each year, tuberculosis is a leading infectious disease claiming millions of death today, mostly in developing countries harboring latent TB infections.[1,2] HIV epidemics in many countries have led to the emergence of new waves of TB infection as co-infection with HIV and mycobacteria render latent TB to an active condition, often with fatal consequences.[3,4] The current cocktail of antitubercular drug regimens can achieve more than 99% efficacy but this is often reduced due to alarming growth of MDR and XDR-TB.[5–9] Although a number of lead molecules exist today[10–12] to develop new drugs but no new chemical entity has emerged for clinical use over the last 40 years. In conjunction with tuberculosis, malaria is also a devastating infectious disease having high morbidity and mortality rate with 300–500 million clinical cases and 1.5–2.7 million deaths every year.[13–15] Nearly all the fatal cases are caused by the malaria parasite *Plasmodium falciparum*.[16] The widespread resistance of malaria parasite to most common antimalarials[17,18] (chloroquine, pyrimethamine), and cross resistance to structurally unrelated drugs makes the current situation more worsening.[19–21] Artemisinine or their structural analogs are potent antimalarial[22,23] but these are associated with the problem of high cost[24] and recently reported resistance to artesunate in Pailin and Western Combodia.[25] Moreover, the adverse effect of co-infection with HIV and malaria is become increasingly apparent.[26] Therefore, new agents that will (i) shorten the current TB treatment, (ii) compatible with HIV drugs and (iii) have novel target with high selectivity for both of diseases are needed.

Mycobacterium tuberculosis and *P. falciparum* allocate enzymatic components of the type II fatty acid biosynthetic pathway (FAS-II)[27,28] for their fatty acid biosynthesis. In *Mycobacterium*, FAS-II pathway comprises a group of enzymes as MabA (FabG), InhA (FabI), FabH as well as Kas A or Kas B which sequentially catalyses the reduction and condensation steps of fatty acid synthesis.[29,30] Among these enzymes InhA and Kas A or Kas B is the most important target for tuberculosis chemotherapy. For Plasmodium, FAS-II is the only fatty acid pathway whose enzymatic components reside at a unique plastid organelle known as

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'apicoplast' and essential for development of the parasite.[28] Another most important metabolic pathway, the isoprenoid pathway DOXP is also known in apicoplast.[31] Both the DOXP and FAS-II pathways are valuable drug targets in antiinfective drug development since these two pathways are absent in the human host.[32] Out of several inhibitors of the FAS-II and DOXP, triclosan (**I**)[33] and fosmidomycin[34] are very important (Fig. 1). Simple acetophenones, benzylideneacetophenones and *p*-nitro-α-acetylamino-β-hydroxypropiophenones are reported to have good antitubercular activties.[35–38] The cyclopropane derivative of fosmidomycin (**II**) (Fig. 1) with limited conformational flexibility in the backbone is as active as fosmidomycin.[39] Moreover, cyclopropyl ring is a common structural element in the mycobacterial cell wall[40] and its chemotherapeutic importance is also well known.[41–43] Aryl cyclopropyl ketones play a prominent role as intermediates in the synthesis of many other biologically active compounds.[44] As a part of our ongoing research devoted for the synthesis of antiinfective agents[45–50] we have already identified the aryloxyphenyl cyclopropyl methanones (**III**)[51] (Fig. 1) as potent antitubercular agent. Keeping in view the above we were prompted to synthesize 4-alkylaminoaryl phenyl cyclopropyl methanones and evaluate them for anti-mycobacterial and antimalarial activities.

2. Results and discussion

2.1. Chemistry

The protocol for the synthesis of 4-alkylamino substituted aryl phenyl cyclopropyl methanones begins with the synthesis of chalcones (**3a** and **3b**).[52,53] The aldol reaction between 4-fluoro acetophenone (**1**) and substituted aromatic aldehydes (**2a** and **2b**) followed by in situ dehydration, leads the desired chalcones (**3a** and **3b**) in quantitative yields. There are three possible pathways to synthesize the title compounds as shown in Figure 2. The first one we discarded as amines may react with ketones and a complex mixture would be obtained (Path 1). The second approach (Path 2) involves the *ipso* nucleophilic substitution at 4-fluoro group in one of the phenyl ring of chalcone **3a** by various amines followed by cyclopropanation. The third approach (Path 3) involves the cyclopropanation of double bond in chalcones followed by *ipso* nucleophilic substitution at 4-fluoro group in one of the phenyl ring of chalcone **3a** to give the title molecules.

The *ipso* nucleophilic substitution at 4-fluoro group in one of the phenyl ring of chalcone **3a** by various amines in presence of K_2CO_3/DMF at 120 °C in an inert atmosphere of nitrogen gave the desired alkylamino substituted chalcones (**4a**–**4e**) in moderate yields only (Scheme 1). The unsatisfactory yield of the products may possibly be due to Michael addition product as we could not isolate the other products of the reaction observed during reaction (TLC). The reaction of the alkylamino substituted chalcones with trimethylsulphoxonium iodide (TMSOI) and 50% aq NaOH at 80 °C in presence of tetrabutylammonium bromide as phase transfer catalyst and CH_2Cl_2 as solvent gave the title compounds (**6a**, **6g**, **6h**, **6j** and **6n**) (Scheme 1). Therefore, the third approach was thought wherein the fluorochalcones **3a** and **3b** were first subjected to cyclopropanation using TMSOI as described above to give the respective cycloproyl derivatives **5a** and **5b** in good yields. The latter on *ipso* nucleophilic substitution of 4-fluoro group using various amines led to the formation of targeted compounds **6b**–**6f**, **6i**, **6k**–**6m** and **6o**–**6u** in quantitative yields (Scheme 1).

In order to see the effect of substitutents in the alkylamine chain we have prepared another series of compounds starting from the above compound **6s** having 2-hydroxyethylamino chain at the 4th position of one of the aromatic ring A. Thus **6s** was reacted with $MeSO_2Cl$ in presence of TEA in CH_2Cl_2 at 0 °C to give respective 2-methanesulphonyloxyethyl amino derivative (**7**). The nucleophilic substitution of $-SO_2Me$ group in compound **7** with several azoles in presence of NaH/DMF at 0–120 °C gave respective 2-(azolyl)-ethylaminoaryl phenyl cyclopropyl methanones (**8a**–**8c**) in good yields (Scheme 2).

The structures of all the compounds as given in Table 1 were determined on the basis of their spectroscopic data and microanalyses. The IR spectra of the compounds, in general, exhibited the absorption band at around 3432 cm^{-1} indicating the presence of aromatic amino group, absorption band of carbonyl group at around 1638–1640 cm^{-1}. The ESMS (mass spectra) of the compounds showed $[M+H]^+$ peaks corresponding to their molecular formulae. The ^1H and ^{13}C NMR spectra are consistent with the proposed structures. The ^1H NMR spectrum of a prototype molecule **6g**, displayed exchangeable N–H proton signal as a singlet at δ 5.39. The four protons of cyclopropyl ring were visible at four different chemical shifts as multiplets at δ 2.76–2.71, 2.60–2.53, 1.85–1.76 and 1.40–1.34 ppm. The aromatic protons appeared as doublet at δ 7.83, 7.23, 7.07 and 6.51 ppm with coupling constant in range of 8.28–8.58 Hz. The protons of alkylamino chain were visible at δ 3.25, 2.42 as triplet and at δ 1.85–1.76 as multiplet along with one proton of cyclopropyl ring. The protons of the *N*,*N*-dimethyl group were observed as a singlet at δ 2.25 ppm. The geometry of the parent chalcone was found to be trans from the coupling constant between the olefinic protons of the propenone moiety (compound **4a**, J = 15.8 Hz) and the TMSOI mediated cyclopropanation (Corey–Chaykovsky reaction) leads the *trans* product with retained stereochemistry as evident from the litrature.[54–56] In the ^{13}C NMR spectrum, the only carbonyl carbon appeared at δ 195.6, while the quaternary aromatic carbon attached to the amine group was observed at δ 153.0. Three carbons of cyclopropyl ring were visible at δ 28.7, 28.2 and 18.7 ppm. The other aromatic quaternary carbons (ArC) were observed at their usual chemical shifts of δ 140.1, 132.3 and 126.8 ppm, while sp^2 aromatic carbons (ArCH) appeared at δ 131.0, 128.9, 127.9 and 111.7 ppm. Almost similar patterns were observed in ^1H NMR and ^{13}C NMR spectra of other compounds (**8a**–**8c**) of the series.

2.2. Biological activities

All of the above synthesized compounds including few of the intermediate chalcones were screened for their antitubercular and antimalarial activities against *M. tuberculosis* H37Rv and *P. falciparum* 3D7 strains in vitro. The antitubercular screening was carried out in vitro using agar microdilution method[57] while the antimalarial activity was assayed as per earlier reported protocols.[58,61]

2.2.1. Antitubercular activity

Antitubercular screening results of all the synthesized compounds and few of the intermediate cahlcones are listed in Table

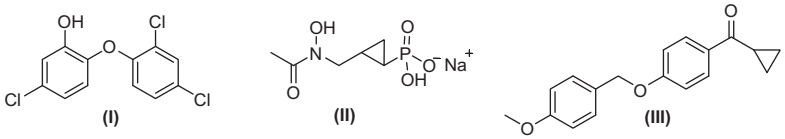


Figure 1. Chemical structure of some FAS-II inhibitor and biologically active cyclopropane ring containing molecules.

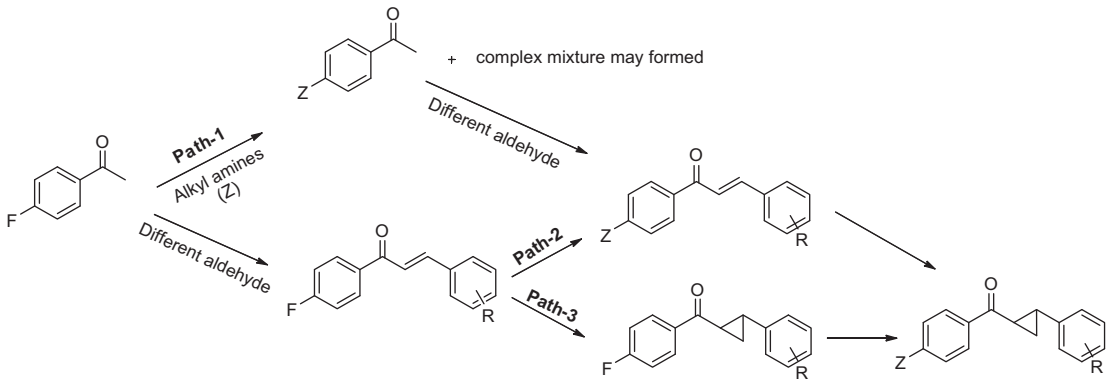
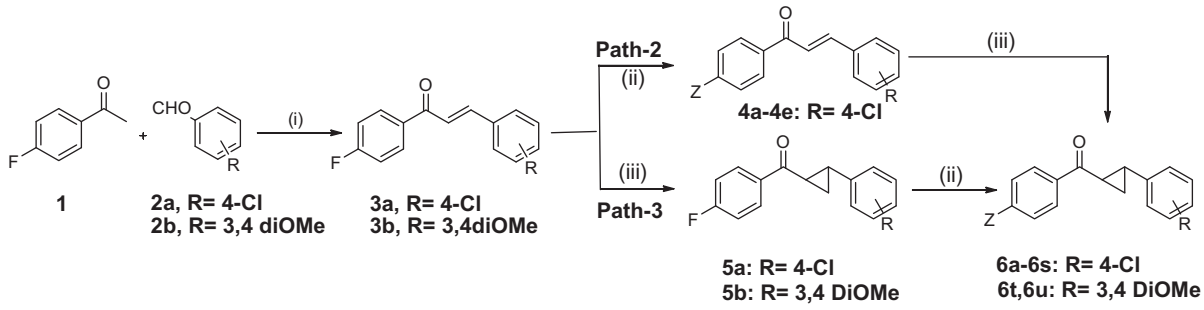
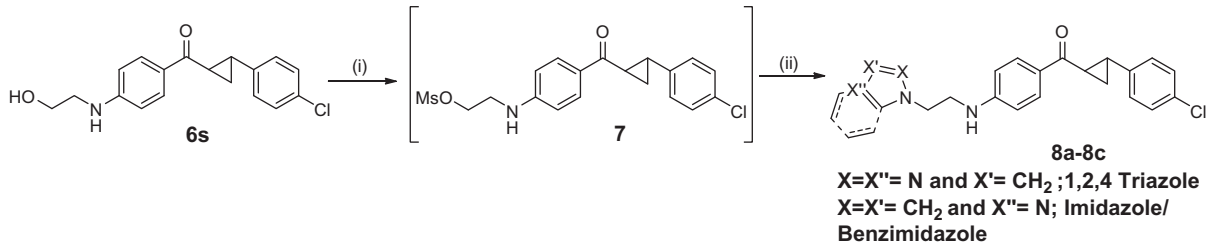


Figure 2. Possible pathways for the formation of alkylaminoaryl phenyl cyclopropyl methanones.



Scheme 1. Synthesis of 4-alkylaminoaryl phenyl cyclopropyl methanones (**6a**–**6u**). Reagents and conditions: (i) KOH, EtOH, rt; (ii) different amines (Z), K_2CO_3, DMF, 120 °C, inert atmosphere; (iii) TMSOI, TBAB (20 mol %), CH_2Cl_2:50% aq NaOH (1:1), 80 °C.



Scheme 2. Synthesis of azolylalkylaminoaryl phenyl cyclopropyl methanones (**8a**–**8c**). Reagents and conditions: (i) CH_3SO_2Cl, Et_3N, CH_2Cl_2, 0 °C–rt; (ii) different azoles, NaH, DMF, 0–120 °C.

2. As evident from the results out of all the alkylaminoaryl phenyl cyclopropyl methanones screened, compounds **6a**, **6d**–**6h**, **6p**, **6q** and **8a**–**8c** showed minimum inhibitory concentration in the range of 3.12–12.5 μg/mL. Among compounds having 4-chloro and 3,4-dimethoxy substituent in aromatic ring B, compounds with 4-chloro substituent (**6a**–**6s** and **8a**–**8c**) were more active than the compounds with 3,4-dimethoxy substituents (**6t** and **6u**). The most active compound of the series was found to be compound **6h** having a furfuryl amine substituent with MIC value 3.12 μg/mL. The compounds **6a** and **6g** having dialkylamino chain as 4-substitutent in one of the phenyl rings (ring A), whether it is cyclic or acyclic have almost similar antitubercular activity with MIC 6.25 μg/mL. On the other hand compounds **6d**, **6f** and **6p** having monoalkylamine chain, dialkylamine chain and cyclic amine with C-chain length ⩽four carbon atoms with comparable lipophilicity displayed only moderate activity with the same MIC value 12.5 μg/mL. However, in contrast compounds with the oleylamine substitutent also displayed only moderate antitubercular activity (MIC 12.5 μg/mL). In the second series of compounds having 2-(azolyl)ethylamino substitutent at 4-position in benzene ring A showed promising to moderate antitubercular activities. Compound **8a** with imidazolyl ethylamino substituent has MIC value 6.25 μg/mL. However, introduction of any lipophilic moiety to the imidazole unit reduces the activity as compounds **8b** and **8c** have MIC values 12.5 μg/mL each. Similar observation was made with the above compounds having piperazinyl substitutents. Replacement of *N*-methyl group (compound **6a**, MIC 6.25 μg/mL) in piprazine by aryl group (compound **6e**) resulted in loss of activity with MIC 12.5 μg/mL.

Encouraged by recent report of antimalrial and antitubercular activities in acetylenic chalcones by Kelly's group[59] we were prompted to see the effect of 4-alkylamino chalcones (**4a**–**4e**) against malaria parasite and *M. tuberculosis* with a view to find out the correlation between the unsaturated system and cyclopropanated system. The antitubercular screening results did not offer any definite correlation between activities with the unsaturated or cyclopropanated compounds. It is evident by the fact that, in compounds **4a** and **4c** (chalcones having double bond, MIC value 12.5 μg/mL each) the activity is less as compared to their cyclopropanated analogues **6g** and **6h** (MICs 6.25 and 3.12 μg/mL), respectively. On the contrary, the chalcones **4b** and **4d** with MIC value 3.12 and 6.25 μg/mL are better antitubercular as compared to their cyclopropanated analogues **6a** and **6j** with MICs values 6.25 and >12.5 μg/mL, respectively.

Table 1
Synthesis of alkylamino substituted chalcones (**4a**–**4e**) and alkylaminoaryl phenyl cyclopropyl methanones (**6a**–**6u** and **8a**–**8c**)

Compound No.	R	*Z* (amine)	Mp (°C)	Yield (%)
4a	4-Cl	*N*,*N*-Dimethyl aminopropylamine	63–65	35
4b	4-Cl	*N*-Me piprazine	100–102	54
4c	4-Cl	Furfuryl amine	72–74	40
4d	4-Cl	Morpholine	98–100	45
4e	4-Cl	Pipridine	111–113	60
6a	4-Cl	*N*-Me piprazine	112–114	80
6b	4-Cl	Cyclohexyl amine	98–100	84
6c	4-Cl	Heptyl amine	97–99	82
6d	4-Cl	Butyl amine	128–130	81
6e	4-Cl	4-(2,3-Dichlorophenyl) piperazin	134–136	77
6f	4-Cl	Dibutyl amine	152–154	78
6g	4-Cl	*N*,*N*-Dimethyl aminopropylamine	94–96	77
6h	4-Cl	Furfuryl amine	96–98	85
6i	4-Cl	1,5-DiMe hexyl amine	128–130	80
6j	4-Cl	Morpholine	115–117	83
6k	4-Cl	Dodecyl amine	92–94	80
6l	4-Cl	Hexadecyl amine	122–124	85
6m	4-Cl	Octyl amine	154–156	87
6n	4-Cl	Pipridine	118–120	79
6o	4-Cl	*N*,*N*-Dimethylamine	132–134	86
6p	4-Cl	Pyrolidine	138–140	86
6q	4-Cl	Oleyl amine	153–155	80
6r	4-Cl	Veratryl amine	140–142	76
6s	4-Cl	Ethanolamine	166–168	73
6t	3,4 Di-OMe	*N*-Me piprazine	156–158	81
6u	3,4 Di-OMe	Heptyl amine	147–149	79
8a	4-Cl	(1*H*-Imidazol-1-yl)ethylamine	110–112	67
8b	4-Cl	(1*H*-1,2,4-Triazol-1-yl)ethylamine	117–119	68
8c	4-Cl	(1*H*-Benzo[*d*]imidazol-1yl) ethylamine	134–136	70

Table 2
Antitubercular activity of the synthesized molecules **4a**–**4e**, **6a**–**6u** and **8a**–**8c**

S. No.	Compound No.	Antitubercular activity (MIC μg/mL)	S. No.	Compound No.	Antitubercular activity (MIC μg/mL)
1	**4a**	12.5	16	**6k**	In*
2	**4b**	3.12	17	**6l**	In
3	**4c**	12.5	18	**6m**	>12.5
4	**4d**	6.25	19	**6n**	>12.5
5	**4e**	>12.5	20	**6o**	In
6	**6a**	6.25	21	**6p**	12.5
7	**6b**	>12.5	22	**6q**	12.5
8	**6c**	>12.5	23	**6r**	>12.5
9	**6d**	12.5	24	**6s**	>12.5
10	**6e**	12.5	25	**6t**	>12.5
11	**6f**	12.5	26	**6u**	>12.5
12	**6g**	6.25	27	**8a**	6.25
13	**6h**	3.12	28	**8b**	12.5
14	**6i**	>12.5	29	**8c**	12.5
15	**6j**	>12.5		Inh*	0.025

In* = Insoluble, Inh* = Isoniazid.

2.2.2. Antimalarial activity

The above alkylamino chalcones and their cyclopropyl derivatives were also screened against malaria parasite *P. falciparum* using the earlier reported protocols.[58,60,61] Most of the compounds showed moderate to high antimalarial activity. Compounds **4a**, **4c**, **6a**–**6d**, **6f**, **6s**, **8a** and **8c** were active against the parasite with IC_{50} in the range of 0.035–0.76 μg/mL. Among all the screened compounds, compound **8a** was the most potent antimalarial agent with MIC and IC_{50} values of 0.062 and 0.035 μg/mL, respectively. Compound **6c** was also found to be a potent antimalarial agent with IC_{50} 0.08 μg/mL and very low MIC (0.3 μg/mL). Majority of the active compounds have shown good correlation between their MIC and IC_{50} values (Table 3). A closure look into structure–activity relationship of the compounds revealed that compounds with lipophilic alkylamino substituent (**6b**, **6c**, **6d** and **6f**) showed good antimalarial activity indicating that the lipophilicity has significant impact on antimalrial activity. Similarly compounds with basic alkylamino chain (compounds **4a** and **6a**) or azole moiety (compounds **8a** and **8c**) also exhibited potent antimalarial activities. It seems that basic alkylamino cahin and lipophilicity are important factors governing the biological activities.

2.2.3. Cytotoxicity

The cytotoxic evaluation of these compounds was carried out on VERO cell line as per earlier reported protocol[62] and the results are shown in Table 3. On the basis of antimalarial/antitubercular and cytotoxic activities, the calculated selectivity indices (SI values) (CC_{50}/IC_{50}) have shown that all the compounds active against malaria and tuberculosis have moderate to high degree of safety. The compound **8a** has shown the best selectivity index (6948.57) as well as potent antimalarial activity. Out of ten antimalarial compounds, nine have shown median cytotoxic concentration to be 82.00–404.03 μg/mL (Table 3).

2.2.4. FAS-II inhibitory activities

2.2.4.1. In silico docking studies. To identify the drug target of the synthesized compounds first the intermediate chalcone **4a** was selected for in silico docking studies.[63,64] Furthermore to characterize the proteinaceous drug target which is most likely to interact with compound **4a**, the ligand file was uploaded into *Inhibitor Identification Tool* (*Is-it?*): (unpublished and implemented in the host laboratory) server and docking jobs were queued by selecting all the 85 drug targets from *M. tuberculosis* enlisted in the server. The top candidates identified by *Is-it*?: server, ranked by interaction energies, included 10 out of the 12 targets from FasII pathway (Fig. 3). It is thus likely that aryl amino derivatives may interact with multiple proteins including fabG or 1UZL (star marked in the Fig. 3), Enoyl-acp reductase (1P44, 2NSD, inhA) and fabD (2QC3) from FAS-II pathway. The compound also showed high affinity with another protein Gyrase or gyrB (another red star marked in the Fig. 3). The target proteins so identified are enlisted in Supplementary Table. The top potential binding partner identified is MabA, which is also known as FabG1, a part of FAS-II enzyme, catalyzing the NADPH-specific reduction of long chain beta-ketoacyl derivatives. The compound **4a** is predicted to be interacting with most of the reported important residues of the NADP binding site with an estimated inhibition constant, K_i value of 261.41 nM. The chlorine atom of the compound **4a** is present in the vicinity of TYR 153 which is reported to be the part of catalytic triad residues. The molecular interactions of the compound **4a** with MabA are shown in Figure 4.

As no ligand variation was done in the final molecule compared to their parent chalcones, the synthesized final molecules directly undergoes to biological assay against FAS-II pathway.

2.2.4.2. FAS-II inhibition assay. FAS-II inhibitory activity was assessed using a recombinant non-pathogenic mycobacterial strain, *Mycobacterium aurum*, which contains *M. tuberculosis kas* operon promoter in fusion with *lacZ* reporter gene.[65] The strain shows continued expression of reporter gene under the influence of *kas* operon promoter during basal conditions, while an increased expression of the reporter gene is noticed only after treatment with FAS-II pathway inhibitors. The preliminary screening of the compounds shows FAS-II inhibitory activity at two different concentration, 25 and 50 μM and results are listed in Table 4. In present

Table 3
Antimalarial activity and selectivity index of the synthesized molecules **4a–4e**, **6a–6u** and **8a–8c**

S. No.	Compound No.	MIC (μg/mL)	IC_{50} (μg/mL)	CC_{50} (μg/mL)	SI
1	**4a**	1.56	0.64	5.92	9.25
2	**4b**	50	11.78	102.46	8.69
3	**4c**	10	0.76	404.03	531.62
4	**4d**	50	4.86	35.64	7.33
5	**4e**	50	8.92	234.59	26.3
6	**6a**	10	0.54	82.06	151.96
7	**6b**	10	0.75	196.18	261.57
8	**6c**	0.3	0.08	398	4975
9	**6d**	0.6	0.33	316.37	958.69
10	**6e**	50	8.82	382.61	43.38
11	**6f**	10	0.73	430.73	590.04
12	**6g**	50	2.86	15.83	5.53
13	**6h**	10	1.71	255.89	149.64
14	**6i**	ND*	ND	ND	ND
15	**6j**	10	3.02	452.76	149.92
16	**6k**	>50	10.4	385.7	37.08
17	**6l**	50	4.57	409.83	89.68
18	**6m**	10	2.13	214.14	100.53
19	**6n**	10	6.05	284.28	46.99
20	**6o**	10	1.43	343.78	240.4
21	**6p**	>50	9.75	431.49	44.26
22	**6q**	>50	75.13	393.35	5.24
23	**6r**	10	8	421.86	52.73
24	**6s**	2	0.6	305	508.33
25	**6t**	50	2.09	77.81	37.23
26	**6u**	10	2.24	272.54	121.67
27	**8a**	0.062	0.035	243.2	6948.57
28	**8b**	10	3.41	39.9	11.7
29	**8c**	2	0.74	285.23	385.45
	Chloroquine	0.05	0.008		

ND* = Not determined.

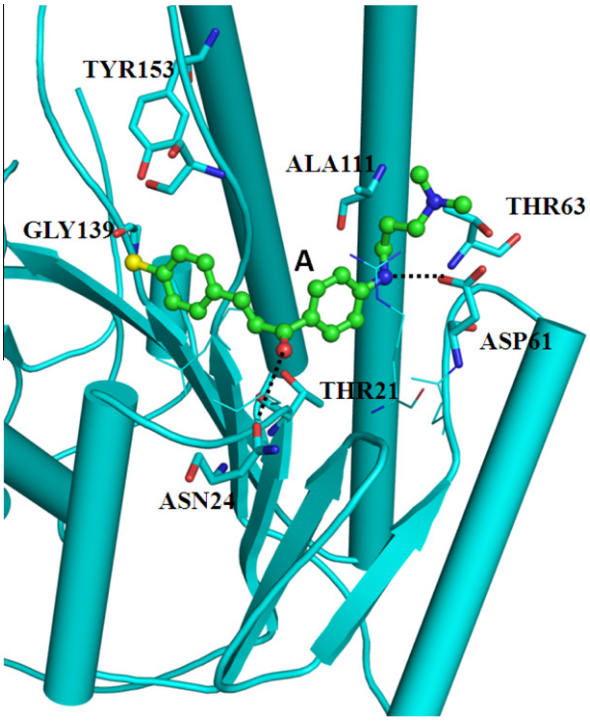


Figure 4. The molecular interactions of compound **4a** within the MabA binding pocket. The interacting residues are labeled and hydrogen bonds are marked by the dashed lines.

studies molecule **4a** was selected for the assessment, the critical concentration of compound at which it inhibited the growth of *M. aurum* culture by ⩾85% was determined by cfu analysis and then β-gal enzyme assay was performed to assess the inducibility under treated condition. We observed an induced level of β-gal enzyme activity after treatment with compound **4a** with respect to untreated control (Fig. 5A). The activity gradually increased with increasing concentration of compound and declined at higher concentration owing to killing of cells at exceeding dose of drugs. It may be noted that we repeated the same experiment using another *M. aurum* recombinant strain carrying *hsp60* promoter wherein no inducibility was observed under similar conditions, rather a decline in reporter gene activity was noticed in line with diminishing viability of bacterial cells (Fig. 5B) as the treatment dose increased. Isoniazid (INH), a known FAS-II pathway inhibitor was used as a positive control in both conditions. All the ongoing results of screening suggest that FAS-II is a viable target of the intermediate

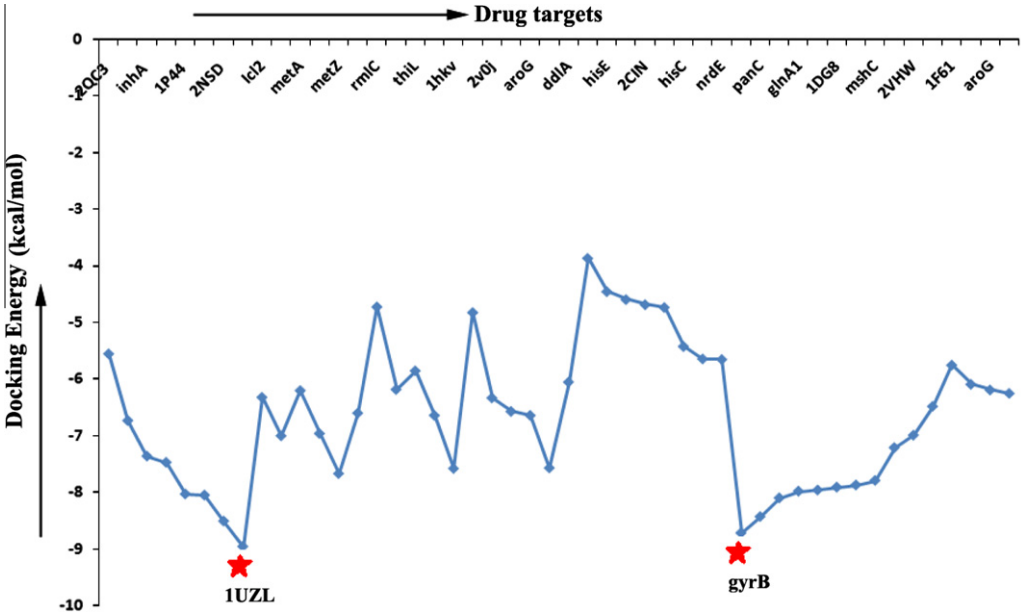


Figure 3. The plot of docking energy calculated by AUTODOCK for aryl amino derivative and the protein targets. Only acceptable scores are used for plot. The most potential binders are 1UZL (a fasII pathway enzyme) and gyrB (Gyrase B) and are denoted by asterisk.

Table 4
FAS-II inhibitory activitiy of selected compounds at two different concentrations

S. No.	Compound No.	% Inhibition (25 μM)	% Inhibition (50 μM)
1	**4a**	**83.40 ± 3.0**	**88.1 ± 0.077**
2	**4b**	13.61 ± 0.64	14.65 ± 0.86
3	**4d**	**47.14 ± 3.19**	42.85 ± 7.99
4	**6a**	0	0.17 ± 0.24
5	**6b**	0	0
6	**6c**	0	0
7	**6d**	39.49 ± 2.37	**60.86 ± 1.15**
8	**6e**	15.66 ± 8.52	31.82 ± 2.12
9	**6f**	**41.52 ± 5.16**	37.55 ± 10.79
10	**6g**	**46.32 ± 7.75**	**57.37 ± 3.48**
11	**6h**	16.48 ± 9.34	27.45 ± 6.04
12	**6i**	17.5 ± 24.74	27.45 ± 6.04
13	**6j**	29.82 ± 4.2	3.81 ± 4.2
14	**6k**	26.99 ± 6.7	32.71 ± 6.9
15	**6l**	36.0 ± 10.17	36.72 ± 3.2
16	**6m**	30.25 ± 7.9	23.9 ± 4.6
17	**8a**	**48.63 ± 2.94**	**50.22 ± 2.31**
18	**8b**	17.87 ± 2.02	30.1 ± 2.57
19	**8c**	1.03 ± 1.46	16.93 ± 0.54

chalcone **4a**. The assessment of the FAS-II activity of the cyclopropylated analogue of **4a**, that is, **6g** was determined by the same protocol and compound shows 57.37% inhibition against *M. aurum* at 50 μM concentration of the compound. Moreover β-gal enzyme assay shows induced level of β-gal enzyme activity after treatment with compound **6g** with respect to untreated control (Fig. 5C). To determine the ligand efficacy against FAS-II pathway some active chalcones and cyclopropyl methanones were screened against the culture of *M. aurum*. Among the screened molecules some compound (**4d** and **6f**) shows moderate inhibition (41–47%) of FAS-II pathway and few of the compounds (**4a**, **6d**, **6g** and **8a**) shows good inhibition in the range of 50–88%. While profiling the activity of synthesized compounds several ligands were identified having good affinity towards the enzymes of FAS-II pathway. In general, the aminoalkylamine chain has prominent role in FAS-II inhibitory activity as evidenced by comparing the effect of compounds **4a**, **4b** and **6g** (Fig. 5C) wherein **4a** and **6g** having *N,N*-dimethylaminopropyl chain have prominent inhibitory effect while **4b** has no significant inhibition. Thus, the double bond or the cyclopropyl moiety has no significant role in eliciting the FAS-inhibitory response. Some of the active compounds which did not respond towards the FAS-II pathway might have some other target and needs further investigation. Moreover, the FAS-II pathway being absent in human may be targeted with such small synthetic molecules to get new chemotherapeutics for tuberculosis and malaria.

3. Conclusion

In conclusion, we have synthesized and evaluated a series of alkylaminoaryl phenyl cyclopropyl cahlcones and methanones in good yields. The compounds were evaluated against *M. tuberculosis* and *P. falciparum*. Few of the compounds showed moderate to significant antimalarial and antitubercular activities. We have also shown one of the possible mode of actions of these compounds may be FAS-II inhibition by in silico screen and in vitro FAS-II enzyme inhibitory activities. Further exploration of this study is currently underway.

4. Experimental

4.1. Chemistry

All glasswares were dried in an open flame before use in connection with an inert atmosphere. Solvents were evaporated under reduced pressure. Thin layer chromatography was performed using Silica Gel 60 F254 plates with detecting agent iodine vapors or by spraying with dragendorf reagent. Silica gel (60–120 mesh) was used for column chromatography. Tetramethylsilane (0.0 ppm) was used as an internal standard in ^{1}H NMR and $CDCl_3$ (77.0 ppm) was used in ^{13}C NMR. The abbreviations used to indicate the peak multiplicity were; s, singlet; br s, broad singlet; d, doublet; dd, double doublet; t, triplet; q, quartet; m, multiplet; Hz, Hertz. FAB MS was recorded on Jeol (Japan)/SX-102. Infrared spectrum was taken with KBr on Perkin-Elmer RX-1. Melting points were determined on a Buchi 535 digital melting point apparatus and were uncorrected. Elemental analysis was performed on a Perkin-Elmer 2400 C, H, N analyzer and values were within ±0.4% of the calculated values.

4.1.1. General procedure for the synthesis of substituted (*E*)-1-phenyl-3-phenylprop-2-en-1-one (3a, 3b)

To a stirring mixture of 4-fluoroacetophenone (8.6 ml, 54.5 mmol) and 4-chlorobenzaldehyde (10 g, 71.13 mmol) or 3,4-dimethoxy benzaldehyde (11.7 g, 70.40 mmol) in ethanol was added KOH (1.98 g, 3.5 mmol) and stirred continued for 10–30 min at room temperature till the disappearance of starting materials. The light green/yellow solid was precipitated, filtered washed with water and dried to get the substituted chalcones (**3a** and **3b**) in good yields.

4.1.2. General procedure for the synthesis of substituted (*E*)-3-(4-chlorophenyl)-1-(4-alkylamino)prop-2-en-1-one (4a–4e)

A mixture of (*E*)-3-(4-chlorophenyl)-1-(4-fluorophenyl)prop-2-en-1-one (**3a**) (1 g, 3.84 mmol), K_2CO_3 (0.637 g, 4.60 mmol) and desired amine (1.2 equiv) in DMF (5 ml) was stirred magnetically at 100–120 °C for 16–18 h under inert atmosphere of nitrogen. After the completion of the reaction (TLC), the reaction mixture was cooled to room temperature and poured in water and extracted with ethyl acetate. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure to get the crude product. The latter was purified by column chromatography (SiO_2, 100–200 mesh) using gradient of hexane/ethyl acetate (9:1→6:4)/0.2:9.8→0.6:9.4% methanol/chloroform to give the desired compounds (**4a**–**4e**, yield 40–56%).

4.1.2.1. (*E*)-3-(4-Chlorophenyl)-1-(4-(3-(dimethylamino) propylamino)phenyl)prop-2-en-1-one (4a). Yellow solid, mp 60–62 °C; yield 46%; R_f 0.43 (0.2:9.8, MeOH/$CHCl_3$); IR (KBr) ν_{max} cm^{-1}: 3426 (N–H), 2928 (C–H), 1605 (C=O). ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.92 (2H, d, J = 8.84 Hz, ArH), 7.71 (1H, d, J = 15.8 Hz, CH=CH), 7.64–7.45 (3H, m, ArH and CH=CH), 7.36 (2H, d, J = 8.90 Hz, ArH), 6.56 (2H, d, J = 8.86 Hz, ArH), 5.53 (1H, br s, NH), 3.27 (2H, q, J = 3.12 Hz $NHCH_2$), 2.44 (2H, t, J = 6.24 Hz, CH_2), 2.24 (6H, s, $N(CH_3)_2$), 1.81 (2H, m, CH_2). ^{13}C NMR (50 MHz, $CDCl_3$): δ 187.5 (ArCO), 153.1, 141.3 (ArC), 136.1 (CH=CH), 134.4, 131.0, 129.7, (ArCH), 131.0, 128.9, 127.9 (ArCH), 128.7 (ArC), 127.0 (CH=CH), 111.8 (ArCH), 58.4 ($NHCH_2$), 45.0 ($(CH_3)_2NCH_2$), 42.9 (NCH_2), 26.3 (CH_2). ESMS (m/z): 343 $(M+H)^+$. Anal. Calcd for $C_{20}H_{23}ClN_2O$: C, 70.06; H, 6.76; N, 8.17. Found: C, 70.13; H, 6.89; N, 8.26.

4.1.2.2. (*E*)-3-(4-Chlorophenyl)-1-(4-(4-methylpiperazin-1-yl)-phenyl)prop-2-en-1-one (4b). Yellow solid, mp 84–86 °C; yield 56%; R_f 0.40 (0.1:9.9, MeOH/$CHCl_3$); IR (KBr) ν_{max} cm^{-1}: 2938 (C–H), 1610 (C=O); ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.92 (2H, d, J = 8.86 Hz, ArH), 7.73 (1H, d, J = 15.54 Hz, CH=CH), 7.54 (2H, d, J = 8.76 Hz, ArH), 7.30–7.16 (3H, m, ArH and CH=CH), 6.85 (2H, d, J = 8.84 Hz, ArH), 3.36–3.30 (4H, m, 2 × CH_2), 2.58–2.53 (4H, m, 2 × CH_2), 2.30 (3H, s, NCH_3). ^{13}C NMR (50 MHz, $CDCl_3$): δ 187.8 (ArCO), 154.6 (ArC), 142.1 (CH=CH), 136.4, 134.2 (ArC), 131.5,

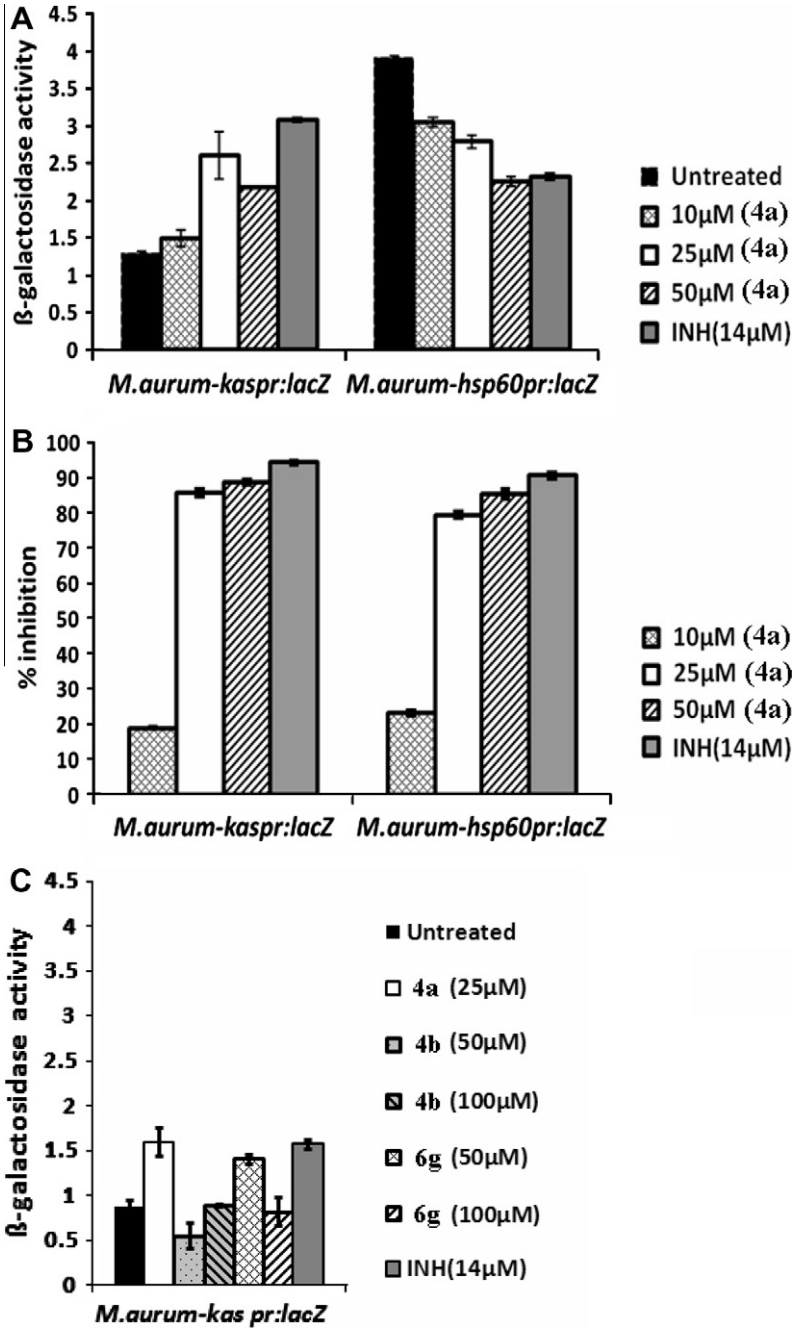


Figure 5. Reporter gene expression and viability assay after treatment with **4a**. (A) Note the induced level of β-gal activity in treated sample in recombinant strain *M. aurum-kaspr:lacZ* with respect to untreated control. INH as a positive control shows maximum inducibility. Recombinant *M. aurum* strain with hsp60 promoter, *M. aurum-hsp60pr:lacZ*, shows decline in β-gal activity in all treated samples including INH with respect to untreated control. (B) Both recombinant strains exhibit similar decline in the viability of bacterial cells; greater inhibition is observed with increasing concentration of compounds. (C) Induced level of β-gal activity in treated cyclopropylated analogue of **4a**, that is, **6g** in recombinant strain *M. aurum-kaspr:lacZ* with respect to untreated control. Recombinant *M. aurum* strain with hsp60 promoter, *M. aurum-hsp60pr:lacZ*, shows decreased in β-gal activity.

129.8, 129.5 (ArCH), 128.8 (ArC), 122.7 (CH═CH), 113.8 (ArCH), 51.4, 48.8 (2 × CH_2), 45.1 (NCH_3). ESMS (*m*/*z*): 341 $(M+H)^+$. Anal. Calcd for $C_{20}H_{21}ClN_2O$: C, 70.48; H, 6.21; N, 8.22. Found: C, 70.38; H, 6.12; N, 8.14.

4.1.2.3. (*E*)-3-(4-Chlorophenyl)-1-(4-(furan-2-ylmethylamino)-phenyl)prop-2-en-1-one (4c). White solid, mp 82–84 °C; yield 40%; R_f 0.37 (0.1:9.9, MeOH/$CHCl_3$); IR (KBr) ν_{max} cm^{-1}: 3445 (N–H), 2932 (C–H), 1600 (C═O). ^1H NMR (200 MHz, $CDCl_3$): δ 8.03 (2H, d, *J* = 8.80 Hz, ArH), 7.76 (1H, d, *J* = 15.60 Hz, CH═CH), 7.57–7.25 (6H, m, ArH, CH═CH and Ar_F-H), 7.06 (2H, d, *J* = 8.86 Hz, ArH), 6.46–6.37 (2H, m, Ar_F-H), 5.06 (2H, s, CH_2). ^{13}C NMR (50 MHz, $CDCl_3$): δ 188.2 (ArCO), 162.5 (ArC), 149.8 (CH═CH), 143.6, 142.8 (ArCH), 136.6, 134.0 (ArC), 131.7 (ArC), 131.1, 129.8, 129.6, 122.6, 115.0, 111.0, 110.8 (ArCH), 62.7 (CH_2). ESMS (*m*/*z*): 351 $(M+H)^+$. Anal. Calcd for $C_{21}H_{18}ClNO_2$: C, 71.69; H, 5.16; N, 3.98. Found: C, 71.58; H, 5.10; N, 3.86.

4.1.2.4. (*E*)-3-(4-Chlorophenyl)-1-(4-morpholinophenyl)prop-2-en-1-one (4d). Light green, mp 82–84 °C; yield 42%; R_f 0.45 (4:6,

EtOAc/Hexane); IR (KBr) ν_{max} cm^{-1}: 2932 (C–H), 1608 (C=O); ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.99 (2H, d, J = 9.26 Hz, ArH), 7.76 (1H, d, J = 15.62 Hz, CH=CH), 7.58 (2H, d, J = 8.72 Hz, ArH), 7.39–7.25 (3H, m, ArH and CH=CH), 6.91 (2H, d, J = 9.00 Hz), 3.88 (4H, t, J = 4.72 Hz, 2 × CH_2), 3.35 (4H, t, J = 5.06 Hz, 2 × CH_2). ^{13}C NMR (50 MHz, $CDCl_3$): δ 187.8 (ArCO), 154.6 (ArC), 142.1 (CH=CH), 136.4, 134.2 (ArC), 131.5, 129.8, 129.5 (ArCH), 128.8 (ArC), 122.7 (CH=CH), 113.8 (ArCH), 66.9, 47.9 (2 × CH_2). ESMS (m/z): 328 (M+H)$^+$. Anal. Calcd for $C_{19}H_{18}ClNO_2$: C, 69.62; H, 5.53; N, 4.27. Found: C, 69.56; H, 5.48; N, 4.14.

4.1.2.5. (*E*)-3-(4-Chlorophenyl)-1-(4-(piperidin-1-yl)phenyl)prop-2-en-1-one (4e). White solid, mp 116–118 °C; yield 54%; R_f 0.55 (10%, EtOAc/Hexane); IR (KBr) ν_{max} cm^{-1}: 2921 (C–H), 1610 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.82 (2H, d, J = 8.76 Hz, ArH), 7.74 (1H, d, J = 15.34 Hz, CH=CH), 7.24 (2H, d, J = 8.72 Hz, ArH), 7.21–7.15 (3H, m, ArH and CH=CH), 6.88 (2H, d, J = 8.78 Hz), 3.67 (4H, br s, 2 × NCH_2), 1.78 (6H, br s, 3 × CH_2). ^{13}C NMR (50 MHz, $CDCl_3$): δ 185.5 (ArCO), 151.6 (ArC), 143.4 (CH=CH), 136.2, 133.2 (ArC), 131.8, 128.8, 128.3 (ArCH), 127.9 (ArC), 122.3 (CH=CH), 113.1 (ArCH), 54.3 (2 × CH_2), 23.7 (2 × CH_2), 22.8 (CH_2). ESMS (m/z): 326 (M+H)$^+$. Anal. Calcd for $C_{20}H_{20}ClNO$: C, 73.72; H, 6.19; N, 4.30. Found: C, 73.76; H, 6.09; N, 4.26.

4.1.3. General procedure for the synthesis of substituted aryl phenyl cyclopropyl methanone (5a, 5b) and alkylamino substituted aryl phenyl cyclopropyl methanone (6a, 6g, 6h, 6j, 6n) from 4a–4e

A mixture of compound **3a** or **3b** (1 equiv), TMSOI (trimethyl sulphoxonium iodide, 2 equiv) and TBAB (tetra butylammonium bromide, 20 mol%) in CH_2Cl_2 (10 ml) was stirred magnetically at ambient temperature for 15 min. 50% aq NaOH (10 ml) solution was subsequently added dropwise and the reaction mixture was refluxed at 80 °C, till the disappearance of chalcone (**3a** or **3b**). After the completion of the reaction (TLC), the reaction mixture was cooled to room temperature, excess of dichloromethane was added and the organic layer was extracted. The organic layer was dried (anhyd Na_2SO_4) and concentrated under reduced pressure to get a crude product. The latter was purified by column chromatography (SiO_2, 100–200 mesh) using gradient of hexane/ethylacetate/chloroform/methanol to give the desired compounds (**5a**, **5b** and **6a**, **6g**, **6h**, **6j** and **6n**) in good yields.

4.1.4. General procedure for the synthesis of alkylamino substituted aryl phenyl cyclopropyl methanone (6b–6f, 6i, 6k–6l and 6o–6u) from 5a and 5b

A mixture of **5a** or **5b** (1 equiv), K_2CO_3 (1.2 equiv) and desired amine (1.2 equiv) in DMF (5 ml) was stirred magnetically at 100–120 °C for 16–18 h under inert atmosphere of nitrogen. After the completion of the reaction (TLC), the reaction mixture was cooled to room temperature and poured in water and extracted with ethyl acetate. The organic layer was dried (anhyd Na_2SO_4) and concentrated under reduced pressure to give a crude product. The latter was purified by column chromatography (SiO_2, 100–200 mesh) using gradient of hexane/ethyl acetate (9:1→6:4)/0.2:9.8→0.6:9.4% methanol/chloroform to give the desired compounds (**6b–6f**, **6i**, **6k–6l** and **6o–6u**) yield 78–86%.

4.1.4.1. (2-(4-Chlorophenyl)cyclopropyl)(4-fluorophenyl)methanone (5a). White solid, mp 118–120 °C; yield 84%; R_f 0.40 (1.0:9.0, EtOAc/Hexanae); IR (KBr) ν_{max} cm^{-1}: 2938 (C–H), 1657 (C=O); ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.03–7.95 (2H, m, ArH), 7.28–7.23 (2H, m, ArH), 7.18–7.06 (4H, m, ArH), 2.82–2.73 (1H, m, H-2), 2.69–2.60 (1H, m, H-3), 1.95–1.86 (1H, m, H-4a), 1.55–1.45 (1H, m, H-4b). ^{13}C NMR (50 MHz, $CDCl_3$): δ 188.7 (ArCO), 165.8, 136.8, 134.5 133.3, (ArC), 131.1, 129.2, 128.4, 115.3 (ArCH), 28.1, 27.3 (C-2 and C-3), 18.2 (C-4). ESMS (m/z): 275 (M+H)$^+$. Anal. Calcd for $C_{16}H_{12}ClFO$: C, 69.95; H, 4.40. Found: C, 69.97; H, 4.42.

4.1.4.2. (2-(3,4-Dimethoxyphenyl)cyclopropyl)(4-fluorophenyl)-methanone (5b). White solid, mp 78–80 °C; yield 90%; R_f 0.55 (1.5:8.5, EtOAc/Hexanae); IR (KBr) ν_{max} cm^{-1}: 2934 (C–H), 1652 (C=O); ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.04–7.97 (2H, m, ArH), 7.15–7.07 (2H, m, ArH), 6.80 (1H, d, J = 8.8 Hz, ArH), 6.69–6.65 (2H, m, ArH), 3.86 (3H, s, OCH_3), 3.85 (3H, s, OCH_3), 2.76–2.70 (1H, m, H-2), 2.64–2.60 (1H, m, H-3), 1.91–1.84 (1H, m, H-4a), 1.55–1.48 (1H, m, H-4b). ^{13}C NMR (50 MHz, $CDCl_3$): δ 188.9 (ArCO), 165.5, 148.5, 146.7, 136.8, 133.5 (ArC), 131.7, 129.1, 127.2, 126.4, 113.3 (ArCH), 28.3, 27.2 (C-2 and C-3), 18.4 (C-4). ESMS (m/z): 301 (M+H)$^+$. Anal. Calcd for $C_{18}H_{17}FO_3$: C, 71.99; H, 5.71. Found: C, 72.06; H, 5.74.

4.1.4.3. (2-(4-Chlorophenyl)cyclopropyl)(4-(4-methylpiperazin-1-yl)phenyl)methanone (6a). Pale white solid, mp 98–100 °C; yield 84%; R_f 0.38 (0.1:9.9, MeOH/$CHCl_3$); IR (KBr) ν_{max} cm^{-1}: 2936 (C–H), 1647 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.90 (2H, d, J = 8.67 Hz, ArH), 7.27 (2H, d, J = 8.28 Hz, ArH), 7.11 (2H, d, J = 8.19 Hz, ArH), 6.86 (2H, d, J = 8.73 Hz, ArH), 3.38–3.35 (4H, m, 2 × CH_2), 2.78–2.72 (1H, m, H-2), 2.62–2.53 (5H, m, 2 × CH_2 and H-3), 2.34 (3H, s, NCH_3), 1.89–1.83 (1H, m, H-4a), 1.44–1.38 (1H, m, H-4b). ^{13}C NMR (50 MHz, $CDCl_3$): δ 195.7 (ArCO), 152.5, 139.8, 131.9 (ArC), 130.7, 128.4, 127.2 (ArCH), 126.5 (ArC), 111.3 (ArCH), 51.1, 48.6 (2 × CH_2), 45.3 (NCH_3), 28.3, 27.5 (C-2 and C-3), 18.6 (C-4). ESMS (m/z): 355 (M+H)$^+$. Anal. Calcd for $C_{21}H_{23}ClN_2O$: C, 71.07; H, 6.53; N, 7.89. Found: C, 71.05; H, 6.58; N, 7.83.

4.1.4.4. (2-(4-Chlorophenyl)cyclopropyl)(4-(cyclohexylamino)-phenyl)methanone (6b). White solid, mp 128–130 °C; yield 81%; R_f 0.50 (15%, EtOAc/Hexane); IR (KBr) ν_{max} cm^{-1}: 3348 (N–H), 2927 (C–H), 1651 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.83 (2H, d, J = 8.70 Hz, ArH), 7.24 (2H, d, J = 8.31 Hz, ArH), 7.08 (2H, d, J = 8.13 Hz, ArH), 6.52 (2H, d, J = 8.52 Hz, ArH), 4.11 (1H, br s, NH), 3.33 (1H, br s, NHCH), 2.74–2.70 (1H, m, H-2), 2.59–2.56 (1H, m, H-3), 2.06–2.02 (2H, m, CH_2), 1.84–1.64 (4H, m, CH_2, H-4a and H-4b), 1.40–1.16 (6H, m, CH_2). ^{13}C NMR (50 MHz, $CDCl_3$): δ 195.6 (ArCO), 151.6, 140.1, 132.4 (ArC), 131.0, 128.9, 127.9 (ArCH), 126.8 (ArC), 112.0 (ArCH), 51.6 (NHCH), 33.5 (CH_2), 28.8, 28.3 (C-2 and C-3), 26.1 (CH_2), 25.2 (CH_2), 18.2 (C-4). ESMS (m/z): 354 (M+H)$^+$. Anal. Calcd for $C_{22}H_{24}ClNO$: C, 74.67; H, 6.84; N, 3.96. Found: C, 74.63; H, 6.81 N, 3.94.

4.1.4.5. (2-(4-Chlorophenyl)cyclopropyl)(4-(heptylamino)phenyl)methanone (6c). White solid, mp 134–136 °C; yield 77%; R_f 0.50 (1:4, EtOAc/Hexane); IR (KBr) ν_{max} cm^{-1}: 3353 (N–H), 2924 (C–H), 1569 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.88 (2H, d, J = 8.61 Hz, ArH), 7.27 (2H, d, J = 8.40 Hz, ArH), 7.11 (2H, d, J = 8.28 Hz, ArH), 6.56 (2H, d, J = 8.61 Hz, ArH), 4.20 (1H, br s, NH), 3.18 (2H, t, J = 6.96 Hz, $NHCH_2$), 2.79–2.74 (1H, m, H-2), 2.63–2.56 (1H, m, H-3), 1.89–1.83 (1H, m, H-4a), 1.67–1.63 (2H, m, CH_2), 1.44–1.32 (9H, m, 4 × CH_2 and H-4b), 0.91 (3H, t, CH_3). ^{13}C NMR (50 MHz, $CDCl_3$): δ 195.7 (ArCO), 152.6, 140.1, 132.4 (ArC), 131.0, 128.9, 127.9 (ArCH), 127.2 (ArC), 111.7 (ArCH), 43.7, 32.2, 29.7, 29.5 ($NHCH_2$ and 3 × CH_2), 28.8, 28.4 (C-2 and C-3), 27.4, 23.0 (2 × CH_2), 18.7 (C-4), 14.5 (CH_3). ESMS (m/z): 370 (M+H)$^+$. Anal. Calcd for $C_{23}H_{28}ClNO$: C, 74.68; H, 7.63; N, 3.79. Found: C, 74.71; H, 7.65; N, 3.76.

4.1.4.6. (4-(Butylamino)phenyl)(2-(4-chlorophenyl)cyclopropyl)-methanone (6d). White solid, mp 97–99 °C; yield 82%; R_f 0.48 (15%, EtOAc/Hexane); IR (KBr) ν_{max} cm^{-1}: 3436 (N–H), 3020 (C–H), 1597 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.85 (2H, d, J = 8.22 Hz, ArH), 7.26 (2H, d, J = 7.74 Hz, ArH), 7.11 (2H, d,

J = 7.83 Hz, ArH), 6.54 (2H, d, J = 8.04 Hz, ArH), 4.11 (1H, br s, NH), 3.21 (2H, d, J = 8.04 Hz, $NHCH_2$), 2.73 (1H, m, H-2), 2.58 (1H, m, H-3), 1.86–1.84 (1H, m, H-4a), 1.68–1.63 (2H, m, CH_2), 1.51–1.39 (3H, m, CH_2 and H-4b), 1.00 (3H, t, J = 7.11 Hz, CH_3). ^{13}C NMR (50 MHz, $CDCl_3$): δ 194.7 (ArCO), 152.1, 139.6, 132.0 (ArC), 130.5, 128.5, 127.5 (ArCH), 126.8 (ArC), 111.2 (ArCH), 42.9 ($NHCH_2$), 31.4 (CH_2) 28.2, 27.7 (C-2 and C-3), 20.2 (CH_2), 18.2 (C-4), 13.9 (CH_3). ESMS (m/z): 328 $(M+H)^+$. Anal. Calcd for $C_{20}H_{22}ClNO$: C, 73.27; H, 6.76; N, 4.27. Found: C, 73.21; H, 6.73; N, 4.24.

4.1.4.7. (2-(4-Chlorophenyl)cyclopropyl)(4-(4-(2,3-dichlorophenyl)piperazin-1-yl)phenyl) methanone (6e). Light green solid, mp 152–154 °C; yield 78%; R_f 0.50 (2%, MeOH/$CHCl_3$); IR (KBr) ν_{max} cm^{-1}: 2936 (C–H), 1593 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.93 (2H, d, J = 8.70 Hz, ArH), 7.25 (2H, d, J = 8.34 Hz, ArH), 7.17 (2H, d, J = 7.44, ArH), 7.09 (2H, d, J = 8.37 Hz, ArH), 6.96–6.89 (3H, m, ArH), 3.52–3.49 (4H, m, 2 × CH_2), 3.19–3.16 (4H, m, 2 × CH_2), 2.80–2.74 (1H, m, H-2), 2.63–2.57 (1H, m, H-3), 1.88–1.82 (1H, m, H-4a), 1.45–1.25 (1H, m, H-4b). ^{13}C NMR (50 MHz, $CDCl_3$): δ 196.0 (ArCO), 154.5, 151.1, 139.9, 134.7, 132.5 (ArC), 130.5, 129.0 (ArCH), 128.7, 128.2 (ArC), 128.0, 127.9, 125.5, 118.9, 114.2 (ArCH), 51.4, 48.2 (2 × CH_2), 28.9, 28.6 (C-2 and C-3), 19.0 (C-4). ESMS (m/z): 485 $(M+H)^+$. Anal. Calcd for $C_{26}H_{23}Cl_3N_2O$: C, 64.28; H, 4.77; N, 5.77. Found: C, 64.25; H, 4.79; N,5.73.

4.1.4.8. (2-(4-Chlorophenyl)cyclopropyl)(4-(dibutylamino)phenyl)methanone (6f). Light green solid, mp 94–96 °C; yield 77%; R_f 0.55 (10%, EtOAc/Hexane); IR (KBr) ν_{max} cm^{-1}: 2959 (C–H), 1594 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.87 (2H, d, J = 9.00 Hz, ArH), 7.24 (2H, d, J = 8.46 Hz, ArH), 7.08 (2H, d, J = 8.43 Hz, ArH), 6.59 (2H, d, J = 9.03 Hz, ArH), 3.31 (4H, m, $N(CH_2)_2$), 2.77–2.71 (1H, m, H-2), 2.58–2.51 (1H, m, H-3), 1.87–1.81 (1H, m, H-4a), 1.63–1.53 (4H, m, 2 × CH_2), 1.41–1.29 (5H, m, 2 × CH_2 and H-4b), 0.93 (6H, t, 2 × CH_3).^{13}C NMR (50 MHz, $CDCl_3$): δ 195.3 (ArCO), 151.6, 140.2, 132.3 (ArC), 130.9, 128.9, 127.9 (ArCH), 125.6 (ArC), 111.0 (ArCH), 51.3 ($N(CH_2)_2$), 30.0 (2 × CH_2), 28.7, 28.2 (C-2 and C-3), 20.7 (CH_2), 18.4 (C-4), 14.3 (CH_3). ESMS (m/z): 384 $(M+H)^+$. Anal. Calcd for $C_{24}H_{30}ClNO$: C, 75.08; H, 7.88; N, 3.65. Found: C, 75.01; H, 7.90; N, 3.62.

4.1.4.9. (2-(4-Chlorophenyl)cyclopropyl)(4-(3-(dimethylamino)-propylamino)phenyl)met-hanone (6g). White solid, mp 96–98 °C; yield 83%; R_f 0.33 (0.1:9.9, MeOH/$CHCl_3$); IR (KBr) ν_{max} cm^{-1}: 3432 (N–H), 2928 (C–H), 1690 (C=O). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.83 (2H, d, J = 8.58 Hz, ArH), 7.23 (2H, d, J = 8.34 Hz, ArH), 7.07 (2H, d, J = 8.28 Hz, ArH), 6.51 (2H, d, J = 8.58 Hz, ArH), 5.39 (1H, s, NH), 3.25 (2H, br s, $NHCH_2$), 2.76–2.71 (1H, m, H-2), 2.60–2.53 (1H, m, H-3), 2.42 (2H, t, J = 6.24 Hz, NCH_2), 2.25 (6H, s, $N(CH_3)_2$), 1.85–1.76 (3H, m, CH_2 and H-4a), 1.40–1.34 (1H, m, H-4b). ^{13}C NMR (50 MHz, $CDCl_3$): δ 195.6 (ArCO), 153.0, 140.1, 132.3 (ArC), 131.0, 128.9, 127.9 (ArCH), 126.8 (ArC), 111.7 (ArCH), 58.8 ($NHCH_2$), 45.7 ($(CH_3)_2NCH_2$), 43.0 (NCH_2), 28.7, 28.2 (C-2 and C-3), 26.4 (CH_2), 18.7 (C-4). ESMS (m/z): 357 $(M+H)^+$. Anal. Calcd for $C_{21}H_{25}ClN_2O$: C, 70.67; H, 7.06; N, 7.85. Found: C, 70.59; H, 7.02; N, 7.81.

4.1.4.10. (2-(4-Chlorophenyl)cyclopropyl)(4-(furan-2-ylmethylamino)phenyl)methanone (6h). White solid, mp 96–98 °C; yield 85%; R_f 0.55 (20%, EtOAc/Hexane); IR (KBr) ν_{max} cm^{-1}: 3445 (N–H), 2928 (C–H), 1600 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.96 (2H, d, J = 8.88 Hz, ArH), 7.43 (1H, m, Furyl-H), 7.25 (2H, d, J = 8.46 Hz, ArH), 7.07 (2H, d, J = 8.46 Hz, ArH), 6.99 (2H, d, J = 8.91 Hz, ArH), 6.42 (1H, m, Furyl-H), 6.36 (1H, m, Furyl-H), 5.04 (2H, s, $NHCH_2$), 2.80–2.74 (1H, m, H-2), 2.64–2.57 (1H, m, H-3), 1.89–1.83 (1H, m, H-4a), 1.47–1.41 (1H, m, H-4b). ^{13}C NMR (50 MHz, $CDCl_3$): δ 195.7 (ArCO), 151.8, 151.7, 142.5, 140.0, 132.4 (ArC), 130.9, 128.9, 128.0, 127.9, 112.2, 110.8, 107.8 (ArCH), 41.1 (CH_2), 28.8, 28.4 (C-2 and C-3), 18.7 (C-4). ESMS (m/z): 352 $(M+H)^+$. Anal. Calcd for $C_{21}H_{18}ClNO_2$: C, 71.69; H, 5.16; N, 3.98. Found: C, 71.63; H, 5.13; N, 3.94.

4.1.4.11. (2-(4-Chlorophenyl)cyclopropyl)(4-(6-methylheptan-2-ylamino)phenyl)methano-ne (6i). White solid, mp 128–130 °C; yield 80%; R_f 0.30 (5%, EtOAc/Hexane); IR (KBr) ν_{max} cm^{-1}: 3422 (N–H), 2926 (C–H), 1596 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.82 (2H, d, J = 8.70 Hz, ArH), 7.24 (2H, d, J = 8.37 Hz, ArH), 7.08 (2H, d, J = 8.37 Hz, ArH), 6.49 (2H, d, J = 8.67 Hz, ArH), 3.95 (1H, br s, NH), 3.53–3.51 (1H, m, NHCH), 2.73–2.67 (1H, m, H-2), 2.57–2.51 (1H, m, H-3), 1.85–1.79 (1H, m, H-4a), 1.56–1.21 (12H, m, 3 × CH_2, CH_3, 2 × CH and and H-4b), 0.87 (6H, d, J = 6.6 Hz $(CH_3)_2$). ^{13}C NMR (50 MHz, $CDCl_3$): δ 195.0 (ArCO), 151.6, 140.1, 132.4 (ArC), 131.0, 128.9, 127.9 (ArCH), 127.1 (ArC), 112.1 (ArCH), 48.7 (CH), 39.3, 37.7 (2 × CH_2), 28.7 (CH), 28.3, 28.2 (C-2 and C-3), 24.3 (CH_2), 23.1, 21.1 (CH_3), 18.5 (CH_2). ESMS (m/z): 384 $(M+H)^+$. Anal. Calcd for $C_{24}H_{30}ClNO$: C, 75.08; H, 7.88; N, 3.65. Found: C, 74.98; H, 7.84; N, 3.61.

4.1.4.12. (2-(4-Chlorophenyl)cyclopropyl)(4-morpholinophenyl)-methanone (6j). Light green solid, mp 115–117 °C; yield 83%; R_f 0.50 (2%, MeOH/$CHCl_3$); IR (KBr) ν_{max} cm^{-1}: 3019 (C–H), 1649 (C=OC=O). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.89 (2H, d, J = 9.09 Hz, ArH), 7.24 (2H, d, J = 8.46 Hz, ArH), 7.08 (2H, d, J = 8.40 Hz, ArH), 6.84 (2H, d, J = 8.91 Hz, ArH), 3.83–3.80 (4H, m, 2 × CH2), 3.28–3.25 (m, 4H, 2 × CH_2), 2.76–2.70 (1H, m, H-2), 2.60–2.54 (1H, m, H-3), 1.88–1.73 (1H, m, H-4a), 1.42–1.36 (1H, m, H-4b). ^{13}C NMR (50 MHz, $CDCl_3$): δ 195.7 (ArCO), 153.3, 140.1, 132.4 (ArC), 130.4, 129.0, 127.9 (ArCH), 126.9 (ArC), 113.8 (ArCH), 66.7 (2 × CH_2), 48.1 (2 × CH_2), 28.8, 28.5 (C-2 and C-3), 18.8 (C-4). ESMS (m/z): 342 $(M+H)^+$. Anal. Calcd for $C_{20}H_{20}ClNO_2$: C, 70.27; H, 5.90; N, 4.10. Found: C, 70.25; H, 5.89; N, 4.07.

4.1.4.13. (2-(4-Chlorophenyl)cyclopropyl)(4-(dodecylamino)phenyl)methanone (6k). White solid, mp 122–124 °C; yield 85%; R_f 0.50 (3%, EtOAc/Hexane); IR (KBr) ν_{max} cm^{-1}: 3355 (N–H), 2921 (C–H), 1639 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.82 (2H, d, J = 8.61 Hz, ArH), 7.23 (2H, d, J = 8.34 Hz, ArH), 7.07 (2H, d, J = 8.31 Hz, ArH), 6.50 (2H, d, J = 8.61 Hz, ArH), 4.13 (1H, br s, NH), 3.15 (2H, t, J = 6.87 Hz, $NHCH_2$), 2.77–2.68 (1H, m, H-2), 2.61–2.52 (1H, m, H-3), 1.84–1.78 (1H, m, H-4a), 1.67–1.57 (2H, m, CH_2), 1.38–1.25 (19H, m, 9 × CH_2 and H-4b), 0.88 (3H, t, J = 6.85 Hz, CH_3). ^{13}C NMR (50 MHz, $CDCl_3$): δ 195.2 (ArCO), 152.4, 140.1, 132.4 (ArC), 130.9, 128.9, 127.9 (ArCH), 127.3 (ArC), 111.8 (ArCH), 43.8, 32.3, 32.2, 30.0, 30.0, 29.8, 29.7 (CH_2), 28.7, 28.2 (C-2 and C-3), 27.5, 27.4, 23.1, 18.6 (CH_2), 18.5 (C-4), 14.6 (CH_3). ESMS (m/z): 440 $(M+H)^+$. Anal. Calcd for $C_{28}H_{38}ClNO$: C, 76.42; H, 8.70; N, 3.18. Found: C, 76.38; H, 8.68; N, 3.14.

4.1.4.14. (2-(4-Chlorophenyl)cyclopropyl)(4-(hexadecylamino)-phenyl)methanone (6l). White solid, mp 154–156 °C; yield 87%; R_f 0.55 (2%, EtOAc/Hexane); IR (KBr) ν_{max} cm^{-1}: 3459 (N–H), 2890 (C–H), 1693 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.82 (2H, d, J = 8.64 Hz, ArH), 7.23 (2H, d, J = 8.34 Hz, ArH), 7.08 (2H, d, J = 8.37 Hz, ArH), 6.50 (2H, d, J = 8.67 Hz, ArH), 4.13 (1H, br s, NH), 3.15 (2H, t, J = 6.96 Hz, $NHCH_2$), 2.71–2.7 (1H, m, H-2), 2.56–2.53 (1H, m, H-3), 1.83–1.80 (1H, m, H-4a), 1.64–1.60 (2H, m, CH_2), 1.38–1.25 (27H, m, 13 × CH_2 and H-4b), 0.90–0.86 (3H, m, CH_3). ^{13}C NMR (50 MHz, $CDCl_3$): δ 195.0 (ArCO), 152.3, 140.1, 132.4 (ArC), 130.9, 128.9, 127.9 (ArCH), 127.4 (ArC), 111.7 (ArCH), 43.8, 32.3, 30.0, 30.0, 29.7 (CH_2), 28.6, 28.1 (C-2 and C-3), 27.5, 23.1, (CH_2), 18.5 (C-4), 14.5 (CH_3). ESMS (m/z): 497 $(M+H)^+$. Anal. Calcd for $C_{32}H_{46}ClNO$: C, 77.46; H, 9.34; N, 2.82. Found: C, 77.40; H, 9.29; N, 2.79.

4.1.4.15. (2-(4-Chlorophenyl)cyclopropyl)(4-(octylamino)phenyl)methanone (6m). White solid, mp 134–136 °C; yield 83%; R_f 0.50 (5%, EtOAc/Hexane); IR (KBr) ν_{max} cm^{-1}: 3354 (N–H), 2922 (C–H),1588 (C=O); ^1H NMR (300 MHz, $CDCl_3$): δ 7.82 (2H, d, J = 8.67 Hz, ArH), 7.24 (2H, d, J = 8.40 Hz, ArH), 7.07 (2H, d, J = 8.40 Hz, ArH), 6.50 (2H, d, J = 8.67 Hz, ArH), 4.16 (1H, br s, NH), 3.15 (2H, t, J = 7.02 Hz, $NHCH_2$), 2.73–2.67 (1H, m, H-2), 2.57–2.51 (1H, m, H-3), 1.84–1.78 (1H, m, H-4a), 1.64–1.57 (2H, m, CH_2), 1.38–1.28 (11H, m, 5 × CH_2 and H-4b), 0.95–0.86 (3H, t, CH_3). ^{13}C NMR (50 MHz, $CDCl_3$): δ 195.0 (ArCO), 152.4, 140.1, 132.4 (ArC), 130.9, 128.9, 127.9 (ArCH), 127.3 (ArC), 111.7 (ArCH), 43.7, 32.2, 29.8, 29.6 ($NHCH_2$ and 3 × CH_2), 28.6, 28.1 (C-2 and C-3), 27.5, 23.0 (2 × CH_2), 18.5 (C-4), 14.5 (CH_3). ESMS (m/z): 384 $(M+H)^+$. Anal. Calcd for $C_{24}H_{30}ClNO$: C, 75.08; H, 7.88; N, 3.65. Found: C, 75.06; H, 7.86; N, 3.67.

4.1.4.16. (2-(4-Chlorophenyl)cyclopropyl)(4-(piperidin-1-yl)phenyl)methanone (6n). Pale white solid, mp 134–136 °C; yield 85%; R_f 0.50 (5%, EtOAc/Hexane); IR (KBr) ν_{max} cm^{-1}: 2921 (C–H), 1596 (C=O); ^1H NMR (300 MHz, $CDCl_3$): δ 7.78 (2H, d, J = 8.76 Hz, ArH), 716 (2H, d, J = 8.28 Hz, ArH), 7.01 (2H, d, J = 8.28 Hz, ArH), 6.74 (2H, d, J = 8.79 Hz, ArH), 3.26 (4H, br s, 2 × NCH_2), 2.68–2.62 (1H, m, H-2), 2.51–2.45 (1H, m, H-3), 1.78–1.72 (1H, m, H-4a), 1.58 (6H, br s, 3 × CH_2), 1.32–1.26 (1H, m, H-4b). ^{13}C NMR (50 MHz, $CDCl_3$): δ 195.5 (ArCO), 152.4, 140.0, 132.1 (ArC), 130.6, 128.8, 127.3 (ArCH), 127.1 (ArC), 111.5 (ArCH), 51.2 (2 × NCH_2), 28.6, 28.4 (C-2 and C-3), 23.8 (2 × CH_2), 23.3 (CH_2), 18.7 (C-4). ESMS (m/z): 341 $(M+H)^+$. Anal. Calcd for $C_{21}H_{22}ClNO$: C, 74.21; H, 6.52; N, 4.12. Found: C, 74.17; H, 6.49; N, 4.14.

4.1.4.17. (2-(4-Chlorophenyl)cyclopropyl)(4-(dimethylamino)-phenyl)methanone (6o). White solid, mp 92–94 °C; yield 80%; R_f 0.45 (15%, EtOAc/Hexane); IR (KBr) ν_{max} cm^{-1}: 3020 (C–H), 1596 (C=O). ^1H NMR (300 MHz, $CDCl_3$): δ 7.87 (2H, d, J = 8.97 Hz, ArH), 7.24 (2H, d, J = 8.43 Hz, ArH), 7.08 (2H, d, J = 8.37 Hz, ArH), 6.63 (2H, d, J = 8.97 Hz, ArH), 3.05 (6H, s, $NHCH_2$), 2.76–2.70 (1H, m, H-2), 2.58–2.52 (1H, m, H-3), 1.85–1.79 (1H, m, H-4a), 1.39–1.32 (1H, m, H-4b). ^{13}C NMR (50 MHz, $CDCl_3$): δ 195.6 (ArCO), 150.8, 139.5, 132.6 (ArC), 130.6 (ArCH), 129.8 (ArC), 129.0, 127.8, 115.5 (ArCH), 43.0 ($N(CH_3)_2$), 29.5, 28.9 (C-2 and C-3), 19.5 (C-4). ESMS (m/z): 300 $(M+H)^+$. Anal. Calcd for $C_{18}H_{18}ClNO$: C, 72.11; H, 6.05; N, 4.67. Found: C, 72.08; H, 6.01; N, 4.65.

4.1.4.18. (2-(4-Chlorophenyl)cyclopropyl)(4-(pyrrolidin-1-yl)phenyl)methanone (6p). White solid, mp 134–136 °C; yield 81%; R_f 0.40 (5%, EtOAc/Hexane); IR (KBr) ν_{max} cm^{-1}: 2960 (C–H), 1607 (C=O); ^1H NMR (200 MHz, $CDCl_3$): δ 7.91 (2H, d, J = 8.90 Hz, ArH), 7.27 (2H, d, J = 8.48 Hz, ArH), 7.11 (2H, d, J = 8.48 Hz, ArH), 6.52 (2H, d, J = 8.94 Hz, ArH), 3.39–3.33 (4H, m, 2 × NCH_2), 2.79–2.73 (1H, m, H-2), 2.63–2.50 (1H, m, H-3), 2.10–1.98 (4H, m, 2 × CH_2), 1.89–1.80 (1H, m, H-4a), 1.43–1.39 (1H, m, H-4b). ^{13}C NMR (50 MHz, $CDCl_3$): δ 195.7 (ArCO), 151.1, 140.2, 132.3 (ArC), 130.8, 128.9, 127.9 (ArCH), 125.9 (ArC), 111.5 (ArCH), 48.2 (2 × NCH_2), 28.8, 28.4 (C-2 and C-3), 25.8 (2 × CH_2), 18.7 (C-4). ESMS (m/z): 326 $(M+H)^+$. Anal. Calcd for $C_{20}H_{20}ClNO$: C, 73.72; H, 6.19; N, 4.30. Found: C, 73.68; H, 6.17; N, 4.32.

4.1.4.19. (*Z*)-(2-(4-Chlorophenyl)cyclopropyl)(4-(octadec-9-enylamino)phenyl)methanone (6q). White solid, mp 137–139 °C; yield 80%; R_f 0.50 (10%, EtOAc/Hexane); IR (KBr) ν_{max} cm^{-1}: 3353 (N–H), 2923 (C–H), 1590 (C=O); ^1H NMR (200 MHz, $CDCl_3$): δ 7.86 (2H, d, J = 8.72 Hz, ArH), 7.26 (2H, d, J = 8.32 Hz, ArH), 7.10 (2H, d, J = 8.48 Hz, ArH), 6.54 (2H, d, J = 8.74 Hz, ArH), 5.35–5.32 (2H, m, CH=CH), 4.20 (1H, br s, NH), 3.18–3.15 (2H, m, $NHCH_2$), 2.81–2.69 (1H, m, H-2), 2.63–2.51 (1H, m, H-3), 2.10–1.89 (3H, m, 1H, H-4a + CH_2), 1.91–1.78 (1H, m, H-4b), 1.73–1.56 (2H, m, CH_2), 1.47–1.21 (24H, m, 12 × CH_2), 0.92 (3H, t, J = 6.64 Hz, CH_3). ^{13}C NMR (50 MHz, $CDCl_3$): δ 195.6 (ArCO), 152.6, 140.1, 132.4 (ArC), 131.0 (ArCH), 130.4, 130.0 (CH=CH) 128.9, 127.9 (ArCH), 127.1 (ArC), 111.7 (ArCH), 43.7, 33.04, 32.3, 30.1, 30.0, 29.7, 29.6 ($NHCH_2$ and 6 × CH_2), 28.7, 28.3 (C-2 and C-3), 27.6, 27.6, 27.5, 23.1 (4 × CH_2), 18.7 (C-4), 14.5 (CH_3). ESMS (m/z): 522 $(M+H)^+$. Anal. Calcd for $C_{34}H_{48}ClNO$: C, 78.20; H, 9.26; N, 2.68. Found: C, 78.11; H, 9.21; N, 2.65.

4.1.4.20. (2-(4-Chlorophenyl)cyclopropyl)(4-(3,4-dimethoxybenzylamino)phenyl)methan-one (6r). White solid, mp 135–137 °C; yield 73%; R_f 0.50 (20%, EtOAc/Hexane); IR (KBr) ν_{max} cm^{-1}: 3350 (N–H), 2938 (C–H), 1587 (C=O); ^1H NMR (200 MHz, $CDCl_3$): δ 7.74 (2H, d, J = 8.74 Hz, ArH), 7.26–7.19 (3H, m, ArH), 7.10 (2H, d, J = 8.48 Hz, ArH), 6.89–6.79 (2H, m, ArH), 6.61 (2H, d, J = 8.72 Hz, ArH), 4.46 (1H, br s, NH), 4.32 (2H, s, $NHCH_2$), 3.87 (3H, s, OCH_3), 3.86 (3H, s, OCH_3), 2.76–2.70 (1H, m, H-2), 2.63–2.55 (1H, m, H-3), 1.89–1.80 (1H, m, H-4a), 1.42–1.34 (1H, m, H-4b). ^{13}C NMR (50 MHz, $CDCl_3$): δ 195.7 (ArCO), 152.6, 148.6, 148.1, 140.1, 133.1, 132.4 (ArC), 130.9, 128.9, 127.9 (ArCH), 127.2 (ArC), 120.0, 112.1, 111.7, 111.0 (ArCH), 56.2 (2 × OCH_3), 48.0 ($NHCH_2$), 28.8, 28.4 (C-2 and C-3), 18.7 (C-4). ESMS (m/z): 422 $(M+H)^+$. Anal. Calcd for $C_{25}H_{24}ClNO_3$: C, 71.17; H, 5.73; N, 3.32. Found: C, 71.11; H, 5.70; N, 3.28.

4.1.4.21. (2-(4-Chlorophenyl)cyclopropyl)(4-(2-hydroxyethylamino)phenyl)methanone (6s). White solid, mp 144–146 °C; yield 75%; R_f 0.50 (5%, MeOH/$CHCl_3$); IR (KBr) ν_{max} cm^{-1}: 3419 (O–H), 3330 (N–H), 2930 (C–H), 1588 (C=O); ^1H NMR (300 MHz, $CDCl_3$): δ 7.83 (2H, d, J = 8.58 Hz, ArH), 7.25 (2H, d, J = 8.46 Hz, ArH), 7.09 (2H, d, J = 8.28 Hz, ArH), 6.59 (2H, d, J = 8.43 Hz, ArH), 3.87–3.71 (2H, m, CH_2), 3.46 (1H, br s, NH), 3.33–3.32 (2H, m, CH_2), 2.79–2.74 (1H, m, H-2), 2.63–2.56 (1H, m, H-3), 1.89–1.83 (1H, m, H-4a), 1.46–1.36 (1H, m, H-4b). ^{13}C NMR (50 MHz, $CDCl_3$): δ 195.9 (ArCO), 152.6, 140.1, 132.4 (ArC), 131.0, 128.9, 127.9 (ArCH), 127.2 (ArC), 111.7 (ArCH), 58.7 (CH_2OH), 43.3 ($NHCH_2$), 28.8, 28.4 (C-2 and C-3), 18.7 (C-4). ESMS (m/z): 316 $(M+H)^+$. Anal. Calcd for $C_{18}H_{18}ClNO_2$: C, 68.46; H, 5.75; N, 4.44. Found: C, 68.39; H, 5.73; N, 4.41.

4.1.4.22. (2-(3,4-Dimethoxyphenyl)cyclopropyl)(4-(4-methylpiperazin-1-yl)phenyl)meth-anone (6t). White solid, mp 112–114 °C; yield 81%; R_f 0.30 (0.1:9.9, MeOH/$CHCl_3$); IR (KBr) ν_{max} cm^{-1}: 2939 (C–H), 1651 (C=O); ^1H NMR (200 MHz, $CDCl_3$): δ 7.89 (2H, d, J = 8.67, 8.70 Hz, ArH), 6.87–6.69 (5H, m, ArH), 3.83 (6H, s, DiOMe), 3.36 (4H, br s, 2 × CH_2), 2.57–2.32 (9H, m, NCH_3, 2 × CH_2 and H-2, H-3), 1.80–1.76 (1H, m, H-4a), 1.46–1.40 (1H, m, H-4b). ^{13}C NMR (50 MHz, $CDCl_3$): δ 195.5 (ArCO), 152.3, 144.7, 139.9, 131.7 (ArC), 128.1, 127.5 (ArCH), 126.7 (ArC), 111.8 (ArCH), 56.3, 56.9 (2 × OMe), 50.5, 48.1 (2 × CH_2), 45.7 (NCH_3), 28.3, 27.6 (C-2 and C-3), 18.3 (C-4). ESMS (m/z): 381 $(M+H)^+$. Anal. Calcd for $C_{23}H_{28}N_2O_3$: C, 72.60; H, 7.42; N, 7.36. Found: C, 72.57; H, 7.39; N, 7.33.

4.1.4.23. (2-(3,4-Dimethoxyphenyl)cyclopropyl)(4-(heptylamino)phenyl)methanone (6u). White solid, mp 144–146 °C; yield 79%; R_f 0.40 (1:4, EtOAc/Hexane); IR (KBr) ν_{max} cm^{-1}: 3357 (N–H), 2921 (C–H), 1556 (C=O); ^1H NMR (300 MHz, $CDCl_3$): δ 7.88 (2H, d, J = 8.70 Hz, ArH), 6.79–6.66 (3H, m, ArH), 6.54 (2H, d, J = 8.73 Hz, ArH), 4.27 (1H, br s, NH), 3.86 (6H, s, DiOMe), 3.17 (2H, m, $NHCH_2$), 2.74–2.71 (1H, m, H-2), 2.57–2.52 (1H, m, H-3), 1.82–1.79 (1H, m, H-4a), 1.65–1.60 (2H, m, CH_2), 1.43–1.30 (9H, m, 4 × CH_2 and H-4b), 0.92 (3H, t, J = 6.27 Hz, CH_3). ^{13}C NMR (50 MHz, $CDCl_3$): δ 195.5 (ArCO), 152.3, 146.3, 140.3, 132.7 (ArC), 128.3, 127.5 (ArCH), 127.1 (ArC), 111.9 (ArCH), 56.4, 56.5 (2 × OMe), 43.5, 32.0, 29.6, 29.3 ($NHCH_2$ and 3 × CH_2), 28.7, 28.3

(C-2 and C-3), 27.1, 23.2 (2 × CH_2), 18.6 (C-4), 14.4 (CH_3). ESMS (*m*/*z*): 396 $(M+H)^+$. Anal. Calcd for $C_{25}H_{33}NO_3$: C, 75.91; H, 8.41; N, 3.54. Found: C, 75.36; H, 8.38; N, 3.57.

4.1.5. General procedure for the synthesis of 2-(azolyl)-ethylaminoaryl phenyl cyclopropyl methanones (8a–8c)

A mixture of 2-(4-chlorophenyl)cyclopropyl)-4-(2-hydroxyethylamino)phenyl methanone (**6s**) (5.0 g, 15.87 mmol), TEA (triethylamine, 2.65 ml, 19.0 mmol) in CH_2Cl_2 (20 ml) was stirred magnetically at 0 °C for 15–20 min. A solution of methanesulphonyl chloride (3.17 ml, 31.7 mmol in 5 ml CH_2Cl_2) was subsequently added dropwise and the reaction mixture was stirred at 0 °C, for 4 h. After completion of the reaction (TLC), the reaction mixture was diluted with excess of dichloromethane and extracted with water. The organic layer was separated and dried (anhyd Na_2SO_4) and concentrated under reduced pressure to get the intermediate 2-(4-(2-(4-chlorophenyl)cyclopropanecarbonyl)phenylamino)ethyl methanesulfonate (**7**) (4.80 g) and it was used as such without further purification in the subsequent reaction with azoles.

To stirring slurry of NaH (0.11 g, 4.58 mmol) in DMF (4 mL) at 0 °C, the desired azole (1.2 equiv) was added and the reaction mixture was stirred at 0 °C for 15–20 min. The above obtained 2-(4-(2-(4-chlorophenyl)cyclopropanecarbonyl) phenylamino) ethyl methanesulfonate (**7**) was added and stirring continued at 100–120 °C till the disappearance of starting material (TLC). The reaction mixture was cooled to room temperature, quenched with ethyl acetate and extracted with water. The organic layer was dried (anhyd Na_2SO_4) and concentrated under reduced pressure to give a crude mass which was purified by column chromatography (SiO_2, 100–200 mesh) using gradient of hexane/ethyl acetate (9:1→6:4)/0.2:9.8→0.6:9.4% methanol/chloroform to give the desired compound (**8a**–**8c**) in varying yields.

4.1.5.1. (4-(2-(1*H*-Imidazol-1-yl)ethylamino)phenyl)(2-(4-chlorophenyl)cyclopropyl)me-thanone (8a). White solid, mp 110–112 °C; yield 67%; R_f 0.40 (5%, MeOH/$CHCl_3$); IR (KBr) ν_{max} cm^{-1}: 3334 (N–H), 2930 (C–H), 1588 (C═O); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.84 (2H, d, J = 8.82 Hz, ArH), 7.50 (1H, s, imidazole-H), 7.27 (2H, d, J = 8.46 Hz, ArH), 7.11 (2H, d, J = 8.46 Hz, ArH), 6.97 (2H, s, imidazole-H), 6.57 (2H, d, J = 8.79 Hz, ArH), 4.19 (2H, t, J = 5.61 Hz, CH_2), 3.58 (2H, t, J = 5.67 Hz, CH_2), 3.35 (1H, m, NH), 2.81–2.75 (1H, m, H-2), 2.59–2.53 (1H, m, H-3), 1.85–1.79 (1H, m, H-4a), 1.48–1.42 (1H, m, H-4b). ^{13}C NMR (50 MHz, $CDCl_3$): δ 195.7 (ArCO), 152.6, 140.1 (ArC), 138.1 (imidazole-CH), 132.4 (ArC), 131.0 (ArCH), 128.5 (imidazole-CH), 128.9, 127.9 (ArCH), 127.2 (ArC), 121.2 (imidazole-CH), 111.7 (ArCH), 46.3 ($N_{imid}CH_2$), 43.3 ($NHCH_2$), 28.8, 28.4 (C-2 and C-3), 18.7 (C-4). ESMS (*m*/*z*): 366 $(M+H)^+$. Anal. Calcd for $C_{21}H_{20}ClN_3O$: C, 68.94; H, 5.51; N, 11.49. Found: C, 68.87; H, 5.49; N, 11.53.

4.1.5.2. (4-(2-(1*H*-1,2,4-Triazol-1-yl)ethylamino)phenyl)(2-(4-chlorophenyl)cyclopropyl) methanone (8b). White solid, mp 117–119 °C; yield 68%; R_f 0.45 (2%, MeOH/$CHCl_3$); IR (KBr) ν_{max} cm^{-1}: 3331 (N–H), 2934 (C–H), 1593 (C═O); ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.17 (1H, s, triazole-H), 7.92 (1H, s, triazole-H), 7.81 (2H, d, J = 8.79 Hz, ArH), 7.25 (2H, d, J = 8.43 Hz, ArH), 7.10 (2H, d, J = 8.43 Hz, ArH), 6.56 (2H, d, J = 8.79 Hz, ArH), 4.40 (2H, t, J = 5.64 Hz, CH_2), 3.58 (2H, t, J = 5.88 Hz, CH_2), 3.34 (1H, m, NH), 2.79–2.74 (1H, m, H-2), 2.57–2.51 (1H, m, H-3), 1.83–1.78 (1H, m, H-4a), 1.46–1.39 (1H, m, H-4b). ^{13}C NMR (50 MHz, $CDCl_3$): δ 195.3 (ArCO), 152.6 (ArC), 150.9, 144.2 (triazole CH), 140.1, 132.4 (ArC), 131.0, 128.9, 127.9 (ArCH), 127.2 (ArC), 111.7 (ArCH), 48.7 ($N_{Triazole}CH_2$), 43.3 ($NHCH_2$), 28.8, 28.4 (C-2 and C-3), 18.7 (C-4). ESMS (*m*/*z*): 367 $(M+H)^+$. Anal. Calcd for $C_{20}H_{19}ClN_4O$: C, 65.48; H, 5.22; N, 15.27. Found: C, 65.54; H, 5.20; N, 15.30.

4.1.5.3. (4-(2-(1*H*-Benzo[d]imidazol-1-yl)ethylamino)phenyl)(2-(4-chlorophenyl)cyclop-ropyl)methanone (8c). White solid, mp 134–136 °C; yield 70%; R_f 0.45 (3%, MeOH/$CHCl_3$); IR (KBr) ν_{max} cm^{-1}: 3337 (N–H), 2932 (C–H), 1585 (C═O); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.89–7.86 (3H, m, ArH), 7.80–7.65 (2H, m, ArH), 7.56–7.50 (1H, m, ArH), 7.36–7.25 (4H, m, ArH), 7.12 (2H, d, J = 8.43 Hz, ArH), 6.58 (2H, d, J = 8.79 Hz, ArH), 4.43 (2H, t, J = 5.31 Hz, CH_2), 3.71 (2H, t, J = 5.70 Hz, CH_2), 3.39 (1H, m, NH), 2.86–2.80 (1H, m, H-2), 2.59–2.53 (1H, m, H-3), 1.85–1.79 (1H, m, H-4a), 1.48–1.42 (1H, m, H-4b). ^{13}C NMR (50 MHz, $CDCl_3$): δ 195.6 (ArCO), 152.3 (ArC), 144.4 ($Ar_{Bz}C$), 143.6 (benzimidazole CH), 140.5 (ArC), 134.1 ($Ar_{Bz}C$), 132.2 (ArC), 131.2, 128.7, 127.5 (ArCH), 127.1 (ArC), 123.6, 123,2, 118.7, 109.9 ($Ar_{Bz}CH$), 111.4 (ArCH), 48.7 ($N_{Benzimid}CH_2$), 43.3 ($NHCH_2$), 28.8, 28.4 (C-2 and C-3), 18.7 (C-4). ESMS (*m*/*z*): 416 $(M+H)^+$. Anal. Calcd for $C_{25}H_{22}ClN_3O$: C, 72.19; H, 5.33; N, 10.10. Found: C, 72.23; H, 5.36; N, 10.13.

4.2. Biology (assay methods)

4.2.1. Antimycobacterial assay

Determination of antitubercular activity against *M. tuberculosis* $H_{37}Rv$ strain (Agar microdilution method): Drug susceptibility and determination of MIC of the test compounds/drugs against *M. tuberculosis* $H_{37}Rv$ was done by agar microdilution method.[57] The MIC of the test compounds was determined by incorporating twofold dilution of this suspension were added to (in tubes) 7H10 middle brook's medium (containing 1.7 mL medium and 0.2 mL OADC supplement) at different concentration of the test compounds keeping the volume constant, that is, 0.1 mL. Medium was allowed to cool keeping the tubes in slanting position. A culture of *M. tuberculosis* $H_{37}Rv$ growing on L-*J* medium was harvested in 0.85% saline with 0.05% Tween-80. A suspension of 1 μg/mL concentration of extracts/compounds was prepared in dimethyl sulphoxide (DMSO). These tubes were then incubated at 37 °C for 24 h followed by streaking of *M. tuberculosis* $H_{37}Rv$ (5×10^5 bacilli per tube). The tubes were then incubated at 37 °C. Growth of bacilli was seen after 30 days of incubation. Tubes having the compounds were compared with control tubes where medium alone was incubated with $H_{37}Rv$. The lowest concentration of the compound at which complete inhibition of colonies occurred was taken as minimum inhibitory concentration (MIC) of test compound.

4.2.1.1. Antimalarial assay. The antimalarial assay was performed in vitro against chloroquine sensitive *Plasmodium falciparum* 3D7 strains reported previously.[58] Culture was maintained in vitro as described by Trager and Jansen[60] with some modifications μL asynchronous culture of *P. falciparum* 3D7 was added. The parasitaemia was maintained to ~0.5% and hematocrit was adjusted to 1.5%. Plates were incubated in CO_2 incubator maintained at 37 °C for 24 h. Radiolabelled hypoxanthine solution containing 0.5 μ Ci/well was added. These plates were further incubated for another 48 h. Cells were harvested on Whattmann filter papers, transferred in scintillation vials, dried overnight. Scintillation cocktail was added in these vials after 24 h, radioactivity was counted under scintillation β-counter. IC_{50} values of tested compounds were calculated on the basis of radiolabelled hypoxanthine uptake by the parasites.

4.2.1.2. Antimalarial assay using minimum inhibitory concentration (MIC). MICs of compounds were determined as described by Rieckmann et al. (1978)[61] with some modifications. Briefly, stock solution of the compounds were prepared at 10 mg/ml in DMSO and stored at 0 °C until use. The test was performed in 96-well microtiter plates, twofold serial drug dilutions were prepared

in complete RPMI 1640 and 50 μL of each dilution was used in each well. Parasitized RBCs (50 μL) were added to each well. The final culture suspension had a hematocrit of 3–4% with 1.0–2.0% infection (>95% rings). Micro culture plates were incubated for 24–32 h at 37 °C in an incubator supplied with 5% CO_2 to allow the development of malaria parasites, culture plates were taken out and maximum supernatant medium was removed, thin blood smear of each well content were made and stained with 15% Giemsa stain. These smears were checked for the maturation of schizonts relative to their controls.

4.2.3. Cell cytotoxicity assay

The cytotoxic assay was carried out against monkey kidney cell line C1008 (Vero cells). The cells were cultivated in 25 cm^2 tissue culture flask supplemented with MEM-medium (9.7 g MEM, 2.2 g/l $NaHCO_3$, 6 g HEPES, Gentamycine sulphate 50 mg, amphotericin B 2.5 mg, TDW-1000 ml) + 15%FBS provided with 5% CO_2 at 37 °C. The culture medium was changed on alternate days. The growth rate was determined as described.[62] For the cytotoxicity assay the cells were washed with PBS, trypsinized with 0.25% trypsin and a cell suspension was made in culture medium. The cells were counted in Neubaur chamber and appropriate dilution was made (1×10^5 cells/ml). Vero cell suspension (100 μL) was added to the microtiter plates and allowed to adhere overnight. Serial dilutions of test compounds were prepared in these plates and Vero cells were incubated with these compounds for 72 h. Resazurin was added in wells and after 4 h these plates were read under florescence reader (Biotek). Cytotoxic concentration (CC_{50}) was determined using MS-EXEL.

4.2.4. FAS-II inhibitory studies

4.2.4.1. In silico studies. The three-dimensional structure of the compound **4a** was built and optimized using the Builder module of Insight II (M/s Accelrys Inc.). The compound was then taken as probe and submitted to an in house developed web-based tool called *Inhibitor Identification Tool (IS-IT)* (unpublished). The tool offers docking against 85 potential drug targets specifically chosen from *Mycobacterium tuberculosis*. Missing residues and atoms of each protein structure were repaired using the biopolymer module of Sybyl 6.8 (Tripos Associates), and Kollman[63,64] charges were assigned to the protein. The grid for docking calculations was centered on the binding site of each protein. Docking simulations were carried out by using AUTODOCK 4.0, and interaction energies between compounds and the proteins were calculated using the scoring function of AUTODOCK 4.0. The protein target with interaction energies greater than the control docking energies was selected for further enzymatic assays.

4.2.4.2. Bacterial strains and viability assay. The generation of recombinant *M. aurum* strains was described earlier.[65] *M. aurum* cultures were grown in Sauton's medium supplemented with 0.05% Tween-80 and kanamycin (25 μg/mL) and were plated on Nutrient-agar plates with 0.05% Tween-80 (NAT) supplemented with kanamycin. For post treatment viability assay, *M. aurum* was grown in Sauton's medium up to 0.6 OD_{600} and the culture was diluted to 0.05 OD with fresh medium. From these diluents, $\sim 1 \times 10^5$ cells were inoculated into different tubes containing 5 ml fresh medium and varying concentration of compounds. The cultures were allowed to grow for 12 h at 37 °C with continuous shaking at 180 rpm. The treated and untreated cultures were plated on NAT-Km plates using 10-fold serial dilution to count the number of viable cells. % inhibition was scored considering the number of bacterial colonies in untreated condition as 100%. Under these experimental conditions we obtained nearly 18.8%, 85.43%, 88.72% and 99.64% inhibition at 10, 25, 50 and 75 μM of **4a** treatment, respectively.

4.2.4.3. Reporter gene expression analysis. Recombinant *M. aurum* strains were grown in Sauton's medium with Kanamycin at 37 °C to 0.5 OD_{600} after which culture was diluted to 0.04–0.05 OD with fresh medium. Ten millilitre of diluted culture were distributed to separate tubes, equilibrated for 2 h at 37 °C and then varying concentrations (10, 25, 50 and 75 μM) of compounds were added to different tubes. Following 12 h incubation at 37 °C, 5 ml cultures from each tube were pelleted, washed and resuspended in PBS (Phosphate Buffer Saline, pH 7.2), sonicated at 4 °C and supernatant was collected by centrifugation at 13000 rpm for 10 min at 4 °C. Protein contents were quantified using Bradford Assay reagent (Sigma B6916) as per manufacturer protocol. β-Gal assay was performed from total cellular protein as described earlier.[65] Briefly, same amount of protein were mixed with 200 μL of ONPG (4 mg/ml) and incubated for 30 min at 37 °C. Reaction was stopped by adding 500 μL of 1 M Na_2CO_3 and optical density was measured at 410 nm. Experiments were carried out in triplicates for each treatment and β-galactosidase units were calculated for each set individually. The culture at each point was also plated to confirm the decline in viability of cells after drug treatment. The whole experiment was repeated twice and similar trends in results were obtained. Mean value and standard deviation were calculated and plotted for each set of data.

4.2.5. Data analysis

All data were expressed as mean ± SD with at least three separate experiments. IC_{50} were determined with linear regression analysis using Microsoft Excel. Statistically significant comparison was calculated using student's *t*-test for unpaired variants. Values of $p < 0.05$ were regarded as statistically significant.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmc.2010.09.071.

References and notes

1. Duncan, K.; Barry, C. E. *Curr. Opin. Microbiol.* **2004**, *7*, 460.
2. World Health Organization. *Global Tuberculosis Control: Surveillance, Planning, and Financing*, WHO Report 2008, WHO Press: Geneva, Switzerland.
3. Jones, D. *Nat. Rev. Drug Disc.* **2005**, *4*, 103.
4. Gandhi, N. R.; Moll, A.; Sturm, A. W. *Lancet* **2006**, *4*, 1575.
5. Gillespie, S. H. *Antimicrob. Agents Chemother.* **2002**, *46*, 267.
6. Tripathi, R. P.; Tewari, N.; Dwivedi, N.; Tiwari, V. K. *Med. Res. Rev.* **2005**, *25*, 93.
7. Ebrahim, G. J. *J. Trop. Pediatr.* **2007**, *53*, 147.
8. Huitric, E.; Verhasselt, P.; Koul, A.; Andries, K.; Hoffner, S.; Andersson, D. I. *Antimicrob. Agents Chemother.* **2010**, *54*, 1022.
9. Raviglione, M. C. *N. Eng. J. Med.* **2008**, *7*, 636.
10. Teresa, M.; Lugo, G.; Bewley, C. A. *J. Med. Chem.* **2008**, *51*, 2606.
11. Zhang, Y.; Martens, K. P.; Denkin, S. *Drug Discovery Today* **2006**, *11*, 21.
12. Janin, Y. L. *Bioorg. Med. Chem.* **2007**, *15*, 2479.
13. Wiesner, J.; Ortmann, R.; Jomaa, H.; Schlitzer, M. *Angew. Chem., Int. Ed.* **2003**, *42*, 5274.
14. Wells, T. N. C.; Alonso, P. L.; Gutteridge, W. E. *Nat. Rev. Drug Disc.* **2009**, *8*, 879.
15. World Health Organization. The World Health Organization website, http://www.who.int/malaria/wmr2008/malaria2008.pdf, World Malaria Report 2008, Geneva, Switzerland.
16. Snow, R. W.; Guerra, C. A.; Noor, A. M.; Myint, H. Y.; Hay, S. I. *Nature* **2005**, *434*, 214.
17. Olliaro, P. L.; Taylor, W. R. J. *J. Exp. Biol.* **2003**, *206*, 3753.
18. Schlitzer, M. *ChemMedChem* **2007**, *2*, 944.
19. McKie, J. H.; Douglas, K. T.; Chan, C.; Roser, S. A.; Yates, R.; Read, M.; Hyde, J. E.; Dascombe, M. J.; Yuthavong, Y.; Sirawaraporn, W. *J. Med. Chem.* **1998**, *41*, 1367.
20. Hyde, J. E. *Trends Parasitol.* **2005**, *21*, 494.
21. White, N. J. *Br. Med. Bull.* **1998**, *54*, 703.

22. White, N. J. *Science* **2008**, *320*, 330.
23. Posner, G. H.; Chang, W.; Hess, L.; Woodard, L.; Sinishtaj, S.; Usera, A. R.; Maio, W.; Rosenthal, A. S.; Kalinda, A. S.; Angelo, J. G. D.; Petersen, K. S.; Stohler, R.; Chollet, J.; Tomas, J. S.; Snyder, C.; Rottmann, M.; Wittlin, S.; Brun, R.; Shapiro, T. A. *J. Med. Chem.* **2008**, *51*, 1035.
24. Hale, V.; Keasling, J. D.; Renninger, N.; Diagana, T. T. *Am. J. Trop. Med. Hyg.* **2007**, *77*, 198.
25. Dondrop, A. M.; Nosten, F.; Yi, P.; Das, D.; Phae, P. A.; Tarning, J.; Lwin, K. M.; Ariey, F.; Hanpithakpong, W.; Lee, S. J.; Ringwald, P.; Silamut, K.; Imwong, M.; Chotivanich, K.; Lim, P.; Herdman, T.; An, S. S.; Yeung, S.; Singhasivanon, P.; Day, N. P. J.; Lindegardh, N.; Socheat, D.; White, N. J. *N. Eng. J. Med.* **2009**, *361*, 455.
26. Kavanagh, E. *Science* **2007**, *315*, 1790.
27. Kuo, M. R.; Morbidoni, H. R.; Alland, D.; Sneddon, S. F.; Gourlie, B. B.; Staveski, M. M.; Leonard, M.; Gregory, J. S.; Janjigian, A. D.; Yee, C.; Musser, J. M.; Kreiswirth, B.; Iwamoto, H.; Perozzo, R.; Jacobs, W. R.; Sacchettini, J. C.; Fidock, D. A. *J. Biol. Chem.* **2003**, *278*, 20851.
28. Waller, R. F.; Ralph, S. A.; Reed, M. B.; Su, V.; Douglas, J. D.; Minnikin, D. E.; Cowman, A. F.; Besra, G. S.; McFadden, G. I. *Antimicrob. Agents Chemother.* **2003**, *47*, 297.
29. Barry, C. E.; Lee, R. E.; Mdluli, K.; Sampson, A. E.; Schroeder, B. G.; Slayden, R. A.; Yuan, Y. *Prog. Lipid Res.* **1998**, *37*, 143.
30. Takayama, K.; Wang, C.; Besra, G. S. *Clin. Microbiol. Rev.* **2005**, *18*, 81.
31. Jana, S.; Paliwal, J. *Int. J. Antimicrob. Agents* **2007**, *30*, 4.
32. Jomaa, H.; Wiesner, J.; Sanderbrand, S.; Altincicek, B.; Weidemeyer, C.; Hintz, M.; Turbachova, I.; Eberl, M.; Zeidler, J.; Lichtenthaler, H. K.; Soldati, D.; Beck, E. *Science* **1999**, *285*, 1573.
33. Kuo, M. R.; Morbidoni, H. R.; Alland, D.; Sneddon, S. F.; Gourlie, B. B.; Staveski, M. M.; Leonard, M.; Gregory, J. S.; Janjigian, A. D.; Yee, C.; Musser, J. M.; Kreiswirth, B. N.; Iwamoto, H.; Perozzo, R.; Jacobs, W. R.; Sacchettini, J. C.; Fidock, D. A. *J. Biol. Chem.* **2003**, *278*, 20851.
34. Wiesner, J.; Henschker, D.; Hutchinson, D. B.; Beck, E.; Jomaa, H. *Antimicrob. Agents Chemother.* **2002**, *46*, 2889.
35. Rajabi, L.; Courreges, C.; Montoya, J.; Aguilera, R. J.; Primm, T. P. *Lett. Appl. Microbiol.* **2005**, *40*, 212.
36. Lin, Y. M.; Zhou, Y.; Flavin, M. T.; Zhou, L. M.; Nie, W.; Chen, F. C. *Bioorg. Med. Chem.* **2002**, *10*, 2795.
37. Morgan, M. A.; Doerr, K. A.; Hampel, H. O.; Goodman, N. L.; Roberts, G. D. *J. Clin. Microbiol.* **1985**, *21*, 634.
38. Rastogi, N.; Goh, K. S.; David, H. L. *Res. Microbiol.* **1989**, *140*, 419.
39. Devreux, V.; Wiesner, J.; Goeman, J. L.; Eycken, J. V. D.; Jomaa, H.; Calenbergh, S. V. *J. Med. Chem.* **2006**, *49*, 2656.
40. Barry, C. E., III; Lee, R. E.; Mdluli, K. *Prog. Lipid Res.* **1998**, *37*, 143.
41. Hansch, C.; Sammes, P. G.; Taylor, J. B.; Dryton, C. J. In *Comprehensive Medicinal Chemistry*; Dryton, C. J., Ed.; Pergamon: Oxford, UK, 1990; Vol. 6.
42. Koshikenen, A. M. P.; Hassila, H. *Acta Chem. Scand.* **1996**, *50*, 323.
43. Burger, A.; Standridge, R. T.; Ariens, E. J. *J. Med. Chem.* **1963**, *6*, 221.
44. Shi, M.; Yang, Y. H.; Xu, B. *Tetrahedron* **2005**, *61*, 1893. and references cited therein.
45. Katiyar, D.; Tiwari, V. K.; Tripathi, R. P.; Srivastava, A.; Chaturvedi, V.; Srivastava, R.; Srivastava, B. S. *Bioorg. Med. Chem.* **2003**, *11*, 4369.
46. Tewari, N.; Tiwari, V. K.; Tripathi, R. P.; Chaturvedi, V.; Srivastava, A.; Srivastava, R.; Shukla, P. K.; Chaturvedi, A. K.; Gaikwad, A.; Sinha, S.; Srivastava, B. S. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 329.
47. Mishra, R. C.; Tripathi, R.; Katiyar, D.; Tewari, N.; Singh, D.; Tripathi, R. P. *Bioorg. Med. Chem.* **2003**, *11*, 5363.
48. Tewari, N.; Tiwari, V. K.; Mishra, R. C.; Tripathi, R. P.; Srivastava, A. K.; Ahmad, R.; Srivastava, R.; Srivastava, B. S. *Bioorg. Med. Chem.* **2003**, *11*, 2911.
49. Tripathi, R. P.; Tiwari, V. K.; Tewari, N.; Katiyar, D.; Saxena, N.; Sinha, S.; Gaikwad, A.; Srivastava, A.; Chaturvedi, V.; Manju, Y. K.; Srivastava, R.; Srivastava, B. S. *Bioorg. Med. Chem.* **2005**, *13*, 5668.
50. Singh, N.; Pandey, J.; Yadav, A.; Chaturvedi, V.; Bhatnagar, S.; Gaikwad, A.; Sinha, S.; Kumar, A.; Shukla, P. K.; Tripathi, R. P. *Eur. J. Med. Chem.* **2009**, *44*, 1705.
51. Dwivedi, N.; Tewari, N.; Tiwari, V. K.; Chaturvedi, V.; Manju, Y. K.; Srivastava, A.; Giakwad, A.; Sinha, S.; Tripathi, R. P. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 4526.
52. Chimenti, F.; Maccioni, E.; Secci, D.; Bolasco, A.; Chimenti, P.; Granese, A.; Befani, O.; Turini, P.; Alcaro, S.; Ortuso, F.; Cirilli, R.; Torre, F. L.; Cardia, M. C.; Distinto, S. *J. Med. Chem.* **2005**, *48*, 7113.
53. Bansal, R. K.; Mathur, S.; Jainendra, J. K.; Sharma, D. *J. Ind. Chem. Soc.* **1988**, *65*, 134.
54. Chandrasekhar, S.; Narasihmulu, C.; Jagadeshwar, V.; Reddy, K. V. *Tetrahedron Lett.* **2003**, *44*, 3629.
55. Paxton, R. J.; Taylor, R. J. K. *Synlett* **2007**, 633.
56. Hartikka, A.; Arvidsson, P. I. *J. Org. Chem.* **2007**, *72*, 5874.
57. Saito, H.; Tomioka, H.; Sato, K.; Emori, M.; Yamane, T.; Yamashita, K.; Hosol, K.; Hidaka, T. *Antimicrob. Agents Chemother.* **1991**, *35*, 542.
58. Desjardins, R. E.; Canfield, C. J.; Haynes, J. D.; Chulay, J. D. *Antimicrob. Agents Chemother.* **1979**, *16*, 710.
59. Hans, R. H.; Guantai, E. M.; Lategan, C.; Smith, P. J.; Wan, B.; Franzblau, S. G.; Gut, J.; Rosenthal, P. J.; Chibale, K. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 942.
60. Trager, W.; Jansen, J. B. *Science* **1976**, *193*, 673.
61. Rieckmann, K. H.; Campbell, G. H.; Sax, L. J.; Ema, J. E. *Lancet* **1978**, *311*, 22.
62. Norma, R. S.; Brun, R. *ChemBioChem* **2003**, *4*, 69.
63. Weiner, S. J.; Kollman, P. A.; Nguyen, D. T.; Case, D. A. *J. Comput. Chem.* **1986**, *7*, 230.
64. Cornell, W. D.; Cieplak, P.; Bayly, C. I.; Gould, I. R.; Merz, K. M., Jr.; Ferguson, D. M.; Spellmeyer, D. C.; Fox, T.; Caldwell, J. W.; Kollman, P. A. *J. Am. Chem. Soc.* **1995**, *117*, 5179.
65. Gupta, N.; Singh, B. N. *J. Appl. Microb.* **2008**, *105*, 1703.