European Journal of Medicinal Chemistry 46 (2011) 4302–4310

Contents lists available at ScienceDirect

European Journal of Medicinal Chemistry

journal homepage: http://www.elsevier.com/locate/ejmech

Original article

Novel aryloxy azolyl chalcones with potent activity against *Mycobacterium tuberculosis* H37Rv

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ARTICLE INFO

Article history:
Received 25 March 2011
Received in revised form
14 June 2011
Accepted 27 June 2011
Available online 3 July 2011

Keywords:
Chalcones
Aryloxy azoles
Anti-tubercular
Isoniazid

ABSTRACT

A series of twenty seven novel aryloxy azolyl chalcones were synthesized and evaluated *in vitro* for the growth inhibition of *Mycobacterium tuberculosis* H37Rv. Ten compounds from this series exhibited good activity with MIC in the range of 3.12–0.78 μg/mL and six of them were found non-toxic against VERO cells and MBMDMøs (mouse bone-marrow derived macrophages), were further evaluated ex-vivo for their potential to kill intracellular bacilli. Two compounds **4** and **19** showed 99% and 71% killing respectively, of intracellular bacilli in MBMDMøs infection model. Further, compound **19**, an imidazolyl chalcone with a 2,4-difluorobenzyloxy moiety also exhibited moderate *in vivo* activity in mice against virulent *M. tuberculosis*, thus providing a new structural lead towards TB drug development.

1. Introduction

Tuberculosis is largely a disease of poverty with the highest cases of the disease occurring in Africa and Asia. The drugs for treatment of tuberculosis have been available for nearly 50 years, still TB remains a global health crisis, killing nearly two million people each year (one person dies every 10 s) [1]. Tuberculosis (TB), caused by *Mycobacterium tuberculosis* (*M.tb*), a facultative intracellular bacillus, is the world's number one killer among infectious diseases and the leading cause of death among women of reproductive age. The World Health Organization (WHO) has estimated that one-third of the world's population is infected with Mycobacterium tuberculosis [2]. Current TB treatment regimen DOTS (directly observed therapy short-course) requires patients to take a combination of three or four drugs, namely, isoniazid (INH), rifampin (RMP), pyrazinamide (PZA), and ethambutol (EMB) (or alternatively streptomycin (SM)), throughout a 6–12 month period. The long treatment regimen, which is necessary due to the presence of a nonreplicating persistent *M.tb* phenotype (NRP-TB) [3], results in poor patient compliance, causes undesired side effects, and makes a significant contribution to the emergence of drug resistant *M.tb* strains [2,4]. TB is aggravated by the spread of HIV and is a major cause of death among HIV/AIDS patients. The emergence of multidrug-resistant (MDR) strains and the increasing prevalence of global human immunodeficiency virus (HIV), as a frequent coinfection, have amplified the incidence of TB [5–7]. Though a number of lead molecules are known today and some of them are at various stages of development [8], however no new drug has been introduced in the past 40 years [9,10]. Hence, there is an urgent need for affordable and effective alternative anti-TB drugs with improved properties such as enhanced activity against MDR strains, reduced toxicity and shortened duration of therapy.

Use of small molecules in the current treatment regimen encouraged us to work on chalcone derivatives [11]. Further, the appeal of working with chalcones (1,3-diarylprop-2-en-1-one) stems from their synthetic accessibility, the various ways the core structure can be diversified. Several reports have documented the wide range of biological properties of natural and synthetic chalcones. They are also cited as being antibacterial, with chemotherapeutic potential against *M. tuberculosis* H37Rv [12]. Licochalcone A (Fig. 1), a chalcone from the roots of *Glycyrrhizae inflata*, showed low MICs against three of the species such as *M. tuberculosis*, *Mycobacterium avium*, and *Mycobacterium bovis* [13]. On the other hand azoles are important as heterocyclic components of many natural products, drugs, and biologically active molecules [14]. They are also reported as potent inhibitor of cell growth of *M. bovis* and *Mycobacterium smegmatis*, two mycobacterial species which closely resemble *M.tb* [15]. Azole

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doi:10.1016/j.ejmech.2011.06.037

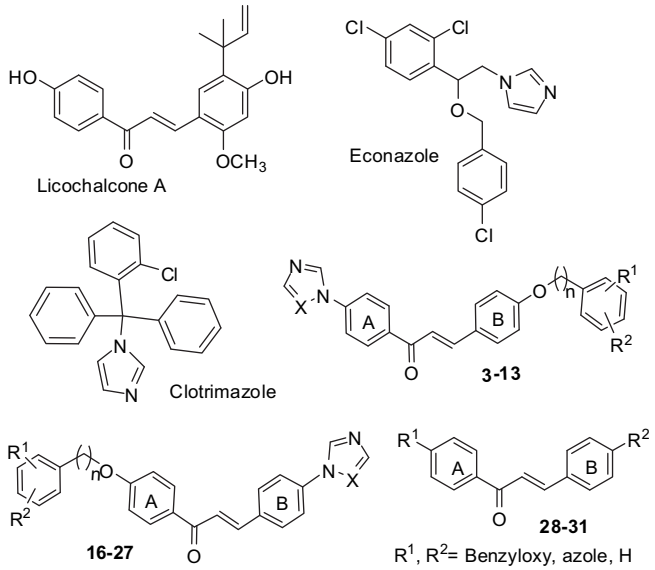


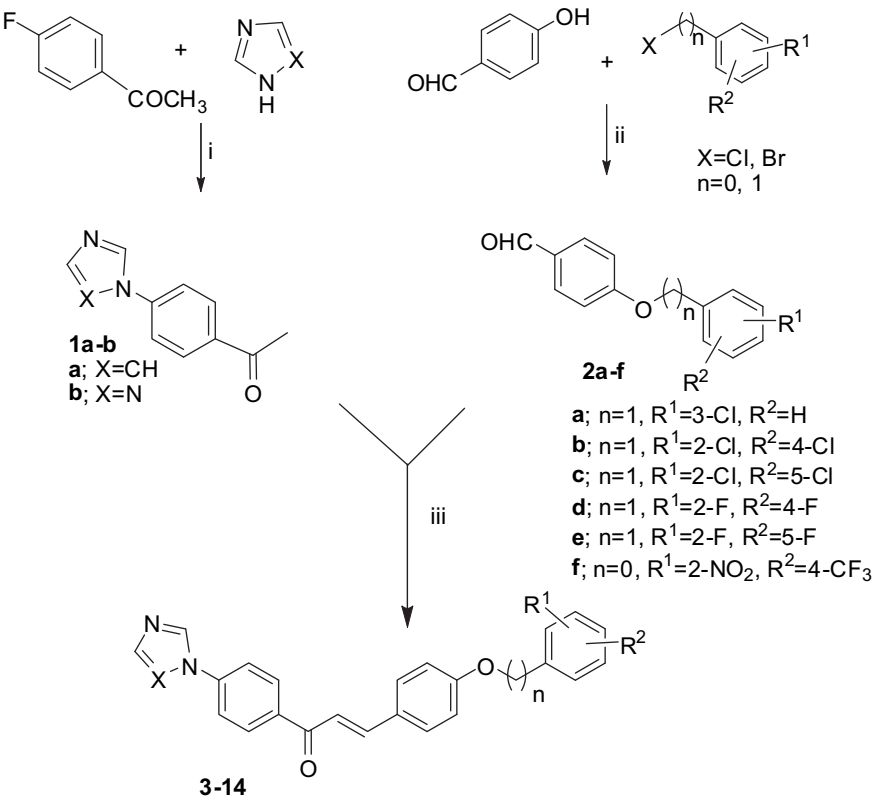
Fig. 1. Representative anti-mycobacterials and target compounds.

antifungal drugs such as econazole and clotrimazole (Fig. 1) are also proved to have anti-tubercular activities in mice [16].

In this context, we would like to mention our ongoing efforts devoted to the synthesis of novel heterocyclics as anti-infective agents. We have recently identified the antileishmanial effectiveness of variously substituted aryloxy cycloalkyl, aryloxy arylalkyl and aryloxy heteroaryl azoles [17]. We presumed that the azolyl and aryloxyl portion of the molecule is crucial for the high activity. Based on above reports and our interest on azole moiety has induced us to extended our studies to the synthesis of some novel chalcone analogues bearing these aryloxyl and the azolyl functionalities (Fig. 1.; **3**–**13** and **16**–**27**) as potential anti-mycobacterial agents. In this communication we described the synthesis of hybrid molecules consisting of chalcones and azoles (imidazoles or triazoles) along with aryloxy moiety and highlighted their anti-tubercular activity against *M. tuberculosis* H37Rv. For structure activity relationship (SAR) studies, variously substituted aryloxy/benzyloxy moieties were chosen and bis azolyl (**28**, **29**), bis benzyloxy (**30**) and monobenzyloxy (**31**) chalcones were also explored.

2. Chemistry

A one-step Claisen–Schmidt condensation was used to prepare the chalcones linked with aryloxyl/benzyloxy and azolyl residues (**3**–**13** and **16**–**27**). As shown in Scheme 1, the new chalcones **3**–**13**,



3; X= CH, n=1, R^1=3-Cl, R^2=H
4; X= CH, n=1, R^1=2-Cl, R^2=4-Cl
5; X= CH, n=1, R^1=2-Cl, R^2=5-Cl
6; X= CH, n=1, R^1=2-F, R^2=5-F
7; X= CH, n=1, R^1=2-F, R^2=4-F
8; X= N, n=1, R^1=3-Cl, R^2=H
9; X= N, n=1, R^1=2-Cl, R^2=4-Cl
10; X= N, n=1, R1=2-Cl, R^2=5-Cl
11; X= N, n=1, R1=2-F, R^2=4-F
12; X= N, n=1, R1=2-F, R^2=5-F
13; X= CH, n=0, R^1=2-NO_2, R^2=4-CF_3

Scheme 1. Reagents and conditions: (i) dry K_2CO_3, DMF, 12–14 h, 110 °C; (ii) t-BuOK, DMSO, 5–6 h, 5 °C–rt; (iii) 10% NaOH-EtOH, 9–10 h, rt.

bearing azole moiety and aryloxy/benzyloxy groups, were prepared by the sodium hydroxide catalyzed condensation of appropriate 4-azolylacetophenones (**1a**–**b**), with the required aryloxy aromatic aldehydes (**2a**–**f**) in moderate to high yield (59–86%). In this case, the 4-azolylacetophenone precursor (**1a**–**b**) were obtained by substitution of 4-fluoro acetophenone with imidazole/triazole. The aryloxy/benzyloxy benzaldehydes (**2a**–**f**) were prepared by alkylation of 4-hydroxy benzaldehydes with variously substituted aryl/benzyl halides in the presence of t-BuOK in DMSO. Similarly the chalcones **16**–**27** (Scheme 2) were obtained by condensation of the appropriate aryloxy/benzyloxy acetophenones (**14a**–**f**) with azolylbenzaldehydes (**15a**–**b**). Condensation gave predominantly single isomer. ^{1}H NMR spectrometry indicated that the chalcone products (**3**–**13** *and* **16**–**27**) to be as the *E*-stereoisomer ($J_{CH=CH}$ = 15.4–16.8 Hz range). For SAR studies bis imidazolyl (**28**), bis triazolyl (**29**), bis benzyloxy (**30**), monobenzyloxy (**31**) chalcones were also prepared from the respective acetophenones and benzaldehydes (Fig. 2).

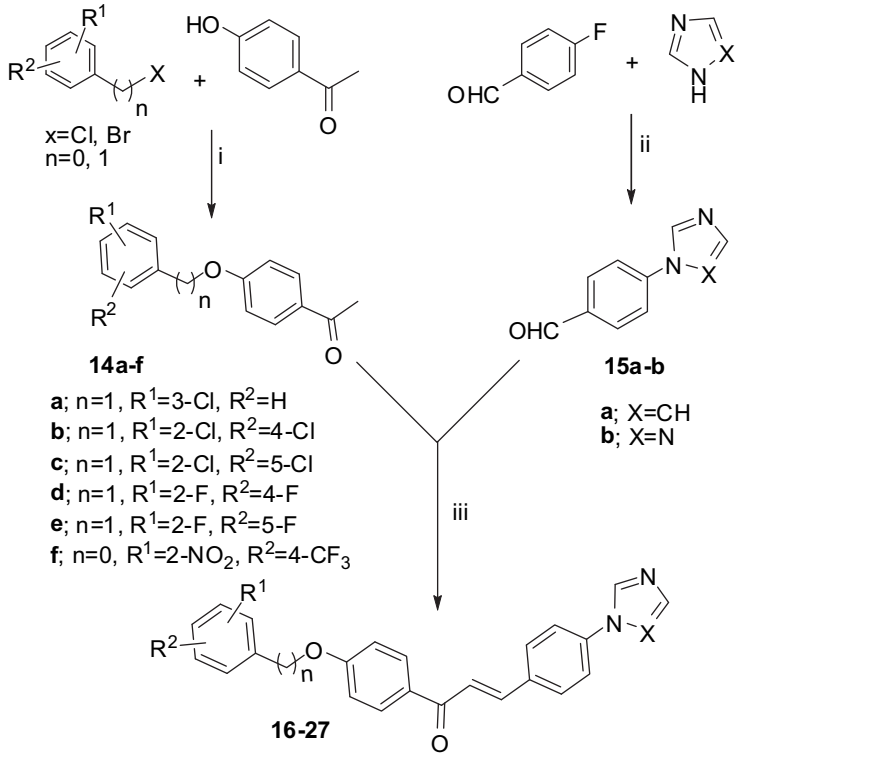
3. Biological activity

3.1. In vitro screening of compounds using virulent strain of M. tuberculosis

The 'proportion method' described by McClachy (1978) was adopted [18]. Test compounds were dissolved in dimethyl sulfoxide (DMSO) to make stocks and their working dilutions were also made in DMSO. To 1.9 mL MB 7H10 agar medium (containing OADC supplement), 0.1 mL of compound or DMSO (negative control) or isoniazid (positive control) was added, mixed and allowed to solidify as slants. Culture of *M. tuberculosis* H37Rv was harvested from Lowenstein–Jensen (L–J) medium and its suspension was made in normal saline containing 0.05% Tween-80. 10 μl of this suspension (~10^5 bacilli) was inoculated into each tube and incubated at 37 °C for 4 weeks. The lowest concentration of a compound which produced no visible bacterial growth was considered as its minimal inhibitory concentration (MIC). Compounds having MIC of ≤3.12 μg/mL were selected for further development.

3.2. Assays for in vitro cytotoxicity against VERO cells and mouse bone-marrow derived macrophages (MBMDMQs)

In vitro cytotoxicity of active compounds (having MIC ≤ 3.12 μg/mL) was measured using Vero cells and mouse bone-marrow derived macrophages [19]. The cell suspensions were plated in 96-well tissue culture plates (20,000 cells/well) and incubated overnight (37 °C, 5% CO_2) to allow their adherence. Test compounds at different concentrations were added to the wells. A known toxic compound was used as a positive control and DMSO was used as negative control. After 24 h incubation, 20 μl of MTS solution (tetrazolium compound) was added to each well and incubated for



16; X= CH, n=1, R^1=3-Cl, R^2=H
17; X= CH, n=1, R^1=2-Cl, R^2=4-Cl
18; X= CH, n=1, R^1=2-Cl, R^2=5-Cl
19; X= CH, n=1, R^1=2-F, R^2=4-F
20; X= CH, n=1, R^1=2-F, R^2=5-F
21; X= N, n=1, R^1=3-Cl, R^2=H
22; X= N, n=1, R^1=2-Cl, R^2=4-Cl
23; X= N, n=1, R^1=2-Cl, R^2=5-Cl
24; X= N, n=1, R^1=2-F, R^2=4-F
25; X= N, n=1, R^1=2-F, R^2=5-F
26; X= CH, n=0, R^1=2-NO_2, R^2=4-CF_3
27; X= N, n=0, R^1=2-NO_2, R^2=4-CF_3

Scheme 2. Reagents and conditions: (i) t-BuOK, DMSO, 5–6 h, 5°C-rt; (ii) dry K_2CO_3, DMF, 12–14 h, 110 °C; (iii) 10% NaOH-EtOH, 9–10 h, rt.

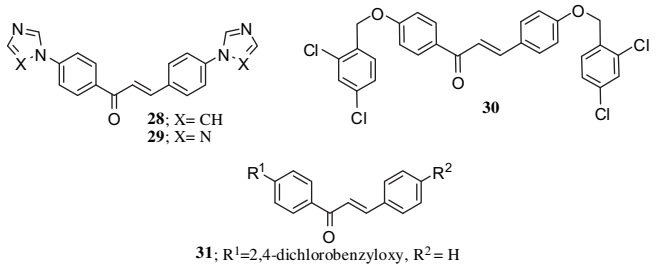


Fig. 2. Bis azolyl and bis benzyloxy chalcones.

further 2 h (37 °C, 5% CO_2). O. D. was read at 490 nm using a plate reader. A compound was considered as potentially toxic if its IC_{50} (concentration causing 50% loss in cell viability) was ≤10 times its MIC.

3.3. Use of ex-vivo (macrophage) model of TB

The macrophage model mimics growth environment of natural infection. Effect of selected test compounds (non-toxic, MIC ≤ 3.12 μg/mL) on the survival and multiplication of *M. tuberculosis* H37Rv within mouse bone-marrow derived macrophages was evaluated as per described protocol [20] (Tuberculosis Drug Screening Program, 2001). 5-day old cultures of adherent macrophages (10^6 cells/well) were infected (3 h) with 5 × 10^6 bacilli in 1 mL of antibiotic-free medium. Later, the wells were washed to remove extra-cellular bacteria and replenished with fresh antibiotic-free medium containing 4× MIC of standard drugs or test compounds. In order to determine the number of bacilli phagocytosed during the 3 h infection period, cells in one well were lysed with 0.1% saponin and the lysate plated on MB7H11 agar. Cells in other wells, after further 4 days of incubation, were washed, lysed and plated on MB7H11 agar. All CFUs were counted after 4 weeks of incubation at 37 °C. Results were expressed as percent reduction in intracellular CFU (100% = CFU of untreated, infected wells). An inhibition of ≥50% was considered as positive.

3.4. In vivo screening of compounds in mouse model of tuberculosis

When infected with a high number of *M. tuberculosis* by *i.v.* route, the mouse harbours a bacillary population that is similar in number and metabolic state to that present in the lung cavity of human TB [21,22]. Outbred Swiss mice were infected with *M. tuberculosis* H37Rv (10^7 CFU/mouse, *i.v.*) and divided into groups of 6–8 animals. Each experimental group received daily oral dose of test compound (100 mg/kg body weight, for 28 days) dissolved in a suitable vehicle (peanut oil). The drug-treated control groups received isoniazid (25 mg/kg) for 28 days. The untreated control group received only the vehicle. At least 3 mice from each group were sacrificed on day 30 for determination of viable bacilli in the lungs. Serial dilutions of lung homogenates were placed on MB7H11 agar medium and colonies (CFU) were counted after 3–4 weeks of incubation at 37 °C.

4. Results and discussion

All the synthesized compounds were tested for their ability to inhibit the growth of *M. tuberculosis* H37Rv by Agar-based proportion Assay (Table 1). Out of twenty seven compounds screened for their *in vitro* anti-tubercular activity against *M. tuberculosis* H37Rv, nineteen compounds were found active with MIC in the range of 12.5–0.78 μg/mL (Table 1) and the rest were with MIC >12.5 μg/mL. Subsequently, cytotoxicity evaluation of 10 compounds, showing anti-tubercular potential (MIC ≤ 3.12 μg/mL), was done against a mammalian cell line (VERO 1008) as well as mouse bone-marrow derived macrophages. Six compounds were considered non-toxic based on their selectivity index (SI ≥ 10, ratio of IC_{50} against mammalian cells and the MIC) and were evaluated ex-vivo to determine their potential to kill intracellular bacilli. On the basis of ex-vivo results (Table 1), two compounds were evaluated for their protective efficacy against tuberculosis infection in mouse model. Results revealed a marginal protective efficacy of compound **19** as it reduced 40% infection load in the lungs of infected mice with reference to untreated control (Table 2). The poor in-vivo activity of compounds **4** and **19** is perhaps attributable to one or more of the following reasons, (a) instability of the compound in gastrointestinal tract, (b) poor absorption from the intestine, (c) rapid biodegradation after absorption and (d) poor bioavailability.

The *in vitro* biological activities of azole-appended chalcones (**3**–**13**, **16**–**31**) have shown encouraging results. Table 1 displays the *in vitro*,cytotoxicity and *ex-vivo* activities of the synthesized compounds against *M. tuberculosis* H37Rv. Some of the compounds showed quite good *in vitro* anti-TB activity as indicated by their low MICs, i.e., 0.78 μg/mL (compound **7** and **21**), 1.56 μg/mL (compounds **17** and **19**), and 3.12 μg/mL (compounds **3**, **4**, **6**, **18**, **20** and **25**). Further, the chalcones **3**–**13**, with azolyl moiety in ring A and aryloxyl moiety in ring B showed the MIC of 0.78–12.5 μg/mL. Surprisingly, on interchanging the positions

Table 1
In vitro and ex-vivo anti-mycobacterial activities of targeted compounds against *M. tuberculosis* H37Rv.

S. no.	Comp.no.	[a]MIC(μg/mL) against *M.tb* H37Rv	[b]Cytotoxicity		[c]Intracellular killing within MBMDM (ex-vivo)
			Vs. VERO	Vs. MBMDM	
1	**3**	3.12	T	ND	ND
2	**4**	3.12	NT	NT	99%
3	**5**	12.50	ND	ND	ND
4	**6**	3.12	T	ND	ND
5	**7**	0.78	NT	NT	<50%
6	**8**	12.50	ND	ND	ND
7	**9**	25.00	ND	ND	ND
8	**10**	>25.00	ND	ND	ND
9	**11**	12.50	ND	ND	ND
10	**12**	>25.00	ND	ND	ND
11	**13**	12.50	ND	ND	ND
12	**16**	6.25	ND	ND	ND
13	**17**	1.56	NT	NT	<50%
14	**18**	3.12	T	ND	ND
15	**19**	1.56	NT	NT	71%
16	**20**	3.12	NT	NT	<50%
17	**21**	0.78	NT	NT	<50%
18	**22**	>25.00	ND	ND	ND
19	**23**	>25.00	ND	ND	ND
20	**24**	12.50	ND	ND	ND
21	**25**	3.12	T	ND	ND
22	**26**	12.50	ND	ND	ND
23	**27**	12.50	ND	ND	ND
24	**28**	>25.00	ND	ND	ND
25	**29**	>25.00	ND	ND	ND
26	**30**	>25.00	ND	ND	ND
27	**31**	12.50	ND	ND	ND
28	INH	0.025	NT	NT	

[a] MIC = Minimum inhibitory concentration, the lowest concentration of the compound which inhibits the growth of mycobacterium >90%; MIC of the drugs used as control (INH).
[b] Non-toxic (at a dose of 10× MIC) against VERO and MBMDMø; ND = not done.
[c] Intracellular (ex-vivo) activity of non-toxic compounds against *M. tuberculosis* in mouse bone-marrow derived macrophages at a concentration of 5× MIC; INH = Isoniazid, NT: non-toxic; T: Toxic (A compound is considered toxic if it causes 50% inhibition at concentration 10 fold higher than its MIC).

Table 2
Detailed *in vivo* efficacy of compounds **4**, **19** and isoniazid against *M. tuberculosis* H37Rv in mice.

Comp.	*In vitro* MIC (μg/mL)	*In vivo*					
		On day 30		On day 40		Viable bacilli (CFUs) in lungs (on day 30)	
		%Survivors	[b]MST	%Survivors	MST	[Per gm tissue]	% Inhibition
Control (no drug)		83	29.66	83	38.00	6.0×10^7	
[a]**4** (100 mg/kg)	3.12	100	30.00	83	38.50	5.2×10^7	13
[a]**19** (100 mg/kg)	1.56	100	30.00	100	40.00	3.6×10^7	40
INH (25 mg/kg)	0.025	100	30.00	100	40.00	1.0×10^4	99.98

[a] Non-toxic against mammalian cell line, VERO and mouse bone-marrow derived macrophages.
[b] MST, mean survival time.

of these two functionalities (**16**–**27**), a similar MIC pattern was observed. However, chalcones with 4-imidazolyl moiety (**3**–**7** and **16**–**20**) were found to be more active than their triazolyl counterparts (**8**–**12** and **21**–**25**) except compound **21** with 1,2,4-triazolyl group in ring B and a 3-chloro benzyloxy group in ring A showed a MIC value of 0.78 μg/mL. Replacement of the benzyloxy group with aryloxy group (2-NO_2, 4-CF_3-aryloxy) in compounds **13, 26** and **27** resulted in loss of activity with MIC values of 12.5 μg/mL indicating that the presence of benzyloxy group is essential for anti-tubercular activity. For SAR studies we also prepared and evaluated the bis azolyl chalcones (Fig. 2, **28** and **29**), however, the bis imidazolyl (**28**) and bis triazolyl (**29**) derivatives were found inactive with MIC values >25 μg/mL. We also explored the bis benzyloxy chalcone **30** and monobenzyloxy chalcone **31**. The activity in these compounds was also significantly dropped as both of them showed MIC ≥ 12.5 μg/mL only. These findings indicate that the occurrence of both the moieties, the benzyloxy group and the imidazolyl group together is necessary for the anti-tubercular activity.

Interestingly, irrespective of substitution in the benzyloxy moiety, compounds (**7** and **21**), (**17** and **19**) and (**3**, **4**, **6**, **18**, **20** and **25**) have shown equal potency with 0.78 μg/mL, 1.56 μg/mL and 3.12 μg/mL MICs respectively. Out of these ten compounds, four compounds viz. **3** (3-chlorobenzyloxy), **6** and **25** (2,5-difluorobenzyloxy), **18** (2,5-dichlorobenzyloxy) were found to be toxic in cytotoxicity assay against VERO cells and MBMDMQs. The six non-toxic compounds **4**, **7**, **17**, **19**, **20** and **21** showing potent *in vitro* activity were evaluated further for their intracellular (ex-vivo) effect on CFU in mouse bone-marrow derived macrophages. Among these, four of the chalcones **7**, **17**, **20** and **21** were found inactive as they reduced <50% of CFU count (Table 1). Compound **4**, with an imidazolyl moiety in ring A and a 2,4-dichlorobenzyloxy moiety in ring B was the most active compound as it led to an inhibition of 99% growth of intracellular bacilli, while compound **19** (imidazolyl moiety in ring B and a 2,4-difluorobenzyloxy moiety in ring A) displayed 71% inhibition. The two promising compounds **4** and **19** were further evaluated for their *in vivo* oral efficacy against *M. tuberculosis* H37Rv in mice and the results are shown in Table 2. Among these, compound **19** exhibited moderate activity with a marginal protection of 40% against virulent *M. tuberculosis*. It is apparent from the activity results (Table 1) that the presence of both the substructures benzyloxy as well as azolyl in A and B rings of chalcone molecule is crucial for the anti-tubercular activity. Further, the benzyloxy moiety with a 2,4-difluoro- and 2,4-dichloro- substituent should be investigated for the development of highly selective anti-tubercular compounds.

5. Conclusion

In conclusion, we have identified a new cheap chalcone molecular scaffold that can be easily prepared from commercially available reagents. The compounds were evaluated against *M. tuberculosis* H37Rv *in vitro* with impressive MIC values. Most of the compounds with potent *in vitro* activities were found non-toxic against VERO cell line and mouse derived macrophages. Two compounds **4** and **19** showed good ex-vivo activity with 99% and 71% inhibition of growth of intracellular bacilli. Thus the newly designed aryloxy azolyl chalcone derivatives represent a highly potent and versatile series of anti-TB compounds and as such present attractive lead compounds for further TB drug development. Further studies on these compounds and optimization of its structure leading to novel analogues with superior biological properties are ongoing in our laboratory.

6. Experimental

All reagents were commercial and were used without further purification. Chromatography was carried on silica gel (60–120 mesh) or basic alumina (pH = 9.5 ± 5, 100 mesh). All reactions were monitored by TLC (silica gel plates with fluorescence F_{254} were used). Melting points were recorded on an electrically heated melting point apparatus and are uncorrected. The ^{1}H NMR and ^{13}C NMR spectra were determined on Bruker Advance DRX-300 MHz spectrometer using TMS as an internal reference. All shifts are given in ppm and multiplicity (s = singlet, d = doublet, m = multiplet). The electrospray mass spectra were recorded on a Thermo Finnigan LCQ Advantage max ion trap mass spectrometer. IR spectra were recorded on Perkin Elmer AC-1 spectrophotometer in the range of 400–4000 cm^{-1}.

6.1. General procedure for the synthesis of compounds (*1a–b* and *15a–b*)

A mixture of 4-fluoro acetophenone/4-fluorobenzaldehyde (10 mmol) and imidazole/triazole (10 mmol) were dissolved in dry DMF (20 mL). K_2CO_3 (12 mmol) was added in small portion within a period of 15 min to the above stirred solution. Mixture was stirred for 10–12 h at 110 °C. Heating discontinued, K_2CO_3 was filtered off, filtrate extracted with ethyl acetate (3 × 15 mL). Organic layer was washed with water (3 × 15 mL), dried over anhydrous sodium sulphate and concentrated to given an oil which was purified on silica gel column (60–120 mesh) taking methanol: chloroform (1:99) as an eluent.

6.1.1. 1-(4-(1H-imiazol-1-yl)phenyl)ethanone (*1a*)

With 4-fluoro acetophenone and 1*H*-imidazole; Yield: 78%; M.P: 112–114 °C; MS(ESI): 187 $[M + 1]^+$; IR (KBr): 3117, 2366, 2213, 1668, 1604, 1523, 1266, 1058, 953, 738 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.64 (s, 3H), 7.25 (s, 1H), 7.35 (s, 1H), 7.53 (d, 2H, J = 8.6 Hz), 7.96 (s, 1H), 8.09 (d, 2H, J = 8.6 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz,): δ 26.6, 117.7, 120.6, 130.3, 131.1, 135.3, 135.7, 140.7, 196.5.

*6.1.2. 1-(4-(1H-1,2,4-triazol-1-yl)phenyl)ethanone (**1b**)*

With 4-fluoro acetophenone and 1*H*-1,2,4-triazole; Yield: 74%; M.P: 142–143 °C; MS(ESI): 188 $[M + 1]^+$; IR (KBr): 3117, 2356, 1677, 1607, 1215, 759 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 2.62 (s, 3H), 7.81–7.84 (d, 2H, $J = 8.5$ Hz), 8.09–8.12 (d, 2H, $J = 8.5$ Hz), 8.13 (s, 1H, *triazole H*), 8.70 (s, 1H, *triazole H*); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 26.4, 118.7, 121.8, 131.6, 133.3, 142.4, 152.9, 196.3.

*6.1.3. 4-(1H-imidazol-1-yl)benzaldehyde (**15a**)*

With 4-fluoro benzaldehyde and 1*H*-imidazole; Yield: 76%; M.P: 147–148 °C; MS(ESI): 173 $[M + 1]^+$; IR (KBr): 3125, 2360, 1697, 1603, 1480, 1260, 1219, 771 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 7.25 (s, 1H, *imidazole H*), 7.39 (s, 1H, *imidazole H*), 7.59 (d, 2H, $J = 12.2$ Hz), 8.00–8.05 (m, 3H, *ArH + imidazole H*), 10.04 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 118.2, 121.7, 131.6, 140.1, 135.6, 135.9, 142.3, 191.2.

*6.1.4. 4-(1H-1,2,4-triazol-1-yl)benzaldehyde (**15b**)*

With 4-fluoro benzaldehyde and 1*H*-1,2,4-triazole; Yield: 72%; M.P: 146–147 °C; MS(ESI): 174 $[M + 1]^+$; IR (KBr): 3123, 2363, 1704, 1600, 1517, 1438, 1204, 830 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 7.92 (d, 2H, $J = 8.5$ Hz), 8.05 (d, 2H, $J = 8.5$ Hz), 8.16 (s, 1H, *triazole H*), 8.71 (s, 1H, *triazole H*), 10.08 (s, 1H, *CHO*); ^{13}C NMR ($CDCl_3 + CD_3OD$, 75 MHz): δ 119.8, 131.3, 135.4, 140.8, 141.4, 152.5, 191.0.

*6.2. General procedure for the synthesis of compounds **2a–f** and **14a–f***

To a stirred suspension of 4-hydroxy benzaldehyde/4-hydroxy acetophenone (1 mmol) in dimethyl sulfoxide (DMSO) (5 mL) at 5–10 °C was added potassium *t*-butoxide (1.2 mmol) was added in small portions in the period of 10 min. After stirring of 30 min, substituted benzyl/aryl halide (1 mmol) was added and then stirring was continued at room temperature for 4–5 h. The reaction mixture was quenched with ice cold water (5 mL) and extracted with ethyl acetate (3 × 5 mL), the combined organic layers were washed with water (3 × 5 mL) dried over Na_2SO_4 and concentrated under reduced pressure to obtain the crude product which was purified by column chromatography by using silica gel (60–120 mesh) and ethyl acetate: Hexane (4:94) as eluent to give the compounds (**2a-f** and **14a-f**).

*6.2.1. 4-(3-Chlorobenzyloxy)benzaldehyde (**2a**)*

With 4-hydroxy benzaldehyde and 3-chloro benzyl chloride; Yield: 79%; M.P: 89–91 °C; MS(ESI): 247 $[M + 1]^+$; IR (KBr): 3052, 2821, 2365, 1690, 1599, 1509, 1265, 1090, 827 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 5.11 (s, 2H), 7.06 (d, 2H, $J = 8.7$ Hz), 7.31–7.34 (m, 3H), 7.43 (s, 1H), 7.82–7.86 (m, 2H), 9.88 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 69.3, 115.1, 125.3, 127.4, 128.4, 130.0, 130.3, 132.0, 134.6, 138.0, 163.3, 190.6.

*6.2.2. 4-(2,4-Dichlorobenzyloxy)benzaldehyde (**2b**)*

With 4-hydroxy benzaldehyde and 2,4-dichlorobenzyl chloride; Yield: 82%; M.P: 93–95 °C; MS(ESI): 281 $[M + 1]^+$; IR (KBr): 3072, 2824, 2357, 1669, 1595, 1254, 1031, 772 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 5.19 (s, 2H), 7.07 (d, 2H, $J = 8.6$ Hz), 7.26–7.30 (m, 1H), 7.42–7.48 (m, 2H), 7.85 (d, 2H, $J = 8.6$ Hz), 9.89 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 67.1, 115.5, 128.1, 129.6, 130.5, 130.7, 131.5, 131.9, 132.9, 136.2, 163.8, 190.1.

*6.2.3. 4-(2,5-Dichlorobenzyloxy)benzaldehyde (**2c**)*

With 4-hydroxy benzaldehyde and 2,5-dichlorobenzyl bromide; Yield: 84%; M.P: 91–93 °C; MS(ESI): 281 $[M + 1]^+$; IR (KBr): 3074, 2826, 2367, 1689, 1604, 1508, 1255, 1035, 863, 817 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 5.20 (s, 2H), 7.10 (d, 2H, $J = 8.7$ Hz), 7.24–7.28 (m, 1H), 7.35 (d, 1H, $J = 8.5$ Hz), 7.54–7.55 (m, 1H), 7.87 (d, 2H, $J = 8.7$ Hz), 9.90 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 66.7, 115.1, 128.5, 129.3, 130.5, 130.6, 131.1, 132.0, 133.2, 135.5, 163.0, 190.7.

*6.2.4. 4-(2,4-Difluorobenzyloxy)benzaldehyde (**2d**)*

With 4-hydroxy benzaldehyde and 2,4-difluorobenzyl bromide; Yield: 73%; M.P: 76–77 °C; MS(ESI): 249 $[M + 1]^+$; IR (KBr): 3036, 2832, 2371, 1674, 1602, 1496, 1215, 1012, 852, 776 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 5.15 (s, 2H), 6.83–6.95 (m, 2H), 7.08 (d, 2H, $J = 8.7$ Hz), 7.43–7.50 (m, 1H), 7.85 (d, 2H, $J = 8.7$ Hz), 9.89 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 63.7, 115.3, 115.4, 116.1, 116.3, 117.3, 130.7, 132.3, 156.9, 161.2, 163.2, 190.1.

*6.2.5. 4-(2,5-Difluorobenzyloxy)benzaldehyde (**2e**)*

With 4-hydroxy benzaldehyde and 2,5-difluorobenzyl bromide; Yield: 71%; M.P: 79–80 °C; MS(ESI): 249 $[M + 1]^+$; IR (KBr): 3084, 2856, 2366, 1690, 1602, 1493, 1258, 1038, 816, 721 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 5.19 (s, 2H), 7.00–7.08 (m, 2H), 7.09 (d, 2H, $J = 8.7$ Hz), 7.19–7.25 (m, 1H), 7.86 (d, 2H, $J = 8.7$ Hz), 9.90 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 63.4, 115.0, 115.6, 115.9, 116.3, 116.7, 130.5, 132.0, 157.6, 160.4, 163.0, 190.6.

*6.2.6. 4-(2-Nitro-4-(trifluoromethyl)phenoxy)benzaldehyde (**2f**)*

With 4-hydroxy benzaldehyde and 1-chloro-2-nitro-4-(trifluoromethyl)benzene; Yield: 77%; M.P: 82–83 °C; MS(ESI): 312 $[M + 1]^+$; IR (KBr): 3051, 2856, 2365, 1697, 1626, 1590, 1531, 1353, 1252, 1136, 1049, 902, 850 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 7.12 (d, 1H, $J = 9.1$ Hz), 7.27 (d, 2H, $J = 8.6$ Hz), 8.00 (d, 2H, $J = 8.6$ Hz), 8.37–8.41 (m, 1H), 8.61 (d, 1H, $J = 2.6$ Hz), 10.02 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 119.4, 120.2, 121.7, 122.2, 123.9, 128.9, 132.2, 133.7, 142.7, 159.2, 159.3, 190.4.

*6.2.7. 1-(4-(3-Chlorobenzyloxy)phenyl)ethanone (**14a**)*

With 4-hydroxy acetophenone and 3-chlorobenzyl chloride; Yield: 73%; M.P: 91–93 °C; MS(ESI): 261 $[M + 1]^+$; IR (KBr): 3315, 3050, 2365, 1662, 1601, 1505, 1275, 1109, 1004, 785 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 2.54 (s, 3H), 5.08 (s, 2H), 6.98 (d, 2H, $J = 8.8$ Hz), 7.30–7.42 (m, 4H), 7.92 (d, 2H, $J = 8.8$ Hz); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 26.3, 69.1, 114.5, 125.3, 127.3, 128.3, 129.9, 130.6, 130.7, 134.5, 138.3, 162.2, 196.6.

*6.2.8. 1-(4-(2,4-Dichlorobenzyloxy)phenyl)ethanone (**14b**)*

With 4-hydroxy acetophenone and 2,4-dichlorobenzyl chloride; Yield: 82%; M.P: 95–97 °C; MS(ESI): 295 $[M + 1]^+$; IR (KBr): 3330, 3095, 2918, 1671, 1597, 1258, 1032, 834 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 2.56 (s, 3H), 5.18 (s, 2H), 7.00 (d, 2H, $J = 8.9$ Hz), 7.26–7.30 (m, 1H), 7.43–7.48 (m, 2H), 7.95 (d, 2H, $J = 8.9$ Hz); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 26.4, 66.3, 114.4, 127.4, 129.3, 129.6, 130.6, 130.7, 132.6, 133.2, 134.4, 162.0, 196.8.

*6.2.9. 1-(4-(2,5-Dichlorobenzyloxy)phenyl)ethanone (**14c**)*

With 4-hydroxy acetophenone and 2,4-dichlorobenzyl bromide; Yield: 86%; M.P: 91–93 °C; MS(ESI): 295 $[M + 1]^+$; IR (KBr): 3097, 2917, 2362, 1669, 1600, 1564, 1257, 1032, 833 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 2.55 (s, 3H), 5.16 (s, 2H), 7.01 (d, 2H, $J = 12.4$ Hz), 7.22–7.35 (m, 2H), 7.54 (s, 1H), 7.95 (d, 2H, $J = 12.4$ Hz); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 26.7, 67.0, 115.2, 127.8, 128.8, 129.5, 130.9, 131.1, 131.4, 133.5, 136.1, 162.3, 197.0.

*6.2.10. 1-(4-(2,4-Difluorobenzyloxy)phenyl)ethanone (**14d**)*

With 4-hydroxy acetophenone and 2,4-difluorobenzyl bromide; Yield: 68%; M.P: 85–87 °C; MS(ESI): 263 $[M + 1]^+$; IR (KBr): 3078, 2923, 2366, 1677, 1603, 1508, 1261, 960, 837 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 2.58 (s, 3H), 5.16 (s, 2H), 6.85–6.90 (m, 1H), 6.91–6.97 (m, 1H), 7.02 (d, 2H, $J = 8.9$ Hz), 7.44–7.52 (m, 1H) 7.97 (d, 2H, $J = 8.9$ Hz); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 26.3, 67.2, 115.2, 126.9, 129.3, 129.8, 130.1, 131.3, 133.1, 159.2, 159.6, 162.3, 198.2.

*6.2.11. 1-(4-(2,5-Difluorobenzyloxy)phenyl)ethanone (**14e**)*

With 4-hydroxy acetophenone and 2,5-difluorobenzyl bromide; Yield: 71%; M.P: 83–85 °C; MS(ESI): 263 $[M + 1]^+$; IR (KBr): 3010, 2928, 1684, 1506, 1210, 896, 787 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 2.56 (s, 3H), 5.16 (s, 2H), 7.01 (d, 2H, $J = 8.9$ Hz), 7.05–7.10 (m, 2H), 7.18–7.26 (m, 1H), 7.95 (d, 2H, $J = 8.9$ Hz); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 26.6, 67.5, 115.3, 125.7, 128.8, 129.4, 130.2, 131.6, 132.9, 158.8, 159.7, 162.4, 198.5.

*6.2.12. 1-(2′-nitro-4′-(trifluoromethyl)biphenyl-4-yl)ethanone (**14f**)*

With 4-hydroxy acetophenone and 1-chloro-2-nitro-4-(trifluoromethyl)benzene; Yield: 73%; M.P: 72–73 °C; MS(ESI): 326 $[M + 1]^+$; IR (KBr): 3123, 3064, 2928, 2364, 1687, 1590, 1525, 1484, 1340, 1251, 1047, 858, 739 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 2.62 (s, 3H), 7.02 (d, 1H, $J = 9.1$ Hz), 7.17 (d, 2H, $J = 8.5$ Hz), 8.06 (d, 2H, $J = 8.5$ Hz), 8.33–8.37 (m, 1H), 8.62 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 26.5, 118.5, 119.4, 121.6, 122.0, 123.9, 128.8, 131.0, 134.6, 142.6, 158.2, 159.6, 196.4.

*6.3. General procedure for the synthesis of chalcones (**3**–**13** and **16**–**31**)*

A mixture of azolyl ketone (**1a**/**1b**) (1 mmol) and aryloxy benzaldehyde (**2a**–**f**) (1 mmol) were dissolved in 10% NaOH-EtOH (5 mL), it was stirred at room temperature for 9–10 h. After completion, 5 mL water was added to the reaction mixture. The separated solid compound was filtered and washed with water. It was purified by crystallization with methanol/chloroform or basic alumina column chromatography to give the desired compounds (**3**–**13**).

The compounds (**16**–**31**) were prepared by the reaction of their corresponding aldehyde and ketone partners.

*6.3.1. (E)-1-(4-(1H-imidazol-1-yl)phenyl)-3-(4-(3-chlorobenzyloxy) phenyl)prop-2-en-1-one (**3**)*

With **1a** and **2a**; Yield: 63%; M.P: 178–179 °C; MS (ESI): 415 (100) $[M + 1]^+$; IR (KBr): 3393, 2362, 1669, 1597, 1487, 1231, 1021, 786; ^1H NMR ($CDCl_3$, 300 MHz): δ 5.09 (s, 2H), 7.00 (d, 2H, $J = 8.6$ Hz), 7.25–7.31 (m, 4H), 7.36–7.44 (m, 3H), 7.52 (d, 2H, $J = 8.5$ Hz), 7.62 (d, 2H, $J = 8.6$ Hz), 7.82 (d, 1H, $J = 15.7$ Hz), 7.96 (s, 1H), 8.14 (d, 2H, $J = 8.5$ Hz); ^{13}C NMR ($CDCl_3$, 75 MHz): 61.9, 115.2, 117.8, 119.1, 120.7, 125.2, 127.2, 127.6, 128.1, 129.8, 130.22, 130.29, 130.3, 134.4, 135.2, 137.1, 138.2, 140.0, 145.3, 160.6, 189.1; Anal. Calcd. for $C_{25}H_{19}ClN_2O_2$: C, 72.37; H, 4.62; N, 6.75. Found C, 72.28; H, 4.58; N, 6.69.

*6.3.2. (E)-1-(4-(1H-imidazol-1-yl)phenyl)-3-(4-(2,4-dichlorobenzyloxy)phenyl)prop-2-en-1-one (**4**)*

With **1a** and **2b**; Yield: 73%; M.P: 168–170 °C; MS(ESI): 449 $[M + 1]^+$; IR (KBr): 3462, 3095, 2368, 1665, 1600, 1518, 1236, 1030, 820 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 5.18 (s, 2H), 7.02 (d, 2H, $J = 8.6$ Hz), 7.26–7.30 (m, 3H), 7.38 (d, 1H, $J = 7.4$ Hz), 7.46 (d, 2H, $J = 7.7$ Hz), 7.50–7.54 (m, 2H), 7.63 (d, 2H, $J = 8.6$ Hz), 7.83 (d, 1H, $J = 15.5$ Hz), 7.96 (s, 1H), 8.14 (d, 2H, $J = 8.5$ Hz); ^{13}C NMR ($CDCl_3$, 75 MHz): 66.7, 115.3, 117.7, 119.3, 120.7, 127.4, 128.0, 129.3, 129.6, 130.41, 130.45, 130.9, 132.7, 133.2, 134.4, 135.4, 137.1, 140.3, 145.1, 160.4, 188.7; Anal. Calcd. for $C_{25}H_{18}Cl_2N_2O_2$: C, 66.83; H, 4.04; N, 6.23; Found C, 66.92; H, 4.11; N, 6.18.

*6.3.3. (E)-1-(4-(1H-imidazol-1-yl)phenyl)-3-(4-(2,5-dichlorobenzyloxy)phenyl)prop-2-en-1-one (**5**)*

With **1a** and **2c**; Yield: 76%; M.P: 171–172 °C; MS(ESI): 449 $[M + 1]^+$; IR (KBr): 3119, 2361, 1651, 1604, 1512, 1153, 1012, 798 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz): δ 5.24 (s, 2H), 7.11–7.16 (m, 3H), 7.46–7.50 (m, 1H), 7.57 (d, 1H, $J = 8.5$ Hz), 7.69 (d, 1H, $J = 2.5$ Hz), 7.75 (d, 1H, $J = 15.4$ Hz), 7.86–7.92 (m, 6H), 8.27–8.33 (m, 2H), 8.45 (s, 1H); Anal. Calcd. for $C_{25}H_{18}Cl_2N_2O_2$: C, 66.83; H, 4.04; N, 6.23; Found C, 66.91; H, 3.92; N, 6.29.

*6.3.4. (E)-1-(4-(1H-imidazol-1-yl)phenyl)-3-(4-(2,4-difluorobenzyloxy)phenyl)prop-2-en-1-one (**6**)*

With **1a** and **2d**; Yield: 68%; M.P: 168–169 °C; MS(ESI): 417 $[M + 1]^+$; IR (KBr): 3428, 3128, 2364, 1659, 1604, 1518, 1252, 1030, 815 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz): δ 5.19 (s, 2H), 7.11–7.16 (m, 4H), 7.27–7.35 (m, 1H), 7.61–7.69 (m, 1H), 7.75 (d, 1H, $J = 15.4$ Hz), 7.86–7.92 (m, 6H), 8.29 (d, 2H, $J = 8.7$ Hz), 8.46 (s, 1H); Anal. Calcd. for $C_{25}H_{18}F_2N_2O_2$: C, 72.11; H, 4.36; N, 6.73; Found C, 72.17; H, 4.43; N, 6.68.

*6.3.5. (E)-1-(4-(1H-imidazol-1-yl)phenyl)-3-(4-(2,5-difluorobenzyloxy)phenyl)prop-2-en-1-one (**7**)*

With **1a** and **2e**; Yield: 66%; M.P: 187–188 °C; MS(ESI): 417 $[M + 1]^+$; IR (KBr): 3468, 3129, 2359, 1653, 1596, 1513, 1223, 1032, 817 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz): δ 5.17 (s, 2H), 7.02–7.11 (m, 4H), 7.22–7.24 (m, 2H), 7.43 (d, 1H, $J = 15.5$ Hz), 7.56–7.58 (m, 1H), 7.65 (d, 2H, $J = 8.6$ Hz), 7.82 (d, 1H, $J = 15.5$ Hz), 7.84–7.91 (m, 2H), 8.15–8.17 (m, 2H), 8.39 (s, 1H); Anal. Calcd. for $C_{25}H_{18}F_2N_2O_2$: C, 72.11; H, 4.36; N, 6.73; Found C, 72.14; H, 4.31; N, 6.76.

*6.3.6. E)-1-(4-(1H-1,2,4-triazol-1-yl)phenyl)-3-(4-(3-chlorobenzyloxy)phenyl)prop-2-en-1-one (**8**)*

With **1b** and **2a**; Yield: 74%; M.P: 197–198 °C; MS(ESI): 416 $[M + 1]^+$; IR (KBr): 3431, 3125, 2924, 2364, 1658, 1600, 1512, 1252, 1026, 812 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz): δ 5.21 (s, 2H), 7.11 (d, 2H, $J = 8.5$ Hz), 7.39–7.44 (m, 3H), 7.53 (s, 1H), 7.74 (d, 1H, $J = 15.5$ Hz), 7.84–7.89 (m, 3H), 8.07 (d, 2H, $J = 8.8$ Hz), 8.31–8.34 (m, 3H), 9.49 (s, 1H); Anal. Calcd. for $C_{24}H_{18}ClN_3O_2$: C, 69.31; H, 4.36; N, 10.10; Found C, 69.38; H, 4.41; N, 10.06.

*6.3.7. (E)-1-(4-(1H-1,2,4-triazol-1-yl)phenyl)-3-(4-(2,4-dichlorobenzyloxy)phenyl)prop-2-en-1-one (**9**)*

With **1b** and **2b**; Yield: 67%; M.P: 183–185 °C; MS(ESI): 450 $[M + 1]^+$; IR (KBr): 3429, 2964, 2329, 1657, 1608, 1512, 1222, 1026, 814 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz): δ 5.23 (s, 2H), 7.13 (d, 2H, $J = 8.7$ Hz), 7.47–7.51 (m, 1H), 7.64 (d, 1H, $J = 8.2$ Hz), 7.70 (d, 1H, $J = 2.0$ Hz), 7.76 (d, 1H, $J = 15.5$ Hz), 7.88 (d, 1H, $J = 15.5$ Hz), 7.90 (d, 2H, $J = 8.8$ Hz), 8.07 (d, 2H, $J = 8.8$ Hz), 8.31 (s, 1H), 8.34 (d, 2H, $J = 8.8$ Hz), 9.47 (s, 1H); Anal. Calcd. for $C_{24}H_{17}Cl_2N_3O_2$: C, 64.01; H, 3.81; N, 9.33; Found C, 64.11; H, 3.86; N, 9.35.

*6.3.8. (E)-1-(4-(1H-1,2,4-triazol-1-yl)phenyl)-3-(4-(2,5-dichlorobenzyloxy)phenyl)prop-2-en-1-one (**10**)*

With **1b** and **2c**; Yield: 71%; M.P: 201–203 °C; MS(ESI): 450 $[M + 1]^+$; IR (KBr): 3451, 3297, 2925, 2367, 1657, 1600, 1513, 1258, 1021, 816 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz): δ 5.24 (s, 2H), 7.15 (d, 2H, $J = 8.6$ Hz), 7.47–7.50 (m, 1H), 7.57 (d, 1H, $J = 8.5$ Hz), 7.70 (d, 1H, $J = 2.2$ Hz), 7.76 (d, 1H, $J = 15.5$ Hz), 7.86–7.92 (m, 3H), 8.07 (d, 2H, $J = 8.6$ Hz), 8.31 (s, 1H), 8.34 (d, 2H, $J = 8.6$ Hz), 9.48 (s, 1H); Anal. Calcd. for $C_{24}H_{17}Cl_2N_3O_2$: C, 64.01; H, 3.81; N, 9.33; Found C, 64.07; H, 3.78; N, 9.29.

*6.3.9. (E)-1-(4-(1H-1,2,4-triazol-1-yl)phenyl)-3-(4-(2,4-difluorobenzyloxy)phenyl)prop-2-en-1-one (**11**)*

With **1b** and **2d**; Yield: 86%; M.P: 199–200 °C; MS(ESI): 418 $[M + 1]^+$; IR (KBr): 3466, 3126, 2923, 2367, 1658, 1601, 1512, 1257, 1215, 1034, 970, 815, 670 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz): δ 5.20 (s, 2H), 7.13 (d, 2H, $J = 8.7$ Hz), 7.17 (d, 1H, $J = 2.4$ Hz), 7.28–7.35 (m, 1H), 7.65 (d, 1H, $J = 6.7$ Hz), 7.76 (d, 1H, $J = 15.5$ Hz), 7.86–7.91 (m, 3H), 8.07 (d, 2H, $J = 8.7$ Hz), 8.31 (s, 1H), 8.34 (d, 2H,

J = 8.7 Hz), 9.48 (s, 1H); Anal. Calcd. for $C_{24}H_{17}F_2N_3O_2$: C, 69.06; H, 4.11; N, 10.07; Found C, 68.97; H, 4.06; N, 9.98.

*6.3.10. (E)-1-(4-(1H-1,2,4-triazol-1-yl)phenyl)-3-(4-(2,5-difluorobenzyloxy)phenyl)prop-2-en-1-one (**12**)*

With **1b** and **2e**; Yield: 61%; M.P: 207–208 °C; MS(ESI): 418 $[M + 1]^+$; IR (KBr): 3467, 3129, 2366, 1654, 1600, 1257, 1034, 815 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz): δ 5.22 (s, 2H), 7.15 (d, 2H, J = 8.6 Hz), 7.27–7.37 (m, 2H), 7.45 (s, 1H), 7.76 (d, 1H, J = 16.0 Hz), 7.87 (d, 2H, J = 8.3 Hz), 7.97 (d, 1H, J = 16.0 Hz), 8.07 (d, 2H, J = 8.5 Hz), 8.31 (s, 1H), 8.34 (d, 2H, J = 8.6 Hz), 9.47 (s, 1H); Anal. Calcd. for $C_{24}H_{17}F_2N_3O_2$: C, 69.06; H, 4.11; N, 10.07; Found C, 69.13; H, 4.17; N, 10.02.

*6.3.11. (E)-1-(4-(1H-imidazol-1-yl)phenyl)-3-(4-(2-nitro-4-(trifluoromethyl)phenoxy)phenyl)prop-2-en-1-one (**13**)*

With **1a** and **2f**; Yield: 59%; M.P: 158–160 °C; MS(ESI): 480 $[M + 1]^+$; IR (KBr): 3433, 3155, 2326, 1657, 1607, 1266, 1031, 842 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 7.03 (d, 2H, J = 9.1 Hz), 7.18 (d, 2H, J = 8.6 Hz), 7.38 (s, 1H), 7.50–7.57 (m, 3H), 7.76 (d, 2H, J = 8.6 Hz), 7.86 (d, 1H, J = 15.6 Hz), 7.98 (s, 1H), 8.17 (d, 2H, J = 8.6 Hz), 8.32–8.36 (m, 1H), 8.61–8.62 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): 114.0, 117.9, 120.2, 120.8, 121.2, 121.8, 123.8, 123.92, 123.99, 128.8, 130.5, 130.7, 131.1, 132.5, 136.6, 140.6, 142.3, 143.6, 156.1, 160.0, 188.4; Anal. Calcd. for $C_{25}H_{16}F_3N_3O_4$: C, 62.63; H, 3.36; N, 8.77; Found C, 62.82; H, 3.42; N, 8.71.

*6.3.12. (E)-3-(4-(1H-imidazol-1-yl)phenyl)-1-(4-(3-chlorobenzyloxy) phenyl)prop-2-en-1-one (**16**)*

With **14a** and **15a**; Yield: 62%; M.P: 136–137 °C; MS(ESI): 415 $[M + 1]^+$; IR (KBr): 3457, 3128, 2363, 1655, 1601, 1523, 1228, 1015, 821 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 5.13 (s, 2H), 7.06 (d, 2H, J = 8.8 Hz), 7.24 (s, 1H), 7.29–7.33 (m, 4H), 7.43–7.46 (m, 3H), 7.57 (d, 1H, J = 15.6 Hz), 7.75 (d, 2H, J = 8.5 Hz), 7.81 (d, 1H, J = 15.6 Hz), 7.92 (s, 1H), 8.05 (d, 2H, J = 8.8 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz): 69.3, 114.7, 117.8, 119.7, 121.4, 122.5, 125.3, 127.4, 128.3, 129.8, 129.9, 130.8, 131.3, 134.2, 134.6, 135.3, 138.2, 138.4, 142.2, 162.3, 188.2; Anal. Calcd. for $C_{25}H_{19}ClN_2O_2$: C, 72.37; H, 4.62; N, 6.75; Found C, 72.42; H, 4.59; N, 6.73.

*6.3.13. (E)-3-(4-(1H-imidazol-1-yl)phenyl)-1-(4-(2,4-dichlorobenzyloxy)phenyl)prop-2-en-1-one (**17**)*

With **14b** and **15a**; Yield: 78%; M.P: 171–173 °C; MS(ESI): 449 $[M + 1]^+$; IR (KBr): 3468, 3136, 2369, 1653, 1600, 1521, 1238, 1031, 820 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz): δ 5.28 (s, 2H), 7.13 (s, IH), 7.20 (d, 2H, J = 8.9 Hz), 7.48–7.52 (m, 1H), 7.66 (d, 1H, J = 8.3 Hz), 7.72 (d, 1H, J = 2.1 Hz), 7.76 (d, 2H, J = 6.1 Hz), 7.78 (s, 1H), 7.85–7.86 (m, 1H), 8.00 (d, 1H, J = 16.8 Hz,), 8.04 (d, 2H, J = 8.8 Hz), 8.20 (d, 2H, J = 8.9 Hz), 8.39 (s, 1H); Anal. Calcd. for $C_{25}H_{18}Cl_2N_2O_2$: C, 66.83; H, 4.04; N, 6.23; Found C, 66.85; H, 4.09; N, 6.16.

*6.3.14. (E)-3-(4-(1H-imidazol-1-yl)phenyl)-1-(4-(2,5-dichlorobenzyloxy)phenyl)prop-2-en-1-one (**18**)*

With **14c** and **15a**; Yield: 76%; M.P: 188–189 °C; MS(ESI): 449 $[M + 1]^+$; IR (KBr): 3468, 3136, 2369, 1653, 1600, 1521, 1238, 1031, 820 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz): δ 5.28 (s, 2H), 7.14 (s, IH), 7.22 (d, 2H, J = 8.5 Hz), 7.51–7.56 (m, 3H), 7.72–7.79 (m, 3H), 7.83 (d, 1H, J = 15.4 Hz), 7.98–8.06 (m, 3H), 8.22 (d, 2H, J = 7.9 Hz), 8.40 (s, 1H); Anal. Calcd. for $C_{25}H_{18}Cl_2N_2O_2$: C, 66.83; H, 4.04; N, 6.23. Found C, 66.91; H, 4.07; N, 6.25.

*6.3.15. (E)-3-(4-(1H-imidazol-1-yl)phenyl)-1-(4-(2,4-difluorobenzyloxy)phenyl)prop-2-en-1-one (**19**)*

With **14d** and **15a**; Yield: 63%; M.P: 143–145 °C; MS(ESI): 417 $[M + 1]^+$; IR (KBr): 3451, 3095, 2366, 1657, 1600, 1258, 1019, 819 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz): δ 5.25 (s, 2H), 7.13–7.14 (m, 2H), 7.20 (d, 2H, J = 8.9 Hz), 7.29–7.36 (m, 1H), 7.62–7.67 (m, 1H), 7.72–7.78 (m, 3H), 7.85–7.86 (m, 1H), 8.00 (d, 1H, J = 15.7 Hz), 8.04 (d, 2H, J = 8.8 Hz), 8.20 (d, 2H, J = 8.9 Hz), 8.39 (s, 1H); Anal. Calcd. for $C_{25}H_{18}F_2N_2O_2$. C, 72.11; H, 4.36; N, 6.73; Found C, 72.15; H, 4.39; N, 6.77.

*6.3.16. (E)-3-(4-(1H-imidazol-1-yl)phenyl)-1-(4-(2,5-difluorobenzyloxy)phenyl)prop-2-en-1-one (**20**)*

With **14e** and **15a**; Yield: 74%; M.P: 149–151 °C; MS(ESI): 417 $[M + 1]^+$; IR (KBr): 3470, 3072, 2363, 1665, 1256, 1035, 879 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz): δ 5.29 (s, 2H), 7.21 (d, 2H, J = 8.8 Hz), 7.49–7.52 (m, 1H), 7.66 (d, 2H, J = 8.4 Hz), 7.71 (d, 2H, J = 2.0 Hz), 7.78 (d, 1H, J = 15.5 Hz), 7.87–7.93 (m, 2H), 8.08 (d, 1H, J = 15.5 Hz), 8.16 (d, 2H, J = 8.6 Hz), 8.22 (d, 2H, J = 8.8 Hz), 8.34 (s, 1H); Anal. Calcd. for $C_{25}H_{18}F_2N_2O_2$: C, 72.11; H, 4.36; N, 6.73; Found C, 72.03; H, 4.24; N, 6.81.

*6.3.17. (E)-3-(4-(1H-1,2,4-triazol-1-yl)phenyl)-1-(4-(3-chlorobenzyloxy)phenyl)prop-2-en-1-one (**21**)*

With **14a** and **15b**; Yield: 75%; M.P: 164–166 °C; MS(ESI): 416 $[M + 1]^+$; IR (KBr): 3459, 3124, 2368, 1657, 1600, 1521, 1226, 1030, 817 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz): δ 5.29 (s, 2H), 7.21 (d, 2H, J = 8.9 Hz), 7.43–7.48 (m, 3H), 7.58 (s, 1H), 7.77 (d, 1H, J = 15.5 Hz), 7.98 (d, 2H, J = 8.7 Hz), 8.04 (d, 1H, J = 15.5 Hz), 8.11 (d, 2H, J = 8.7 Hz), 8.22 (d, 2H, J = 8.8 Hz), 8.30 (s, 1H), 9.42 (s, 1H); Anal. Calcd. for $C_{24}H_{18}ClN_3O_2$; C, 69.31; H, 4.36; N, 10.10; Found C, 69.34; H, 4.33; N, 10.17.

*6.3.18. (E)-3-(4-(1H-1,2,4-triazol-1-yl)phenyl)-1-(4-(2,4-dichlorobenzyloxy)phenyl)prop-2-en-1-one (**22**)*

With **14b** and **15b**; Yield: 77%; M.P: 168–170 °C; MS(ESI): 450 $[M + 1]^+$; IR (KBr): 3468, 3125, 2364, 1655, 1600, 1518, 1236, 1165, 1030, 820 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz): δ 5.28 (s, 2H), 7.20 (d, 2H, J = 8.8 Hz), 7.48–7.52 (m, 1H), 7.66 (d, 1H, J = 8.3 Hz), 7.72 (d, 1H, J = 2.0 Hz), 7.76 (d, 1H, J = 15.6 Hz), 7.96 (d, 2H, J = 8.6 Hz), 8.03 (d, 1H, J = 15.6 Hz), 8.10 (d, 2H, J = 8.6 Hz), 8.21 (d, 2H, J = 8.9 Hz), 8.28 (s, 1H), 9.41 (s, 1H). Anal. Calcd. for $C_{24}H_{17}Cl_2N_3O_2$; C, 64.01; H, 3.81; N, 9.33; Found C, 64.06; H, 3.84; N, 9.42.

*6.3.19. (E)-3-(4-(1H-1,2,4-triazol-1-yl)phenyl)-1-(4-(2,5-dichlorobenzyloxy)phenyl)prop-2-en-1-one (**23**)*

With **14c** and **15b**; Yield: 69%; M.P: 204–205 °C; MS(ESI): 450 $[M + 1]^+$; IR (KBr): 3446, 3111, 2910, 2364, 1657, 1603, 1519, 1250, 1035, 813, cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz): δ 5.29 (s, 2H), 7.23 (d, 2H, J = 8.8 Hz), 7.48–7.52 (m, 1H), 7.58 (d, 1H, J = 8.6 Hz), 7.73 (d, 1H, J = 2.7 Hz), 7.76 (d, 1H, J = 15.6 Hz), 7.97 (d, 2H, J = 8.6 Hz), 8.03 (d, 1H, J = 15.6 Hz), 8.10 (d, 2H, J = 8.7 Hz), 8.22 (d, 2H, J = 8.8 Hz), 8.28 (s, 1H), 9.40 (s, 1H). Anal. Calcd. for $C_{24}H_{17}Cl_2N_3O_2$. C, 64.01; H, 3.81; N, 9.33; Found C, 63.92; H, 3.79; N, 9.37.

*6.3.20. (E)-3-(4-(1H-1,2,4-triazol-1-yl)phenyl)-1-(4-(2,4-difluorobenzyloxy)phenyl)prop-2-en-1-one (**24**)*

With **14d** and **15b**; Yield: 76%; M.P: 197–198 °C; MS(ESI): 418 $[M + 1]^+$; 3447, 2928, 2369, 1663, 1600, 1520, 1247, 1032, 818, ^1H NMR (DMSO-d_6, 300 MHz): δ 5.24 (s, 2H), 7.11–7.14 (m, 1H),7.20 (d, 2H, J = 8.8 Hz), 7.28–7.36 (m, 1H), 7.63–7.73 (m, 1H), 7.76 (d, 1H, J = 15.6 Hz), 7.96 (d, 2H, J = 8.6 Hz), 8.02 (d, 1H, J = 15.6 Hz), 8.09 (d, 2H, J = 8.6 Hz), 8.20 (d, 2H, J = 8.9 Hz), 8.28 (s, 1H), 9.40 (s, 1H); Anal. Calcd. for $C_{24}H_{17}F_2N_3O_2$. C, 69.06; H, 4.11; N, 10.07; Found C, 69.12; H, 4.14; N, 10.04.

*6.3.21. (E)-3-(4-(1H-1,2,4-triazol-1-yl)phenyl)-1-(4-(2,5-difluorobenzyloxy)phenyl)prop-2-en-1-one (**25**)*

With **14e** and **15b**; Yield: 74%; M.P: 168–170 °C; MS(ESI): 418 $[M + 1]^+$; IR (KBr): 3427, 3117, 2364, 1658, 1586, 1518, 1256, 1027,

820 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz): δ 5.29 (s, 2H), 7.23 (d, 2H, $J = 8.8$ Hz), 7.48–7.52 (m, 1H), 7.58 (d, 1H, $J = 8.4$ Hz), 7.72 (d, 1H, $J = 2.4$ Hz), 7.78 (d, 1H, $J = 15.7$ Hz), 7.91 (d, 2H, $J = 8.5$ Hz), 8.03 (d, 1H, $J = 15.7$ Hz), 8.15 (d, 2H, $J = 8.6$ Hz), 8.23 (d, 2H, $J = 8.7$ Hz), 8.30 (s, 1H), 9.59 (s, 1H). Anal. Calcd. for $C_{24}H_{17}F_2N_3O_2$. C, 69.06; H, 4.11; N, 10.07; Found C, 69.11; H, 4.08; N, 10.16.

*6.3.22. (E)-3-(4-(1H-imidazol-1-yl)phenyl)-1-(4-(2-nitro-4-(trifluoromethyl)phenoxy)phenyl)prop-2-en-1-one (**26**)*

With **14f** and **15a**; Yield: 71%; M.P: 159–161 °C; MS(ESI): 480 $[M + 1]^+$; IR (KBr): 3427, 3126, 2358, 1658, 1263, 1052, 819 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 7.09 (d, 1H, $J = 9.0$ Hz), 7.24–7.28 (m, 3H), 7.37 (s, 1H), 7.50 (d, 2H, $J = 7.4$ Hz), 7.57 (d, 1H, $J = 15.7$ Hz), 7.80 (d, 2H, $J = 8.3$ Hz), 7.89 (d, 1H, $J = 15.6$ Hz), 7.96 (s, 1H), 8.18 (d, 2H, $J = 7.4$ Hz), 8.40 (d, 1H, $J = 9.0$ Hz), 8.66 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): 114.0, 117.8, 118.5, 120.0, 121.4, 122.0, 124.0, 128.4, 128.8, 130.0, 130.8, 131.2, 133.8, 135.3, 135.4, 138.7, 142.6, 143.5, 158.1, 159.6, 188.3; Anal. Calcd. for $C_{25}H_{16}F_3N_3O_4$. C, 62.63; H, 3.36; N, 8.77; Found C, 62.69; H, 3.31; N, 8.83.

*6.3.23. (E)-3-(4-(1H-1,2,4-triazol-1-yl)phenyl)-1-(4-(2-nitro-4-(trifluoromethyl)phenoxy)phenyl)prop-2-en-1-one (**27**)*

With **14f** and **15b**; Yield: 77%; M.P: 162–163 °C; MS(ESI): 481 $[M + 1]^+$; IR (KBr): 3423, 3130, 2364, 1655, 1268, 1047, 830 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 7.06 (d, 1H, $J = 9.3$ Hz), 7.24–7.27 (m, 3H), 7.54 (s, 1H), 7.56 (d, 1H, $J = 15.6$ Hz), 7.77–7.80 (m, 2H), 7.87 (d, 1H, $J = 15.6$ Hz), 8.14–8.17 (m, 3H), 8.35–8.39 (m, 1H), 8.61–8.64 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): 118.5, 120.0, 120.1, 121.6, 122.3, 123.9, 124.0, 128.8, 129.9, 131.2, 134.5, 135.4, 138.2, 140.8, 142.6, 143.4, 152.8, 158.2, 159.6, 188.3; Anal. Calcd. for $C_{24}H_{15}F_3N_4O_4$. C, 60.00; H, 3.15; N, 11.66; Found C, 60.08; H, 3.18; N, 11.61.

*6.3.24. (E)-1,3-bis(4-(1H-imidazol-1-yl)phenyl)prop-2-en-1-one (**28**)*

With **1a** and **15a**; Yield: 74%; M.P: 188–190 °C; MS(ESI): 341 $[M + 1]^+$; IR (KBr): 3462, 3125, 2364, 1655, 1600, 1165, 1037, 845 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 7.29 (s, 1H), 7.38 (s, 1H), 7.52–7.64 (m, 2H), 7.81 (d, 1H, $J = 15.5$ Hz), 7.92 (d, 2H, $J = 8.5$ Hz), 8.03–8.09 (m, 3H), 8.17 (d, 2H, $J = 8.6$ Hz), 8.21–8.26 (m, 2H), 8.31 (s, 1H), 8.38 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): 118.2, 118.9, 120.8, 125.3, 126.7, 126.9, 129.7, 130.8, 131.1, 133.4, 136.4, 136.9, 137.5, 138.8, 141.4, 144.8, 188.4; Anal. Calcd. for $C_{21}H_{16}N_6O$. C, 74.10; H, 4.74; N, 16.46; Found C, 74.79; H, 4.21; N, 16.34.

*6.3.25. (E)-1,3-bis(4-(1H-1,2,4-triazol-1-yl)phenyl)prop-2-en-1-one (**29**)*

With **1b** and **15b**; Yield: 68%; M.P: 195–197 °C; MS(ESI): 343 $[M + 1]^+$; IR (KBr): 3462, 3125, 2364, 1655, 1600, 1165, 1037, 845 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 7.84 (d, 1H, $J = 15.6$ Hz), 7.98 (d, 2H, $J = 8.6$ Hz), 8.06 (d, 2H, $J = 8.7$ Hz), 8.11–8.17 (m, 3H), 8.28 (s, 1H), 8.38 (s, 1H), 8.38 (d, 2H, $J = 8.7$ Hz), 9.41 (s, 1H), 9.49 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): 121.4, 121.9, 127.3, 129.1, 133.5, 136.7, 136.8, 137.2, 141.3, 143.7, 144.1, 157.1, 158.6, 188.6; Anal. Calcd. for $C_{19}H_{14}N_6O$. C, 66.66; H, 4.12; N, 24.55; Found C, 66.79; H, 4.21; N, 23.96.

*6.3.26. (E)-1,3-bis(4-(2,4-dichlorobenzyloxy)phenyl)prop-2-en-1-one (**30**)*

With **2c** and **14c**; Yield: 67%; M.P: 151–153 °C; MS(ESI): 557 $[M + 1]^+$; IR (KBr): 3223, 3129, 2371, 1657, 1251, 1039, 812 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 5.23 (s, 2H), 5.28 (s, 2H), 7.24 (d, 2H, $J = 8.5$ Hz), 7.31–7.34 (m, 2H), 7.38 (d, 2H, $J = 8.7$ Hz), 7.43–7.49 (m, 3H), 7.73 (d, 1H, $J = 15.4$ Hz), 7.77–7.80 (m, 3H), 8.07 (d, 1H, $J = 15.4$ Hz), 8.28–8.31 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): 67.1, 68.2, 114.5, 115.6, 120.8, 126.3, 126.7, 126.9, 128.7, 129.0, 129.7, 131.3, 131.6, 131.7, 131.8, 132.3, 132.4, 134.3, 134.6, 134.9, 135.1, 145.1, 159.4, 162.6, 188.2; Anal. Calcd. for $C_{29}H_{20}Cl_4O_3$. C, 62.39; H, 3.61; Found C, 62.28; H, 3.53.

*6.3.27. (E)-1-(4-(2,4-dichlorobenzyloxy)phenyl)-3-phenylprop-2-en-1-one (**31**)*

With **14c** and benzaldehye; Yield: 76%; M.P: 137–138 °C; MS(ESI): 383 $[M + 1]^+$; IR (KBr): 3411, 3223, 3129, 2371, 1657, 1251, 1039, 812 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 5.25 (s, 2H), 7.21 (d, 2H, $J = 8.6$ Hz), 7.24–7.28 (m, 2H), 7.31–7.33 (m, 2H), 7.39–7.43 (m, 1H), 7.69 (d, 1H, $J = 15.6$ Hz), 7.72–7.78 (m, 2H), 7.98 (d, 1H, $J = 15.6$ Hz), 8.09–8.13 (m, 1H), 8.16–8.22 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): 66.4, 114.4, 126.4, 126.7, 127.2, 127.4, 129.2, 129.3, 130.7, 130.9, 131.1, 132.4, 134.1, 134.3, 134.7, 144.7, 162.3, 187.8; Anal. Calcd. for $C_{22}H_{16}Cl_2O_2$. C, 68.94; H, 4.21; Found C, 68.79; H, 4.16.

Acknowledgements

V.K.M. thanks the Council of Scientific and Industrial Research (India) for the award of Senior Research Fellowship. Authors are thankful to S.A.I.F. Division, CDRI, Lucknow, for providing spectroscopic data. Thanks are also due to Anoop K Srivastava, Ajay S. Verma and Hori Lal for technical assistance. CDRI communication No: 8093.

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