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Synthesis and biological evaluation of substituted 4,6-diarylpyrimidines and 3,5-diphenyl-4,5-dihydro-1*H*-pyrazoles as anti-tubercular agents

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ABSTRACT

Various substituted 4,6-diarylpyrimidin-2-amine (**4**), 4,6-diaryl-2-(heteroaryl)pyrimidine (**6**) and 1-(3,5-diaryl-4,5-dihydro-1*H*-pyrazol-1-yl)ethanone (**7**) derivatives were synthesized in good yields using simple methodology. The synthesized compounds (**4-7**) were evaluated for their *in vitro* anti-tubercular activity against *Mycobacterium tuberculosis* H37Rv strain. Compounds **4a**, **6b**, **7b,** and **7c** exhibited significant anti-tubercular activity at MIC values 25, 25, 12.5 and 12.5 µM concentration. *In vitro* cytotoxicity data using non cancerous hepatic monocytes (THP-1) cells indicated that most active compounds **7b** and **7c** were safe as their MIC values were much lower than their cytotoxic values.

Tuberculosis (TB) remains a major global health problem as per eighteenth global report on tuberculosis (TB) published by WHO in 2013.[1] According to this report, an estimated 8.6 million people developed TB and 1.3 million died from the disease in 2012. The majority of cases worldwide in 2012 were in the South-East Asia (29%), African (27%) and Western Pacific (19%) regions. India and China alone accounted for 26% and 12% of total cases, respectively. [1]

Globally in 2012, data from drug resistance surveys and continuous surveillance among notified TB cases suggest that 3.6% of newly diagnosed TB cases and 20% of those previously treated for TB had MDR-TB. 84,000 people with confirmed MDR-TB (i.e. resistance to both rifampicin, the most powerful TB drug and isoniazid), plus 10,000 with rifampicin resistance detected using Xpert MTB/ RIF. The largest increases between 2011 and 2012 were in India, South Africa and Ukraine.[1] Thus, as resistant strains of *Mycobacterium tuberculosis* (MTB) have slowly emerged; treatment failure is a main reality. However, various drugs such as streptomycin (**i**), rifampicin (**ii**), isoniazid (**iii**), ethionamide (**iv**), ethambutol (**v**) and pyrazinamide (**vi**) etc (Fig. 1) are used for the treatment of TB. Since, these drugs are taking more than six month treatment; therefore, there is a need for regular efforts to search new chemical entities which can serve better treatment against tuberculosis. Some nitrogenous derivatives such as pyrimidine and pyrazole analogs (**vii** & **viii**) are reported to be highly effective against *Mycobacterium tuberculosis* in *in vitro* model at 0.78 and 0.35 µg/mL concentration respectively (Fig. 1).[2]

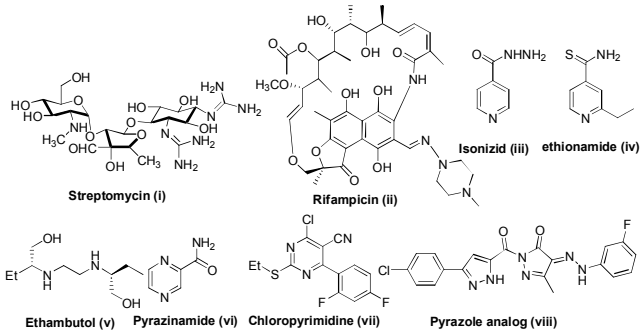

Figure 1. Lead anti-tubercular agents

In the recent past, 2-amino-4,6-diarylpyrimidine derivatives[3-5] have been reported to exhibit diverse biological activities such as antiplatelet,[3] reverse-transecriptase inhibitory,[4] antifungal and antibacterial activities[5] whereas another nitrogenous molecule, 3,5-diaryl-1*H*-pyrazole derivatives[6-7] have presented potential aryl-*N*-acetyltransferase inhibitory[6] and cytotoxic activities.[7] Recently, we could explore the anti-tubercular activity of conformationally rigid 2-amino-4,6-diarylpyrimidine (**ix**)[8] and 3,5-diaryl-1*H*-pyrazole derivatives (**x**)[8] on cyclic framework, Fig. 2.

On the other side, structure activity relationship (SAR) study of some biologically active natural products such as combretastatin (**xi**),[7,9] phenastatin (**xii**)[9] and podophyllotoxin (**xiii**)[9] revealed that

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trimethoxyphenyl group present in these molecules is mainly responsible for their potent cyctotoxic activity,[9] Fig. 2.

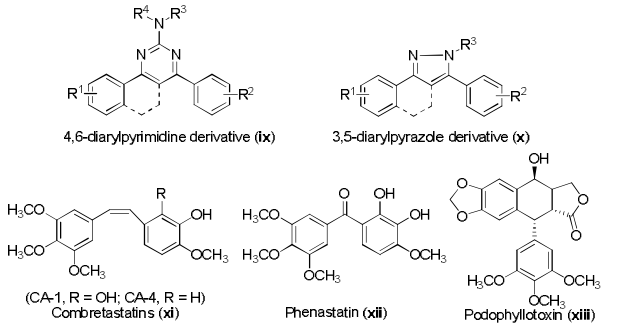
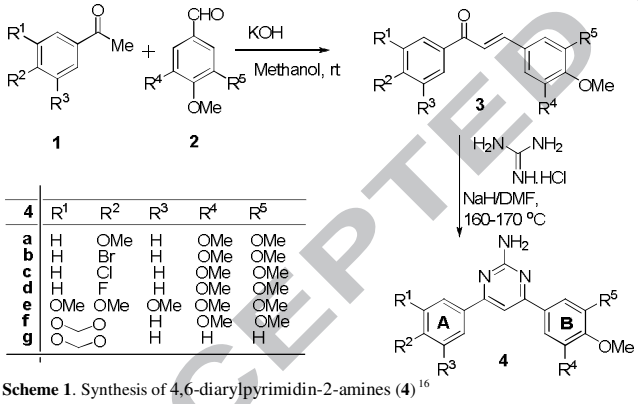


Figure 2.

Inspired from our previous findings on 2-amino-4,6-diarylpyrimidine[8] and 3,5-diaryl-1*H*-pyrazole fragment containing molecules[8] and observed impact of trimethoxyphenyl group on biological cytotoxic activities,[9] we further designed some 2-amino-4,6-diarylpyrimidine derivatives (**4** and **6**) and 3,5-diaryl-1*H*-pyrazole derivatives (**7**) as potential anti-tubercular agents. The proposed molecules will have a trimethoxyphenyl fragment (phenyl ring **B** of **4**, scheme 1) to important cytotoxic activity, along with a diatomic five and six member heterocyclic ring.

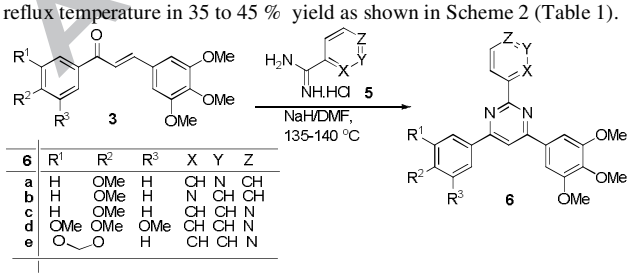
In our approach, synthesis of target molecules was started using 1-arylethanone (**1**) and arylaldehyde (**2**) as starting materials following reported procedure.[10] Reaction of **1** with arylaldehyde (**2**) using base KOH in methanol with stirring for 24-25 h at room temperature produced chalcones (**3**) in 67-85 % yields. Chalcones (**3**) on further reaction with guanidine hydrochloride in the presence of sodium hydride and DMF at reflux temperature gave 4,6-diarylpyrimidin-2-amines (**4**) in 51-66 % yield, Scheme 1.



4	R^1	R^2	R^3	R^4	R^5
a	H	OMe	H	OMe	OMe
b	H	Br	H	OMe	OMe
c	H	Cl	H	OMe	OMe
d	H	F	H	OMe	OMe
e	OMe	OMe	OMe	OMe	OMe
f	O–O		H	OMe	OMe
g	O–O		H	H	H

Scheme 1. Synthesis of 4,6-diarylpyrimidin-2-amines (**4**)[16]

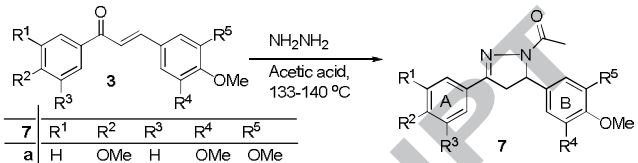
In anticipation to study structure activity relationship (SAR) of 4,6-diarylpyrimidin-2-amines (**4**), we have also synthesized novel 4,6-diaryl-2-(heteroaryl)pyrimidine (**6**) from chalcone (**3**) and heteroarylamidines (**5**) in the presence of sodium hydride and DMF at reflux temperature in 35 to 45 % yield as shown in Scheme 2 (Table 1).



6	R^1	R^2	R^3	X	Y	Z
a	H	OMe	H	CH	N	CH
b	H	OMe	H	N	CH	CH
c	H	OMe	H	CH	CH	N
d	OMe	OMe	OMe	CH	CH	N
e	O–O		H	CH	CH	N

Scheme 2. Synthesis of 4,6-diaryl-2-(heteroaryl)pyrimidine (**6**)[16]

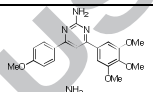
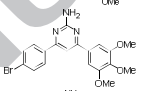
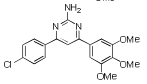
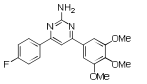
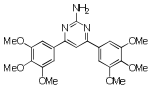
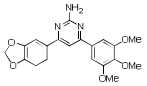
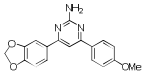
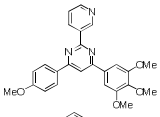
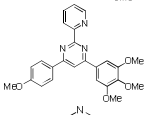
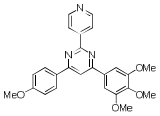
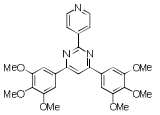
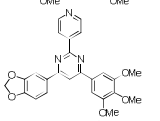
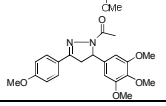
In our strategy to see the effect of size of pyrimidine ring on biological efficacy of compound **4** and **6**, we further synthesized 1-(3,5-diaryl-4,5-dihydro-1*H*-pyrazol-1-yl)ethanone (**7**) from the reaction of chalcones (**3**) with hydrazine hydrate in presence of acetic acid at reflux temperature following reported methods which yielded desired compounds 52-72% in yield as shown in Scheme 3 (Table 1).[11-15]

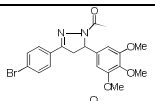
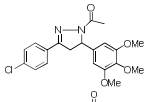
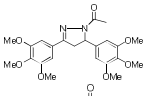
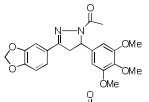
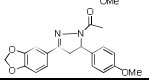


7	R^1	R^2	R^3	R^4	R^5
a	H	OMe	H	OMe	OMe
b	H	Br	H	OMe	OMe
c	H	Cl	H	OMe	OMe
d	OMe	OMe	OMe	OMe	OMe
e	O–O		H	OMe	OMe
f	O–O		H	H	H

Scheme 3. Synthesis 1-(3,5-diaryl-4,5-dihydro-1*H*-pyrazol-1-yl)ethanone (**7**)[16]

Table 1. Structure, melting point and yield of synthesized compounds[16]

Com.	Structure	Mp (°C)	Yield (%)
4a[10]		173-174	66
4b[10]		155-156	64
4c[10]		149-150	53
4d[a]		133-134	51
4e		202-203	55
4f		175-176	57
4g[a]		189-190	62
6a		152-153	37
6b		67-68	35
6c		185-186	45
6d		172-173	39
6e		248-249	40
7a[11,12]		148-149	56

7b[11,13]		143-144	63
7c[11]		141-142	52
7d		163-164	72
7e[14]		141-142	65
7f[15]		119-120	64

[a] Commercially available

The synthesized compounds were characterized by the use of different spectroscopic techniques *viz* NMR (^{1}H NMR, ^{13}C NMR, Dept 135), IR and mass spectrometry.[16]

Compounds **4, 6** and **7** (Table 1) were evaluated for their anti-tubercular activity against *Mycobacterium tuberculosis* H37Rv strain using micro plate alamar blue assay (MABA) and results are reported in Table 2. Out of eighteen compounds *viz* **4a-g**, **6a-e** and **7a-f** with high log p values, eleven compounds **4a-d**, **6a-b**, **7a-c** and **7e-f** were found to be active (Table 2). In order to assess lipophilic nature of compounds and compare it with standard anti-tubercular drugs, their lipophilicity was calculated using ChemBioDraw Ultra 11.0 which is expressed in the terms log P value, Table 2.

Table 2.
In vitro anti-tubercular activity against *Mycobacterium tuberculosis* H37Rv strain using micro plate alamar blue assay (MABA) and *in vitro* cytotoxicity in THP-1 cells (CC_{50})

Compounds	Log P[a]	MIC (µM)	CC_{50} (µM)
4a	3.50	25	100
4b	4.45	50	100
4c	4.18	50	-
4d	3.78	50	-
4e	3.25	>100	-
4f	3.40	>100	200
4g	3.66	>100	-
6a	5.02	100	200
6b	5.44	25	50
6c	5.02	>100	-
6d	4.77	>100	-
6e	4.93	>100	400
7a	2.34	50	200
7b	2.09	12.5	100
7c	3.02	12.5	100
7d	2.09	>100	200
7e	2.25	100	200
7f	2.50	100	200
Isonizid[8]	-0.60	0.2	-
Rifampicin[8]	2.61	2.0	-
Streptomycin[8]	-4.11	6.0	-
vii (Fig. 1)[2a]	4.74	0.78 [b]	-
viii (Fig. 1)[2b]	3.40	0.35 [b]	-

[a]liphophilicity was calculated using ChemBioDraw Ultra 11.0, [b] µg/mL

The anti-tubercular activity results of synthesized compounds (**4**-**7**) revealed that 4,6-diarylpyrimidin-2-amines, **4a** and **4b-d** exhibited good anti-tubercular activity at MIC 25 and 50 µM respectively while compounds **4e, 4f** and **4d** were inactive at 100 µM concentration (MIC value).

The 2-heteroaryl substituted 4,6-diaryl-pyrimidine derivatives, **6a** and **6b** exhibited considerable anti-tubercular activity at MIC 25 and 100 µM respectively. However, compounds **6c, 6d** and **6e** in this series were found to be inactive at 100 µM concentrations (MIC value).

Similarly, the 3,5-diarylpyrazole derivatives, **7a, 7b** and **7c** exhibited significant anti-tubercular activity at MIC 50, 12.5 and 12.5 µM respectively whereas compounds **7e** and **7f** were found active at MIC 100 µM and **7d** was found inactive at 100 µM.

Structure activity relationship (SAR) of compounds **4**-**7** revealed that in case of 4,6-diarylpyrimidine derivatives **4** and **6**, methoxy group in phenyl ring A of 4,6-diarylpyrimidin-2-amines (e.g. **4a,** Scheme 1) had impact on anti-tubercular activity. Additional methoxy group in phenyl ring **A** or replacement of methoxy groups by methylenedioxy brought decline in biological activity of compounds. Similarly, replacement of methoxy group of phenyl ring **A** of **4a** by halogen atoms (F, Cl, and Br) attenuated anti-tubercular activity. Further, substitution of 2-amino group of **4a** by pyridinyl fragment such as pyridin-2-yl, pyridin-3-yl and pyridin-4-yl could not bring further enhancement in biological activity of compound **4a**.

The biological activity of compounds **7a-f** showed that ring contraction of pyrimidine ring of 4,6-diarylpyrimidine derivatives **4a-c** and **4e-g** had incremental effect on their anti-tubercular activity e.g. compounds **7b, 7c, 7e** and **7f** had better activity over compound **4b, 4c, 4f** and **4g.** Interestingly, in contrast to compound **4a**, replacement of methoxy group in phenyl ring A of **7a** (Scheme 3) by halogen atoms (F, Cl and Br) had profound effect on its anti-tubercular activity.

In view of good anti-tubercular activity of compounds **4a-b**, **6a-b**, **7a-c** and **7e-f**, their cytoxicity was evaluated *in vitro* using MTT assay in non cancerous hepatic monocytes (THP-1) cells.[9] In this assay, cytotoxicity concentration (CC_{50}) values of **4a-b, 7b-c** was 100 µM and compounds **6a**, **7a**, **7e-f** had 200 µM (Table 2). However, compound **6b** presented CC_{50} value of 50 µM.

Since, theoretically, MIC values are approximately double of IC_{50} values therefore considering the *in-vitro* anti-tubercular and cytotoxic activities of compounds (MIC *Vs* IC_{50} values), the most active compound **7b** and **7c** are considered to be eight times selective towards tubercular *Vs* healthy cells whereas compound **4a** and **7a** are four times selective with significant high log p values and were found to be safe with respect to their MIC values.

In conclusion, we have synthesized trimethoxy benzene moiety containing diarylpyrimidin-2-amine derivatives (**4** and **6**) and 1-(3,5-diaryl-4,5-dihydro-1*H*-pyrazol-1-yl)ethanone (**7**) in moderate to good yields. Compounds **4a**, **6b**, **7b** and **7c** exhibited significant anti-tubercular activity at MIC values 25, 25, 12.5 and 12.5 µM concentration respectively in *in vitro* assay against *Mycobacterium tuberculosis* H37Rv strain. The biological activity profile of most active derivatives **7b** and **7c** showed significant anti-tubercular activity with eight times selectivity towards tubercular *Vs* healthy cells and safe with respect to their MIC values.

Overall, out of three pharmacophores studied *viz* **4**, **6** and **7**, diarylpyrazole derivatives (**7**) have further scope for investigation as novel anti-tubercular agents for better treatment of MTB.

Acknowledgements

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bmcl.....These data include experimental methods, spectral data and scan copy of some compounds, MOL files and InChiKeys of compounds described in this article.

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16. a) *Representative procedure for synthesis of chalcone* (**3**): 1-arylethanone (**1**, 10 mmol) and arylaldehyde (**2**, 10 mmol) in the presence of base KOH (30 mmol) were stirred in methanol (50 mL) for 24 h at room temperature. After the completion of reaction, methanol was distilled and the crude was diluted with ethyl acetate and extracted with water. The organic layer was separated, dried over anhydrous sodium sulphate and concentrated to give crude material which on recrystallized with methanol to give desired compound (**3**) in 70-80 % yields. *1-(4-methoxyphenyl)-3-(3,4,5-trimethoxyphenyl)prop-2-en-1-one* (**3a**): yellow solid; yield 83%; R_f: 0.34 (30% EtOAc in Hexane); mp 131-132 ^oC; IR (KBr, ν_{max}/cm^{-1}): 1656 (C=O), ^1H NMR ($CDCl_3$, 300 MHz, δ ppm): 3.87 (s, 3H, OCH_3), 3.88 (s, 3H, OCH_3), 3.89 (s, 6H, 2xOCH_3), 6.85 (s, 2H, ArH), 6.97 (d, 2H, *J*=9.0 Hz, ArH), 7.36 (d, *J*=15.6 Hz, 1H, CH), 7.65 (d, *J*=15.3 Hz, 1H, CH), 8.02 (d, *J*=9.0 Hz, 2H, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz, δ ppm): 55.89 (OCH_3), 56.63 (2xOCH_3), 61.39 (OCH_3), 106.02 (2xArH), 114.24 (2xArH), 121.66 (CH), 130.99, 131.20 (2xArH), 131.54, 140.71, 144.53 (CH), 153.88 (2xAr), 163.81, 189.09 (C=O); MS ($C_{19}H_{20}O_5$): 329 [MH^+].

b) *4,6-diarylpyrimidin-2-amines* (**4**): In a 50 mL R.B. flask, chalcone (**3**, 2.0 mmol) and guanidine hydrochloride (4.0 mmol) in the presence of base NaH (3.0 mmol) were stirred in DMF (20 ml) at 160-170 ^oC. After the completion of reaction, mixture was diluted with water and extracted with ethyl acetate. The organic layer was separated, dried over anhydrous sodium sulphate and concentrated to give crude material which on column chromatography on basic alumina using chloroform in hexane (40 to 50%) as eluent gave desired compound (**4**). *4-(benzo[d][1,3]dioxol-5-yl)-6-(4-methoxyphenyl)pyrimidin-2-amine* (**4g**): Pale yellow solid; yield 62%; R_f: 0.5 (10% methanol in $CHCl_3$); mp 189-190 ^oC; IR (KBr, ν_{max}/cm^{-1}): 3361.92 (NH_2); ^1H NMR ($CDCl_3$+DMSO-d_6, 300 MHz, δ ppm): 3.80 (s, 3H, OCH_3), 5.57 (s, 2H, NH_2), 5.97 (s, 2H, CH_2), 6.84 (d, *J*=8.1 Hz, 1H, Ar-H), 6.92 (d, *J*=8.7 Hz, 2H, Ar-H), 7.25 (s, 1H, CH), 7.53-7.58 (m, 2H, ArH), 7.98 (d, 2H, *J*=8.7, ArH); ^{13}C NMR ($CDCl_3$+DMSO-d_6, 75 MHz, δ ppm): 54.54 (OMe), 100.65 (OCH_2), 101.23 (ArH), 106.42 (CH) 107.45 (ArH), 113.16 (2xArH), 120.68 (ArH), 127.71 (2xArH), 129.24, 131.22, 147.33, 148.69, 160.69, 162.83, 164.00, 164.30; MS ($C_{18}H_{15}N_3O_3$): 322.2 [MH^+].

c) *4,6-diarylpyrimidin-2-amines* (**6**): In a 50 mL R.B. flask, chalcone (**3**, 2 mmol) and amidine (**5**, 2 mmol) in the presence of base NaH (3 mmol) were stirred in DMF (10 ml) at 135-140 ^oC. After the completion of reaction, reaction mixture was poured in cold water with vigorous stirring and neutralized it with N/5 HCl solution. The precipitate was filtered and dried. The crude was purified by column chromatography with a mixture of chloroform-methanol to give the desired product **6**. *4-(4-methoxyphenyl)-2-(pyridin-3-yl)-6-(3,4,5-trimethoxyphenyl)pyrimidine* (**6a**): creamy solid; R_f: 0.7 (EtOAc); mp 152-153 ^oC; ^1H NMR ($CDCl_3$, 300 MHz, δ ppm): 3.91 (s, 3H, OCH_3), 3.95 (s, 3H, OCH_3), 4.02 (s, 6H, 2xOCH_3), 7.75 (d, *J*=9.0 Hz, 2H, ArH), 7.44-7.48 (m, 1H, ArH), 7.50 (s, 2H, ArH), 7.70 (s, 1H, ArH), 8.25 (d, *J*=9.0 Hz, 2H, ArH), 8.72-8.75 (m, 1H, ArH), 8.89-8.92 (m, 1H, ArH), 9.87 (s, 1H, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz, δ ppm): 55.85 (OMe), 56.81 (2xOMe), 61.40 (OMe) 105.03 (2xArH), 109.98 (ArH), 114.73 (2xArH), 123.66 (ArH), 129.20 (2xArH), 129.83, 133.05, 134.05, 136.00 (ArH), 141.24, 150.56 (ArH), 151.57 (ArH), 154.05 (2xAr), 162.56, 162.87, 164.60, 164.75.; MS ($C_{25}H_{23}N_3O_4$) : 430.3 [MH^+].

d) *1-(3,5-diaryl-4,5-dihydro-1H-pyrazol-1-yl)ethanone* (**7**): In a 50 mL R.B. flask, chalcone (**3,** 1.5 mmol) and hydrazine hydrate (7.5 mmol) were stirred in acetic acid (20 mL) at 133-140 ^oC. On completion of the reaction, mixture was diluted with water and extracted with ethyl acetate. The organic layer was separated, dried over anhydrous sodium sulphate and concentrated to give crude material which on column chromatography on basic alumina using chloroform in hexane (40-50%) as eluent gave desired compound **7**. *1-(3-(benzo[d][1,3]dioxol-5-yl)-5-(4-methoxyphenyl)-4,5-dihydro-1H-pyrazol-1-yl)ethanone* (**7f**): white solid; yield 64%; R_f: 0.64 (10% methanol in $CHCl_3$); mp 119-120 ^oC; IR (KBr, ν_{max}/cm^{-1}): 1646 (C=O); ^1H NMR ($CDCl_3$, 300 MHz, δ ppm): 2.40 (s, 3H, CH_3), 3.11 (dd, *J*=4.5 & 17.7 Hz, 1H, CH_2), 3.64-3.73 (m, 1H, CH), 3.79 (s, 3H, OCH_3), 5.54 (dd, *J*=4.2 & 11.4 Hz, 1H, CH), 6.04 (s, 2H, CH_2), 6.83-6.87 (m, 3H, ArH), 7.10-7.19 (m, 3H, ArH), 7.28 (s, 1H, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz, δ ppm): 22.34 (CH_3) , 42.79 (CH_2), 55.67 (OCH_3), 55.83 (CH), 101.94 (OCH_2), 106.62 (ArH), 108.63, 114.63 (2xArH), 121.99 (ArH), 126.25, 127.31 (2xArH), 134.56, 148.62, 149.94, 153.84, 159.42, 169.03 (C=O); MS ($C_{19}H_{18}N_2O_4$): 339 [MH^+].

Graphical Abstract