Bioorganic & Medicinal Chemistry Letters 22 (2012) 7426–7430

Contents lists available at SciVerse ScienceDirect

Bioorganic & Medicinal Chemistry Letters

journal homepage: www.elsevier.com/locate/bmcl

# Molecular hybridization of bioactives: Synthesis and antitubercular evaluation of novel dibenzofuran embodied homoisoflavonoids via Baylis–Hillman reaction

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ARTICLE INFO

*Article history:*
Received 19 July 2012
Revised 22 September 2012
Accepted 11 October 2012
Available online 22 October 2012

*Keywords:*
Dibenzofuran
Homoisoflavonoids
Baylis–Hillmann (BH) reaction
Antimycobacterial activity
Molecular hybridization

ABSTRACT

A novel series of natural product like dibenzofuran embodied homoisoflavonoids [(*E*)-3-(dibenzo[*b*,*d*]-furan-2-ylmethylene)chroman-4-ones] designed by molecular hybridization were synthesized in very good yields via a sequence of reactions involving base catalyzed Baylis–Hillmann (BH) reaction of 2-dibenzofuran carboxaldehyde and methyl acrylate; bromination of BH adduct; condensation of resulted allylic bromide with substituted phenols or 2-dibenzofuranol followed by cyclization. Among the all 11 new compounds screened for in vitro antimycobacterial activity against *Mycobacterium tuberculosis* H37Rv (MTB), (*E*)-3-(dibenzo[*b*,*d*]furan-2-ylmethylene)-6-fluorochroman-4-one (**7f**) and (*E*)-3-(dibenzo[*b*,*d*] furan-2-ylmethylene)-6-fluorochroman-4-one (**7g**) were found to be active with MIC 12.5 μg/mL.



Tuberculosis (TB) is an ancient chronic infectious disease caused mainly by *Mycobacterium tuberculosis* (MTB).[1] It has become more prevalent disease claiming over two million lives worldwide each year and dwells hidden in as many as two billion people. Additionally, the evolution of its new virulent forms like multi drug resistant (MDR–TB) and extremely drug resistant (XDR-TB) has become a major threat to human kind.[2] The resurgence of TB is more alarming in HIV infected people due to the development of pathogenic synergy.[2,3] The worsening situation has prompted the world health organization (WHO) to declare tuberculosis a global public health crisis.[3] All the above facts also stressed an urgent need for development of fast acting new antitubercular drugs with diverse and unique structural features.[4]

Molecular hybridization[5] is a fairly new concept in drug design and development based on the combination of pharmacophoric moieties of different bioactive natural or synthetic substances to produce a new hybrid compound with improved affinity and efficacy, when compared to the parent drugs. Additionally, this strategy can result in compounds presenting different and/or dual modes of action, modified selectivity profile and reduced undesired side effects.[6] Homoisoflavonoids[7] (Fig. 1) constitute a class of natural products prevalently isolated from the bulbs, rhizomes, or roots of several genera of Hyacinthaceae and Caesal pinioideae. Several natural and synthetic homoisoflavonoids were found to possess various biological properties such as antifungal, antiviral, antitubercular antimutagenic, antiproliferative, antioxidant, antiallergic and antihistaminic, anti-inflammatory, and protein tyrosine kinase (PTK) inhibitor activities.[8] On the other hand, dibenzofuran is a basic framework in several natural products with pronounced biological properties.[9] Simple dibenzofurans are also occurring in higher plants, where they often act as antifungal phytoalexins.[9] Synthetic heterocycles derived from dibenzofuran manifests a number of important and therapeutically useful biological activities such as antibacterial, antidepressant, and antituberculasis[10] (Fig. 1).

We therefore envisaged that designing newer heterocycles through molecular hybridization of bioactive dibenzofuran derivatives with natural homoisoflavonoids in one molecular frame (Fig. 2) could result pharmacologically relevant natural product like newer analogues as potential candidates for biological evaluation. Continuing our work[11] on synthesis of dibenzofuran derived antitubercular agents, we herein report an efficient synthesis and antitubercular evaluation of natural product like dibenzofuran conjugated homoisoflavonoids [(*E*)-3-(dibenzo[*b*,*d*]furan-2-yl methylene)chroman-4-ones] in very good yields via Baylis–Hillmann (BH) reaction. Screening all new compounds **7a–k** for in vitro activity against Mycobacterium tuberculosis H37Rv (MTB) resulted (*E*)-3-(dibenzo[*b*,*d*]furan-2-ylmethylene)-6-fluorochroman-4-one **(7f)** and (*E*)-3-(dibenzo[*b*,*d*]furan-2-ylmethylene)-6-fluorochroman -4-one (**7g**) as active antitubercular agents with MIC of 12.5 μg/mL.

Dibenzo[*b*,*d*]furan-2-carbaldehyde (**1**), being versatile substrate in the synthesis of heterocyclic compounds, is chosen as starting

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http://dx.doi.org/10.1016/j.bmcl.2012.10.056

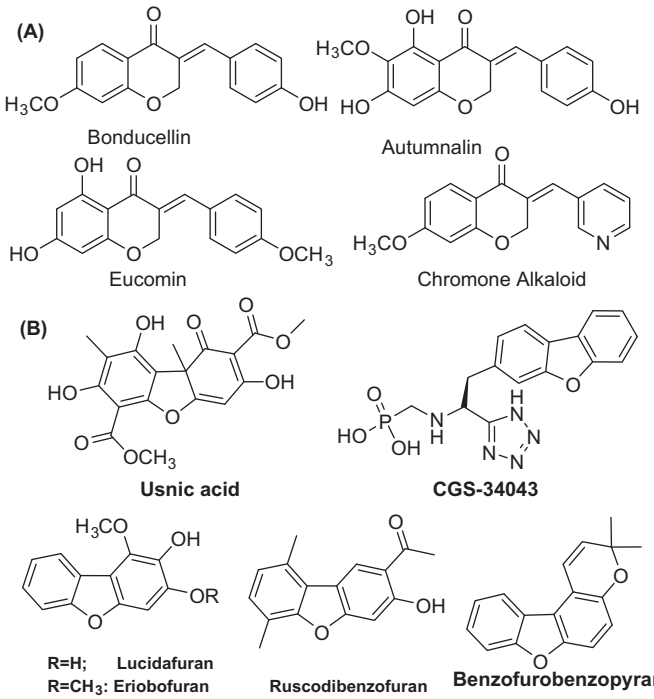



**Figure 1.** Representative bioactive analogues of (A) natural homo isoflavonoids (B) natural and synthetic dibenzofuran.

material. It was prepared from dibenzofuran following the modified literature protocol developed in our laboratory.[11] Having dibenzo[*b*,*d*]furan-2-carboxaldehyde (**1**) in hand, efforts were focused on Baylis–Hillmann (BH) reaction[12] of **1** with methyl acrylate and base. Several reaction conditions examined to achieve the best yield of Baylis–Hillmann adduct **2** are shown in Table 1. The reaction was proceeded effectively, when **1** was reacted with 8 equivalents of methyl acrylate at room temperature in the presence of DABCO for 7 days to give Baylis–Hillmann adduct **2** in 70% yield (Table 1, entry 6). The use of solvents such as methanol, THF or combination of THF and water in the Baylis–Hillmann (BH) reaction did not give good yield even after 6 days of reaction (Table 1, entries 1–3). Change of base to DBU or $K_2CO_3$ or $N(Et)_3$ are also not fruitful. Also prolonging the BH reaction to 12 days did not show any significant improvement in product yield (Table 1, entry 7). The BH adduct 2 was fully characterized by $^1H$ and $^{13}C$ NMR, IR and mass (EI-MS) spectral data.[13]

Further, Allylic bromide analogue **3**[14], prepared in excellent yield through bromination of Methyl 2-(dibenzo[*b*,*d*]furan-2-yl(hydroxy)methyl)acrylate **(2)** with $HBr/H_2SO_4$ in dichloro methane at 0 °C, was reacted with series of phenols **4a–k** (Fig. 3) to give alkylated esters **5a–k** (Scheme 1).[15] Base hydrolysis of **5a–k**

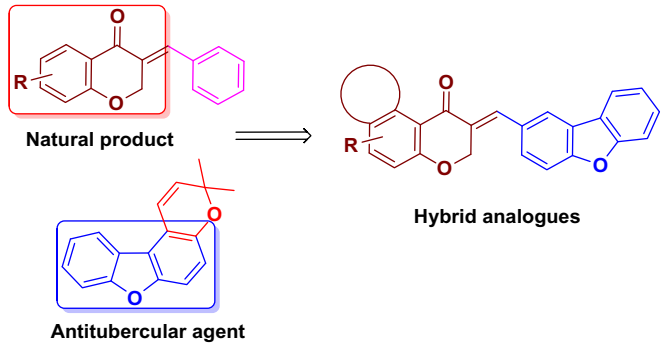
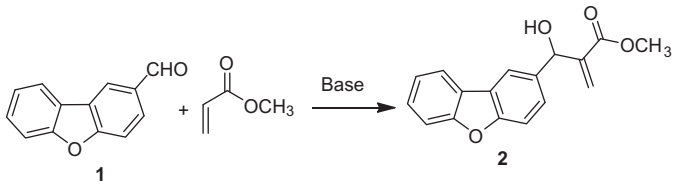



**Figure 2.** Design strategy for new dibenzofuran-chromanone hybrids.

**Table 1**
Optimization of Baylis-Hillmann reaction conditions[a]




| Entry | Base | Solvent | Time (days) | Yield[b] of **2** (%) |
|---|---|---|---|---|
| 1 | DABCO | Methanol | 6 | 15 |
| 2 | DABCO | THF | 6 | 12 |
| 3 | DABCO | THF: Water (1:1) | 6 | 12 |
| 4 | DABCO | Neat | 4 | 32 |
| 5 | DABCO | Neat | 6 | 49 |
| 6 | DABCO | Neat | 7 | 70 |
| 7 | DABCO | Neat | 12 | 72 |
| 8 | DBU | Neat | 12 | 22 |
| 9 | $K_2CO_3$ | Neat | 12 | 25 |
| 10 | $N(Et)_3$ | Neat | 12 | 20 |

[a] All the reactions were performed with 1 (1.0 mmol), Base (1.0 mmol), methyl acrylate (8.0 mmol) and the progress of reaction was monitored by TLC.
[b] Isolated yield.

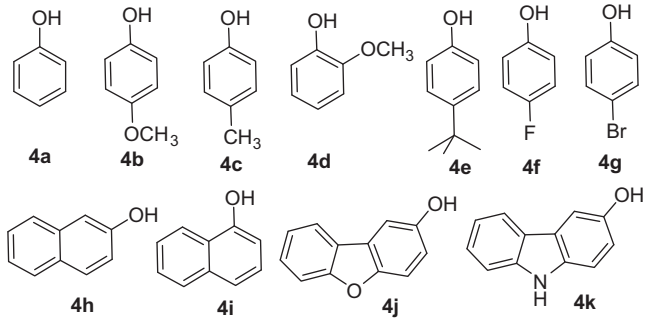
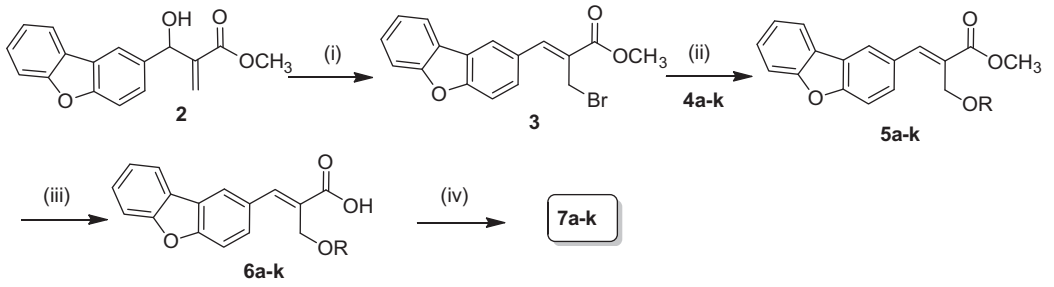



**Figure 3.** Phenols **4a–k** used in the present study.

resulted aklenyl acids **6a–k** in 82–90% overall yield from **3** to **6a–k.** The compounds **6a–k** was characterized by $^1H$ NMR, IR and mass spectral data.[16] To obtain desired products with enhanced lipophilic nature, aklenyl acids **6a–k** was cyclized with TFAA in dichloromethane to give hybrid homoisoflavonoids **7a–k** (Fig. 4) in very good yields. All the new compounds **7a–k** was fully characterized by $^1H$ and $^{13}C$ NMR, IR and mass (EI-MS & HR-MS) spectral data[17] (see Supplementary data).

The antimycobacterial activity of the synthesized dibenzofuran embodied homoisoflavonoids **7a–k** has been screened against *M. tuberculosis* H37Rv (MTB) by agar dilution method for the determination of minimum inhibitory concentration (MIC) in triplicates.[18] The MIC is defined as the minimum concentration of compound required to completely inhibit the bacterial growth. The MIC values of **7a–k** along with the standard drugs for comparison are furnished in Table 2. Eleven new compounds screened have showed in vitro activity against MTB with MIC ranging from 12.5–25.0 μg/mL. Two compounds **7f** and **7g** inhibited MTB with MIC of 12.5 μg/mL.When compared to pyrazinamide (MIC 50.8 μg/mL), all the 11 compounds were found to be more potent, though all the compounds were less potent than other anti-TB drugs isoniazid (0.1 μg/mL) and ethambutol (MIC 3.13 μg/mL). Structure–activity correlations of the new compounds **7a–k** with respect to their antitubercular activity reveal that natural homoisoflavonoids were tuned for first time to act as antitubercular agents by conjugating with dibenzofuran unit. Also fluoro/bromo substituent on phenyl ring of homoisoflavonoid architecture (Table 1) profoundly




**Scheme 1.** Synthesis of dibenzofuran conjugated homoisoflavonoids **7a–k**. Reaction conditions: (i) $HBr/H_2SO_4$, DCM, 12 h (ii) **4a**–**k**, $K_2CO_3$, Acetone, 6–7 h (iii) aq KOH, Acetone, 12 h (iv) TFAA, DCM, reflux, 8 h.

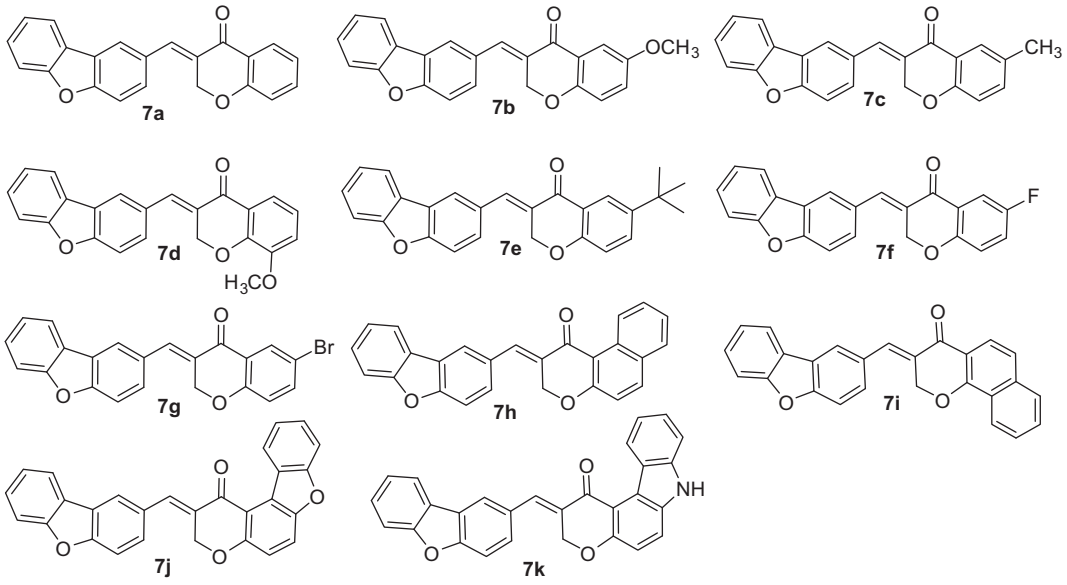



**Figure 4.** Structures of dibenzofuran embodied homoisoflavonoids **7a–k**.

**Table 2**
Physical data and antitubercular evaluation of **7a–k**. against *M. tuberculosis* $H_{37}RV$

| Entry | Phenols **4** | Intermediate compounds | | | homoisoflavonoids | | Mp (°C) | Log*P*/CLogP[b] | MIC (μg/mL) |
|---|---|---|---|---|---|---|---|---|---|
| | | **5** | **6** | Yield[a] **3** to **6** (%) | **7** | Yield[a] (%) | | | |
| 1 | **4a** | **5a** | **6a** | 90 | **7a** | 82 | 115 | 3.69/5.69 | 25.0 |
| 2 | **4b** | **5b** | **6b** | 86 | **7b** | 80 | 88 | 3.56/5.72 | 25.0 |
| 3 | **4c** | **5c** | **6c** | 83 | **7c** | 76 | 96 | 4.17/6.19 | 25.0 |
| 4 | **4d** | **5d** | **6d** | 88 | **7d** | 73 | 98 | 3.56/5.72 | 25.0 |
| 5 | **4e** | **5e** | **6e** | 82 | **7e** | 70 | 116 | 5.39/7.52 | 25.0 |
| 6 | **4f** | **5f** | **6f** | 85.5 | **7f** | 71 | 119 | 3.84/5.88 | 12.5 |
| 7 | **4g** | **5g** | **6g** | 90 | **7g** | 89 | 67 | 4.51/6.60 | 12.5 |
| 8 | **4h** | **5h** | **6h** | 90 | **7h** | 85 | 119 | 4.68/6.86 | 25.0 |
| 9 | **4i** | **5i** | **6i** | 86 | **7i** | 80 | 126 | 4.68/6.86 | 25.0 |
| 10 | **4j** | **5j** | **6j** | 83 | **7j** | 68 | 85 | 4.35/7.63 | 25.0 |
| 11 | **4k** | **5k** | **6k** | 88 | **7k** | 75 | 96 | 4.38/7.20 | 25.0 |
| 12 | — | — | | — | Isoniazid | — | — | 0.1 | |
| 13 | — | — | | — | Ethambutol | — | — | 3.13 | |
| 14 | — | — | | — | Pyrazinamide | — | — | 50.0 | |

[a] Isolated yields.
[b] Calculated using chemdraw ultra 11.0.

decreased their MIC values 25 μg/mL to 12.5 μg/mL. log*P*/C log*P* values of studied compounds **7a**–**k** were calculated using Chem Bio Draw Ultra 11.0. The described log*P* (*C*log*p*) values are the mean of lipophilic contributions of individual atoms, fragments and the pairs of interacting fragments in the chemical structure. Structural correlations of the newly synthesized compounds **7a**–**k** with respect to their antitubercular activity reveal that introduction of electron with drawing groups such as fluoro/ bromo decreases log *P* (Clog p) values with increased antitubercular activity (Table 2, entries 6 and 7)

In conclusion we have synthesized a novel series of dibenzofuran embodied homoisoflavonoids **7a**–**k** designed by molecular

hybridization. The sequence of reactions employed are (i) base catalyzed Baylis–Hillmann (BH) reaction of 2-dibenzofuran carboxaldehyde and methyl acrylate (ii) bromination of BH adduct (iii) condensation of resulted allylic bromide with substituted phenols or 2-dibenzofuranol followed by cyclization. All the products obtained in very good yields were characterized by spectra data. Screening all these new derivatives against *M. tuberculosis* H37Rv (MTB) resulted homoisoflavonoids **7f** and **7g** as most potent antitubercular agents with MIC 12.5 μg/mL. Structure–activity correlations of the new compounds **7a–k** with respect to their antitubercular activity reveal that natural homoisoflavonoids were tuned for first time to act as potent antitubercular agents by conjugating with dibenzofuran unit. The results observed here is useful to generate novel natural product like potent antimycobacterial homoisoflavonoids.

## Acknowledgments

Authors (S.K. and T.Y.) are thankful to Dr. J. S. Yadav, Director and Dr. V.J. Rao, Head, CPC Division (Organic Chemistry Division-II), CSIR-IICT, Hyderabad for their continuous support, encouragement and financial assistance from MLP & Net Work projects. T.Y. (SRF) is thankful to CSIR for fellowship.

## Supplementary data

Supplementary data (copies of $^{1}H$, $^{13}C$ NMR and mass spectra of all the new compounds **2**, **3** & **7a–k** and $^{1}H$ NMR of **6a–k**) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bmcl.2012.10.056.

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13. *Methyl 2-(dibenzo[b,d]furan-2-yl(hydroxy)methyl)acrylate 2* dibenzo[*b,d*]furan-2-carbaldehyde **1** (1.0 g, 5 mmol) and DABCO (0.571 g, 5 mmol) was added methyl acrylate (2.75 mL, 40 mmol) at room temperature and continue stirring. After 7 days (tlc) the reaction mixture was diluted with ethyl acetate (20 mL), washed successively with 2 N HCl (2 × 5 mL), water (2 × 5 mL) and saturated $NaHCO_3$ solution (5 mL) and dried over anhyd. $Na_2SO_4$. The solvent was evaporated under vacuum and crude residue thus obtained was chromatographed over silica gel (hexane: ethyl acetate; 8:1) to give methyl 2-(dibenzo[*b,d*]furan-2-yl(hydroxy) methyl)acrylate **2** as pale red thick syrup. $^{1}H$ NMR (300 MHz, $CDCl_3$) $\delta$: 7.94–7.82 (m, 2H), 7.58–7.44 (m, 2H), 7.43–7.35 (m, 2H), 7.28 (t, *J* = 7.5 Hz, 1H), 6.31 (s, 1H), 5.86–5.82 (m, 1H), 5.65 (s, 1H), 3.70 (s, 3H), 3.10 (br, s, 1H). $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$: 166.7, 156.5, 142.1, 140.9, 135.8, 127.2, 126.0, 125.8, 122.7, 121.2, 120.7, 118.8, 111.6, 111.4, 109.2, 73.1, 51.9. IR (KBr, $Cm^{-1}$) 3450(br), 2951, 1718, 1629, 1478, 1446, 1196, 1149, 1040, 816, 750. ESI-MS found $(M+Na)^{+}$ =305 for $C_{17}H_{14}O_4$.
14. *(Z)-methyl 2-(bromomethyl)-3-(dibenzo[b,d]furan-2-yl)acrylate 3*: Methyl 2-(dibenzo[*b,d*]furan-2-yl(hydroxy)methyl)acrylate **2** (2.05 g, 8.8 mmol) in dry dichloromethane (30 mL) at 0 °C was added slowly aq. HBr (1.43 mL, 26 mmol) and conc. $H_2SO_4$ (2.59 mL, 48.7 mmol) and stirred at room temperature for 12 h. The reaction mixture was diluted with dichloromethane (20 mL), poured in water (20 mL). The organic layer was separated, washed with water (2 × 10 mL), dried over anhyd. $Na_2SO_4$ and evaporated to dryness. The crude residue thus obtained chromatographed over silica gel column eluted with hexane: ethyl acetate (9:1) to give required (*Z*)-methyl 2-(bromomethyl)-3-(dibenzo[*b,d*]furan-2-yl) acrylate **3** (2.5 g, 83%) as brown colored solid. mp 108–112 °C. $^{1}H$ NMR (300 MHz, $CDCl_3$) $\delta$: 8.26(s,1H), 8.02–7.92(m, 2H), 7.70–7.53(m, 3H), 7.47(t, *J* = 8.309 Hz, 1H), 7.36 (t, *J* = 7.3 Hz, 1H), 4.46(s, 1H), 3.90(s, 3H). $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$: 166.6, 156.6, 156.5, 143.1, 129.2, 128.9, 127.8, 127.5, 124.9, 124.7, 123.1, 122.1, 120.8, 112.1, 111.8, 52.4, 27.2. IR (KBr, $Cm^{-1}$) 2923, 1699, 1582, 1433, 1313, 1196, 1075, 839, 756. EI-MS found M+ =344 for $C_{17}H_{13}BrO_3$.
15. *General procedure for the condensation of phenols **4a–k** with (Z)-methyl 2-(bromomethyl)-3-(dibenzo[b,d]furan-2-yl)acrylate*: To a mixture of (*Z*)-methyl 2-(bromomethyl)-3-(dibenzo[*b,d*]furan-2-yl)acrylate **3** (0.5 mmol) and $K_2CO_3$ (0.5 mmol) in acetone (4 mL) was added phenols **4a–k** (0.5 mmol) and refluxed for 6–7 h. After completion, reaction mixture was concentrated under reduced pressure, residue was dissolved in ethyl acetate (20 mL) and water (10 mL), and organic layer was separated, washed with brine solution (2 × 10 mL, dried over $Na_2SO_4$ and concentrate on rotary evaporator to give **5a–k** as colorless thick syrup. Usually the products **5a–k** obtained were pure enough to proceed directly to the next step without any further characterization.
16. *General procedure for the synthesis of compounds **6a–k***: to a solution of acrylates **5a–k** (1.0 mmol) in acetone (4 mL) was added KOH (1.5 mmol) and 3 drops of water with stirring at room temperature for about 12 h. After completion of reaction, the solvent was evaporated, water (10 mL) was added and acidified with AcOH to a PH of 6.0, extracted the reaction mixture with ethyl acetate (3 × 10 mL). The combined organic layer was washed with brine, dried over $Na_2SO_4$ and evaporated under reduced pressure. The residue obtained was chromatographed over silica gel (hexane: ethyl acetate, 1:1) resulted pure compounds **6a–k**.
*(E)-3-(dibenzo[b,d]furan-2-yl)-2-(phenoxymethyl)acrylicacid (**6a**)* white solid. $^{1}H$ NMR (300 MHz, DMSO-$d_6$) $\delta$: 8.17(s, H), 8.14 (d, *J* = 1.5 Hz, 1H), 7.63–7.54(m, 4H), 7 .45(t, *J* = 7.3 Hz, 1H), 7.37–7.31(m, 3H), 7.27(t, *J* = 7.3 Hz, 1H), 7.06–6.99(m, 2H), 4.87(s, 2H). *(E)-3-(dibenzo[b,d]furan-2-yl)-2-((4-methoxyphenoxy)methyl) acrylic acid (**6b**)* white solid. $^{1}H$ NMR(300 MHz, DMSO-$d_6$) $\delta$: 8.14(d, *J* = 8.1, 2H), 7.62–7.49(m, 4H), 7.42(t, *J* = 7.7 Hz, 1H), 7.27(t, *J* = 7.7, 1H), 6.96(d, *J* = 9.0 Hz, 2H), 6.84(d, *J* = 9.0 Hz, 2H), 4.80(s, 2H), 3.79(s, 3H). *(E)-3-(dibenzo[b,d]furan-2-yl)-2-(p-tolyloxy methyl)acrylic acid (**6c**)* light yellow solid. $^{1}H$ NMR (300 MHz, DMSO-$d_6$) $\delta$: 8.13(d, *J* = 7.9, 2H), 7.64–7.50(m, 4H), 7.43(t, *J* = 7.5 Hz, 1H), 7.25(t, *J* = 7.5, 1H), 7.12(d, *J* = 8.4 Hz, 2H), 6.91(d, *J* = 8.4 Hz, 2H), 4.82(s, 2H), 2.34(s,3H). *(E)-3-(dibenzo[b,d]furan-2-yl)-2-((2-methoxy phenoxy)methyl) acrylic acid (6d)* yellow solid. $^{1}H$ NMR (300 MHz ,DMSO-$d_6$) $\delta$: 8.26(s, 1H), 8.15(s, 1H), 7.67(d, *J* = 8.0 Hz, 2H), 7.57 (t, *J* = 9.5 Hz, 2H), 7.46 (t, *J* = 7.3 Hz, 1H), 7.30(t, *J* = 7.3 Hz, 1H), 7.04 (d, *J* = 8.0 Hz, 1H), 7.01–6.94(m, 2H), 6.92–6.85(m, 1H), 4.85(s, 2H), 3.84(s, 3H). *(E)-2-((4-tert-butylphenoxy)methyl)-3-(dibenzo[b,d]furan-2-yl)acrylic acid(**6e**)* white solid. $^{1}H$ NMR (300 MHz, DMSO-$d_6$) $\delta$: 8.14(s, 1H), 8.07(s, 1H), 7.79(d, *J* = 12.8 Hz, 1H), 7.62–7.50(m, 2H), 7.48–7.38(m ,2H), 7.34(d, *J* = 8.6 Hz, 2H), 7.21 (t, *J* = 7.3 Hz, 1H), 6.95 (d, *J* = 8.6 Hz, 2H), 4.83(s, 2H), 1.35(s, 9H).*(E)-3-(dibenzo[b,d]furan-2-yl)-2-((4-fluorophenoxy)methyl) acrylic acid (**6f**)* pale yellow solid. $^{1}H$ NMR (300 MHz, DMSO-$d_6$) $\delta$: 8.17(s, 1H), 8.11(s, 1H), 7.66–7.50(m, 4H), 7.43(t, *J* = 7.7 Hz, 1H), 7.29(t, *J* = 7.3 Hz, 1H), 7.06–6.94(m, 4H), 4.83(s, 2H). *(E)-2-((4-*

*bromophenoxy)methyl)-3-(dibenzo[b,d]furan-2-yl) acrylic acid (**6g**)* White solid . $^1$H NMR(300 MHz, DMSO-$d_6$) $\delta$ : 8.19(s, 1H), 8.11(s, 1H), 7.67–7.54(m, 4H), 7.50–7.39(m, 3H), 7.31(t, $J$ = 7.3 Hz, 1H), 6.98(d, $J$ = 8.8 Hz, 2H), 4.83(s, 2H). *(E)-3-(dibenzo[b,d]furan-2-yl)-2-((naphthalen-2-yloxy)methyl) acrylic acid(**6h**)* white solid. $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$: 8.19(s, 1H), 8.16(s, 1H), 7.82(t, $J$ = 8.8 Hz, 2H), 7.74–7.27(m, 10H), 7.15(t, $J$ = 7.9 Hz, 1H), 4.85(s, 2H). *(E)-3-(dibenzo[b,d]furan-2-yl)-2-((naphthalen-1-yloxy)methyl) acrylic acid(**6i**)* white solid. $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$: 8.34 (d, $J$ = 8.1 Hz, 1H), 8.25(s, 1H), 8.17(s, 1H), 7.86(d, $J$ = 7.9 Hz, 1H) 7.62(d, $J$ = 8.4 Hz, 1H), 7.56–7.32(m, 8H), 7.13-7.02(m, 1H), 6.97(d, $J$ = 7.3 Hz, 1H), 5.03(s, 2H). *(E)-3-(dibenzo[b,d]furan-2-yl)-2-((dibenzo[b,d]furan-2-yloxy)methyl) acrylic acid (B)* White solid. $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$: 8.23(s, 1H), 8.20(s, 1H), 8.00–7.80(m, 2H), 7.68–7.58(m, 3H), 7.57–7.50(m, 3H), 7.47–7.36(m, 2H), 7.28(t, $J$ = 7.3 Hz, 1H), 7.23–7.14(m, 2H),4.98(s, 2H). *(E)-2-((9H-carbazol-3-yloxy)methyl)-3-(dibenzo [b,d]furan-2-yl)acrylic acid (**6k**)* White solid. $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$: 10.72(br s, 1H), 8.24–8.14(m, 2H), 7.99–7.89(m, 2H), 7.63(d, $J$ = 8.8 Hz, 1H), 7.59–7.43(m, 3H), 7.42–7.31(m, 2H), 7.26(t, $J$ = 7.7 Hz, 1H), 7.15–7.03(m, 3H), 6.91(dd, $J$ = 1.1, 8.4 Hz, 1H), 4.96(s, 2H).

17. *General procedure for the synthesis of dibenzofuran embodied homoisoflavonoids **7a–k***: to a solution of **6a–k** (1 mmol) in anhydrous dichloro methane (4 mL) was added trifluoroacetic anhydride (TFAA, 1.2 mmol). After refluxing for 8 h, the reaction mixture was concentrated and chromatographed over silica gel column eluted with hexane: ethylacetate (7:1) to give required homoisoflavonoids (**7a–k**) as white solids. *(E)-3-(dibenzo[b,d]furan-2-ylmethylene) chroman-4-one (7a)* white solid; mp 140 °C. $^1$H NMR (300 MHz, $CDCl_3$) $\delta$: 8.05–7.93(m, 3H), 7.88(t, $J$ = 1.5 Hz, 1H), 7.65–7.55(m, 2H), 7.53–7.43(m, 2H), 7.42–7.28(m, 2H), 7.06(t, $J$ = 8.3 Hz, 1H), 6.94(d, $J$ = 8.3 Hz, 1H), 5.43(d, $J$ = 2.2, 2H). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$: 182.3, 161.0, 156.6, 156.5, 137.8, 135.9, 130.0, 129.3, 127.9, 127.8, 125.1, 124.8, 123.4, 123.1, 122.3, 121.9, 120.8, 117.8, 112.9, 112.0, 111.8, 67.6. IR (KBr, $Cm^{-1}$) 2923, 2853, 1670, 1604, 1469, 1320, 1197, 1020, 840, 743 .EI-MS found $M^+$ =326 for $C_{22}H_{14}O_3$. *(E)-3-(dibenzo[b,d]furan-2-ylmethylene)-6-methoxy chroman-4-one (**7b**)* pale yellow solid; mp130 °C. $^1$H NMR (300 MHz, $CDCl_3$) $\delta$: 8.03–7.92(m, 2H), 7.88(d, $J$ = 1.5 Hz, 1H), 7.65–7.55(m, 2H), 7.48 (dt, $J$ = 1.1, 7.7, 1H), 7.43–7.32(m, 3H), 7.06 (dd, $J$ = 3.1, 9.0 Hz, 1H), 6.88(d, $J$ = 8.8 Hz, 1H), 5.38 (d, $J$ = 1.1, 2H), 3.85(s, 3H). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$: 182.0, 156.6, 156.4, 154.4, 137.5, 130.4, 130.2, 129.3, 127.8, 127.3, 125.0, 123.9, 123.4, 123.15, 122.3, 121.9, 120.7, 119.1, 112.0, 111.8, 108.1, 67.6, 55.8. IR (KBr, $Cm^{-1}$) 2923, 1670, 1603, 1490, 1429, 1287, 1198, 1136, 1037, 815, 743. EI-MS found $M^+$ =356 for $C_{23}H_{16}O_4$ and HRMS calculated for $[M+H]^+$ is 357.1126, found 357.1144. *(E)-3-(dibenzo[b,d]furan-2-ylmethylene)-6-methylchroman-4-one (**7c**)* brown solid; mp 146 °C. $^1$H NMR (300 MHz, $CDCl_3$) $\delta$: 8.02–7.93(m, 2H), 7.88(d, $J$ = 1.5 Hz, 1H), 7.80(d, $J$ = 2.2 Hz, 1H), 7.64–7.55(m, 2H), 7.53–7.31(m, 3H), 7.30–7.24(m, 1H), 6.84(d, $J$ = 8.3 Hz, 1H), 5.39 (d, $J$ = 1.5 Hz, 2H), 2.37(s, 3H). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$: 182.2, 159.0, 156.6, 156.4, 137.4, 136.8, 131.3, 130.3, 129.3, 127.8, 127.4, 125.0, 124.8, 123.4, 123.1, 122.3, 121.6, 120.7, 117.6, 111.9, 111.8, 67.6, 29.6. IR (KBr, $Cm^{-1}$) 2923, 1659, 1590, 1483, 1421, 1292, 1188, 1023, 823, 749. EI-MS found $M^+$ =340 for $C_{23}H_{16}O_3$. **(E)-3-(dibenzo[b,d]furan-2-ylmethylene)-8-methoxychroman-4-one (7d)** black solid; mp125 °C. $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ : 8.03–7.86(m, 2H), 7.69–7.27(m, 5H), 7.10–6.84(m, 3H), 5.48(d, $J$ = 2.2 Hz, 2H), 3.87(s, 3H). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$: 182.0, 156.5, 156.4, 150.9, 137.7, 129.6, 129.5, 129.3, 127.8, 127.4, 123.1, 122.9, 122.4, 122.2, 121.3, 120.7, 119.0, 116.5, 111.9, 111.8, 111.6, 68.1, 56.1. IR (KBr, $Cm^{-1}$) 2922, 2852, 1706, 1669, 1486, 1258, 1196, 1021, 839, 747. EI-MS found $M^+$ =356 for $C_{23}H_{16}O_4$ and HRMS calculated for $[M+H]^+$ is 357.1126, found 357.1134. *(E)-6-tert-butyl-3-(di benzo[b,d]furan-2-ylmethylene)chroman-4-one (**7e**)* White solid; mp 132 °C. $^1$H NMR (300 MHz, $CDCl_3$) $\delta$: 8.01–7.92(m, 2H), 7.88(d, $J$ = 1.5 Hz, 1H), 7.64–7.28(m, 7H), 6.87 (d, $J$ = 8.3 Hz, 1H), 5.40(d, $J$ = 2.2 Hz, 2H), 1.37(s, 9H). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$: 182.4, 158.9, 156.6, 156.4, 144.8, 137.3, 133.5, 130.4, 129.3, 127.8, 124.8, 123.8, 123.5, 123.1, 122.3, 121.2, 120.8, 117.4, 111.9, 111.8, 67.5, 34.3, 31.2. IR (KBr, $Cm^{-1}$) 2957, 2925, 1678, 1615, 1475, 1418, 1292, 1250, 1193, 1122, 1014, 829, 755. EI-MS found $M^+$ =382 for $C_{26}H_{22}O_3$ and HRMS calculated for $[M+H]^+$ is 383.1647, found 383.1652. *(E)-3-(dibenzo[b,d]furan-2-ylmethylene)-6-fluoro chroman-4-one (**7f**)* yellow solid; mp 124 °C. $^1$H NMR (300 MHz, $CDCl_3$) $\delta$: 8.04(m, 1H), 7.97(dd, $J$ = 0.5,7.3 Hz, 1H), 7.89(d, $J$ = 1.5 Hz, 1H), 7.73–7.58(m, 3H), 7.56–7.46(m, 1H), 7.45–7.32(m, 2H), 7.26–7.15(m, 2H) 7.03–6.92(m, 1H), 5.44(d, $J$ = 1.7, 2H). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$: 182.3, 156.7, 156.0, 154.1, 138.3, 129.7, 129.3, 127.9, 123.4, 123.2, 123.1, 122.7, 122.4, 120.8, 119.5, 119.4, 114.0, 113.0, 112.7, 112.1, 111.9, 67.8. IR (KBr, $Cm^{-1}$) 2924, 2854, 1738, 1662, 1579, 1492, 1291, 1194, 1126, 1032, 816, 741. EI-MS found $M^+$ =344 for $C_{22}H_{13}FO_3$ and HRMS calculated for $[M+H]^+$ is 345.0926, found 345.0912. *(E)-3-(dibenzo[b,d]furan-2-yl methylene)-6-bromochroman-4-one(**7g**)* pale yellow solid; mp 60 °C. $^1$H NMR (300 MHz, $CDCl_3$) $\delta$: 8.07–8.03(m, 1H), 7.98(s, 1H), 7.68–7.62(m, 2H), 7.61–7.52(m, 3H), 7.51–7.42(m, 2H), 7.38(t, $J$ = 7.3 Hz, 1H), 6.91(d, $J$ = 8.6 Hz, 1H), 5.48(d, $J$ = 1.3 Hz, 2H). IR (KBr, $Cm^{-1}$) 2924, 2853, 1740, 1670, 1599, 1467, 1282, 1197, 1125, 1020, 818, 742. EI-MS found $M^+$ =404 for $C_{22}H_{13}BrO_3$. *(E)-2-(dibenzo [b,d]furan-2-ylmethylene)-2,3-dihydro-1H-benzo[f]chromen-1-one (**7h**)* white solid; mp 114 °C. $^1$H NMR (300 MHz, $CDCl_3$) $\delta$: 9.45 (d, $J$ = 8.4 Hz, 1H), 8.04(s, 1H), 7.98–7.85(m, 3H), 7.76–7.55(m, 4H), 7.53–7.29(m, 4H), 7.07(d, $J$ = 8.8 Hz, 1H), 5.46(d, $J$ = 1.5 Hz, 2H). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$: 182.3, 162.9, 156.6, 156.3, 138.8, 137.3, 136.8, 131.8, 131.3, 130.0, 129.4, 129.1, 128.4, 127.7, 127.2, 126.4, 124.9, 123.5, 123.1, 122.1, 120.7, 118.6, 114.2, 111.9, 111.8, 67.4. IR (KBr, $Cm^{-1}$) 2922, 1653, 1594, 1432, 1238, 1195, 1141, 815, 744. EI-MS found $M^+$ =376 for $C_{26}H_{16}O_3$ and HRMS calculated for $[M+H]^+$ is 377.1177, found 377.1181 . *(E)-3-(dibenzo [b,d]furan-2-ylmethylene)-2H-benzo[h]chromen-4(3H)-one (**7i**)* yellow solid; mp 180 °C. $^1$H NMR (300 MHz, $CDCl_3$) $\delta$: 8.23 (d, $J$ = 8.309 Hz, 1H), 8.08–7.90(m, 4H), 7.78(d, $J$ = 8.3 Hz, 1H), 7.76–7.42(m, 7H), 7.37(t, $J$ = 7.5 Hz, 1H), 5.69(d, $J$ = 2.2 Hz, 2H). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$: 182.5, 162.2, 156.7, 156.4, 140.0, 139.6, 137.4, 137.1, 136.9, 130.6, 129.6, 129.3, 127.8, 127.3, 126.2, 125.0, 124.8, 123.4, 123.1, 122.5, 122.3, 121.5, 120.8, 112.0, 111.9, 68.3. IR (KBr, $Cm^{-1}$) 2923, 2854, 1742, 1663, 1594, 1453, 1283, 1195, 1100, 813, 740. EI-MS found $M^+$ =376 for $C_{26}H_{16}O_3$. *(E)-2-(di benzo[b,d]furan-2-ylmethylene)-2,3-dihydro-1H-benzofuro [3,2-f]chromen-1-one (**7j**)* White solid; mp 194 °C. $^1$H NMR (300 MHz, $CDCl_3$) $\delta$: 9.14 (d, $J$ = 7.5 Hz, 1H), 8.11(s, 1H), 7.99–7.90 (m, 2H), 7.71–7.30(m, 9H), 7.06(d, $J$ = 9.0 Hz, 1H), 5.44(d, $J$ = 1.5 Hz, 2H). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$: 183.2, 168.7, 165.2, 158.8, 157.8, 156.7, 156.5, 147.3, 139.9, 137.5, 130.4, 129.3, 128.4, 127.8, 127.2, 123.5, 123.1, 122.6, 122.3, 120.8, 119.0, 117.1, 117.0, 112.0, 111.9, 111.7, 111.2, 67.8. IR (KBr $Cm^{-1}$) 2923, 2853, 1669, 1591, 1434, 1307, 1274, 1193, 1081, 1019, 816, 743. EI-MS found $M^+$ =416 for $C_{28}H_{16}O_4$. *(E)-2-(dibenzo[b,d]furan-2-ylmethylene)-2,3-dihydro pyrano [2,3-c]carbazol-1(7H)-one (**6l**)* yellow solid; mp 178 °C. $^1$H NMR (300 MHz, $CDCl_3$) $\delta$: 11.82-11.80(br, 1H), 8. 27–8.11(m, 3H), 8.03–7.95(m, 2H), 7.79–7.48(m, 5H), 7.42(t, $J$ = 7.1 Hz, 1H), 7.33(t, $J$ = 7.3 Hz, 1H), 7.18(t, $J$ = 7.3 Hz, 1H), 6.76(d, $J$ = 8.3 Hz, 1H), 5.59 (d, $J$ = 0.9 Hz, 2H). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$: 181.3, 168.6, 155.8, 155.6, 144.7, 142.9, 140.1, 138.4, 137.8, 135.2, 133.5, 130.2, 129.7, 128.9, 128.3, 127.7, 124.4, 123.0, 122.7, 121.6, 119.5, 118.9, 117.4, 112.2, 111.7, 111.4, 107.7, 67.5. IR (KBr, $Cm^{-1}$) 2923, 2854, 1742, 1653, 1596, 1457, 1319, 1192, 1117, 1011, 818, 750. EI-MS found $M^+$ =415 for $C_{28}H_{17}NO_3$.

18. *Antitubercular evaluation assay*: tenfold serial dilutions of each test compounds **7a–k** and drugs were prepared and incorporated into Middlebrook 7H11 agar medium with OADC Growth Supplement. Inoculum of *M. tuberculosis* $H_{37}Rv$ ATCC 27294 was prepared from fresh Middlebrook 7H11 agar slants with OADC (oleic acid, albumin, dextrose and catalase; Difco) Growth Supplement adjusted to 1 mg/mL (wet weight) in Tween 80 (0.05%) saline diluted to $10^{-2}$ to give a concentration of $\sim 10^7$ cfu/mL. A 5 μL amount of bacterial suspension was spotted into 7H11 agar tubes containing 10-fold serial dilutions of drugs per mL. The tubes were incubated at 37 C, and final readings were recorded after 28 days. This method is similar to that recommended by the National Committee for Clinical Laboratory Standards for the determination of MIC in triplicate.