Chem Biol Drug Des 2012; **80:** 1003–1008

doi: 10.1111/j.1747-0285.2012.01436.x

Research Letter

Evaluation of Structurally Diverse Benzoazepines Clubbed with Coumarins as *Mycobacterium tuberculosis* Agents

Kuldip Upadhyay[1], Atul Manvar[2,†], Kena Rawal[3], Sudhir Joshi[4], Jalpa Trivedi[5], Ravi Chaniyara[6] and Anamik Shah[2,*]

[1]R & D Division, Gujarat Narmada Valley Fertilizers Company Limited, Narmadanagar-392015, Gujarat, India
[2]National Facility for Drug Discovery, Department of Chemistry, Saurashtra University, Rajkot-360005, Gujarat, India
[3]Alembic Research Centre, Alembic Pharmaceuticals Limited, Gujarat, Vadodara-390003, India
[4]Department of Chemistry, H & H. B. Kotak Science Institute, Rajkot-360004, Gujarat, India
[5]Department of Medicinal Chemistry, ISF College of Pharmacy, Moga-142001, Punjab, India
[6]New Drug Discovery Division, Wockhardt Research Centre, Aurangabad-431136, Maharashtra, India
**Corresponding author: Anamik K. Shah, anamik_shah@hotmail.com*
[†]Present address: Centre for Synthesis & Chemical Biology, School of Chemistry & Chemical Biology, University College Dublin, Belfield, Dublin 4, Ireland.

Tuberculosis caused by *Mycobacterium tuberculosis* remains a leading cause of mortality worldwide into 21st century. In continuation with our anti-tuberculosis research programme, in this work, we have prepared molecularly diverse coumarins clubbed with benzothiazepines as well as its aza-analogues-benzodiazepines by molecular hybridization. The resulting compounds were screened for their *M. tuberculosis* activity against H_{37}Rv strains using microplate alamar blue assay. Among the designed diversity, the compounds 5k, 5n and 5o were found significantly active in primary anti-tuberculosis assay at minimum inhibitory concentration <6.25 μM. Moreover, the IC_{50} values of 5k and 5o in level-2 screening were observed as >10 μg/mL and 3.63 μg/mL, respectively. Design and synthesis of more focused library and its three-dimensional quantitative structure activity relationship analysis are underway.

Key words: benzodiazepines, benzothiazepines, coumarins, H_{37}Rv, microplate alamar blue assay, *Mtb*

Received 11 January 2012, revised 13 May 2012 and accepted for publication 5 June 2012

Tuberculosis (TB) is one of the most devastating and second infectious diseases causes of mortality followed by *acquired immune deficiency syndrome (*AIDS). According to world health organization (WHO) statistics, 33% world's population has been exposed to TB bacterium[a]. In the last year, it was anticipated that there may be around 9.8 million new cases[a]. A number of anti-TB drugs are ineffective against TB because of the development of resistant strains (1). The limited effectiveness of current chemotherapy stems largely from the lengthy and complicated nature of first-line anti-TB drugs (2,3). The most problematic issue with the current TB regimen is insufficient adherence to the treatment course, attributable to its length, complexity and adverse effects, led to difficult- and expensive-to-treat multidrug-resistant tuberculosis (MDR-TB) (4). The world's two most populous countries, India and China, account for more than 50% of the world's MDR-TB cases (5). Treatment for MDR-TB typically requires 18–24 months of combination therapy with second-line drugs those are less efficacious, more toxic and expensive than the first-line drugs (6). In few regions, almost 20% of MDR-TB cases were classified as extensively drug-resistant tuberculosis (XDR-TB) (7). The treatment options for XDR-TB are very limited as XDR-TB bacilli are resistant not only to isoniazid and rifampicin, but also to fluoroquinolones and aminoglycosides (8). More recently, another definition of XDR-TB as MDR-TB resistant to any fluoroquinolone and at least one of the second-line drugs (capreomycin, kanamycin and amikacin) used in TB treatment (9). There are serious adverse effects with most MDR-TB and XDR-TB drugs, such as nephrotoxicity and ototoxicity with aminoglycosides, hepatotoxicity with ethionamide and dysglycaemia with gatifloxacin (10). In few cases, XDR-TB has been shown aggressive form of TB, causing very high mortality (10).

The improvement in TB chemotherapy can be achieved by four primary goals: (i) Shorten and simplify TB treatment; (ii) improve efficacy, safety and reduce long-lasting therapy; (iii) develop drugs for HIV-TB co-infection, which can be readily co-administered with antiretrovirals; and (iv) shorten therapy of latent TB infection (11). Moreover, to effectively treat and control MDR- and XDR-TB patients, physicians and national TB treatment programs require regimens based on safer, tolerable and efficacious drugs having new mechanisms of action (12,13). At present, the global TB development pipeline has nine candidates, but a key issue is how to develop them simultaneously in combination trials to identify the best candidate (14).

In this context, recently, we have explored ubiquitous heterocycles, such as coumarins (15–17), 1,4-dihydropyridines (18,19) and quinolines (20) based scaffolds as promising antituberculars. To understand the structure–activity relationship among the designed conjugates, three-dimensional quantitative structure–activity relationship (3D-QSAR) was also conceived. More recently, we have patented tetrahydropyrimidines as potent anti-TB agents (21–23). The molecules were rationally designed and latter synthesized based on its predicted activities by comparative molecular field analysis and comparative molecular similarity index analysis. Among the naturally occurring pyranocoumarins (calanolide A, calanolide B and its stereoisomer), calanolide A is significantly interesting. The biological activity of calanolide A is not only restricted to anti-TB but also found active for HIV infections (24). Moreover, calanolide B is also claimed to have similar range of activity to calanolide A against mycobacteria. Consequently, we focused on coumarin derivatives such as, 4-styryl coumarins (15), 4-arylamino coumarins (16), coumarin-4-acetic acid benzylidenehydrazides (17) and more recently phenylhydrazono-chroman dione (25) as a potent antituberculars. Furthermore, the coumarin nucleuses have also been found as potent antimycobacterials (26–28) (Figure 1). Interestingly, novel acrylic esters (α,β-unsaturated carbonyls) of versatile (hetero)arenes were also proved as potent antituberculars (29). The 1,5-benzo(thi)diazepine motifs are of particular interest for drug discovery because they have been found active against different families of targets (30). Successful introduction of diltiazem and clentiazem for angina pectoris, hypertension, arrhythmias and other related cardiac disorders have proved the potentials of benzothiazepines skeleton (31,32). At present, in an extensive review, we have highlighted the therapeutic significance of 1,5-benzothiazipine pharmacophore (33). Although the biological evaluation of (benzo)azepines, particularly in the anti-TB research area, is still in its infancy (34–36). Consequently, in a present work, we have envisioned to probe molecular hybrids of coumarins with benzoazepines for their activity against *Mycobacterium tuberculosis* $H_{37}Rv$ strains (Figure 2).

At the outset, the syntheses of a versatile library of coumarin clubbed with benzoazepines, compounds **5a**–**o** and **7a**–**k** are depicted in Scheme 1. The chalcone derivatives were prepared by Claisen–Schmidt condensations (37). The 3-acetyl-4-hydroxycoumarin **3** was treated with (hetero)aromatic aldehydes using mild base, afforded chalcone derivatives **4**. The resulting chalcones were treated with 2-aminothiophenol by employing piperidine as a catalyst at elevated temperature, afforded compounds **5a**–**o** in good to excellent

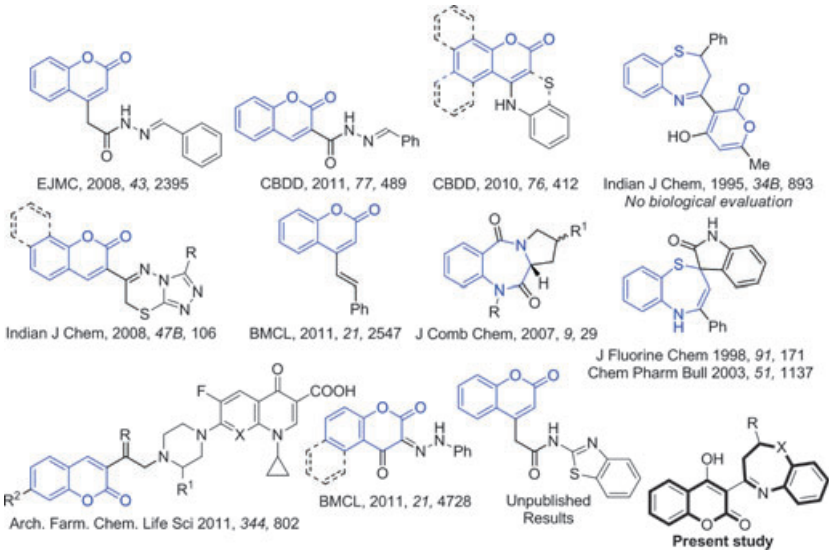


Figure 1: Examples of coumarines and benzoazepines as a potent *Mycobacterium tuberculosis* agents **(1)**.

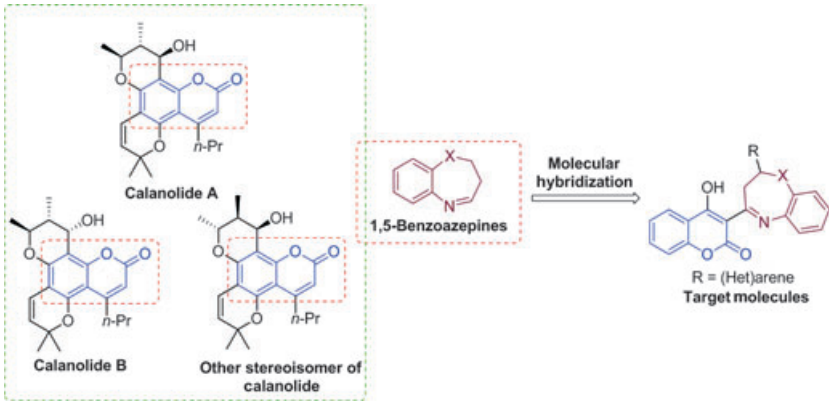
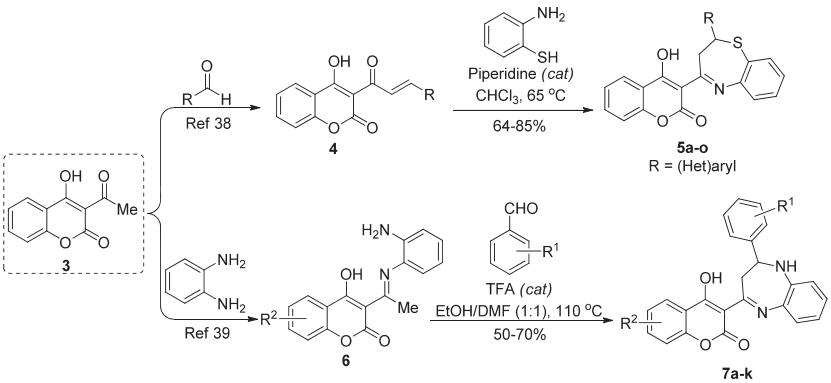
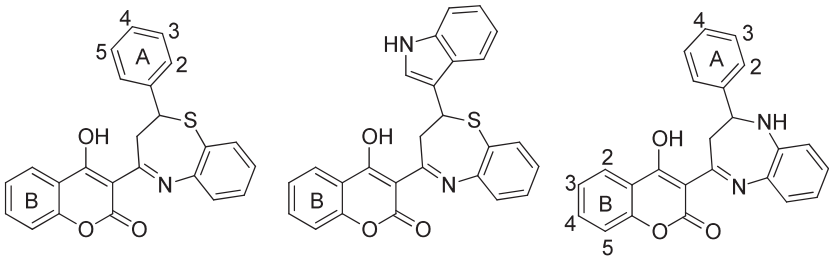


Figure 2: Molecular hybridization concept for design of the target molecules **(2)**.



Scheme 1: Synthesis of compounds **5a**–**o** and **7a**–**k**.

Table 1: Antimycobacterial activity of the compounds **5a–o** and **7a–k**



Compounds	Ring A	Ring B	GI (%)[a]	MIC (μg/mL)[b]	ClogP[c]
5a	2-NO_2	H	4	<6.25	5.717
5b	3-NO_2	H	2	<6.25	5.797
5c	2-OMe	H	8	<6.25	5.973
5d	3-OMe	H	3	<6.25	5.973
5e	4-OMe	H	2	<6.25	5.973
5f	2-Cl	H	60	<6.25	6.767
5g	3-Cl	H	8	<6.25	6.767
5h	4-Cl	H	13	<6.25	6.767
5i	4-F	H	72	<6.25	6.197
5j	4-OH	H	32	<6.25	5.387
5k[d]	4-NO_2	H	93	<6.25	5.797
5l	3,4,5-tri OMe	H	9	<6.25	5.354
5m	3-OH	H	3	<6.25	5.387
5n	Indolyl	H	80	<6.25	6.044
5o[d]	2-OH	H	94	<6.25	5.337
7a	3-OPh	3-Me	35	>6.25	7.471
7b	4-OH	3-Me	30	>6.25	4.706
7c	3-OH	2,5-di Me	27	>6.25	5.205
7d	4-OH	H	19	>6.25	4.207
7e	4-SMe	3-Me	12	>6.25	5.932
7f	4-SMe	2,5-di Me	11	>6.25	6.431
7g	3-OH	3-Me	9	>6.25	4.706
7h	4-OMe	2,5-di Me	7	>6.25	5.791
7i	4-Cl	2,5-di Me	4	>6.25	6.585
7j	3-Br	H	2	>6.25	5.737
7k	4-OMe	3-Me	0	>6.25	5.292

MIC, minimum inhibitory concentration.

[a](GI) Growth inhibitions of virulent strain of *Mycobacterium tuberculosis*.

[b]MIC of Rifampin: 0.015–0.125 μg/mL against *M. tuberculosis* $H_{37}Rv$ (97% inhibition).

[c]ClogP is calculated on ChemDraw Ultra 12.0.

[d]The IC_{50} (μg/mL) values of **5k** and **5o** were found as >10 and 3.63, respectively.

yields. The imine derivatives **6** were prepared by literature described method (38). Latter, the corresponding imines were treated with aldehydes by employing trifluoroacetic acid as a catalyst at higher temperature, afforded easy accessible compounds **7a**–**k** in moderate to good yields (see Appendix S1). Both electron-rich and electron-deficient as well as sterically hindered functional groups were well tolerated under the established reaction conditions. The antimycobacterial activities of synthesized compounds were assessed using the microplate alamar blue assay (MABA) against *Mtb* $H_{37}Rv$ strains (see Appendix S1). The drug rifampin was used as a positive control. The growth inhibitions of rifampin were observed 97% at minimum inhibitory concentration (MIC) (0.015–0.125 μg/mL). The antimycobacterial activities of synthesized compounds are summarized in Table 1. The molecules bearing electron-rich methoxy group in the ring A, compounds **5c, 5d, 5e** and **5l** have shown poor activity. The hydrogen bond donor hydrophilic analogue, compound **5j** has shown 32% growth inhibition, while **5m** has shown very poor potency. The results were quite surprising for the compound **5o** bearing hydroxy group at C2 in the ring A, and have exhibited highest growth inhibition and found significantly active in the designed series. Consequently, we may conclude that the potency of the compounds is not only dependent on the presence of particular functional group but regioselectivity may also play a significant role to determine anti-TB activity in this class of compounds. Among three regio-isomers, compounds **5a, 5b** and **5k** having nitro group in the ring A, the only analogue **5k** has shown excellent activity, while the activities of other two isomers were decreased by manyfolds. Next, we replaced the aromatic ring A by heteroarene indole, compound **5n** was observed noteworthy. Comparison of the regio-isomers (compounds **5f, 5g** and **5h**) having moderate electron-poor chloro group in the ring A, the compound **5f** was found notable. The incorporation of fluorine group into organic molecules can serve to dramatically alter many of the physical properties of the molecules, for instances, lipophilicity, metabolic stability, conformational behaviour, *etc*. For these reasons, we have rationally incorporated electro-negative fluoro surrogate, as a result compound **5i** has shown promising activity. Having elucidated a few potent inhibitors of *Mtb,* we next examined the aza-analogues of benzothiazepines. Few benzodiazepines in the designed series have shown moderate activity. The compound **7a** having sterically hindered phenoxy group in the ring A have exhibited 35% inhibitions. Despite the lower potency, the ClogP values of the compounds **7b, 7d** and **7g** having hydrophilic hydroxyl group in the ring A were found <5. The compound **7k** was observed least active in the designed series. The compounds demonstrating at least 90% inhibitions in the primary screening were retested at lower concentration against *M. tuberculosis* $H_{37}Rv$ to determine the actual MIC in the MABA. The MIC is defined as the lowest concentration effecting a reduction in fluorescence of 90% relative to controls such as isoniazid (ATCC 35822) or rifampin (ATCC 35838). Concurrent with the determination of MICs, the compounds were tested for their cytotoxicity (IC_{50}) in Vero cells at concentrations ≤62.5 mg/mL or ten times the MIC for *M. tuberculosis* $H_{37}Rv$. After 72 h exposure, viability was assessed on the basis of cellular conversion of 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) into a formazan product using the promega cell titre 96 non-radioactive cell proliferation assays. The IC_{50} values of the compounds **5k** and **5o** in level-2 screening were observed as >10 and 3.63 μg/mL respectively. Finally, the effect on compound polarity was estimated by calculating the ClogP for each compounds synthesized on ChemDraw Ultra 12. The thumb rule for ClogP values to a drug-like molecule must be <'5′ to by-pass the cell barrier. The ClogP seems to correlate with some extent in three analogues. Our findings confirmed that electron density, lipophilicity and regioselectivity of the functional groups are enabling to determine the antimycobacterial activity in such compounds.

In summary, a hybrid of coumarins with benzoazepines were synthesized and evaluated for their anti-TB activity against *M. tuberculosis* $H_{37}Rv$ strain. In a primary screening, compounds **5k, 5n** and **5o** have shown 93, 80 and 94 percentage growth inhibitions, respectively, at MIC <6.25 μM. The IC_{50} values of compounds **5k** and **5o** were found to be >10 μg/mL and 3.63 μg/mL, respectively. The coumarin clubbed with benzodiazepines were not found significant scaffold for anti-TB activity. However, the benzothiazepine is considered as one of the scaffolds for further development of potent anti-TB drugs. The syntheses of more focused library especially having small heterocycles instead of ring A in the core structure and its energy minimization prediction by 3D-QSAR is in progress in our laboratory. The findings will be disseminated in due course.

Acknowledgment

Financial support of the Department of Science and Technology (DST), New Delhi (India) under the project entitled 'National Facility for Drug Discovery through New Chemical Entities (NCEs) Development and Instrumentation Support to Small Manufacturing Pharma Enterprise' is gratefully acknowledged. The authors are also thankful to Dr. Cecil Kwong for antimycobacterial screening at Tuberculosis Antimicrobial Acquisition and Coordinating Facility (TAACF), USA.

References

1. Duncan K. (2003) Progress in TB drug development and what is still needed. Tuberculosis;83:201–207.
2. Ginsberg A.M., Spigelman M. (2007) Challenges in tuberculosis drug research and development. Nat Med;13:290–294.
3. Tripathi R.P., Bisht S.S., Ajay A., Sharma A., Misra M., Gupt M.Pd. (2012) Developments in chemical approaches to treat tuberculosis in the last decade. Curr Med Chem;30:488–517.
4. Gandhi N.R., Nunn P., Dheda K., Schaaf H.S., Zignol M., Van Soolingen D., Jensen P., Bayona J. (2010) Multidrug-resistant and extensively drug-resistant tuberculosis: a threat to global control of tuberculosis. Lancet;375:1830–1843.
5. Koul A., Arnoult E., Lounis N., Guillemont J., Andries K. (2011) The challenge of new drug discovery for tuberculosis. Nature;469:483–490.
6. Janin Y.L. (2007) Antituberculosis drugs: ten years of research. Bioorg Med Chem;15:2479–2513.
7. Mitton-Fry M.J., Hanna D. (2012) Current approaches to tuberculosis drug discovery and development, Series No. 14, Chapter 9. Neglected Disease and Drug Discovery. Cambridge, UK: RSC publishing.

8. Raviglione M.C., Smith I.M. (2007) XDR Tuberculosis-implications for global public health. N Engl J Med;356:656–659.
9. Moraski G.C., Markley L.D., Hipskind P.A., Boshoff H., Cho S., Franzblau S.G., Miller M.J. (2011) Advent of imidazo[1,2-*a*]pyridine-3-carboxamides with potent multi- and extended drug resistant antituberculosis activity. ACS Med Chem Lett;2:466–470.
10. Dover L.G., Coxon G.D. (2011) Current status and research strategies in tuberculosis drug development. J Med Chem;54:6157–6165.
11. Yew W.W., Lange C., Leung C.C. (2011) Treatment of tuberculosis: update 2010. Eur Respir J;37:441–462.
12. Nayyar A., Jain R. (2005) Recent advances in new structural classes of anti-tuberculosis agents. Curr Med Chem;12:1873–1886.
13. Da Silva P.E.A., Palomino J.C. (2011) Molecular basis and mechanisms of drug resistance in *Mycobacterium tuberculosis*: classical and new drugs. J Antimicrob Chemother;66:1417–1430.
14. Yew W.W., Cynamon M., Zhang Y. (2011) Emerging drugs for the treatment of tuberculosis. Expert Opin Emerging Drugs;16:1–21.
15. Upadhyay K., Bavishi A., Thakrar S., Radadiya A., Vala H., Parekh S., Bhavsar D., Savant M., Parmar M., Adlakha P., Shah A. (2011) Synthesis and biological evaluation of 4-styrylcoumarin derivatives as inhibitors of TNF-α and IL-6 with anti-tubercular activity. Bioorg Med Chem Lett;21:2547–2549.
16. Virsodia V., Shaikh M.S., Manvar A., Desai B., Parecha A., Loriya R., Dholariya K., Patel G., Vora V., Upadhyay K., Denish K., Shah A., Coutinho E.C. (2010) Screening for in vitro antimycobacterial activity and three-dimensional quantitative structure-activity relationship (3D-QSAR) study of 4-(arylamino)coumarin derivatives. Chem Biol Drug Des;76:412–424.
17. Manvar A., Malde A., Verma J., Virsodia V., Mishra A., Upadhyay K., Acharya H., Coutinho E.C., Shah A. (2008) Synthesis, antitubercular activity and 3D-QSAR study of coumarin-4-acetic acid benzylidene hydrazides. Eur J Med Chem;43:2395–2403.
18. Manvar A., Pissurlenkar R.R.S., Virsodia V., Upadhyay K., Manvar D., Mishra A., Acharya H., Parecha A., Dholakia C., Shah A., Coutinho E.C. (2011) Synthesis, in vitro antitubercular activity and 3D-QSAR study of 1,4-dihydropyridines. Mol Divers;14:285–305.
19. Kharkar P.S., Desai B., Gaveria H., Varu B., Loriya R., Naliapara Y., Shah A., Kulkarni V.M. (2002) Three-dimensional quantitative structure-activity relationship of 1,4-dihydropyridines as antitubercular agents. J Med Chem;45:4858–4867.
20. Dodia N., Shah A. (2000) Synthesis and antitubercular activity of some substituted 3-nitro and 3-bromo-4-hydroxy-2-quinolones. Indian J Heterocy Ch;10:69–70.
21. Virsodia V., Pissurlenkar R.R.S., Manvar D., Dholakia C., Adlakha P., Shah A., Coutinho E.C. (2008) Synthesis, screening for antitubercular activity and 3D-QSAR studies of substituted *N*-phenyl-6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydro-pyrimidine-5-carboxamides. Eur J Med Chem;43:2103–2115.
22. Sarkar D., Sarkar S., Joshi R.R., Khedkar V.M., Pissurlenkar R.R., Coutinho E.C., Shah A.K. (2011) 1,6-Methyl-4-phenyl-5-(phenyl or cycloalkyl) carbamoyl-1,2,3,4-tetrahydropyrimidin-2-one derivatives as antitubercular agents. PCT Int Appl, WO 2011/151701 A1 20111208.
23. Sarkar D., Sarkar S., Joshi R.R., Khedkar V.M., Pissurlenkar R.R., Coutinho E.C., Shah A.K. (2012) Preparation of 6-methyl-4-phenyl-5-(phenyl or cyclohexyl)carbamoyl-1,2,3,4-tetrahydropyrimidin-2-one derivatives as antitubercular agents. Indian Pat Appl IN 2010DE01244 A 20120302.
24. Currens M.J., Gulakowski R.J., Mariner J.M., Moran R.A., Buckheit R.W., Gustafson K.R., McMahon J.B., Boyd M.R. (1996) Antiviral activity and mechanism of action of calanolide A against the human immunodeficiency virus type-1. J Pharmacol Exp Ther;279:645–651.
25. Manvar A., Bavishi A., Radadiya A., Patel J., Vora V., Dodia N., Rawal K., Shah A. (2011) Diversity oriented design of various hydrazides and their in vitro evaluation against *Mycobacterium tuberculosis* H_{37}Rv strains. Bioorg Med Chem Lett;21:4728–4731.
26. Dandia A., Sati M., Arya K., Sharma R., Loupyb A. (2003) Facile one pot microwave induced solvent-free synthesis and antifungal, antitubercular screening of spiro[1,5]-benzothiazepin-2,3′[3′*H*]indol-2[1′*H*]-ones. Chem Pharm Bull;51:1137–1141.
27. Dandia A., Upreti M., Rani B., Pant U.C., Gupta I.J. (1998) Synthesis and antimicrobial evaluation of some new fluorinated spiro[[1,5]-benzothiazepin-2,3′[3′*H*]-indol]-2′(1′*H*)-ones. J Fluorine Chem;91:171–174.
28. Kamal A., Reddy K.L., Devaiah V., Shankaraiah N., Reddy G.S.K., Raghvan S. (2007) Solid-phase synthesis of a library of pyrrolo[2,1-*c*][1,4]benzodiazepine-5,11-diones with potential antitubercular activity. J Comb Chem;9:29–42.
29. Kabir M.S., Namjoshi O.A., Verma R., Polanowski R., Krueger S.M., Sherman D., Rott M.A., Schwan W.R., Monte A., Cook J.M. (2010) A new class of potential anti-tuberculosis agents: synthesis and preliminary evaluation of novel acrylic acid ethyl ester derivatives. Bioorg Med Chem;18:4178–4186.
30. Omelchenko A., Bouchard R., Le H.D., Choptiany P., Visen N., Hnatowich M., Hryshko L.V. (2003) Inhibition of canine (NCX1.1) and *Drosophila* (CALX1.1) Na^+-Ca^{2+}exchangers by 7-chloro-3,5-dihydro-5-phenyl-1*H*-4,1-benzothiazepine-2-one (CGP-37157). J Pharmacol Exp Ther;306:1050–1057.
31. Campiani G., Fiorini I., De Filippis M.P., Ciani S.M., Garofalo A., Nacci V., Giorgi G., Sega A., Botta M., Chiarini A., Budriesi R., Bruni G., Romeo M.R., Manzoni C., Mennini T. (1996) Cardiovascular characterization of pyrrolo[2,1-d][1,5]benzothiazepines derivatives binding selectively to the peripheral-type benzodiazepine receptor (PBR): from dual PBR affinity and calcium antagonist activity to novel and selective calcium entry blockers. J Med Chem;39:2933–2938.
32. Bolli M.H., Marfurt J., Grisostomi C., Boss C., Binkert C., Hess P., Treiber A., Thorin E., Morrison K., Buchmann S., Bur D., Ramuz H., Clozel M., Fischli W., Weller T. (2004) Novel benzo[1,4]diazepin-2-one derivatives as endothelin receptor antagonists. J Med Chem;47:2776–2795.
33. Bariwal J.B., Upadhyay K.D., Manvar A.T., Trivedi J.C., Singh J.S., Jain K.S., Shah A.K. (2008) 1,5-Benzothiazepine, a versatile pharmacophore: a review. Eur J Med Chem;43:2279–2290.
34. Mogilaih K., Sudhakar G.R. (2003) Synthesis of pyrazoline, pyrimidine and 1,5-benzodiazepine derivatives of 1,8-naphthyridine and evaluation of antibacterial activity. Indian J Chem;42B:636–640.
35. Kumar P.V., Rao V.R. (2008) Synthesis of pyrazoline, pyrimidine and 1,5-benzodiazepine derivatives of 1,8-naphthyridine and evaluation of antibacterial activity. Indian J Chem;47B:106–111.

36. Guo Q., Liu M.–.L., Feng L.–.S., Lv K., Guan G., Guo H.–.Y., Xiao C.–.L. (2011) Synthesis and in vitro antimycobacterial activity of fluoroquinolone derivatives containing a coumarin moiety. Arch Pharm Chem Life Sci;344:802–809.
37. Trivedi J.C., Bariwal J.B., Upadhyay K.D., Naliapara Y.T., Joshi S.K., Pannecouque C.C., Clercq E.C., Shah A.K. (2007) Improved and rapid synthesis of new coumarinyl chalcone derivatives and their antiviral activity. Tetrahedron Lett;48:8472–8474.
38. Kloss R.A., Wiener C. (1963) The reaction of 3-acyl-4-hydroxycoumarins with ammonium salts. J Org Chem;28:1671–1673.

Note

[a]World Health Organization (WHO), global tuberculosis control (2010) http://www.who.int/tb/publications/global_report/2010/en/index.html.

Supporting information

Additional Supporting Information may be found in the online version of this article:

Appendix S1. Antimycobacterial activity of the compounds **5a**–**o** and **7a**–**k**.

Table S1. Substrate scope of the reaction.

Please note: Wiley-Blackwell is not responsible for the content or functionality of any supporting materials supplied by the authors. Any queries (other than missing material) should be directed to the corresponding author for the article.