European Journal of Medicinal Chemistry 53 (2012) 416–423

Contents lists available at SciVerse ScienceDirect

European Journal of Medicinal Chemistry

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

Preliminary communication

A solvent free, four-component synthesis and 1,3-dipolar cycloaddition of 4(*H*)-pyrans with nitrile oxides: Synthesis and discovery of antimycobacterial activity of enantiomerically pure 1,2,4-oxadiazoles

Abdulrahman I. Almansour [a], Raju Suresh Kumar [a,*], Natarajan Arumugam [a], Dharmarajan Sriram [b]

[a] *Department of Chemistry, College of Science, King Saud University, P.O. Box 2455, Riyadh 11451, Saudi Arabia*
[b] *Medicinal Chemistry & Antimycobacterial Research Laboratory, Pharmacy Group, Birla Institute of Technology & Science – Pilani, Hyderabad Campus, Jawahar Nagar, Hyderabad 500 078, Andhra Pradesh, India*

ARTICLE INFO

Article history:
Received 7 February 2012
Received in revised form
5 April 2012
Accepted 12 April 2012
Available online 21 April 2012

Keywords:
Antitubercular activity
Mycobacterium tuberculosis
Multi-drug resistant tuberculosis
1,3-Dipolar cycloaddition
Pyrans
1,2,4-Oxadiazoles

ABSTRACT

Four-component reactions of (*R*)-1-(1-phenylethyl)tetrahydro-4(1*H*)-pyridinone, aromatic aldehydes and malononitrile in a 1:2:1 molar ratio in the presence of solid sodium ethoxide under solvent free conditions afforded an inseparable mixture of two diastereomeric 4(*H*)-pyrans in near quantitative yields. These compounds upon 1,3-dipolar cycloaddition with nitrile oxides furnished two enantiomerically pure 1,2,4-oxadiazoles in moderate yields, which were screened for *in vitro* activity against *Mycobacterium tuberculosis* H37Rv (MTB) and multi-drug resistant *M. tuberculosis* (MDR-TB). Among the compounds screened, compound **10h** was found to be the most active *in vitro* with a MIC value of 0.07 and 0.14 μM against MTB and MDR-TB respectively.

1. Introduction

Tuberculosis (TB), caused by *Mycobacterium tuberculosis* (MTB), has become an important world-wide public health problem with one-third of the world's population infected by the TB bacillus. About 9 million people, mostly from developing countries, develop active TB yearly, and the death toll is about 2 million in each year [1,2]. The pathogenic synergy of tuberculosis with HIV [3] enhances the overall incidence of TB in HIV-positive patients by 50 times relative to the rate for HIV-negative individuals [4]. Single agent TB therapy rapidly leads to drug-resistant organisms [5], while multi-drug treatment needs to be prolonged as MTB divides slowly and it is metabolically capable of becoming drug insensitive and/or bacilli may become sequestered [6,7]. The emergence of multi-drug and extensively drug-resistant tuberculosis (MDR-TB and XDR-TB) further aggravates the problems associated with TB treatment, as patients could become virtually untreatable using currently available anti-TB drugs. Furthermore, no new drugs have been introduced in the last four decades, except the recently introduced fluoroquinolones [8,9], which testifies to the lack of significant research in this area in the pharmaceutical industry. Hence the development of new drugs, capable of overcoming MDR- and XDR-TB, to efficiently treat this disease is imperative.

Pyran derivatives occupy an important place in the realm of natural and synthetic organic chemistry, because of their biological and pharmacological properties as antisterility and anticancer agents [10,11]. Polyfunctionalised dihydropyran is a common structural unit in a number of natural products such as secoiridoid monoterpenes and biogenetically related indole alkaloids [12,13]. 2-Amino-3-cyano-4*H*-pyrans possess photochemical activity [14], and the synthesis of 4*H*-pyran in recent years has attracted considerable interest as an important intermediate for the construction of many heterocycles. The 4*H*-pyran ring can also be transformed into pyridine systems which are also pharmacologically important [15,16].

The 1,2,4-oxadiazole ring system, known as an ester isostere [17], is prevalent in various biologically interesting benzodiazepine receptor ligands [18,19], muscarinic receptor agonists (**1**, Fig. 1) [20–22] and $5HT_3$ receptor antagonists (**2**, Fig. 1) [23]. Marine alkaloids, phidianidines A (**3**, R = Br) and B (**3**, R = H) (Fig. 1) isolated from the aeolid opisthobranch *Phidiana militaris* exhibit high

* Corresponding author. Tel.: +966 4675907; fax: +966 4675992.
E-mail addresses: sraju@ksu.edu.sa, drrajusureshkumar@gmail.com (R. Suresh Kumar).

0223-5234/$ – see front matter © 2012 Elsevier Masson SAS. All rights reserved.
doi:10.1016/j.ejmech.2012.04.021

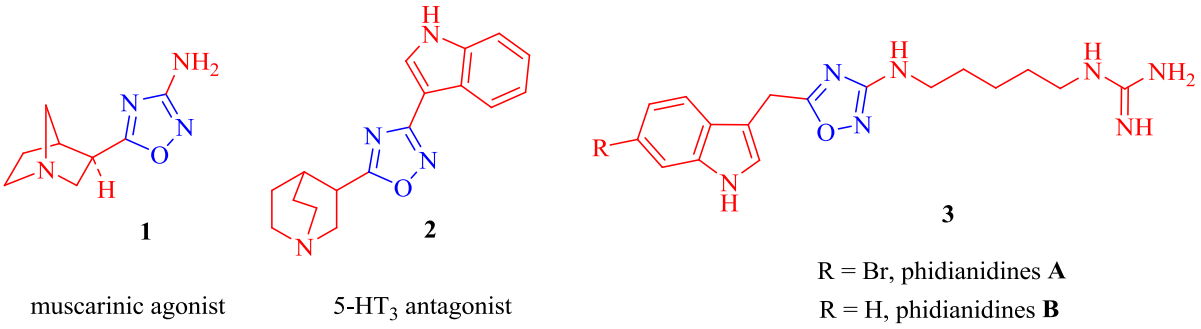


Fig. 1. Examples of biologically active 1,2,4-oxadiazoles.

cytotoxicity against tumour and nontumor mammalian cell lines in *in vitro* assays [24]. 1,2,4-Oxadiazoles have also been found to possess analgesic [25], anti-inflammatory [26] and antitumour [27] activities. These observations lead to the conclusion that 1,2,4-oxadiazoles satisfy the definition of privileged scaffolds, that is, molecular frameworks that are able to bind to a diverse array of receptors [28]. Molecules with piperidine sub-structure possesses analgesic [29,30], anti-inflammatory [29], central nervous system (CNS) depressant [31–33], local anaesthetic [31,34], anticancer [35], and antimicrobial activities [36].

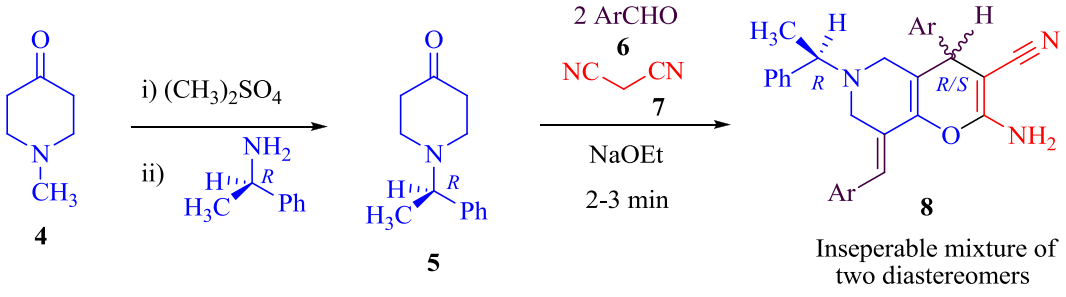
Recently, we have initiated a research programme aimed at studying the application of multi-component, domino and cycloaddition reactions to the construction of novel heterocycles [37–42], and their screening for antimycobacterial activities, which has unearthed several compounds with activities comparable to or superior to those of some of the currently employed first-line drugs for TB [43–51]. In this context, we report here our findings on the antitubercular properties of enantiomerically pure hybrid heterocycles incorporating piperidine, pyran and oxadiazoles.

2. Chemistry

In the present investigation, the reaction of (*R*)-1-(1-phenylethyl)tetrahydro-4(1*H*)-pyridinone **5**, a series of aromatic aldehydes **6** and malononitrile **7** in a 1:2:1 molar ratio in the presence of solid sodium ethoxide under solvent free condition afforded a mixture of two diastereomers of tetrahydro-4*H*-pyrano [3,2-*c*]pyridine-3-carbonitriles **8** in near quantitative yields (94–97%) (Scheme 1, Table 1). Enantiomerically pure (*R*)-1-(1-phenylethyl)tetrahydro-4(1*H*)-pyridinone **5**, required for this investigation, was prepared from 1-methyltetrahydro-4(1*H*)-pyridinone **4** following a literature procedure [52]. A mixture of (*R*)-1-(1-phenylethyl)tetrahydro-4(1*H*)-pyridinone, aromatic aldehyde and malononitrile in solid sodium ethoxide was ground well in a semimicro boiling tube at ambient temperature for about 2–3 min and after completion of the reaction, water (50 mL) was added to the mixture and the product was filtered and dried *in vacuo*. In all the cases, the product was obtained as a mixture of two diastereomers of **8** with almost similar R_f values, which could not be separated through column chromatography. However, the products were identified from the ^{1}H NMR spectrum of the mixture and the ratio of diastereomers was calculated from the intensities of the singlets due to H-4 of major and minor isomers of **8b** respectively occurring at 3.91 and 3.84 ppm. The other notable signals of the diastereomers of **8b** are: a singlet from the NH_2 protons at 4.57 ppm, two singlets at 6.81 and 6.84 ppm from the arylmethylidene hydrogen, doublets and multiplets in the region, 2.76–3.31 ppm and 3.52–3.75 ppm, due to 5-CH_2 and 7-CH_2 protons of the major and minor isomers. The doublets at 1.20 ppm ($J = 6.6$ Hz) and 1.27 ppm ($J = 7.2$ Hz) are due to the methyl protons of the phenylethyl group. The signals for CH hydrogen of the mixture overlap and appear as a quartet at 3.42 ppm ($J = 6.6$ Hz). The methyl hydrogens of the aryl rings appear as singlets at 2.31, 2.33 and 2.34 ppm and the aromatic hydrogens appear as a multiplet at 6.93–7.30 ppm.

With the diastereomeric mixture of 4(*H*)-pyrans (**8a–e**) in our hand, next our aim is to synthesize oxadiazole derivatives using –C≡N functionality as the dipolarophile. The 1,3-dipolar cycloaddition of nitrile oxide, generated *in situ* from *N*-hydroxyarylimidoyl chloride and triethylamine, to the inseparable diastereomeric mixture of 2-amino-4-aryl-6-[(*R*)-1-phenylethyl]-8-[(*E*)-1-arylmethylidene]-5,6,7,8-tetrahydro-4*H*-pyrano[3,2-*c*]-pyridine-3-carbonitriles **8a–e** (Scheme 2) furnished two diastereomeric 1,2,4-oxadiazoles **9** and **10**, which could be separated through column chromatography using petroleum ether/ethyl acetate as eluent. These enantiomerically pure oxadiazoles **9** and **10** were obtained in 30–38% and 15–29% yields respectively.

The cycloadducts were characterized by one- and two-dimensional NMR spectroscopic data as illustrated for **9a**. The ^{1}H NMR spectrum of **9a** has a singlet at 4.36 ppm readily assignable to H-4, whose C,H-COSY correlation assigns 40.8 ppm to C-4. The H-4 shows HMBCs (Fig. 2) with (i) C-5 at 50.4 ppm and (ii) C-4a at 114.0 ppm. Further, H-4 also shows HMBCs with (i) C-3 at 74.1 ppm, (ii) C-2 at 156.6 ppm and (iii) C-5′ of the oxadiazole ring at 175.9 ppm. The C,H-COSY spectrum assigns the 5-CH_2 hydrogens to a doublet at



Scheme 1. Synthesis of 4(*H*)-pyrans **8**.

Table 1
Diastereomeric ratio and yield of compounds **8a–e**.

Comp	Ar	Ratio of diastereomers of **8**	Yield of **8** (*RR*) + (*RS*) (%)
a	C_6H_5	1:0.6	96
b	*p*-MeC_6H_4	1:0.4	97
c	*o*-ClC_6H_4	1:0.9	95
d	*o*,*p*-$Cl_2C_6H_3$	1:0.9	96
e	1-Naphthyl	1:0.9	94

3.02 ($J = 15.9$ Hz) and a multiplet at 3.32–3.37 ppm. The 5-CH_2 hydrogens show a HMBC with a carbon at 49.7 ppm assigning it to C-7. From C,H-COSY spectrum, the doublet and a multiplet at 3.76 ($J = 14.1$ Hz) and 3.32–3.37 ppm can be assigned to 7-CH_2 hydrogens, which show HMBC with C-8a at 139.9 ppm. The benzylidene hydrogen H-9 appears as a singlet at 6.97 ppm, the C,H-COSY of which assigns the signal at 123.1 ppm to C-9. The carbon signal at 166.7 ppm can be assigned to C-3′ of oxadiazole ring. The methine and methyl hydrogens of 1-phenylethylamine appear as a quartet and a doublet at 3.47 and 1.17 ppm ($J = 6.6$ Hz) and the aromatic hydrogens appear as multiplets at 7.06–8.03 ppm. The assignment of hydrogen and carbon signals of **10a** has also been done by similar straightforward considerations. The ^1H and ^{13}C chemical shifts of **9a** and **10a** are depicted in Figs. 3 and 4 respectively.

The absolute configuration at C-4 of **9** and **10** could not be deduced from NMR data alone. However, no compound belonging to **9** and **10** afforded crystals suitable for X-ray crystallographic study rendering the assignment of their complete stereochemistry difficult. To obtain crystals suitable for X-ray crystallographic structure determination to deduce the absolute configuration at C-4, the cycloadduct **10** was acetylated with acetic anhydride (Scheme 3). However, the product **11** was obtained as a viscous liquid impeding X-ray crystallographic study. Hence, with a view to arriving at the most likely relative configuration at C-4, optimization of the cycloadducts **9a** and **10a** was done using AM1 calculations (Arguslab 4.0.1). From the optimized geometries, it is clear that the two diastereomers have almost equal energy (−1,53,115.0997 kcal/mol and −1,53,115.0153 kcal/mol), showing that both the isomers are almost equally stable. This is also evident from the formation of the diastereomers, **9** and **10** in most cases in approximately equal amounts Scheme 2.

Although the tetrahydro-4*H*-pyrano[3,2-*c*]pyridine-3-carbonitriles **8a–e** possess two dipolarophilic functionalities, *viz.* –C=C and –C≡N, nitrile oxide adds preferentially to the cyano functionality furnishing only the 1,2,4-oxadiazoles, **9** and **10** showing that this reaction proceeds chemoselectively. The cycloadduct **12** arising from the addition of nitrile oxide to C=C was not formed, even when an excess of nitrile oxide was used (Scheme 4).

3. Biological results and discussion

The enantiomerically pure 1,2,4-oxadiazoles, **9** and **10**, bearing diastereomeric relationship, were screened for their *in vitro* antimycobacterial activity against MTB and MDR-TB by agar dilution method similar to that recommended by the National Committee for Clinical Laboratory Standards for the determination of MIC in duplicate. The MDR-TB clinical isolate was resistant to the first-line anti-TB drugs, isoniazid, rifampicin and ethambutol. The MIC, defined as the minimum concentration of the compound required to completely inhibit the bacterial growth, the MIC values of the synthesized compounds and the standard drugs for comparison are reported in Table 2.

In the first phase of screening against MTB, all the compounds showed excellent *in vitro* activity with MIC ranging from 0.07 to 18.80 μM. Twelve compounds (**9b**, **9d–h**, **10a–j**) inhibited MTB with MIC of less than 5.22 μM and are more potent than the standard, ethambutol (MIC: 7.64 μM). Three compounds (**9h**, **10f** and **10h**) were found to be more active against MTB than isoniazid (MIC: 0.36 μM). Compound **10h** was found to be the most active *in vitro* with MIC of 0.07 μM against MTB displaying 1.7, 5.1, 67.3 and 109 times greater activity than rifampicin, isoniazid, ciprofloxacin and ethambutol respectively.

Subsequently, compounds having MIC < 3 μM were evaluated against MDR-TB, which inhibited MDR-TB with MIC ranging from 0.14 to 5.54 μM. All the twelve compounds screened were found to be more active than isoniazid (MIC: 11.38 μM), ciprofloxacin (MIC: 37.73 μM) and ethambutol (MIC: 61.18 μM). Eleven compounds with MIC ≤ 2.60 were more active than rifampicin (MIC: 3.80 μM). Compounds **9h** and **10h** display the maximum activity *in vitro* with MIC of 0.14 μM against MDR-TB, being 27.1, 81.3, 269.5 and 437 times more potent than rifampicin, isoniazid, ciprofloxacin and ethambutol respectively.

In general, oxadiazoles belonging to the diastereomer **10** display enhanced activity (2–4 times) relative to the diastereomer **9** against MTB disclosing that the activity is sensitive to the stereochemistry of the pyran. On the contrary, the activities of the diastereomers of each compound tested against MDR-TB appear to be insensitive to their stereochemistry, in the range of compounds investigated, as evident from the fact that their MIC values are equal.

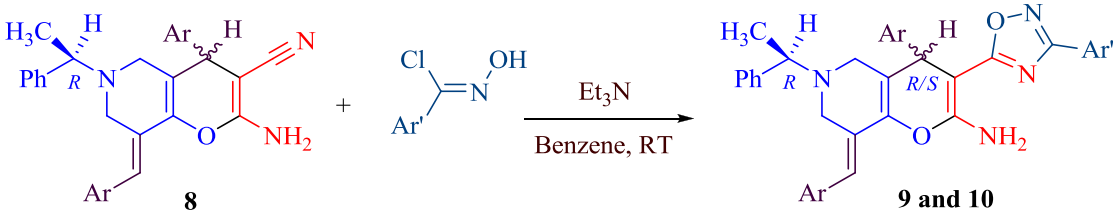
4. Conclusion

The present investigation describes a facile access to highly functionalised 4*H*-pyrans from (*R*)-1-(1-phenylethyl)tetrahydro-4(1*H*)-pyridinone, a series of aromatic aldehydes and malononitrile using solid sodium ethoxide under solvent free conditions in near quantitative yields and their chemoselective 1,3-dipolar cycloaddition with nitrile oxides furnishing two enantiomerically pure 1,2,4-oxadiazoles in moderate yields. These novel oxadiazoles showed excellent *in vitro* activity against *M. tuberculosis* H37Rv (MTB) and multi-drug resistant *M. tuberculosis* (MDR-TB). The novel oxadiazole derivatives discovered in this study may provide valuable therapeutic intervention for the treatment of tuberculosis.

5. Experimental

5.1. General methods

The melting points were measured using open capillary tubes and are uncorrected. ^1H, ^{13}C and two-dimensional NMR spectra



Scheme 2. Synthesis of enantiomerically pure oxadiazoles **9** and **10**.

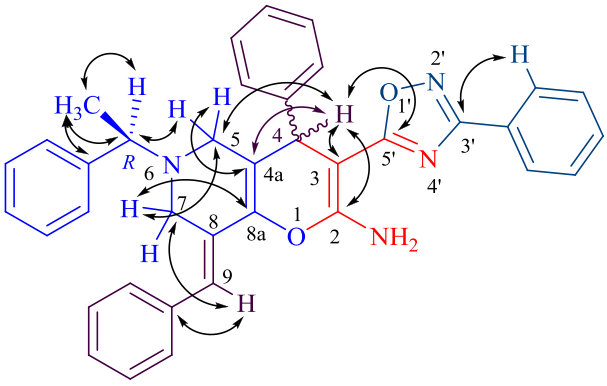


Fig. 2. Selected HMBCs of **9a**.

were recorded on a Bruker 300 MHz instrument in $CDCl_3$ using TMS as internal standard. Chemical shifts are given in parts per million (δ-scale) and the coupling constants are given in hertz. IR spectra were recorded on a JASCO FT IR instrument (KBr pellet in case of solids and $CHCl_3$ in case of liquids). Elemental analyses were performed on a Perkin Elmer 2400 Series II Elemental CHNS analyser. Mass spectra were recorded on JEOL-DX303 HF mass spectrometer. Column chromatography was performed on silica gel (230–400 mesh) using petroleum ether–ethyl acetate as eluent. Optical rotation values were measured using an autopol IV automatic polarimeter at sodium D line at 25 °C. Ten fold serial dilutions of each test compound/drug were incorporated into Middlebrook 7H11 agar medium with OADC Growth Supplement. Inoculum of *M. tuberculosis* $H_{37}Rv$ were prepared from fresh Middlebrook 7H11 agar slants with OADC Growth Supplement adjusted to 1 mg/mL (wet weight) in Tween 80 (0.05%) saline diluted to 10^{-2} to give a concentration of approximately 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. The minimum inhibitory concentration (MIC) is defined as the minimum concentration of compound required to give complete inhibition of bacterial growth.

5.2. General procedure for the synthesis of pyrans (*8a–e*)

A mixture of (*R*)-1-(1-phenylethyl)tetrahydro-4(1*H*)-pyridinone (1 mmol), aromatic aldehyde (2 mmol), and malononitrile (1 mmol), in solid sodium ethoxide was ground well in a semimicro

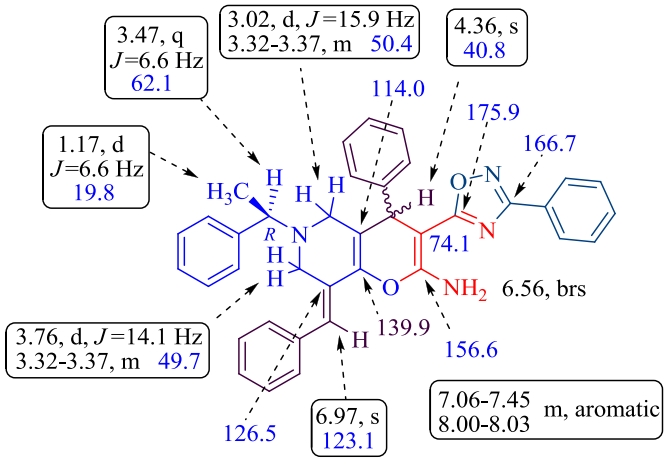


Fig. 3. ^1H and ^{13}C chemical shifts of **9a**.

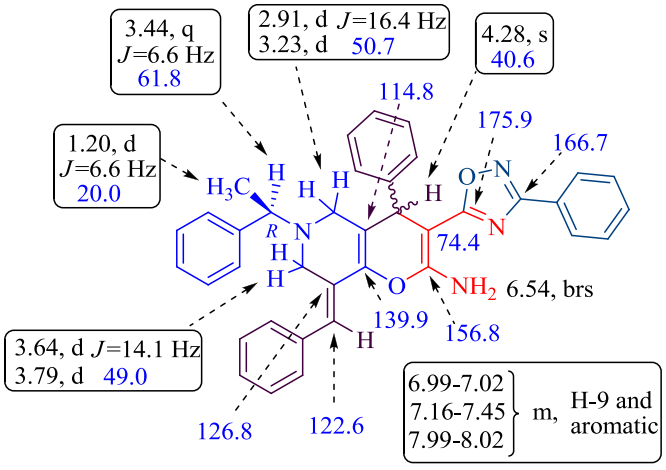


Fig. 4. ^1H and ^{13}C chemical shifts of **10a**.

boiling tube at ambient temperature for about 2–3 min. After completion of the reaction as evident from TLC, water (50 mL) was added to the reaction mixture and the product was filtered, washed with water, and dried *in vacuo*.

5.2.1. 2-Amino-4-phenyl-6-(1-phenylethyl)-8-[(E)-phenylmethylidene]-5,6,7,8-tetrahydro-4H-pyrano[3,2-c]pyridine-3-carbonitrile (*8a*) [dr = 1:0.6]

Obtained as pale yellow solid; ^1H NMR (300 MHz, $CDCl_3$): δ_H 1.18 (d, J = 6.6 Hz, CH_3), 1.19 (d, J = 7.2 Hz, CH_3), 2.77–3.31 (m, 5-CH_2 and 7-CH_2), 3.40–3.43 (m, CH), 3.52–3.88 (m, 5-CH_2 and 7-CH_2), 3.93 (s, 1H, H-4), 3.95 (s, 1H, H-4), 4.59 (s, NH_2), 6.85–7.39 (m, aromatic), 7.83 (s, H-9).

5.2.2. 2-Amino-4-(4-methylphenyl)-8-[(E)-(4-methylphenyl) methylidene]-6-(1-phenylethyl)-5,6,7,8-tetrahydro-4H-pyrano [3,2-c]pyridine-3-carbonitrile (*8b*) [dr = 1:0.4]

Obtained as white solid; ^1H NMR (300 MHz, $CDCl_3$): δ_H 1.20 (d, J = 6.6 Hz, CH_3), 1.27 (d, J = 7.2 Hz, CH_3), 2.76–3.31 (m, 5-CH_2 and 7-CH_2), 3.42 (q, J = 6.6 Hz, CH), 3.52–3.75 (m, 5-CH_2 and 7-CH_2), 3.84 (s, 1H, H-4), 3.91 (s, 1H, H-4), 4.57 (s, NH_2), 6.81 (s, H-9), 6.84 (s, H-9), 6.93–7.30 (m, aromatic).

5.2.3. 2-Amino-4-(2-chlorophenyl)-8-[(E)-(2-chlorophenyl) methylidene]-6-(1-phenylethyl)-5,6,7,8-tetrahydro-4H-pyrano[3,2-c] pyridine-3-carbonitrile (*8c*) [dr = 1:0.9]

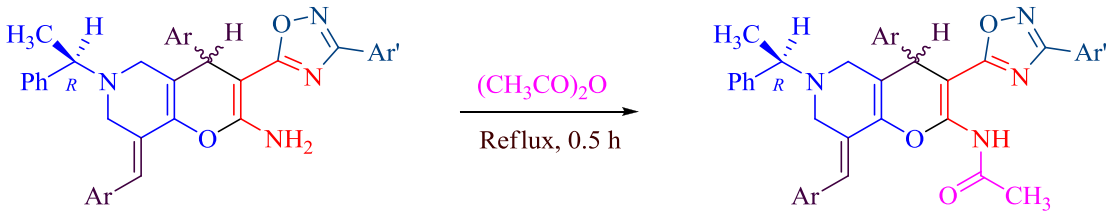
Obtained as pale yellow solid; ^1H NMR (300 MHz, $CDCl_3$): δ_H 1.14 (d, J = 6.6 Hz, CH_3), 1.18 (d, J = 6.9 Hz, CH_3), 2.79–3.30 (m, 5-CH_2 and 7-CH_2), 3.36–3.54 (m, CH, 5-CH_2 and 7-CH_2), 4.66–4.80 (m, CH and NH_2), 6.82–7.40 (m, aromatic and H-9).

5.2.4. 2-Amino-4-(2,4-dichlorophenyl)-8-[(E)-(2,4-dichlorophenyl) methylidene]-6-(1-phenylethyl)-5,6,7,8-tetrahydro-4H-pyrano [3,2-c]pyridine-3-carbonitrile (*8d*) [dr = 1:0.9]

Obtained as pale yellow solid; ^1H NMR (300 MHz, $CDCl_3$): δ_H 1.17 (d, J = 6.6 Hz, CH_3), 1.18 (d, J = 6.3 Hz, CH_3), 2.73–2.84 (m, 5-CH_2 and 7-CH_2), 3.06–3.50 (m, CH, 5-CH_2 and 7-CH_2), 4.60 (s, NH_2), 4.68 (s, NH_2), 6.73–7.45 (m, aromatic and H-9).

5.2.5. 2-Amino-4-(1-naphthyl)-8-[(E)-1-naphthylmethylidene]-6-(1-phenylethyl)-5,6,7,8-tetrahydro-4H-pyrano[3,2-c]pyridine-3-carbonitrile (*8e*) [dr = 1:0.9]

Obtained as solid; ^1H NMR (300 MHz, $CDCl_3$): δ_H 0.98–1.02 (m, CH_3), 2.64–3.22 (m, 5-CH_2 and 7-CH_2), 3.28–3.32 (m, CH), 3.37–3.60 (m, CH, 5-CH_2 and 7-CH_2), 4.64 (s, NH_2), 6.83–8.24 (m, aromatic and H-9).



10 **11**

Scheme 3. Acetylation of oxadiazole **10**.

5.3. General procedure for the synthesis of 1,2,4-oxadiazoles **9** and **10**

To a solution of 4*H*-pyran **8** (1 mmol) in benzene (5 mL), *N*-hydroxyarylcarboximidoyl chloride (1 mmol) was added and the mixture stirred at room temperature. A solution of triethylamine (1 mmol) in benzene (3 mL) was added dropwise to the above mixture and the stirring was continued for 7–8 h. After completion of the reaction as evident from TLC, the resulting mixture was filtered to remove the triethylamine hydrochloride, the solvent evaporated *in vacuo* and the residue subjected to flash column chromatography on silica gel using petroleum ether/ethyl acetate (5:1 v/v) to obtain enantiomerically pure **9** and **10**.

5.3.1. 4-Phenyl-6-[(R)-1-phenylethyl]-8-[(E)-1-phenylmethylidene]-3-(3′-phenyl-1,2,4-oxadiazol-5-yl)-5,6,7,8-tetrahydro-4H-pyrano [3,2-c]pyridin-2-amine (**9a**)

Obtained as white solid (0.069 g, 36%); mp = 174–175 °C; $[\alpha]_D = +142.8$ (*c* 0.20, $CHCl_3$); IR (KBr): 1093, 1290, 1362, 1409, 1537, 1635, 1676, 2920, 3452 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ_H 1.17 (d, 3H, *J* = 6.6 Hz, CH_3), 3.02 (d, 1H, *J* = 15.9 Hz, H-5a), 3.32–3.37 (m, 2H, H-5b and H-7a), 3.47 (q, 1H, *J* = 6.6 Hz, CH), 3.76 (d, 1H, *J* = 14.1 Hz, H-7b), 4.36 (s, 1H, H-4), 6.56 (br s, 2H, NH_2), 6.97 (s, 1H, H-9), 7.06–7.45 (m, 18H, aromatic), 8.00–8.03 (m, 2H, aromatic). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 19.8, 40.8, 49.7, 50.4, 62.1, 74.1, 114.0, 123.1, 126.5, 127.0, 127.3, 127.4, 128.0, 128.1, 128.2, 128.3, 128.5, 128.6, 128.8, 129.2, 130.0, 130.7, 136.1, 139.9, 142.8, 144.0, 156.6, 166.7, 175.9. EI-MS: *m*/*z* 564.60 (M^+). Anal. Calcd for $C_{37}H_{32}N_4O_2$: C, 78.70; H, 5.71; N, 9.92. Found: C, 78.76; H, 5.76; N, 9.85.

5.3.2. 4-Phenyl-6-[(R)-1-phenylethyl]-8-[(E)-1-phenylmethylidene]-3-(3′-phenyl-1,2,4-oxadiazol-5-yl)-5,6,7,8-tetrahydro-4H-pyrano [3,2-c]pyridin-2-amine (**10a**)

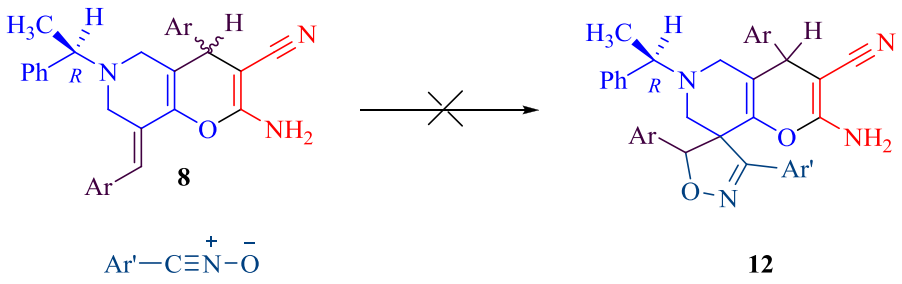
Obtained as viscous liquid (0.046 g, 24%); $[\alpha]_D = -115.2$ (*c* 0.23, $CHCl_3$); IR ($CHCl_3$): 1095, 1292, 1365, 1408, 1535, 1633, 1678, 2923, 3450 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ_H 1.20 (d, 3H, *J* = 6.6 Hz, CH_3), 2.91 (d, 1H, *J* = 16.4 Hz, H-5a), 3.23 (d, 1H, *J* = 16.4 Hz, H-5b), 3.44 (q, 1H, *J* = 6.6 Hz, CH), 3.64 (d, 1H, *J* = 14.1 Hz, H-7a), 3.79 (d, 1H, *J* = 14.1 Hz, H-7b), 4.28 (s, 1H, H-4), 6.54 (br s, 2H, NH_2), 6.99–7.02 (m, 3H, H-9 and aromatic), 7.16–7.45 (m, 16H, aromatic), 7.99–8.02 (m, 2H, aromatic). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 20.0, 40.6, 49.0, 50.7, 61.8, 74.4, 114.8, 122.6, 126.8, 126.9, 127.0, 127.3, 127.4, 128.0, 128.2, 128.3, 128.5, 128.6, 129.0, 130.7, 136.3, 139.9, 143.2, 144.1, 156.8, 166.7, 175.9. EI-MS: *m*/*z* 564.74 (M^+). Anal. Calcd for $C_{37}H_{32}N_4O_2$: C, 78.70; H, 5.71; N, 9.92. Found: C, 78.75; H, 5.66; N, 9.96.

5.3.3. 3-[3′-(4-Chlorophenyl)-1,2,4-oxadiazol-5-yl]-4-phenyl-6-[(R)-1-phenylethyl]-8-[(E)-1-phenylmethylidene]-5,6,7,8-tetrahydro-4H-pyrano[3,2-c]pyridin-2-amine (**9b**)

Obtained as white solid (0.075 g, 37%); mp = 184–185 °C; $[\alpha]_D = +139.0$ (*c* 0.20, $CHCl_3$); IR (KBr): 1091, 1290, 1369, 1407, 1533, 1635, 1678, 2924, 3451 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ_H 1.18 (d, 3H, *J* = 6.3 Hz, CH_3), 2.98 (d, 1H, *J* = 16.2 Hz, H-5a), 3.27–3.33 (m, 2H, H-5b and H-7a), 3.44 (q, 1H, *J* = 6.3 Hz, CH), 3.73 (d, 1H, *J* = 14.1 Hz, H-7b), 4.78 (s, 1H, H-4), 6.53 (br s, 2H, NH_2), 6.95 (s, 1H, H-9), 7.06–7.36 (m, 15H, aromatic), 7.41 (d, 2H, *J* = 8.1 Hz, aromatic), 7.95 (d, 2H, *J* = 8.1 Hz, aromatic). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 20.1, 40.9, 50.1, 50.9, 62.7, 74.2, 114.7, 122.5, 125.9, 126.9, 127.0, 127.1, 127.3, 127.9, 128.2, 128.3, 128.5, 128.6, 128.8, 128.9, 136.2, 136.7, 140.0, 143.4, 144.0, 156.7, 165.9, 176.1. EI-MS: *m*/*z* 599.10 (M^+). Anal. Calcd for $C_{37}H_{31}ClN_4O_2$: C, 74.17; H, 5.22; N, 9.35. Found: C, 74.12; H, 5.26; N, 9.30.

5.3.4. 3-[3′-(4-Chlorophenyl)-1,2,4-oxadiazol-5-yl]-4-phenyl-6-[(R)-1-phenylethyl]-8-[(E)-1-phenylmethylidene]-5,6,7,8-tetrahydro-4H-pyrano[3,2-c]pyridin-2-amine (**10b**)

Obtained as white solid (0.052 g, 26%); mp = 163–164 °C; $[\alpha]_D = -102.7$ (*c* 0.20, $CHCl_3$); IR (KBr): 1093, 1292, 1367, 1409, 1535, 1633, 1679, 2921, 3450 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ_H 1.20 (d, 3H, *J* = 6.6 Hz, CH_3), 2.89 (d, 1H, *J* = 16.4 Hz, H-5a), 3.21 (d, 1H, *J* = 16.4 Hz, H-5b), 3.43 (q, 1H, *J* = 6.6 Hz, CH), 3.61 (d, 1H, *J* = 14.1 Hz, H-7a), 3.78 (d, 1H, *J* = 14.1 Hz, H-7b), 4.27 (s, 1H, H-4), 6.51 (br s, 2H, NH_2), 6.98–7.35 (m, 16H, H-9 and aromatic), 7.40 (d, 2H, *J* = 8.6 Hz, aromatic), 7.94 (d, 2H, *J* = 8.6 Hz, aromatic). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 20.0, 40.6, 49.1, 50.9, 61.9, 74.3, 115.0, 122.6, 125.9, 127.0, 127.3, 128.0, 128.2, 128.3, 128.6, 128.9, 129.0, 136.2, 136.7, 140.0, 143.4, 144.0, 156.9, 165.9, 176.1. EI-MS: *m*/*z* 599.02 (M^+). Anal. Calcd for $C_{37}H_{31}ClN_4O_2$: C, 74.17; H, 5.22; N, 9.35. Found: C, 74.23; H, 5.27; N, 9.28.



8 **12**

Ar′—C≡N⁺—O⁻

Scheme 4. Non formation of isoxazoline **12**.

Table 2
Minimum inhibitory concentrations (μM) of compounds **9** and **10** against mycobacterial species.

Comp	Ar	Ar′	Yield (%)[a]		MTB	MDR-TB	MTB	MDR-TB
			9 (*RR* or *RS*)[b]	**10** (*RS* or *RR*)[b]	**9**		**10**	
a	C_6H_5	C_6H_5	36	24	11.07	NT	2.76	5.54
b	C_6H_5	*p*-ClC_6H_4	37	26	5.22	NT	2.60	2.60
c	*p*-MeC_6H_4	C_6H_5	38	18	10.54	NT	5.28	NT
d	*p*-MeC_6H_4	*p*-ClC_6H_4	37	15	2.49	1.24	0.64	1.24
e	*o*-ClC_6H_4	C_6H_5	30	27	1.23	1.23	0.63	1.23
f	*o*-ClC_6H_4	*p*-ClC_6H_4	30	28	0.60	0.60	0.15	0.60
g	*o*,*p*-$Cl_2C_6H_3$	C_6H_5	32	26	1.11	0.57	0.57	0.57
h	*o*,*p*-$Cl_2C_6H_3$	*p*-ClC_6H_4	33	25	0.27	0.14	0.07	0.14
i	1-Naphthyl	C_6H_5	30	28	18.80	NT	4.71	NT
j	1-Naphthyl	*p*-ClC_6H_4	32	29	8.94	NT	4.48	NT
Rifampicin	–	–	–	–	–	–	0.12	3.80
Isoniazid	–	–	–	–	–	–	0.36	11.38
Ciprofloxacin	–	–	–	–	–	–	4.71	37.73
Ethambutol	–	–	–	–	–	–	7.64	61.18

MTB: *Mycobacterium tuberculosis*; MDR-TB: multi-drug resistant *Mycobacterium tuberculosis*; NT: not tested.
[a] Isolated yield.
[b] The absolute configurations of these diastereomers at C-4 not distinctly assigned.

*5.3.5. 4-(4-Methylphenyl)-8-[(E)-1-(4-methylphenyl)methylidene]-6-[(R)-1-phenylethyl]-3-(3′-phenyl-1,2,4-oxadiazol-5-yl)-5,6,7,8-tetrahydro-4H-pyrano[3,2-c]pyridin-2-amine (**9c**)*

Obtained as white solid (0.071 g, 38%); mp = 186–187 °C; $[\alpha]_D = +126.0$ (*c* 0.20, $CHCl_3$); IR (KBr): 1091, 1292, 1366, 1409, 1536, 1630, 1679, 2921, 3451 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ_H 1.21 (d, 3H, *J* = 6.6 Hz, CH_3), 2.28 (s, 1H, CH_3), 2.32 (s, 1H, CH_3), 2.99 (d, 1H, *J* = 15.9 Hz, H-5a), 3.22–3.33 (m, 2H, H-5b and H-7a), 3.45 (q, 1H, *J* = 6.6 Hz, CH), 3.76 (d, 1H, *J* = 14.1 Hz, H-7b), 4.31 (s, 1H, H-4), 6.53 (br s, 2H, NH_2), 6.91 (s, 1H, H-9), 6.96–8.02 (m, 18H, aromatic). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 19.2, 21.1, 21.2, 40.5, 50.1, 51.0, 62.7, 74.4, 114.5, 122.3, 126.4, 127.0, 127.3, 127.4, 127.8, 128.3, 128.6, 128.8, 128.9, 129.2, 130.7, 130.9, 133.4, 136.4, 136.7, 140.0, 141.1, 143.5, 156.6, 166.7, 176.0. EI-MS: *m*/*z* 592.60 (M^+). Anal. Calcd for $C_{39}H_{36}N_4O_2$: C, 79.03; H, 6.12; N, 9.45. Found: C, 79.08; H, 6.18; N, 9.50.

*5.3.6. 4-(4-Methylphenyl)-8-[(E)-1-(4-methylphenyl)methylidene]-6-[(R)-1-phenylethyl]-3-(3′-phenyl-1,2,4-oxadiazol-5-yl)-5,6,7,8-tetrahydro-4H-pyrano[3,2-c]pyridin-2-amine (**10c**)*

Obtained as viscous liquid (0.034 g, 18%); $[\alpha]_D = -114.4$ (*c* 0.19, $CHCl_3$); IR ($CHCl_3$): 1094, 1292, 1365, 1410, 1534, 1631, 1678, 2925, 3451 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ_H 1.20 (d, 3H, *J* = 6.8 Hz, CH_3), 2.31 (s, 1H, CH_3), 2.36 (s, 1H, CH_3), 2.89 (d, 1H, *J* = 16.5 Hz, H-5a), 3.21 (d, 1H, *J* = 16.5 Hz, H-5b), 3.43 (q, 1H, *J* = 6.8 Hz, CH), 3.64 (d, 1H, *J* = 14.3 Hz, H-7a), 3.82 (d, 1H, *J* = 14.3 Hz, H-7b), 4.23 (s, 1H, H-4), 6.52 (br s, 2H, NH_2), 6.95 (s, 1H, H-9), 7.01–8.01 (m, 18H, aromatic). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 19.2, 21.1, 21.2, 40.1, 49.1, 50.8, 61.8, 74.5, 114.2, 122.4, 126.2, 126.9, 127.2, 127.4, 127.9, 128.2, 128.6, 128.8, 128.9, 129.0, 129.2, 130.6, 130.9, 133.5, 136.4, 136.8, 141.2, 143.4, 156.8, 166.6, 176.1. EI-MS: *m*/*z* 592.72 (M^+). Anal. Calcd for $C_{39}H_{36}N_4O_2$: C, 79.03; H, 6.12; N, 9.45. Found: C, 79.10; H, 6.05; N, 9.51.

*5.3.7. 3-[3′-(4-Chlorophenyl)-1,2,4-oxadiazol-5-yl]-4-(4-methylphenyl)-8-[(E)-1-(4-methylphenyl)methylidene]-6-[(R)-1-phenylethyl]-5,6,7,8-tetrahydro-4H-pyrano[3,2-c]-pyridin-2-amine (**9d**)*

Obtained as white solid (0.074 g, 37%); mp = 192–193 °C; $[\alpha]_D = +134.4$ (*c* 0.20, $CHCl_3$); IR (KBr): 1093, 1291, 1365, 1406, 1536, 1630, 1675, 2922, 3450 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ_H 1.21 (d, 3H, *J* = 6.6 Hz, CH_3), 2.29 (s, 1H, CH_3), 2.32 (s, 1H, CH_3), 2.98 (d, 1H, *J* = 16.5 Hz, H-5a), 3.22–3.32 (m, 2H, H-5b and H-7a), 3.45 (q, 1H, *J* = 6.6 Hz, CH), 3.75 (d, 1H, *J* = 13.8 Hz, H-7b), 4.30 (s, 1H, H-4), 6.49 (br s, 2H, NH_2), 6.90 (s, 1H, H-9), 6.96–7.96 (m, 17H, aromatic). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 20.2, 21.1, 21.2, 40.5, 50.2, 51.0, 62.8, 74.3, 114.5, 122.3, 125.9, 126.4, 127.0, 127.4, 127.8, 128.3, 128.6, 128.8, 128.9, 129.2, 133.3, 136.5, 136.6, 136.7, 140.0, 141.1, 143.5, 156.7, 165.9, 176.2. EI-MS: *m*/*z* 626.80 (M^+). Anal. Calcd for $C_{39}H_{35}ClN_4O_2$: C, 74.69; H, 5.62; N, 8.93. Found: C, 74.75; H, 5.68; N, 8.87.

*5.3.8. 3-[3′-(4-Chlorophenyl)-1,2,4-oxadiazol-5-yl]-4-(4-methylphenyl)-8-[(E)-1-(4-methylphenyl)methylidene]-6-[(R)-1-phenylethyl]-5,6,7,8-tetrahydro-4H-pyrano[3,2-c]-pyridin-2-amine (**10d**)*

Obtained as viscous liquid (0.030 g, 15%); $[\alpha]_D = -106.2$ (*c* 0.21, $CHCl_3$); IR ($CHCl_3$): 1093, 1290, 1368, 1408, 1537, 1631, 1679, 2924, 3454 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ_H 1.20 (d, 3H, *J* = 6.8 Hz, CH_3), 2.31 (s, 1H, CH_3), 2.36 (s, 1H, CH_3), 2.87 (d, 1H, *J* = 16.2 Hz, H-5a), 3.20 (d, 1H, *J* = 16.2 Hz, H-5b), 3.42 (q, 1H, *J* = 6.6 Hz, CH), 3.63 (d, 1H, *J* = 14.1 Hz, H-7a), 3.82 (d, 1H, *J* = 14.1 Hz, H-7b), 4.22 (s, 1H, H-4), 6.50 (br s, 2H, NH_2), 6.95 (s, 1H, H-9), 7.01–7.20 (m, 9H, aromatic), 7.40 (d, 2H, *J* = 8.6 Hz, aromatic), 7.53–7.55 (m, 2H, aromatic), 7.71–7.73 (m, 2H, aromatic), 7.94 (d, 2H, *J* = 8.6 Hz, aromatic). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 19.2, 21.1, 21.2, 40.1, 49.2, 50.9, 61.8, 74.5, 114.7, 122.5, 125.9, 126.9, 127.4, 127.9, 128.2, 128.6, 128.8, 128.9, 129.0, 129.1, 129.2, 130.9, 136.4, 136.7, 136.8, 141.1, 156.9, 165.9, 176.5. EI-MS: *m*/*z* 626.92 (M^+). Anal. Calcd for $C_{39}H_{35}ClN_4O_2$: C, 74.69; H, 5.62; N, 8.93. Found: C, 74.63; H, 5.67; N, 8.86.

*5.3.9. 4-(2-Chlorophenyl)-8-[(E)-1-(2-chlorophenyl)methylidene]-6-[(R)-1-phenylethyl]-3-(3′-phenyl-1,2,4-oxadiazol-5-yl)-5,6,7,8-tetrahydro-4H-pyrano[3,2-c]pyridin-2-amine (**9e**)*

Obtained as viscous liquid (0.055 g, 30%); $[\alpha]_D = +161.0$ (*c* 0.23, $CHCl_3$); IR ($CHCl_3$): 1092, 1294, 1367, 1407, 1537, 1635, 1676, 2920, 3452 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ_H 1.13 (d, 3H, *J* = 6.6 Hz, CH_3), 2.98 (d, 1H, *J* = 16.5 Hz, H-5a), 3.09 (d, 1H, *J* = 14.1 Hz, H-7a), 3.37 (q, 1H, *J* = 6.6 Hz, CH), 3.52–3.57 (m, 2H, H-5b and H-7b), 5.10 (s, 1H, H-4), 6.62 (br s, 2H, NH_2), 6.84 (d, 1H, *J* = 7.8 Hz, aromatic), 6.96–8.04 (m, 18H, H-9 and aromatic). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 20.2, 41.0, 50.0, 50.4, 62.3, 72.8, 114.6, 120.1, 126.2, 127.0, 127.2, 127.3, 127.4, 128.1, 128.2, 128.3, 128.6, 129.3, 129.5, 130.2, 130.7, 133.4, 133.8, 134.4, 139.7, 143.5, 157.1, 166.7, 175.8. EI-MS: *m*/*z* 632.73 (M^+). Anal. Calcd for $C_{37}H_{30}Cl_2N_4O_2$: C, 70.14; H, 4.77; N, 8.84. Found: C, 70.20; H, 4.83; N, 8.91.

*5.3.10. 4-(2-Chlorophenyl)-8-[(E)-1-(2-chlorophenyl)methylidene]-6-[(R)-1-phenylethyl]-3-(3′-phenyl-1,2,4-oxadiazol-5-yl)-5,6,7,8-tetrahydro-4H-pyrano[3,2-c]pyridin-2-amine (**10e**)*

Obtained as viscous liquid (0.050 g, 27%); $[\alpha]_D = -134.7$ (*c* 0.18, $CHCl_3$); IR ($CHCl_3$): 1091, 1292, 1366, 1409, 1539, 1633, 1677, 2922, 3453 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ_H 1.19 (d, 3H, *J* = 6.6 Hz, CH_3), 2.98 (d, 1H, *J* = 17.0 Hz, H-5a), 3.37 (d, 1H, *J* = 17.0 Hz, H-5b), 3.42–3.57 (m, 3H, CH, H-7a and H-7b), 5.02 (s, 1H, H-4), 6.61 (br s,

2H, NH_2), 6.99 (s, 1H, H-9), 7.01–8.03 (m, 18H, aromatic). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 19.7, 40.2, 49.1, 50.3, 61.4, 73.0, 114.8, 120.1, 126.3, 126.9, 127.2, 127.3, 127.4, 128.0, 128.1, 128.5, 128.6, 128.8, 129.5, 130.2 130.4, 130.7, 133.5, 133.9, 134.5, 139.7, 143.3, 157.3, 166.7, 175.7. EI-MS: *m*/*z* 632.59 (M^+). Anal. Calcd for $C_{37}H_{30}Cl_2N_4O_2$: C, 70.14; H, 4.77; N, 8.84. Found: C, 70.21; H, 4.68; N, 8.80.

*5.3.11. 4-(2-Chlorophenyl)-8-[(E)-1-(2-chlorophenyl)methylidene]-3-[3′-(4-chlorophenyl)-1,2,4-oxadiazol-5-yl]-6-[(R)-1-phenylethyl]-5,6,7,8-tetrahydro-4H-pyrano[3,2-c]-pyridin-2-amine (**9f**)*

Obtained as viscous liquid (0.058 g, 30%); $[\alpha]_D = +142.4$ (*c* 0.22, $CHCl_3$); IR ($CHCl_3$): 1090, 1291, 1366, 1409, 1538, 1633, 1676, 2924, 3449 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ_H 1.13 (d, 3H, $J = 6.6$ Hz, CH_3), 2.97 (d, 1H, $J = 16.5$ Hz, H-5a), 3.09 (d, 1H, $J = 14.1$ Hz, H-7a), 3.37 (q, 1H, $J = 6.6$ Hz, CH), 3.52–3.57 (m, 2H, H-5b and H-7b), 5.09 (s, 1H, H-4), 6.61 (br s, 2H, NH_2), 6.83 (d, 1H, $J = 7.5$ Hz, aromatic), 6.96–7.97 (m, 17H, H-9 and aromatic). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 19.2, 40.4, 50.0, 50.4, 62.3, 72.8, 114.3, 120.1, 125.3, 125.8, 126.2, 127.1, 127.3, 127.5, 128.0,128.2, 128.3, 128.4, 128.6, 128.8, 128.9, 129.0, 129.3, 129.5, 130.2, 133.4, 133.8, 134.3, 136.8, 139.7, 143.4, 157.2, 165.9, 175.9. EI-MS: *m*/*z* 666.95 (M^+). Anal. Calcd for $C_{37}H_{29}Cl_3N_4O_2$: C, 66.53; H, 4.38; N, 8.39. Found: C, 66.46; H, 4.33; N, 8.46.

*5.3.12. 4-(2-Chlorophenyl)-8-[(E)-1-(2-chlorophenyl)methylidene]-3-[3′-(4-chlorophenyl)-1,2,4-oxadiazol-5-yl]-6-[(R)-1-phenylethyl]-5,6,7,8-tetrahydro-4H-pyrano[3,2-c]-pyridin-2-amine (**10f**)*

Obtained as viscous liquid (0.055 g, 28%); $[\alpha]_D = -118.5$ (*c* 0.24, $CHCl_3$); IR ($CHCl_3$): 1089, 1294, 1365, 1406, 1537, 1635, 1678, 2921, 3451 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ_H 1.19 (d, 3H, $J = 6.6$ Hz, CH_3), 2.97 (d, 1H, $J = 16.7$ Hz, H-5a), 3.37 (d, 1H, $J = 16.7$ Hz, H-5b), 3.42–3.57 (m, 3H, CH, H-7a and H-7b), 5.01 (s, 1H, H-4), 6.60 (br s, 2H, NH_2), 6.99–7.96 (m, 18H, H-9 and aromatic). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 19.7, 40.5, 49.1, 50.3, 61.4, 72.9, 115.0, 120.1, 125.8, 126.3, 126.9, 127.3, 127.4, 127.9, 128.2, 128.5, 128.9, 129.0, 129.5, 130.2, 130.3, 130.9, 133.4, 133.9, 134.4, 136.7, 139.7, 143.2, 157.4, 165.9, 175.9. EI-MS: *m*/*z* 667.08 (M^+). Anal. Calcd for $C_{37}H_{29}Cl_3N_4O_2$: C, 66.53; H, 4.38; N, 8.39. Found: C, 66.59; H, 4.31; N, 8.45.

*5.3.13. 4-(2,4-Dichlorophenyl)-8-[(E)-1-(2,4-dichlorophenyl) methylidene]-6-[(R)-1-phenylethyl]-3-(3′-phenyl-1,2,4-oxadiazol-5-yl)-5,6,7,8-tetrahydro-4H-pyrano[3,2-c]-pyridin-2-amine (**9g**)*

Obtained as viscous liquid (0.058 g, 32%); $[\alpha]_D = +112.0$ (*c* 0.24, $CHCl_3$); IR ($CHCl_3$): 1093, 1290, 1362, 1407, 1535, 1630, 1676, 2923, 3449 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ_H 1.18 (d, 3H, $J = 6.6$ Hz, CH_3), 2.90 (d, 1H, $J = 16.2$ Hz, H-5a), 3.10 (d, 1H, $J = 14.1$ Hz, H-7a), 3.35 (q, 1H, $J = 6.6$ Hz, CH), 3.43–3.48 (m, 2H, H-5b and H-7b), 5.02 (s, 1H, H-4), 6.66 (br s, 2H, NH_2), 6.76 (d, 1H, $J = 8.1$ Hz, aromatic), 6.89 (s, 1H, H-9), 6.97 (dd, 1H, $J = 8.1$, 2.0 Hz, aromatic), 7.14–8.03 (m, 14H, aromatic). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 20.2, 49.9, 50.5, 62.7, 72.3, 114.8, 119.0, 126.5, 127.1, 127.2, 127.8, 128.3, 128.6, 128.7, 129.2, 130.8, 132.8, 133.1, 133.4, 134.0, 134.5, 139.7, 143.3, 157.0, 166.7, 175.5. EI-MS: *m*/*z* 702.48 (M^+). Anal. Calcd for $C_{37}H_{28}Cl_4N_4O_2$: C, 63.26; H, 4.02; N, 7.98. Found: C, 63.34; H, 4.08; N, 7.90.

*5.3.14. 4-(2,4-Dichlorophenyl)-8-[(E)-1-(2,4-dichlorophenyl) methylidene]-6-[(R)-1-phenylethyl]-3-(3′-phenyl-1,2,4-oxadiazol-5-yl)-5,6,7,8-tetrahydro-4H-pyrano[3,2-c]-pyridin-2-amine (**10g**)*

Obtained as viscous liquid (0.047 g, 26%); $[\alpha]_D = -128.0$ (*c* 0.25, $CHCl_3$); IR ($CHCl_3$): 1090, 1292, 1364, 1405, 1538, 1632, 1679, 2925, 3447 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ_H 1.18 (d, 3H, $J = 6.6$ Hz, CH_3), 2.93 (d, 1H, $J = 16.8$ Hz, H-5a), 3.35 (d, 1H, $J = 16.8$ Hz, H-5b), 3.41–3.55 (m, 3H, CH, H-7a and H-7b), 4.96 (s, 1H, H-4), 6.62 (br s, 2H, NH_2), 6.91–8.03 (m, 17H, H-9 and aromatic). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 19.7, 41.1, 49.0, 50.1, 61.2, 72.5, 114.6, 119.2, 126.7, 127.1, 127.2, 127.3, 127.8, 128.3, 128.4, 128.7, 128.8, 129.3, 129.4, 130.8, 131.0, 133.0, 133.2, 133.6, 134.1, 134.6, 139.7, 143.1, 157.1, 166.8, 175.5. EI-MS: *m*/*z* 702.61 (M^+). Anal. Calcd for $C_{37}H_{28}Cl_4N_4O_2$: C, 63.26; H, 4.02; N, 7.98. Found: C, 63.30; H, 4.09; N, 7.92.

*5.3.15. 3-[3′-(4-Chlorophenyl)-1,2,4-oxadiazol-5-yl]-4-(2,4-dichlorophenyl)-8-[(E)-1-(2,4-dichlorophenyl)methylidene]-6-[(R)-1-phenylethyl]-5,6,7,8-tetrahydro-4H-pyrano-[3,2-c]-pyridin-2-amine (**9h**)*

Obtained as viscous liquid (0.063 g, 33%); $[\alpha]_D = +124.6$ (*c* 0.21, $CHCl_3$); IR ($CHCl_3$): 1114, 1295, 1357, 1408, 1529, 1633, 1683, 2923, 3442 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ_H 1.19 (d, 3H, $J = 6.5$ Hz, CH_3), 2.90 (d, 1H, $J = 16.2$ Hz, H-5a), 3.10 (d, 1H, $J = 14.1$ Hz, H-7a), 3.36 (q, 1H, $J = 6.5$ Hz, CH), 3.44–3.48 (m, 2H, H-5b and H-7b), 5.03 (s, 1H, H-4), 6.62 (br s, 2H, NH_2), 6.76 (d, 1H, $J = 8.4$ Hz, aromatic), 6.89 (s, 1H, H-9), 6.98 (dd, 1H, $J = 8.1$, 1.8 Hz, aromatic), 7.16–7.37 (m, 9H, aromatic), 7.42 (d, 2H, $J = 8.4$ Hz, aromatic), 7.95 (d, 2H, $J = 8.4$ Hz, aromatic). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 20.2, 40.8, 50.0, 50.5, 62.7, 72.2, 114.4, 119.1, 125.6, 126.5, 127.2, 127.8, 128.4, 128.5, 128.6, 128.9, 129.2, 130.8, 131.0, 132.8, 133.2, 133.4, 133.9, 134.5, 136.8, 139.7, 140.0, 143.2, 157.1, 166.0, 175.7. EI-MS: *m*/*z* 736.80 (M^+). Anal. Calcd for $C_{37}H_{27}Cl_5N_4O_2$: C, 60.31; H, 3.69; N, 7.60. Found: C, 60.23; H, 3.76; N, 7.67.

*5.3.16. 3-[3′-(4-Chlorophenyl)-1,2,4-oxadiazol-5-yl]-4-(2,4-dichlorophenyl)-8-[(E)-1-(2,4-dichlorophenyl)methylidene]-6-[(R)-1-phenylethyl]-5,6,7,8-tetrahydro-4H-pyrano-[3,2-c]-pyridin-2-amine (**10h**)*

Obtained as viscous liquid (0.047 g, 25%); $[\alpha]_D = -108.6$ (*c* 0.19, $CHCl_3$); IR ($CHCl_3$): 1114, 1294, 1359, 1406, 1530, 1632, 1680, 2923, 3445 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ_H 1.18 (d, 3H, $J = 6.6$ Hz, CH_3), 2.92 (d, 1H, $J = 16.7$ Hz, H-5a), 3.34 (d, 1H, $J = 16.7$ Hz, H-5b), 3.40–3.50 (m, 3H, CH, H-7a and H-7b), 4.94 (s, 1H, H-4), 6.60 (br s, 2H, NH_2), 6.91–7.51 (m, 14H, H-9 and aromatic), 7.94 (d, 2H, $J = 8.4$ Hz, aromatic). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 19.6, 40.8, 48.9, 50.1, 61.3, 72.5, 114.3, 119.3, 125.7, 126.7, 127.1, 127.2, 127.8, 128.3, 128.6, 128.8, 129.0 129.3, 129.4, 131.0, 132.9, 133.2, 133.6, 134.0, 134.6, 136.9, 139.7, 143.0, 157.2, 166.0, 175.6. EI-MS: *m*/*z* 736.68 (M^+). Anal. Calcd for $C_{37}H_{27}Cl_5N_4O_2$: C, 60.31; H, 3.69; N, 7.60. Found: C, 60.38; H, 3.62; N, 7.68.

*5.3.17. 4-(1-Naphthyl)-8-[(E)-1-(1-naphthyl)methylidene]-6-[(R)-1-phenylethyl]-3-(3′-phenyl-1,2,4-oxadiazol-5-yl)-5,6,7,8-tetrahydro-4H-pyrano[3,2-c]pyridin-2-amine (**9i**)*

Obtained as pale yellow solid (0.055 g, 30%); mp = 124–125 °C; $[\alpha]_D = +156.0$ (*c* 0.21, $CHCl_3$); IR (KBr): 1089, 1291, 1365, 1402, 1531, 1634, 1676, 2922, 3454 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ_H 0.93 (d, 3H, $J = 6.6$ Hz, CH_3), 2.76 (d, 1H, $J = 16.1$ Hz, H-5a), 3.06 (d, 1H, $J = 14.0$ Hz, H-7a), 3.25 (q, 1H, $J = 6.6$ Hz, CH), 3.41 (d, 1H, $J = 16.1$ Hz, H-7a), 3.53 (d, 1H, $J = 14.0$ Hz, H-7b), 5.35 (s, 1H, H-4), 6.67 (br s, 2H, NH_2), 6.96–7.99 (m, 23H, H-9 and aromatic), 8.07 (d, 1H, $J = 8.7$ Hz, aromatic), 8.37 (d, 1H, $J = 8.1$ Hz, aromatic). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 19.9, 41.8, 50.3, 51.1, 62.3, 74.2, 120.6, 122.8, 124.9, 125.0, 125.5, 125.7, 125.8, 125.9, 126.2, 126.4, 126.9, 127.1, 127.2, 127.3, 127.6, 128.0, 128.2, 128.4, 128.5, 128.6, 128.8, 128.9, 129.0, 130.7, 130.9, 131.7, 131.9, 133.2, 133.4, 139.6, 143.2, 157.2, 166.6, 176.1. EI-MS: *m*/*z* 664.88 (M^+). Anal. Calcd for $C_{45}H_{36}N_4O_2$: C, 81.30; H, 5.46; N, 8.43. Found: C, 81.38; H, 5.52; N, 8.48.

*5.3.18. 4-(1-Naphthyl)-8-[(E)-1-(1-naphthyl)methylidene]-6-[(R)-1-phenylethyl]-3-(3′-phenyl-1,2,4-oxadiazol-5-yl)-5,6,7,8-tetrahydro-4H-pyrano[3,2-c]pyridin-2-amine (**10i**)*

Obtained as pale yellow solid (0.051 g, 28%); mp = 112–113 °C; $[\alpha]_D = -132.4$ (*c* 0.20, $CHCl_3$); IR (KBr): 1088, 1289, 1366, 1405, 1534, 1630, 1675, 2924, 3455 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ_H 0.89 (d, 3H, $J = 6.6$ Hz, CH_3), 2.68 (d, 1H, $J = 16.5$ Hz, H-5a), 3.22–3.31 (m, 2H, CH and H-5b), 3.41 (d, 1H, $J = 14.1$ Hz, H-7a), 3.64 (d, 1H, $J = 14.1$ Hz, H-7b), 5.24 (s, 1H, H-4), 6.64 (br s, 2H, NH_2), 6.69–7.97 (m, 23H, H-9

and aromatic), 8.09 (d, 1H, $J = 7.2$ Hz, aromatic), 8.24 (d, 1H, $J = 7.8$ Hz, aromatic). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 19.5, 40.6, 49.3, 51.1, 61.4, 74.3, 120.5, 122.7, 124.9, 125.1, 125.4, 125.6, 125.9, 126.0, 126.1, 126.5, 126.6, 127.0, 127.1, 127.2, 127.7, 127.9, 128.1, 128.4, 128.5, 128.8, 129.0, 129.1, 130.6, 131.6, 131.9, 133.2, 133.5, 139.5, 142.9, 157.0, 166.5, 176.0. EI-MS: m/z 664.72 (M^+). Anal. Calcd for $C_{45}H_{36}N_4O_2$: C, 81.30; H, 5.46; N, 8.43. Found: C, 81.37; H, 5.39; N, 8.50.

*5.3.19. 3-[3′-(4-Chlorophenyl)-1,2,4-oxadiazol-5-yl]-4-(1-naphthyl)-8-[(E)-1-(1-naphthyl)methylidene]-6-[(R)-1-phenylethyl]-5,6,7,8-tetrahydro-4H-pyrano[3,2-c]pyridin-2-amine (**9j**)*

Obtained as pale yellow solid (0.062 g, 32%); mp = 114–115 °C; $[\alpha]_D = +152.6$ (*c* 0.20, $CHCl_3$); IR (KBr): 1101, 1288, 1367, 1407, 1533, 1633, 1679, 2925, 3470 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 0.92 (d, 3H, $J = 6.6$ Hz, CH_3), 2.75 (d, 1H, $J = 16.2$ Hz, H-5a), 3.06 (d, 1H, $J = 14.1$ Hz, H-7a), 3.24 (q, 1H, $J = 6.6$ Hz, CH), 3.40 (d, 1H, $J = 16.2$ Hz, H-7a), 3.52 (d, 1H, $J = 14.1$ Hz, H-7b), 5.33 (s, 1H, H-4), 6.63 (br s, 2H, NH_2), 6.95–7.01 (m, 5H, H-9 and aromatic), 7.20–7.91 (m, 17H, aromatic), 8.06 (d, 1H, $J = 8.7$ Hz, aromatic), 8.35 (d, 1H, $J = 8.1$ Hz, aromatic). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 19.8, 41.3, 50.3, 51.0, 62.3, 74.1, 120.6, 122.7, 124.9, 125.0, 125.5, 125.7, 125.8, 125.9, 126.2, 126.4 126.8, 127.1, 127.6, 128.0, 128.4, 128.5, 128.9, 131.6, 131.9, 133.1, 133.4, 136.7, 139.6, 143.1, 157.1, 165.8, 176.2. EI-MS: m/z 698.50 (M^+). Anal. Calcd for $C_{45}H_{35}ClN_4O_2$: C, 77.30; H, 5.05; N, 8.01. Found: C, 77.24; H, 4.98; N, 8.08.

*5.3.20. 3-[3′-(4-Chlorophenyl)-1,2,4-oxadiazol-5-yl]-4-(1-naphthyl)-8-[(E)-1-(1-naphthyl)methylidene]-6-[(R)-1-phenylethyl]-5,6,7,8-tetrahydro-4H-pyrano[3,2-c]pyridin-2-amine (**10j**)*

Obtained as pale yellow solid (0.056 g, 29%); mp = 109–110 °C; $[\alpha]_D = -121.5$ (*c* 0.19, $CHCl_3$); IR (KBr): 1087, 1288, 1367, 1407, 1536, 1632, 1678, 2926, 3457 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 0.86 (d, 3H, $J = 6.6$ Hz, CH_3), 2.68 (d, 1H, $J = 16.5$ Hz, H-5a), 3.21–3.31 (m, 2H, CH and H-5b), 3.41 (d, 1H, $J = 14.1$ Hz, H-7a), 3.65 (d, 1H, $J = 14.1$ Hz, H-7b), 5.24 (s, 1H, H-4), 6.63 (br s, 2H, NH_2), 6.70–7.02 (m, 4H, H-9 and aromatic), 7.17 (d, 1H, $J = 6.9$ Hz, aromatic), 7.36–7.91 (m, 18H, aromatic), 8.09 (d, 1H, $J = 8.4$ Hz, aromatic), 8.24 (d, 1H, $J = 8.7$ Hz, aromatic). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 19.6, 40.3, 49.3, 51.2, 61.5, 74.3, 120.6, 122.7, 125.0, 125.1, 125.5, 125.7, 125.8, 126.0, 126.1, 126.2, 126.6, 126.7, 127.1, 127.8, 127.9, 128.4, 128.5, 128.9, 131.7, 131.9, 133.3, 133.5, 136.7, 139.5, 157.1, 165.8, 176.2. EI-MS: m/z 698.74 (M^+). Anal. Calcd for $C_{45}H_{35}ClN_4O_2$: C, 77.30; H, 5.05; N, 8.01. Found: C, 77.37; H, 5.11; N, 8.07.

Acknowledgements

This project was supported by Research Center, College of Science, King Saud University.

Appendix A. Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.ejmech.2012.04.021.

References

[1] D.E. Snider, M. Raviglione, A. Kochi, Global Burden of Tuberculosis, in: B. Bloom (Ed.), Tuberculosis: Pathogenesis, Protection and Control, ASM, Washington, DC, 1994, p. 3.
[2] C. Dye, S. Scheele, P. Dolin, V. Pathania, M.C. Raviglione, J. Am. Med. Assoc. 282 (1999) 677.
[3] K.M. De Cock, R.E. Chaisson, Int. J. Tubercul. Lung Dis. 3 (1999) 457.
[4] E.L. Corbett, C.J. Watt, N. Walker, D. Maher, B.G. Williams, M.C. Raviglione, C. Dye, Arch. Intern. Med. 163 (2003) 1009.
[5] K. Honer zu Bentrup, D.G. Russell, Trends Microbiol. 9 (2001) 597.
[6] C. Dye, B.G. Williams, M.A. Espinal, M.C. Raviglione, Science 295 (2002) 2042.
[7] T.B. Agerton, S.E. Valway, R.J. Blinkhorn, K.L. Shilkret, R. Reves, W.W. Schluter, B. Gore, C.J. Pozsik, B.B. Plikaytis, C. Woodley, I.M. Onorato, Clin. Infect. Dis. 29 (1999) 85.
[8] P.R. Mohapatra, Am. J. Respir. Crit. Care Med. 170 (2004) 920.
[9] H.L. Rieder, Lancet 373 (2009) 1148.
[10] Y. Morianka, K. Takahashi, Jpn. Kokai 17 (1977) 498.
[11] J.B. Montandon, F.J. Zijlstra, J.H.P. Wilson, J. Int. Tissue React. 11 (1989) 107.
[12] L.-F. Tietze, Angew. Chem., Int. Ed. Engl 22 (1983) 828 and references cited therein.
[13] S. Hatakeyama, N. Ochi, H. Numata, S. Takano, J. Chem. Soc., Chem. Commun. (1988) 1202.
[14] C.N. Ocallaghan, T.B.H. Mcmurry, J. Chem. Res. (S) 8 (1999) 457.
[15] J.L. Marco, N. Martin, A.M. Grau, C. Seoane, A. Albert, F.H. Cano, Tetrahedron 50 (1994) 3509.
[16] A. Albert, F.H. Cano, N. Martin, A. Ramos, M. Rodriguez, J.L. Segara, C. Seoane, J. Chem. Soc., Perkin Trans. 1 (1997) 3401.
[17] J. Saunders, A.M. MacLeod, K. Merchant, G.A. Showell, R.J. Snow, L.J. Street, R. Baker, J. Chem. Soc., Chem. Commun. (1988) 1618.
[18] F. Watjen, R. Baker, M. Engelstoff, R. Herbert, A. MacLeod, A. Knight, K. Merchant, J. Moseley, J. Saunders, C.J. Swain, E. Wong, J.P. Springer, J. Med. Chem. 32 (1989) 2282.
[19] W.R. Tully, C.R. Gardner, R.J. Gillespie, R. Westwood, J. Med. Chem. 34 (1991) 2060.
[20] J. Saunders, M. Cassidy, S.B. Freedman, E.A. Harley, L.L. Iversen, C. Kneen, A.M. MacLeod, K.J. Merchant, R.J. Snow, R. Baker, J. Med. Chem. 33 (1990) 1128.
[21] B.S. Orlek, F.E. Balaney, F. Braun, M.S.G. Clark, M.S. Hadley, J. Hatcher, G.J. Riley, H.E. Rosenberg, H.J. Wadsworth, P. Wyman, J. Med. Chem. 34 (1991) 2726.
[22] L.J. Street, R. Baker, T. Book, C.O. Kneen, A.M. MacLeod, K.J. Merchant, G.A. Showell, J. Saunders, R.H. Herbert, S.B. Freedman, E.A. Harley, J. Med. Chem. 33 (1990) 2690.
[23] C.J. Swain, R. Baker, C. Kneen, J. Moseley, J. Saunders, E.M. Seward, G. Stevenson, M. Beer, J. Stanton, K. Watlina, J. Med. Chem. 34 (1991) 140.
[24] M. Carbone, Y. Li, C. Irace, E. Mollo, F. Castelluccio, A. Di Pascale, G. Cimino, R. Santamaria, Y.W. Guo, M. Gavagnin, Org. Lett. 13 (2011) 2516.
[25] R.M. Srivastava, A. Lima, O.S. Viana, M.J.C. Silva, M.T.J.A. Catanho, J.O.F. Morais, Bioorg. Med. Chem. 11 (2003) 1821.
[26] P. Afiatpour, R.M. Srivastava, M.L. Oliveira, E.J. Barreiro, Braz. J. Med. Biol. Res. 27 (1994) 1403.
[27] N.M.M. Bezerra, S.P. De Oliveira, R.M. Srivastava, J.R. De Silva, II Farmaco 60 (2005) 955.
[28] For a review of the application of the privileged scaffold concept to drug discovery, see: M.E. Welsch, S.A. Snyder, B.R. Stockwell Curr. Opin. Chem. Biol. 14 (2010) 347.
[29] G.J. Richardo, B.C. Juan, R.A. Mario, M. Rolder, C.R. Peinado, Fernando Spen. 47 (1979) 168.
[30] B.R. Jerom, K.H. Spencer, Eur. Pat. Appl. EP 277794, 1998.
[31] R.V. Perumal, M. Adiraj, P. Shanmugapandian, Indian Drugs 38 (2001) 156.
[32] C.R. Ganellin, R.G. Spickett, J. Med. Chem. 8 (1965) 619.
[33] M. Nikolov, D. Stefanara, D. Chardanov, Acta. Nerv. Super. 16 (1974) 264.
[34] R.E. Hangenbach, H. Gysin, Experientia 8 (1952) 184.
[35] B. Heana, V. Dobre, I. Niculesar-Duvaz, J. Prakt. Chem. 327 (1985) 667.
[36] I.G. Mobio, A.T. Soldatenkov, V.O. Federov, E.A. Ageer, N.D. Sergeeva, S. Lin, E.E. Stashenko, N.S. Prostakov, E.I. Andreeva, Khim.-Farm. Zh. 23 (1989) 421.
[37] M. Ashraf Ali, R. Ismail, T.S. Choon, R. Suresh Kumar, H. Osman, N. Arumugam, A.I. Almansour, K. Elumalai, A. Singh, Bioorg. Med. Chem. Lett. 22 (2012) 508.
[38] R. Suresh Kumar, H. Osman, S. Perumal, J.C. Menendez, M. Ashraf Ali, R. Ismail, T.S. Choon, Tetrahedron 67 (2011) 3132.
[39] R. Suresh Kumar, M. Ashraf Ali, H. Osman, R. Ismail, T.S. Choon, Y.K. Yoon, A.C. Wei, S. Pandian, E. Manogaran, Bioorg. Med. Chem. Lett. 21 (2011) 3997.
[40] M. Ashraf Ali, R. Ismail, T.S. Choon, Y.K. Yoon, A.C. Wei, S. Pandian, R. Suresh Kumar, H. Osman, E. Manogaran, Bioorg. Med. Chem. Lett. 20 (2010) 7064.
[41] R. Suresh Kumar, S. Perumal, Tetrahedron Lett. 48 (2007) 7164.
[42] R. Suresh Kumar, S. Perumal, H.B. Kagan, R. Guillot, Tetrahedron: Asymmetry 18 (2007) 170.
[43] S. Michael Rajesh, R. Suresh Kumar, L.A. Libertsen, S. Perumal, P. Yogeeswari, D. Sriram, Bioorg. Med. Chem. Lett. 21 (2011) 3012.
[44] M. Ashraf Ali, R. Ismail, T.S. Choon, E. Manogaran, R. Suresh Kumar, H. Osman, J. Govindasamy, R. Yadav, G. Yadav, R. Kour, S. Vyas, J. Enzyme Inhib. Med. Chem. 27 (2012) 155.
[45] R. Suresh Kumar, S. Perumal, K.A. Shetty, P. Yogeeswari, D. Sriram, Eur. J. Med. Chem. 45 (2010) 124.
[46] R. Suresh Kumar, S.M. Rajesh, S. Perumal, D. Banerjee, P. Yogeeswari, D. Sriram, Eur. J. Med. Chem. 45 (2010) 411.
[47] R. Suresh Kumar, S. Michael Rajesh, S. Perumal, P. Yogeeswari, D. Sriram, Tetrahedron: Asymmetry 21 (2010) 1315.
[48] R. Suresh Kumar, S. Michael Rajesh, S. Perumal, D. Banerjee, P. Yogeeswari, D. Sriram, Chem. Pharm. Bull. 58 (2010) 602.
[49] S.R. Malwal, D. Sriram, P. Yogeeswari, V. Badireenath Konkimalla, H. Chakrapani, J. Med. Chem. 55 (2012) 553.
[50] R. Ranjith Kumar, S. Perumal, P. Senthilkumar, P. Yogeeswari, D. Sriram, J. Med. Chem. 51 (2008) 5731.
[51] D. Sriram, P. Yogeeswari, R. Thirumurugan, R.K. Pavana, J. Med. Chem. 49 (2006) 3448.
[52] M.E. Kuehne, P.A. Matson, W.G. Bornmann, J. Org. Chem. 56 (1991) 513.