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Synthesis of 3-Isopropylbenzo[D]Oxazol-2(3H)-One Amides and Urea Derivatives; Evaluation of their Anti-Mycobacterial and Cytotoxic Activity

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Abstract

Tuberculosis (TB) is a traditional disease caused by infection with *Mycobacterium tuberculosis*, it is a serious public health issue due to its risk of person-to-person transmission, and high level of morbidity and humanity. The World Health Organization (WHO) estimates 11.4 million people worldwide are infected with both *Mycobacterium tuberculosis* (Mtb) and HIV. Currently, there are approximately 8 million new infections and 3 million deaths attributed to *M. tuberculosis* annually. One of the major problems associated in comprehensive control of TB is that the restart of the disease in patients who carry a latent syndrome, in which the bacteria is in slow budding or non growing state and is refractory to treat with predictable anti-TB drugs. Directly observed treatment (DOT) is presently practicing for standard TB chemotherapy. It is well known that the resistance levels are poor in the areas with a strongly performing DOTS programmes. However, various drugs available in the market cannot be used for prolonged times due to diverse side effects. Therefore, the development of new and safe anti-TB drugs is in high demand. The major investigation on sEH inhibitors focused on urea, amide, amino- heterocycles and carbamate derivatives, but research on new compound structures is limited. Benzoxazolones are widely distributed in plants and are of increasing interest for a variety of pharmacological properties, such as detoxification, antibacterial, anti-HIV, anti-inflammatory, and transequilizers. Since benzoxazolones are active and inexpensive, many structural modification and preliminary bioactivity evaluation studies have been performed based on benzoxazol-ones. In this paper, 3-isopropyl benzo[d]oxazol-2(3H)-one amides and urea analogues were synthesized and evaluated as sEH inhibitors *in vitro*, and their anti-tuberculosis activities were determined *in vivo*. The 3-isopropylbenzo[d]oxazol-2(3H)-one heterocycles has received considerable attention from the medicinal chemists owing to their capacity to mimic a benzamides or a phenyl urea moiety in a metabolically stable template. This class of compounds has led to the discovery of a number of derivatives endowed with antibacterial-antifungal, analgesic-anti-inflammatory, anticonvulsant, dopaminergic, HIV-1 reverse transcriptase activity, and normolipenic agents. Usually functionalization of the nitrogen atom is of interest, since the electronic characteristic of this atom can be decisive for the biological activity. Nevertheless, most efforts have focused on N-, 5-, or 6-substituted benzoxazol-ones. Presently, 5-substituted benzoxazolone derivatives have been scarcely prepared, and few reports have described the sEH inhibitory activities or anti-tuberculosis activities. The pronounced biological activity of benzoxazolone derivatives and the lack of structure-bioactivity relationships prompted our investigation on 5-substituted-3-isopropylbenzo[d]oxazol-2(3H)-one.

Keywords: *Mycobacterium tuberculosis*; Anti-mycobacterial; HIV; Cytotoxic

Introduction

As part of our research on biologically active heterocycles,23 we herein reported an efficient method for the synthesis of 3-isopropylbenzo[d]oxazol-2(3H)-one amides and phenyl urea analogues. It is known that estrification is an important method for structural modification [1-15]. Hence, benzoate and besilate, the most common modified groups, were introduced to optimize the skeleton structure 2(3H)-benzoxazolones at 5-position (Tables 1 and 2). The synthetic route is outlined in Scheme 1. The starting material 2-amino-4-bromophenol 1 was reacted with ethyl 1H-imidazole-1-carboxylate under a nitrogen atmosphere in THF reflux to provide 5-bromobenzo[d]oxazol-2(3H)-one 2, which reacted with isopropyl iodide to afford the corresponding 5-bromo-3-isopropylbenzo[d] oxazol-2(3H)-ones 3. This compound 3 was underwent suzuki cross-coupling reaction with 3-aminophenylboronic acid in Pd(II)Cl2(dppf) and K2CO3 offered compound 4 [16-24]. The 4-bromo benzoyl chloride reacted with compound 4 yield the compound 5 in good yield. The compound 5 reacted with 2-amino phenyl boronic acid provide scaffold 6. The coupling reaction carried out with compound 6 and different acid chlorides obtained amide 7a-n in excellent yields (Scheme 1). Corresponding urea derivatives in good yields (Scheme 2). The general, practical and established method was successfully applied for the synthesis of 3-isopropylbenzo[d]oxazol-2(3H)-one amides 7a-n and urea derivatives 8a-d. Thus synthesized compounds 7a–n and 8a–d are well characterized by spectral data. These 3-isopropylbenzo[d] oxazol-2(3H)-one amides 7a-n and urea derivatives 8a-d were screened for their anti-mycobacterial activity [25-29].

In Vitro Anti-Mycobacterial Activity

Compound 6 reacts with various phenyl, pyrazole, pyridine and cyclobutyl acid chlorides or isocyanates were synthesized 3-isopropylbenzo[d]oxazol-2(3H)-one amides 7a-n and urea derivatives 8a-d. The synthesized compounds were screened for their

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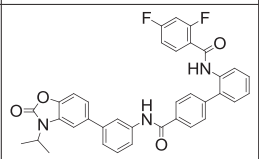
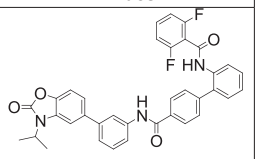
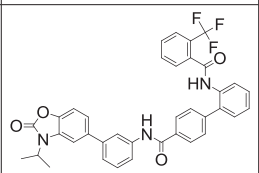
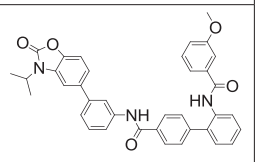
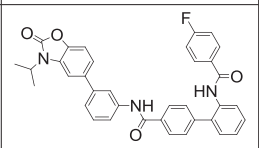
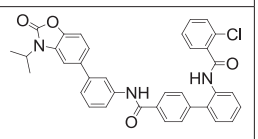
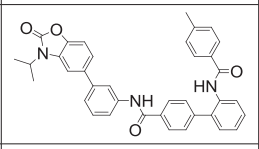
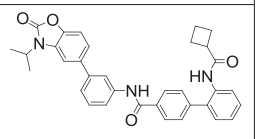
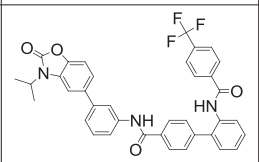
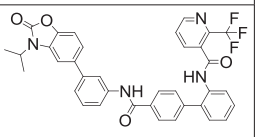
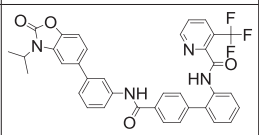
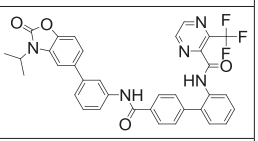
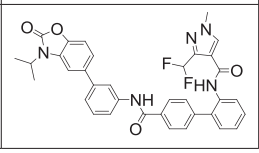
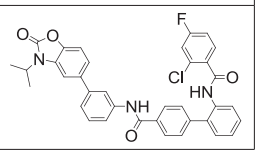
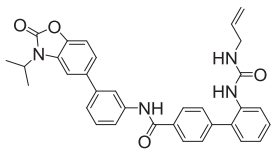
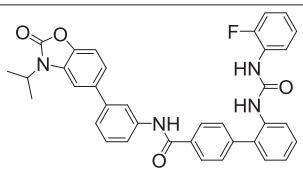
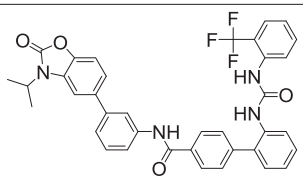
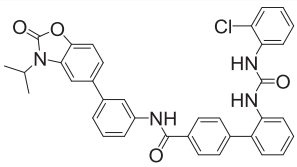
Compd	Amides[a]	Compd	Amides[a]
7a		7h	
7b		7i	
7c		7j	
7d		7k	
7e		7l	
7f		7m	
7g		7n	

[a]All products were characterized by NMR, IR and mass spectrometry.

Table 1: Synthesis of 3-isopropylbenzo[d]oxazol-2(3H)-one amide derivatives (7a-n).

in vitro anti-mycobacterial activity against *M. tuberculosis* H37Rv (MTB) by agar dilution method recommended by National Committee for Clinical Laboratory Standards for the determination of MIC and the values of the synthesized compounds along with standard drugs Isoniazid, Ethambutol and Ciprofloxacin for comparison are presented in Table 3. Based on MIC values we could observe structure–activity relationship by the influence of substituted amides and urea derivatives. Anti-mycobacterial screening of 7a–n and 8a-d reveals that all the tested compounds showed moderate to good activity against the tested anti-mycobacterial assay and MIC's ranging from 1.56 to 50.0 µg/mL. The compound 8a showed excellent activity against anti-mycobacteria same as Ethambutol (MIC=1.56). The compounds 7a, 7e, 7f, 7g, 8c, and 8d showed good activity. Unfortunately, the compounds 7d, 7j, 7k, 7l and 8b showed poor anti-mycobacterial activity against 8a. The activity of the 4-CF3 compound 7e, 3-(trifluoromethyl) picolinamide compound 7f and 8c were same (MIC=6.5) potent against both replicating and non-replicating *M. tuberculosis*. When the 4-CF3 in the compound 7e and 7f with MIC=6.5 was replace with 2-CF3 group of compound 7b with a MIC of 25, was 4-fold less active. All experiments were carried out in triplicates and the results were reported as ± SD. From the anti-mycobacterial activity, the MIC values are calculated and presented in Table 3. The values presented in the Table 3 suggested that electronic effect may play a role in the anti-tuberculosis activity in this series.

Compd	Urea derivatives[a]
8a	
8b	
8c	
8d	

[a]All products were characterized by NMR, IR and mass spectrometry.

Table 2: Synthesis of 3-isopropylbenzo[d]oxazol-2(3H)-one urea derivatives (8a-d).

Cytotoxic Evaluation

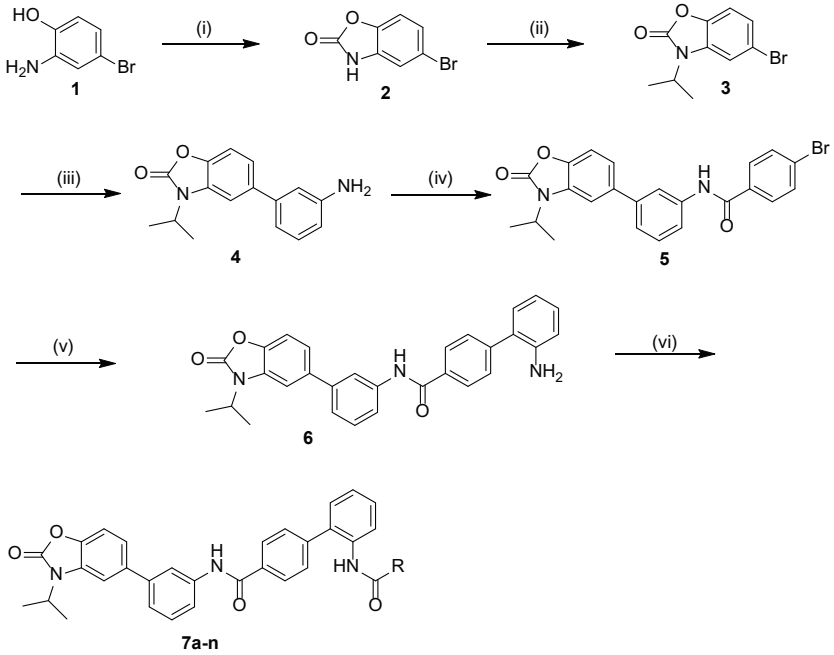
All the synthesized compounds 7a-n and 8a-d were subjected to WST-1 cytotoxicity assay against Panc-1 (human pancreatic adenocarcinoma) and H460 (human non-small cell lung carcinoma) cell lines. These compounds were inactive towards to cytotoxicity against both the cancer cell lines tested, hence the % cytotoxicity at various concentrations of the compounds were obtained and the respective IC50 value for the corresponding cell lines were obtained through the plot.

Conclusions

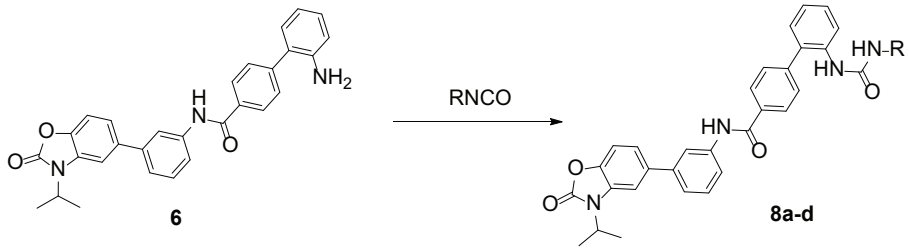
In summary, we have developed a simple method for the synthesis of 3-isopropylbenzo[d]oxazol-2(3H)-one amides 7a-n and urea 8a-d derivatives. The suzuki coupling reaction of boronic acid with bromo benzene in the presence of Pd(II) catalyst under reflux conditions provides the novel class of amide and urea derivatives which are found to possess interesting anti-micobactirial properties. This method also describes the synthesis of benzoxazol moiety which is found to possess interesting anti-mycobacterial properties.

General

All chemicals used possess a purity of >95%. Yields refers to pure products after purification and are unoptimized. Melting points were determined in open capillaries on Gallenkamp apparatus and are uncorrected. Microanalyses were conducted on Perkin-Elmer 240C or Perkin-Elmer Series II CHNS/O Analyzer 2400 instrument. Silica gel 60 (230–400 mesh) was used for the column chromatography. TLC plates (Silica Gel 60 F254) were used for thin-layer chromatography (TLC). Aluminum oxide (activity II–III), Brockmann grade was used.



Scheme 1: Reagents and conditions. (i) ethyl 1H-imidazole-1-carboxylate, THF, 70°C, 12 h; (ii) Isopropyl iodide, K2CO3, THF, 70°C, 12 h; (iii) Pd(II)Cl2(dppf), K2CO3, Boronic acid, EtOH+Toluene, reflux; iv) 4-bromo benzoyl Chloride, DCM, 2h, RT; (v) Pd(11)Cl2(dppf), K2CO3 , Boronic acid, EtOH+Toluene, reflux; (vi). RCOCl, DCM, 2 h, RT.



Scheme 2: Reagent and conditions. (i) RNCO, DCM, RT.

Entry	Compd	CLogP[a]	MIC (μg/ml)	MIC (μm)
1	7a	5.83	125	48.28
2	7b	5.73	25	25.42
3	7c	6.04	25	23.42
4	7d	6.24	50	11.63
5	7e	6.94	6.25	101.70
6	7f	5.06	6.25	101.85
7	7g	4.08	12.5	49.73
8	7h	5.42	25	24.14
9	7i	5.90	25	23.90
10	7j	5.78	50	12.04
11	7k	5.16	50	10.91
12	7l	4.71	50	12.73
13	7m	4.20	25	25.48
14	7n	5.98	25	24.76
15	7o	6.00	1.56	350.39
16	7p	7.09	50	12.01

Table 3: Anti-mycobacterial activity of 7a-n and 8a-d against *Mycobacterium smegmatis*.

Experimental procedure:

1. General procedure for the synthesis of substituted Benzoxazolidine-one amides (7a-n): The compound 6 react with benzoyl chlorides in CH2Cl2 as a solvent for 2 h at RT. Upon completion, the solvent was removed under reduced pressure and the residue was purified by column chromatography to produce substituted benzoxazolidine-one amides.

2. General procedure for the synthesis of substituted Benzoxazolidine-one urea derivatives (8a-d): The compound 6 react with isocyanates in CH2Cl2 as a solvent for 2 h at RT. Upon completion, the solvent was removed under reduced pressure and the residue was purified by column chromatography to afford benzoxazolidine-one urea derivatives.

Supplementary Data

Supplementary data contains spectral data of compounds 7a-n (Table 1) and 8a-d (Table 2).

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