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Design, Synthesis and Biological evaluation of some novel biphenyl substituted oxazole derivatives

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Abstract: Novel 2,5-dimethyl-4-substituted biphenyl-1,3-oxazole derivatives have been synthesized by the suzuki reaction of 4-(4-bromophenyl)-2,5-dimethyloxazole [obtained by the bromination reaction of p-bromo phenyl ethanone and further cyclisation reaction with acetamide under microwave] with substituted phenylboronic acid in presence of bis(triphenylphosphine)palladium(ii) chloride and potassium carbonate in dimethyl formamide. These were screened for in-vitro antimicrobial activity against two gram positive (*Streptococcus pyogenes* and *Staphylococcus aureus*) and two gram negative bacteria (*Pseudomonas aeruginosa* and *Escherichia coli*) as well as for antifungal and antimalarial activity against *Plasmodium falciparum strain*. Compound 3(c) and 3(i) exhibited good antimicrobial and antimalarial activity.

Keywords: p-bromo phenyl ethanone, acetamide, phenylboronic acid, Antimicrobial and antimalarial activity.

Introduction

In recent decades, microbial diseases are more prevalent than they were during the first half of the last century and are still difficult to be diagnosed clinically. To combat them, various synthetic and semi-synthetic antimicrobial drugs have been used in clinical practice[1,2]. In literature, a number of research paper are available describing the antimicrobial behaviour of aromatic and heterocyclic compound [3-6]. But, in the treatment of microbial infections only limited numbers of efficacious antimicrobial drugs are used even after availability of a number of antimicrobial agents. Many of the currently available drugs are toxic, enable recurrence because they are bacteriostatic/ fungistatic and not bactericidal/fungicidal or lead to the development of resistance due in part to the prolonged periods of administration. The impact is more acute in developing countries due to non-availability of desired medicines

[7,8]. There is a real perceived need for the discovery of new compounds that are endowed with antibacterial and antifungal activities, possibly acting through mechanism of actions, which are distinct from those of well known classes of antimicrobial agents to which many clinically relevant pathogens are now resistant [9-11].

Oxazole are a class of heterocyclic compounds that are believed to occur in nature from post- translational modification of serine and threonine residues in peptides [12,13]. They are key building blocks of natural products, pharmaceuticals and synthetic intermediates [14-16]. Oxazole have not only attracted great interests due to their appearance as subunits of various biologically active natural products but also because of their utilities as valuable precursors in many useful synthetic transformations [17]. Among the numerous heterocyclic moieties of biological and pharmacological interest, the oxazole ring is endowed with various activities such as hypoglycemic[18], anti-inflammatory [19], and antibacterial [20] activities. It is reported that new D2-isoxazoline derivatives can be as betaadrenergic receptor antagonist [21]. The oxazole derivatives have raised considerable attention to medicinal research, and a large number of investigations on their synthesis and biological activities have been reported during the last ten years [22-24].

Looking at the importance of these heterocyclic nuclei, it is thought of interest to devote some attention for the synthesis of biphenyl substituted oxazole derivatives and to evaluate these derivatives for antimicrobial and antimalarial activity against *plasmodium falciparum* strain.

2.1 Antimicrobial activity :

All the synthesized compounds were tested against two gram positive bacteria (*Staphylococcus aureus*, *Streptococcus Pyogenes*) and two gram negative bacteria (*Escherichia coli* ,*Pseudomonas aeruginosa*) using micro broth dilution method [25-28] for the determination of minimal inhibition concentration . For the antifungal activity the common standard strains that were used, are *C.Albicans*, *A,Niger* and *A.Clavatus*. Muller Hinton broth (Microcare laboratory & Tuberculosis Research Centre, Surat-3, India) was used as nutrient medium to grow and dilute the drug suspension for the test bacteria. Inoculum Size for Test Strain was adjust to 10^8Cfu [Colony Forming Unit] per milliliter by comparing the turbidity. DMSO was used as diluents / vehicle to get desired concentration of drugs to test upon Standard bacterial strains. Serial dilutions were prepared in primary and secondary screening. In primary screening 1000 µg/ml, 500 µg/ml, and 250 µg/ml concentrations of the synthesized compounds were taken. The active synthesized compounds found in this primary screening were further tested in a second set of dilution against all microorganisms. The highest dilution showing at least 99 % inhibition zone is taken as MIC. The test mixture should contain 10^8 organism/ml. Standard drugs Ampicillin and Chloramphenicol were used as antibacterial for comparison. Standard drugs Nystatin and Greseofulvin were used as antifungal for comparison.

2.2 Antimalarial activity :

The in vitro antimalarial assay was carried out in 96 well microtitre plates according to the microassay protocol reference. The cultures of*Plasmodium falciparum* strain were maintained in medium RPMI 1640 supplemented with 25 mM HEPES, 1% D-glucose, 0.23% sodium bicarbonate and 10% heat inactivated human serum. The asynchronous parasites of *Plasmodium falciparum* were synchronized after 5% D-sorbitol treatment to obtain only the ring stage

parasitized cells. For carrying out the assay, an initial ring stage parasitaemia of 0.8 to 1.5% at 3% haematocrit in a total volume of 200 µ l of medium RPMI-1640 was determined by Jaswant Singh Bhattacharya (JSB) staining to assess the percent parasitaemia (rings) and uniformally maintained with 50% RBCs (O+). A stock solution of 5mg/ml of each of the test samples was prepared in DMSO and subsequent dilutions were prepared with culture medium. The diluted samples in 20 µ l volume were added to the test wells so as to obtain final concentrations (at fivefold dilutions) ranging between 0.4 µ g/ml to 100 µ g/ml in duplicate well containing parasitized cell preparation. The culture plates were incubated at 37oC in a candle jar. After 36 to 40 h incubation, thin blood smears from each well were prepared and stained with JSB stain. The slides were microscopically observed to record maturation of ring stage parasites into trophozoites and schizonts in presence of different concentrations of the test agents. The test concentration which inhibited the complete maturation into schizonts was recorded as the minimum inhibitory concentrations (MIC). Quinine was taken as the reference drug.

3.MATERIALS AND METHODS

3.1 General Procedures:

Reagent grade chemicals were used without further purification. All the melting points were taken in open capillaries and are uncorrected. The purity and mass of the synthesized compounds was checked by MS . 1H NMR spectral was recorded in CDCl3 /DMSO with tetramethylsilane (TMS) as the internal standard at 400 MHz on a Bruker DRTX-400 spectrophotometer. The chemical shifts are reported as parts per million (ppm). Elemental analysis was performed using a (EURO EA 3000 instrument). Acme silica gel-G and Merck silica gel (100 to 200, 60 to 120 meshes) were used for analytical TLC and Column chromatography respectively.

3.2 Chemistry:

We have prepared the novel 2,5-dimethyl-4-substituted biphenyl-1,3-oxazole derivatives in three steps, using p-bromo phenyl ethanone, acetamide and substituted phenyl boronic acid as the starting materials. p-bromo phenyl ethanone on bromination reaction with bromine results 2-bromo-1-(4-bromophenyl) propan-1-one which oncyclisation reaction with acetamide results 4-(4-bromophenyl)-2,5-dimethyloxazoleand further by Suzuki coupling reaction with substituted phenyl boronic acidin presence of potassium carbonate and bis tri phenyl phosphine palladium(II) dichloride in DMF results the desired 2,5-dimethyl-4-biphenyl substituted-1,3- oxazole derivatives. The clear procedure for the preparation of desired 2,5-dimethyl-4-biphenyl substituted-1,3-oxazole derivatives are given below.

4.Preparation of desired 2,5-dimethyl-4-biphenyl substituted-1,3- oxazolederivatives:

4.1 Preparation of 2-bromo-1-phenylpropan-1-one (Intermediate-A):

To a solution of p-bromo phenyl ethanone (0.01mole) in diethyl ether was added bromine (0.013 mole) dropwise at 0 ^{0}C and then it was stirred at ambient temperature for 1hr. After completion, the reaction mixture was quenched with Sat.sodium bicarbonate solution. The compound was extracted with ethyl acetate and washed with water. The organic layer was dried over Na_2SO_4, evaporated and purified by column chromatography by using 100-200 silica gelat 4% ethyl acetate in hexane which results to give desiredIntermediate-A.(Yield:85%).

Spectral data of intermediate-A:

^{1}H-NMR (400MHz, $CDCl_3$): δ 7.88 (d,*J* = 8.4Hz, 2H),7.63 (d,*J* = 8.4Hz, 2H), 5.21 (q,*J* = 6.4Hz, 1H),1.89 (d, *J* = 6.8Hz, 3H), MS: 290.7 (M+).

4.2 Preparation of 4-(4-bromophenyl)-2,5-dimethyloxazole (Intermediate-B):

A mixture of compound (Intermediate-A) (0.01 mole) and acetamide (0.04 mole) was heated under microwave for 1hr. Progress of reaction mass was monitored through TLC.After completion, the reaction mixture was quenched with Sat.sodium bicarbonate solution. The compound was extracted with ethyl acetate and washed with water. The organic layer was dried over Na_2SO_4, evaporated and purified by column chromatography by using 100-200 silica gelat 20% ethyl acetate in hexane which results to give desiredIntermediate-B. (Yield:45%).

Spectral data of intermediate-B:

^{1}H-NMR (400MHz, $CDCl_3$): δ7.51 (m, 4H), 2.46 (s, 6H), MS: 251.8.

4.3 General procedure for the synthesis of desired 2,5-dimethyl-4-biphenyl substituted-1,3- oxazolederivatives:

A mixture of compound (Intermediate-B) (0.01mole) and potassium carbonate (0.015mole) was dissolved in 10 mL DMF. Then to it was added bis(triphenylphosphine) palladium(ii) chloride (0.001 mole) followed by substituted phenyl boronic acid (0.015 mole) under nitrogen atmosphere at room temperature and the reaction mixture was heated at 95^{0}C for 2hrs. After completion, the reaction mixture was diluted with ethyl acetate and washed with water. The organic layer was dried over Na_2SO_4 and evaporated. The crude compound was purified by using column chromatography with 100-200 silica gel to give compound 3(a-i) Scheme 1.

Spectral data of desired 2,5-dimethyl-4-biphenyl substituted-1,3- oxazole derivatives:

2,5-dimethyl-4-(3'-(trifluoromethyl) biphenyl-4-yl)oxazole 3(a) :^{1}H-NMR (400MHz, $CDCl_3$): δ 7.86 (s, 1H), 7.80 (d, *J* = 7.2Hz, 1H), 7.74(d,*J* = 8.4Hz, 2H), 7.65 (d,*J* = 8.4Hz, 2H),7.54-7.61(m, 2H),2.54 (s, 3H),2.48 (s, 3H), MS (ESI+)m/z: 318.2 (M^++1). Anal. Calcd for$C_{18}H_{14}F_3NO$:C- 68.13%, H- 4.45%, F- 17.96%, N- 4.41%, O- 5.04%, Found : C- 68.11%, H- 4.41%, F- 17.93%, N- 4.38%, O- 5.01%.

2,5-dimethyl-4-(2'-(trifluoromethoxy) biphenyl-4-yl)oxazole 3(b) :

^{1}H-NMR (400MHz, $CDCl_3$): δ 7.73 (d, *J*= 8.4Hz, 2H), 7.55 (d, *J* = 2.0 Hz, 2H), 7.48-7.50 (m,1H), 7.37-7.41 (m, 3H), 2.56 (s, 3H),2.49 (s, 3H),MS (ESI+)m/z: 334.2 (M^++1). Anal. Calcd for$C_{18}H_{14}F_3NO_2$:C- 64.86%, H- 4.23%, F-17.10%, N- 4.20%, O- 9.60%, Found : C- 64.83%, H- 4.21%, F-17.05%, N- 4.15%, O- 9.55%.

2,5-dimethyl-4-(4'-(trifluoromethyl) biphenyl-4-yl)oxazole 3(c) :

^{1}H-NMR (400MHz, $CDCl_3$): δ 7.75 (m, 2H), 7.70-7.73 (m, 4H), 7.64-7.66 (m,2H), 2.54 (s, 3H),2.48 (s, 3H),MS (ESI+)m/z: 318.1 (M^++1). Anal.Calcd for$C_{18}H_{14}F_3NO$:C- 68.13%, H- 4.45%, F- 17.96%, N- 4.41%, O- 5.04%, Found : C- 68.11%, H- 4.41%, F- 17.92%, N- 4.39%, O- 5.01%.

4-(2',5'-dichlorobiphenyl-4-yl)-2,5-dimethyloxazole 3(d) :

^{1}H-NMR (400MHz, $CDCl_3$): ^{1}HNMR: (400MHz, CDCl3): δ 7.71 (d, *J* = 8.4 Hz, 2H), 7.47 (d, *J* = 8.4 Hz, 2H), 7.40 (d, *J* = 8.4 Hz, 1H),7.36 (d, *J* = 2.4 Hz, 1H),7.24-7.27 (m, 1H), 2.54 (s, 3H),2.47 (s, 3H),MS (ESI+)m/z:

318.1 (M^++1). Anal.Calcd for$C_{17}H_{13}Cl_2NO$:C- 64.17%, H- 4.12%, Cl- 22.28%, N- 4.40%, O- 5.03%, Found : C- 64.12%, H- 4.09%, Cl- 22.25%, N- 4.35%, O- 5.01%.

4-(3',5'-dichlorobiphenyl-4-yl)-2,5-dimethyloxazole 3(e):

^{1}H-NMR (400MHz, $CDCl_3$): ^{1}HNMR: (400MHz, CDCl3): δ 7.73 (s, 1H), 7.71 (s,1H),7.58 (d, *J* = 8.4 Hz, 2H), 7.49 (d, *J* = 1.6 Hz, 2H),7.33 (m,1H), 2.54 (s, 3H),2.47 (s, 3H),MS (ESI+) m/z: 318.3 (M^++1). Anal.Calcd for$C_{17}H_{13}Cl_2NO$:C- 64.17%, H- 4.12%, Cl- 22.28%, N- 4.40%, O- 5.03%, Found : C- 64.13%, H- 4.10%, Cl- 22.26%, N- 4.37%, O- 5.02%.

2,5-dimethyl-4-(2'-(methylthio)biphenyl-4-yl)oxazole 3(f) :

^{1}H-NMR (400MHz, $CDCl_3$): ^{1}HNMR: (400MHz, CDCl3): δ 7.70 (m,2H), 7.47 (d,*J* = 8.0 Hz, 2H), 7.28-7.34 (m,2H),7.22-7.23 (m, 2H), 2.53 (s, 3H), 2.47 (s, 3H), 2.37(s, 3H),MS (ESI+)m/z: 296.1 (M^++1). Anal.Calcd for$C_{18}H_{17}NOS$:C- 73.19%, H- 5.80%, N- 4.74%, O- 5.42%, S- 10.85%, Found : C- 73.17%, H- 5.78%, N- 4.72%, O- 5.40%, S- 10.83%.

4-(biphenyl-4-yl)-2,5-dimethyloxazole 3(g) : ^{1}H-NMR (400MHz, $CDCl_3$): ^{1}HNMR: (400MHz, CDCl3): δ 7.71 (d,*J* = 8.4 Hz, 2H), 7.62-7.66 (m,4H), 7.43-7.46 (m,2H),7.33-7.36 (m, 1H), 2.53 (s, 3H), 2.47 (s, 3H),MS (ESI+) m/z: 250.4 (M^++1). Anal.Calcd for$C_{17}H_{15}NO$:C- 81.90%, H- 6.06%, N- 5.62%, O- 6.42%, Found : C-81.88%, H- 6.04%, N- 5.59%, O- 6.39%.

2,5-dimethyl-4-(3',4',5'-trifluorobiphenyl-4-yl)oxazole 3(h) :

^{1}H-NMR (400MHz, $CDCl_3$): δ 7.71 (d,*J* = 8.4 Hz, 2H), 7.54 (d,*J* = 8.4 Hz, 2H), 7.20-7.23 (m,2H), 2.53 (s, 3H), 2.47 (s, 3H),MS (ESI+)m/z: 304.1 (M^++1). Anal.Calcd for$C_{17}H_{12}F_3NO$:C-67.32%, H- 3.99%, F- 18.79%, N- 4.62%, O- 5.28%, Found : C-67.30%, H- 3.97%, F- 18.77%, N- 4.61%, O- 5.25%.

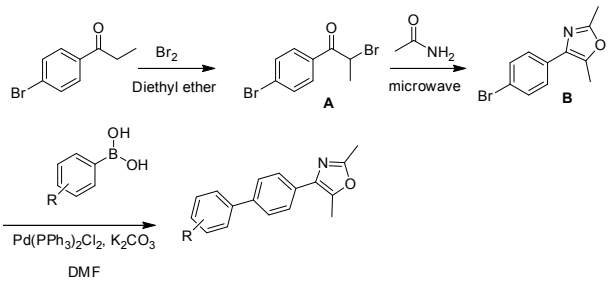
4-(4'-fluorobiphenyl-4-yl)-2,5-dimethyloxazole 3(i) :

^{1}H-NMR (400MHz, $CDCl_3$): δ δ 7.70 (d,*J* = 8.4 Hz, 2H), 7.56-7.60 (m,4H), 7.11-7.15 (m,2H), 2.53 (s, 3H), 2.47 (s, 3H),MS (ESI+)m/z: 268.2 (M^++1). Anal.Calcd for$C_{17}H_{14}FNO$:C-76.39%, H- 5.28%, F- 7.11%, N- 5.24%, O- 5.99%, Found : C-76.37%, H- 5.25%, F- 7.09%, N- 5.21%, O- 5.97%.

5. Result and discussion :

p-bromo phenyl ethanone on bromination reaction with bromine in diethyl ether results 2-bromo-1-(4-bromophenyl)propan-1-one (Intermediate-A)which oncyclisation reaction with acetamide under microwave heating results 4-(4-bromophenyl)-2,5-dimethyloxazole (Intermediate-B). The obtained compound (Intermediate-B) on Suzuki coupling reaction with substituted phenyl boronic acidin presence of potassium carbonate and bis tri phenyl phosphine palladium(II) dichloride in DMF results the desired 2,5-dimethyl-4-biphenyl substituted-1,3- oxazole derivatives. The list of synthesized compounds are represented by Table-1.

Scheme :



List of synthesized compound Table-1

Compound	R	M.P(^{0}C)	Yield(%)
3a	3-CF3	140-142	57
3b	2-OCF3	158-160	67
3c	4-CF3	167-169	44
3d	2,5-Dichloro	178-180	66
3e	3,5-Dichloro	165-167	56
3f	2-SCH3	159-161	43
3g	H	172-174	54
3h	3,4,5-Trifluoro	187-189	65
3i	4-F	162-164	69

5.2 Antibacterial activity:

The antibacterial activity of all the synthesized compounds were tested in-vitro against pathogenic *E. coli*, *P.aeruginosa*,*S. aureus*and *S.pyogenus* and the results were compared with standard drugs (Ampicillin and Chloramphenicol). In case of *S.aureus* compounds 3(b), 3(c), 3(d), 3(f), and 3(i)exhibit good activity while rest of the compounds show moderate activity. In case of *S.pyogenus* compounds 3(a), 3(b), and 3(e) exhibit good activity while rest of the compounds show moderate activity. In case of *E. coli* Compound 3(c) shows higher activity and 3(d), 3(f) and 3(i) show moderate activity while rest of the compounds possess less activity. In case of *P.aeruginosa* compound 3(f) shows higher activity and compound 3(c), 3(d) and 3(h) shows good activity while rest of the compounds possess less activity. The results are given in Table-2.

Table-2 Antibacterial activity (minimum inhibitory concentration in µg/ml)

Compound	E.COLI	P. AERUGINOSA	S. AUREUS	S. PYOGENUS
3(a)	250	500	250	100
3(b)	200	250	100	100
3(c)	62.5	100	125	125
3(d)	100	100	100	200
3(e)	250	250	250	100
3(f)	100	62.5	100	250
3(g)	500	250	200	200
3(h)	500	100	200	250
3(i)	100	200	100	250
Ampicillin	100	100	250	100
Chloramphenicol	50	50	50	50

Table-3: Antifungal Activity (In MIC)

Compound	C.Albicans	A.Niger	A.Clavatus
3(a)	1000	500	1000
3(b)	>1000	>1000	>1000
3(c)	500	>1000	>1000
3(d)	250	500	>1000
3(e)	>1000	>1000	>1000
3(f)	500	>1000	>1000
3(g)	500	>1000	>1000
3(h)	1000	500	500
3(i)	250	>1000	>1000
Nystatin	100	100	100
Greseofulvin	500	100	100

Table-4: Antimalarial Activity

Compound	Mean IC50 (µg/ml)
3(a)	1.43
3(b)	0.85
3(c)	0.52
3(d)	0.72
3(e)	1.07
3(f)	1.53
3(g)	2.22
3(h)	1.09
3(i)	0.61
Quinine	0.268

5.2 Antifungal activity:

The antifungal activity of all the synthesized compounds were tested in-vitro against fungi *C.Albicans*, *A.Niger* and *A.Clavatus* and the

results were compared with standard drugs (Nystatin and Greseofulvin). In case of *C.Albicans* compound 3(d) and 3(i) exhibit higher activity while 3(c), 3(f) and 3(g) show good activity and rest of the compounds possess less activity. In case of *A,Niger* and *A.Clavatus* all the compounds possess less activity. The results are given in Table-3.

5.4 Antimalarial activity:

For antimalarial activity, Compounds 3(c) and 3(i) exhibit good activity closer to reference compound Quinine against *plasmodium falciparum* strain while rest of the compounds possess lessactivity. The results are given inTable-4.

6. Conclusion :

All the newly synthesized compounds were screened for antibacterial, antifungal and antimalarial activity. The data in the Table-2 indicate that among the synthesized compounds, compounds 3(c) and 3(i) exhibit excellent and compounds 3(a), 3(b), 3(d), 3(e) and 3(f) possess good antibacterial activity. However, the activities of the tested compounds are much less than those of standard agents used. Compounds 3(c) and 3(i) also show potent antimalarial activity. From the results of various biological activities it is clear that these compounds would be of better use in drug development to combat bacterial infections and as antimalarial agents in the future.

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