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Design and Synthesis of some Novel oxazole derivatives and their biomedical efficacy

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Abstract: Some new 5-substituted aryl (or heteroaryl)-2-methyl-4-phenyloxazole derivatives have been synthesized by the suzuki reaction of 5-bromo-2-methyl-4-phenyloxazole [obtained by the bromination of 2-methyl-4-phenyloxazole, which is obtained by the cyclization of 2-bromo-1-phenylethanone with acetamide under microwave] with substituted aryl(or heteroaryl) boronic acid. All the synthesized compounds were characterized by elemental analysis, NMR(¹H & ¹³C) and MS. 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.

Keywords: Oxazole, Acetamide, Substituted phenyl boronic acid, Antibacterial, Antifungal, Antimalarial activity.

Introduction

The derivatives of Oxazole have become increasingly important in the past few years because of their use in intermediates for the preparation of new biological materials. The oxazole ring is present in numerous pharmacologically important compounds, including those used as antibiotics [1] and antiproliferative [2]. The wide range of biological activities of oxazoles includes anti-inflammatory [3], analgesic [4],

antibacterial, antifungal [5], hypoglycaemic [6], antiproliferative [7], anti-tuberculosis [8], muscle relaxant [9] and HIV inhibitor activity [10]. In addition, oxazole derivatives are useful synthetic intermediates and can be used as diversity scaffolds in combinatorial chemistry[11] and also as peptidomimetics [12]. Standard drugs used in some of the medicinally important derivatives containing oxazole are Trimethadione etc. which possess antiepileptic [13] properties.

Oxazoles play a vital role in the manufacture of various biologically active drugs as brain-derived neurotrophic factor inducers [14], analgesic [15], trypanocidal activity [16], antimitotic agents with pro-apoptotic activity [17]. Over the years, a number of methods have been devised for the synthesis of oxazoles [18]. Classically, the Robinson–Gabriel synthesis was the most common route to oxazoles, which involves dehydration of 2-acylamino-ketones [19].

Looking at the importance of these heterocyclic nuclei, it is thought of interest to devote some attention for the synthesis of new 2-methyl-4-phenyl oxazole derivatives having different substitution at 5-position and to evaluate these derivatives for antimicrobial and antimalarial activity.

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 [20-23] 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 adjusted to 108 CfU [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 dilution were prepared in primary and secondary screening. In primary screening 1000 micro/ml, 500 micro/ml, and 250 micro/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 108 organism/ml. Standard drugs Ampicillin and Chloramphenicol were used as antibacterial for comparison. Standard drugs Nystatin and Griseofulvin were used as antifungal for comparison.

Antimalarial activity :

The in vitro antimalarial assay was carried out in 96 well microtitre plates according to the microassay protocol reference. The cultures of *P. 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 *P. 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 uni-formally 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 five fold 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 37°C 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.

Material & methods

Reagent grade chemicals were used without further purification. All the melting points were taken in open capillaries and are uncorrected. The mass of the synthesized compounds were checked by MS. ¹H NMR spectra (CDCl₃/DMSO-d₆) were recorded on FTIR RXI Perkin-Elmer 1800 spectrophotometer and Bruker DRTX-400 spectrophotometer (400 MHz) using TMS as internal standard, respectively. 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.

Experimental

Synthesis of 2-methyl-4-phenyl oxazole (1):

A solution of 2-bromo-1-phenylethanone, (7.0 gm., 35.16 mmol) and acetamide, (8.3 gm., 140.67) was heated under microwave for 1 hr. The reaction mixture was diluted with Ethyl acetate and washed with saturated solution of sodium bicarbonate followed by water. Organic layer was dried over magnesium sulphate, filtered and evaporated under reduced pressure and crude compound was purified by using column chromatography. (4.9 gm, 87.6%).
¹HNMR: (400MHz, CDCl₃): δ 7.80 (s, 1H), 7.69-7.71 (m, 2H), 7.37-7.41 (m, 2H), 7.27-7.31 (m, 1H), 2.51 (s, 3H).

Synthesis of 5-bromo-2-methyl-4-phenyl oxazole (2):

To a solution of synthesized compound(1) 2-methyl-4-phenyloxazole (4.9 gm., 30.78 mmol) in 150 ml acetic acid was added NBS (6.5 gm., 36.93) at 00C and stirred at RT for 8hrs. The reaction mixture was diluted with Ethyl acetate and washed with saturated solution of sodium bicarbonate followed by water. Organic layer was dried over magnesium sulphate, filtered and evaporated under reduced pressure and crude compound was purified by using column chromatography. (6.5 gm, 89.05%)
¹HNMR: (400MHz, CDCl₃): δ 7.92-7.94 (m, 2H), 7.41-7.45 (m, 2H), 7.32-7.36 (m, 1H), 2.51 (s, 3H).

General procedure for the synthesis of desired 5-substituted aryl (or heteroaryl) -2-methyl-4-phenyloxazole derivative :

To a solution of 5-bromo-2-methyl-4-phenyl oxazole (compound-2) (0.01mole) in DMF and water (8:2) was added potassium carbonate (0.015mole) followed by bis(triphenylphosphine)palladium(ii) chloride (0.001 mole) under nitrogen atmosphere at room temperature. Then to it was added substituted aryl(or heteroaryl) boronic acid (0.015 mole) and the reaction mixture was heated at 80 0C for 2hrs. The reaction mixture was diluted with ethyl acetate and washed with water. The organic layer was dried over Na₂SO₄ and evaporated. The crude compound was purified by using column chromatography with 100-200 silica gel to give compound 3(a-j) Table-1.

5-(3-(trifluoromethyl) phenyl)-2-methyl-4-phenyloxazole 3(a):

¹HNMR: (400MHz, CDCl₃): δ 7.87 (s, 1H), 7.73 (d, J = 8.0Hz, 1H), 7.59-7.62 (m, 2H), 7.55 (d, J = 7.6Hz, 1H), 7.33-7.46 (m, 4 H), 2.58 (s, 3H). ¹³C NMR (CDCl₃): δ 160.9 (C of methyl substituted oxazole ring), 136.6-143.8 (C of oxazole ring). 132.2 (C of phenyl ring), 129.9-131.8 (CH of phenyl ring), 128.02-129.25 (CH of CF₃ Substituted phenyl ring) 125.3 (CF₃),

14.1 (CH₃). MS; m/z = 304.19 (M⁺). Anal. calcd. For C₁₇H₁₂F₃NO: C, 67.32; H, 3.99; F, 18.79; N, 4.62; O, 5.28.

5-(2-methyl-4-phenyloxazol-5-yl) pyrimidine 3 (b):

¹HNMR: (400MHz, CDCl₃): δ 9.12 (s, 1H), 8.93 (s, 2H), 7.57-7.59 (m, 2H), 7.38-7.43 (m, 3H), 2.6 (s, 3H). ¹³C NMR (CDCl₃): δ 162.3 (C of methyl substituted oxazole ring), 158.8 (CH of pyrimidine ring), 147.7 (CH of pyrimidine ring), 136.4-146.3 (C of oxazole ring), 135.2 (C of phenyl ring), 131.2 (C of pyrimidine ring), 127.7-129.5 (CH of phenyl ring), 14.1 (CH₃). MS; m/z = 238.2 (M⁺). Anal. calcd. For C₁₄H₁₁N₃O: C, 70.87; H, 4.67; N, 17.71; O, 6.74.

5-(4-fluorophenyl)-2-methyl-4-phenyl oxazole 3 (c):

¹HNMR: (400MHz, CDCl₃): δ 7.53-7.61 (m, 4H), 7.32-7.39 (m, 3H), 7.03-7.07 (m, 2H), 2.56 (s, 3H). ¹³C NMR (CDCl₃): δ 166.3 (C of methyl substituted Oxazole ring), 163.1 (CH-F), 137.4-145.4 (C of oxazole ring), 134.1 (C of phenyl ring), 127-129.8 (CH of phenyl ring), 126.9 (C of fluoro substituted phenyl ring), 118-126.3 (CH of fluoro substituted phenyl ring), 14.1 (CH₃). MS; m/z = 254.08 (M⁺). Anal. calcd. For C₁₆H₁₂FNO: C, 75.88; H, 4.78; F, 7.50; N, 5.53; O, 6.32.

2-methyl-4-phenyl-5-(4-(trifluoro methoxy) phenyl)oxazole 3 (d) :

¹HNMR: (400MHz, CDCl₃): δ 7.59-7.61 (m, 4H), 7.32-7.41 (m, 3H), 7.19 (d, J = 7.6Hz, 2H), 2.56 (s, 3H). ¹³C NMR (CDCl₃): δ 165.9 (C of methyl substituted Oxazole ring), 162.1 (CH-OCF₃), 137-146.4 (C of oxazole ring), 135.1 (C of phenyl ring), 126-1130.8 (CH of phenyl ring), 123.8 (C of O-CF₃ substituted phenyl ring), 114.2-125.3 (CH of O-CF₃ substituted

phenyl ring), 14.3 (CH₃). MS; m/z = 320.24 (M⁺). Anal. calcd. For C₁₇H₁₂F₃NO₂: C, 63.95; H, 3.79; F, 17.85; N, 4.39; O, 10.02.

5-(3, 5-dichlorophenyl) -2- methyl -4- phenyl oxazole 3 (e) :

¹HNMR: (400MHz, CDCl₃): δ 7.63 (s, 1H), 7.56 (d, J = 6.8Hz, 2H), 7.41-7.47 (m, 5H), 2.46 (s, 3H). ¹³C NMR (CDCl₃): δ 165.1 (C of methyl substituted oxazole ring), 146.5 (C of 3,5-di chloro phenyl substituted oxazole ring) 137.3 (C-Phenyl of oxazole ring), 136.9 (C-Cl), 135.6 (C of 3, 5 -di chloro phenyl), 130.2-132.9- (CH of 3, 5-di chloro phenyl), 128.5-132.5 (CH of phenyl substituted), 14.1 (CH₃). MS; m/z = 306.4 (M+3) Anal. calcd. For C₁₆H₁₁Cl₂NO: C, 63.18; H, 3.65; Cl, 23.31; N, 4.60; O, 5.26.

5-(4-chloro-3-(trifluoromethyl) phenyl) -2-methyl- 4 – phenyloxazole 3 (f) :

¹HNMR: (400MHz, CDCl₃): δ 7.93 (s, 1H), 7.63-7.65 (m, 1H), 7.57-7.59 (m, 2H), 7.35-7.45 (m, 4H), 2.57 (s, 3H). ¹³C NMR (CDCl₃): δ 165.8 (C of methyl substituted oxazole ring), 146.5 (C of 4- chloro, 3-trifluoro methyl phenyl substituted oxazole ring) 137.3 (C-Phenyl of oxazole ring), 137.1 (C of substituted 4- Chloro, 3-trifluoro methyl phenyl), 136.9 (C-Cl), 134.6 (C-CF₃), 133.2-132.9- (CH of 4- chloro, 3-trifluoro methyl phenyl), 128.5-132.5 (CH of phenyl substituted), 14.1 (CH₃). MS; m/z = 338.4 (M⁺). Anal. calcd. For C₁₇H₁₁ClF₃NO: C, 60.46; H, 3.28; Cl, 10.50; F, 16.88; N, 4.15; O, 4.74.

2-chloro-4-(2-methyl-4-phenyloxazol-5-yl) pyridine 3 (g):

¹HNMR: (400MHz, DMSO-d₆): δ 8.41 (d, J = 5.2Hz, 1H), 7.58-7.61 (m, 2H), 7.43-7.52 (m, 5H), 2.561 (s, 3H). ¹³C NMR (CDCl₃): δ 165.7 (C of methyl substituted oxazole ring), 151.8 (CH of pyridine ring), 149.3 (C-Cl), 148.3 (C of

pyridine ring), 146.3 (C of substituted 3-chloro pyridine oxazole ring), 137.6 (C of Phenyl of oxazole ring), 129.5-131.5 (CH of phenyl substituted), 112.8-114.3 (CH of 3-chloro pyridine), 14.1 (CH₃). MS; m/z = 271.14 (M⁺), 273.18 (M+2). Anal. calcd. For C₁₅H₁₁ClN₂O: C, 66.55; H, 4.10; Cl, 13.10; N, 10.35; O, 5.91.

3-(2-methyl-4-phenyloxazol-5-yl) pyridine 3 (h) :

¹HNMR: (400MHz, CDCl₃): δ 8.84 (s, 1H), 8.53-8.55 (m, 1H), 7.84-7.87 (m, 1H), 7.59-7.61 (m, 2H), 7.28-7.41 (m, 4H), 2.56 (s, 3H). ¹³C NMR (CDCl₃): δ 165.1 (C of methyl substituted oxazole ring), 150.8 (CH of pyridine ring), 145.8.3 (C of substituted pyridine oxazole ring), 136.6 (C of Phenyl of oxazole ring), 128.5-130.2 (CH of phenyl substituted), 111.9-113.1 (CH of pyridine), 14.1 (CH₃). MS; m/z = 237.1 (M⁺). Anal. calcd. For C₁₅H₁₂N₂O: C, 76.25; H, 5.12; N, 11.86; O, 6.77.

2-methyl-5-(2-(methylthio) phenyl)-4-phenyloxazole 3 (i) :

¹HNMR: (400MHz, CDCl₃): δ 7.50-7.52 (m, 2H), 7.42-7.46 (m, 1H), 7.28-7.33 (m, 2H), 7.17-7.27 (m, 4H), 2.56 (s, 3H), 2.39 (s, 3H). ¹³C NMR (CDCl₃): δ 165.9 (C of methyl substituted oxazole ring), 146.2 (C of ethyl (phenyl)sulfane substituted oxazole ring), 136.5 (C of S-ethyl substituted phenyl), 136.1 (C of phenyl substituted oxazole), 128.3-129.6 (CH of substituted phenyl), 125.8-126.5 (CH of S-ethyl substituted phenyl), 14.8-30.6 (S-CH₂CH₃), 14.1 (CH₃). MS; m/z = 282.2 (M⁺). Anal. calcd. For C₁₇H₁₅NOS: C, 72.57; H, 5.37; N, 4.98; O, 5.69; S, 11.40.

3-fluoro-5-(2-methyl-4-phenyloxazol-5-yl) pyridine 3 (j) :

¹HNMR: (400MHz, CDCl₃): δ 8.66 (s, 1H), 8.38-8.57 (m, 1H), 7.57-7.62 (m, 3H), 7.36-

7.44 (m, 3H), 2.58 (s, 3H). ¹³C NMR (CDCl₃): δ 165.1 (C of methyl substituted Oxazole ring), 160.1 (C-F), 146.4 (C of 3-fluoro pyridine substituted oxazole ring), 135.1 (C of phenyl substituted oxazole ring), 134-136.6 (CH of 3-fluoro pyridine ring), 125.2-127.3 (CH of phenyl ring), 14.3 (CH₃). MS; m/z = 255.08 (M⁺). Anal. calcd. For C₁₅H₁₁FN₂O: C, 70.86; H, 4.36; F, 7.47; N, 11.02; O, 6.29.

Result and discussion

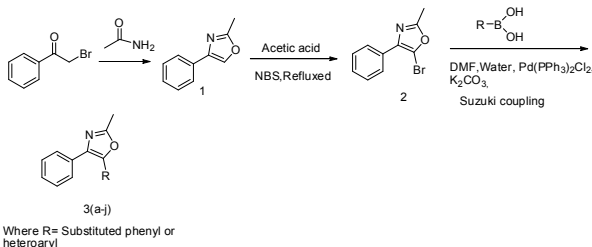
Chemistry :

In this present investigation a novel series of substituted oxazoles compounds were synthesized. Cyclization of 2-bromo-1-Phenylethanone with acetamide results 2-methyl-4-phenyloxazole, which on bromination and further by the Suzuki reaction with substituted boronic acid gives desired product.

Table-1

Compound	R	Physical State	M.P (°C)	Yield (%)
3a	3-CF ₃ Phenyl	White solid	228-229	72.2
3b	Pyrimidine-5-yl	Yellow solid	321-322	81.9
3c	4-F Phenyl	Yellow oil	-	77.1
3d	4-OCF ₃ Phenyl	Brown oil	-	63.1
3e	3,5-DiChloro Phenyl	White solid	286-287	77.5
3f	4-Cl,3-CF ₃ Phenyl	White solid	272-273	40.5
3g	2-Cl-pyridine-4-yl	Yellow solid	304-305	52.9
3h	Pyridine-3-yl	Brown oil	-	42.9
3i	2-methylthio phenyl	Brown solid	259-260	72.2
3j	5-F-pyridine-3-yl	Brown solid	274-275	62.2

Scheme



Antibacterial activity

The antibacterial activity of all the synthesized compounds were tested in-vitro against pathogenic *E. coli* MTCC 443, *P.aeruginosa* MTCC 1688, *S.aureus* MTCC96 and *S.pyogenus* MTCC 442 and the results were compared with standard drugs (Ampicillin and Chloramphenicol). In case of *S.aureus* MTCC96 compounds 3(b), 3(g), exhibit good activity while 3(c), 3(d), 3(h) and 3(i) show moderate activity. In case of *S.pyogenus* MTCC 442 compounds 3(a), 3(b) and 3(e) exhibit higher activity while 3(c), and 3(h) show moderate activity. In case of *E. coli* MTCC 443 Compound 3(b), 3(c) and 3(d) show higher activity and 3(e), 3(f) and 3(g) show moderate activity while rest of the compounds possess less activity. In case of *P.aeruginosa* MTCC 1688 compounds 3(d) and 3 (f) show good activity while 3(g) and 3(i) show moderate activity while rest of the compounds possess less activity. The results are given in Table-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(j) exhibit good activity while 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.

Table-2: Antibacterial activity (In Minimum inhibitory concentration)

Compound	E.COLI MTCC 443	P.AERUGINOSA MTCC 1688	S.AUREUS MTCC 96	S.PYOGENUS MTCC 442
3(a)	250	500	250	100
3(b)	100	250	100	100
3(c)	125	200	125	125
3(d)	200	62.5	200	200
3(e)	250	250	250	100
3(f)	250	100	250	250
3(g)	250	200	100	250
3(h)	500	250	200	200
3(i)	500	200	200	250
3(j)	250	200	500	250
Ampicillin	100	100	250	100
Chloramphenicol	50	50	50	50

Antimalarial activity

For antimalarial activity, Compounds 3(b) and 3(d) exhibit good activity closer to reference compound Quinine against plasmodium falciparum strain while rest of the compounds possess less activity. The results are given in Table-4.

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 compound 3(b), 3(d) and 3(g) possesses good antibacterial activity. However, the activities of the tested compounds are much less than those of standard agents used. These compounds also show potent antimalarial activity against plasmodium falciparum strain except compound 3(g). 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.

Table-3: Antifungal Activity(In MIC)

Compound	C.Albicans MTCC 227	A.Niger MTCC 282	A.Clavatus MTCC 1323
3(a)	1000	500	1000
3(b)	>1000	>1000	>1000
3(c)	>1000	>1000	>1000
3(d)	>1000	>1000	>1000
3(e)	>1000	>1000	>1000
3(f)	>1000	500	500
3(g)	500	>1000	>1000
3(h)	500	>1000	>1000
3(i)	1000	500	500
3(j)	250	>1000	>1000
Nystatin	100	100	100
Greseofulvin	500	100	100

Table-4: Antimalarial Activity

Compound	Mean IC ₅₀ (micrograme/ml)
3(a)	0.96
3(b)	0.55
3(c)	1.43
3(d)	0.68
3(e)	1.07
3(f)	1.38
3(g)	1.15
3(h)	2.22
3(i)	1.09
3(j)	1.43
Quinine	0.268

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