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REVIEW ARTICLE

DESIGNED SYNTHESIS OF A NOVEL SERIES PYRAZOLO (1, 5-A) PYRIMIDINE ANALOGOUS AND BIOEVLUATION

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ABSTRACT

"High-functioning In this investigation,the synthesis of a series of Pyrazolo (1, 5-a) pyrimidine analogous andwas examination of biological study. A novel procedure for the synthesis of 1, 3, 4-oxidiazole analogous was bearing 6-chloropyrazolo (1, 5-a) pyrimidine-3-carboxylic acid. This moiety was transformed into 2-(6-chloropyrazolo (1, 5-a) pyrimidin-3-yl)-5-phenyl-1, 3, 4-oxadiazole derivatives in three steps. The novel series of 1, 3, 4oxidiazole can be obtained from compound (3) treated with aryl carboxylic acid and $POCl_3$. The compound (3) can be prepared from compound (2) treated with hydrazine hydrate at reflux in ethanol. The compound (2) can be obtained by the 6-chloropyrazolo (1, 5-a) pyrimidine-3-carboxylic acid with thionyl chloride. These analogous can estimated toanalyse by spectral analysis such as ^{1}HNMR, ^{13}NMR and LCMS. In addition to examined by activity of antimicrobial.

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INTRODUCTION

Five-membered aromatic rings with three heteroatoms are a type of aromatic compound in which the various heteroatoms contribute very differently to the formation of aromaticconjugation. Among them, 1,3,4-oxadiazole and 1,3,4-thiadiazole scaffolds constitute an important core structure in chemotherapeutic agents and have attracted significant attention due to their interesting biological activities and medicinal properties(1-4). Pyrimidine, a six membered heterocyclic compound bearing two N-atoms in the ring, constitutes an important component of nucleic acid and is widespread in Nature.The pyrimidine system is an important pharamacophores endowed with drug likeproperties However, the synthesis of pyrimidine derivatives containing a 1,3,4-oxadiazole ring or 1,3,4-thiadiazole ring, as well as their biological activities are seldom described in the literature. The titled nucleus exhibited biological activity including antimicrobial activity (5-9). Cytotoxic activity (10, 11), anti-inflammatory activity (12), HIV-1-RT inhibitors (13), antiarrhythmic activities (14), anti-tubercular activity (15), Cyclooxygenase Inhibitors (16).etc.

During the course of a medicinal chemistry program, the synthesis of a pyrimidine intermediate containing a 1,3,4-oxadiazole ring and became important for further transformations. Despite the simple structural features of this compound. Herein, we report optimized conditions, substrate scope, and applications of the CuI_2-catalyzed C-N cross-coupling of of 2-(6-chloropyrazolo (1, 5-a) pyrimidin-3-yl)-5-phenyl-1, 3, 4-oxadiazole derivatives which provide facile access to these compounds and their derivatives. This desired compound can be synthesized from 6-chloropyrazolo (1, 5-a) pyrimidine-3-carbohydrazide with aromatic carboxylic acid in cyclization reagent such as $POCl_3$.

METHODS AND MATERIALS

All chemicals, reagents, solvents and also starting materials required for the reactions were procured from Sigma-Aldrich with and used without further purification. The melting point of the all newly synthesized compounds were find out using an Aggarwal thermal apparatus and uncorrected. The NMR spectra of selective analogous were measured on a Bruker for 400 ^{1}HNMR spectra and 100 MHz for ^{13}C NMR spectra in

$CDCl_3$ solvent using TMS as internal standard. The reaction was monitored by thin layer chromatography using silica gel as an adsorbent and ethyl acetate-hexane in different ratios as eluent. All the synthesized compounds find the molecular weight using LCMS.

2.1. The preparation of 6-chloropyrazolo (1,5-a)pyrimidine-3-carbonyl chloride (2): To take clean and dry 50mL RBF and 20mL of MDC was poured. The starting material 6-chloropyrazolo (1,5-a)pyrimidine-3-carboxylic acid (1mol) was dissolved in above solvent and thionylchloride (1.25mol) added drop wise by using dropping funnel portion wise . The reaction was continued after completion of the addition of acid chloride for four hours. The reaction was identified by TLC. The unconsumed acid chloride evaporated by heating above 40^0C. The reaction was quenched in 100gms ice in a 250mL beaker and extracted with MDC and also washed with water .The separated organic layer and distilled off and get desired product. Palered; Yield-95%; M.P-194-196^0C; 1HNMR (400MHz, DMSO) δppm: 8.894(s, 1H), 8.654(s, 1H), 8.291(s, 1H);^{13}CNMR (100MHz,DMSO)δppm,189.32, 154.77, 151.06, 144.28,141.25, 128.87, 109.07; Molecular weight (m/z):216.37(M+2); Formula of the compound – $C_7H_3Cl_2N_3O$.

2.2.The preparation of 6-chloropyrazolo (1,5-a) pyrimidine-3-carbohydrazide (3): The mixture of compound (2) (1mol) and hydrazine hydrate (1.125mol) is dissolved in ethanol (25mL) in 50mL RBF. The mixture starting material continued at reflux for five hrs. The consumption of reactants was recognized by TLC.The solvent was evaporated by heating above 80^0C and obtained a solid compound. The desired material got after washing with water. Brown compound; Yield-92%; M.P-214-216^0C; ^{1}HNMR (400MHz, DMSO) δppm: 9.357(s,1H,-NH-); 8.907(s, 1H), 8.714(s, 1H), 8.304(s, 1H) , 5.187(s,2H,NH2), ; 13CNMR (100MHz, DMSO) δppm: 169.22, 155.09, 151.39, 144.33,142.58, 128.66, 110.05; Molecular weight (m/z):213.07(M+2); Formula of the compound – $C_7H_6ClN_5O$.

2.3.The general preparation of 2-(6-chloropyrazolo (1, 5-a) pyrimidin-3-yl)-5-phenyl-1, 3, 4-oxadiazole derivatives (5a-5i): To take dry and clean RBF. The mixture of compound (3) and aryl carboxylic acid are taken in RBFand few drops of phosphorus oxychloride into RBF at room temperature . The reaction mixture continuous carried the reaction at 60^0C for 5 hrs. The progress of the reaction was examined by the TLC (EtOAc: n-hexane = 5:5). After all the reactants were consumed and then cooled the reaction mixture at RT. The crude dissolved in ethyl acetate and washed with as saturated solution of sodium bicarbonate and separated the ethyl acetate layer and also washed with water separated the organic layer. The organic layer can be distilled off under vacuums and solid compound obtained.

2.3.1.2-(6-chloropyrazolo (1, 5-a) pyrimidin-3-yl)-5-phenyl-1, 3, 4-oxadiazole (5a): Pale red ; Yield-84%; M.P-221-223^0C; ^{1}HNMR (400MHz, DMSO) δppm: 8.932(s, 1H), 7.935(s, 1H), 7.816(s, 1H) , 7.736-7.426(m,5H) ; ^{13}CNMR (100 MHz, DMSO) δppm: 163.78, 155.11, 152.62, 144.64, 132.73, 130.05, 129.04, 128.83, 128.12, 127.45,110.35; Molecular weight (m/z):299.72(M+2); Formula of the compound – $C_{14}H_8ClN_5O$

2.3.2.4-(5-(6-chloropyrazolo (1, 5-a) pyrimidin-3-yl)-1, 3, 4-oxadiazol-2-yl)phenol (5b): Pale yellow compound ; Yield-86%; M.P-229-231^0C; ^{1}HNMR (400MHz, DMSO) δppm: 9.452 (s,1H,-OH);8.908(s, 1H), 8.475(s, 1H), 7.657(s, 1H) , 7.487-7.276(m,4H) ; ^{13}CNMR (100 MHz, DMSO) δppm: 166.04, 156.27, 154.13, 152.12, 132.12, 129.46, 128.82, 126.65, 124.28, 108.64;Molecular weight (m/z): 315.34(M+2); Formula of the compound: $C_{14}H_8ClN_5O_2$.

2.3.3.2-(6-chloropyrazolo (1,5-a)pyrimidin-3-yl)-5-(4-methoxyphenyl)-1,3,4-oxadiazole(5c): Pale yellow compound; Yield-88%; M.P-234-236^0C; ^{1}HNMR (400MHz, DMSO) δppm: 8.674(s, 1H), 7836(s, 1H), 7.653(s, 1H) , 7.610-7.284(m,4H), 3.712(s,3H,OCH_3) ; 13CNMR (100 MHz, DMSO) δppm:165.26, 163.02, 158.23, 153.57, 142.62, 131.26, 129.04, 128.84, 128.35, 117.64, 115.38, 105.03, 55.12; Molecular weight (m/z): 329.71(M+2); Formula of the compound: $C_{15}H_{10}ClN_5O_2$.

2.3.4.4-(5-(6-chloropyrazolo (1,5-a)pyrimidin-3-yl)-1,3,4-oxadiazol-2-yl)-2-methoxy phenol(5d): Palered compound; Yield-89%; M.P-234-2360C; ^{1}HNMR (400MHz, DMSO) δppm: 9.672 (s,1H,-OH), 8.946(s, 1H), 7.912(s, 1H), 7.722(s, 1H) , 7.514-7.3264(m,3H), 3.626(s,3H, OCH_3) ; ^{13}CNMR (100 MHz, DMSO) δppm:163.74, 155.27, 154.02, 146.62, 144.43, 140.07, 132.39, 129.06, 120.02, 117.65, 115.39, 110.62, 105.37, 55.02; Molecular weight (m/z): 345.66(M+2); Formula of the compound: $C_{15}H_{10}ClN_5O_3$.

2.3.5.2-(4-bromophenyl)-5-(6-chloropyrazolo (1,5-a) pyrimidin-3-yl)-1,3,4-oxadiazole (5e): Red compound; Yield-88%; M.P-245-247^0C; 1HNMR (400MHz, DMSO) δppm: 8.914(s, 1H), 8.065(s, 1H), 7.814(s, 1H), 7.586-7.396(m,4H,Ar-H), ; ^{13}CNMR (100 MHz, DMSO) δppm:168.46, 155.03, 151.26, 145.08, 132.44, 129.37, 128.84, 128.21, 127.02, 127.15, 106.02; Molecular weight (m/z): 376.04(M+2); Formula of the compound : $C_{14}H_7BrClN_5O$.

2.3.6.2-(6-chloropyrazolo (1, 5-a) pyrimidin-3-yl)-5-(4-iodophenyl)-1, 3, 4-oxadiazole (5f): Pale red compound; Yield-88%; M.P-251-253^0C; 1HNMR (400MHz, DMSO) δppm: 8.942(s, 1H), 7.906(s, 1H), 7.764(s, 1H), 7.762-7.484(m, 4H, Ar-H); ^{13}CNMR (100 MHz, DMSO) δppm:169.19, 155.65, 153.72, 143.04, 1321.81, 129.65, 128.88, 128.52, 127.94, 127.05, 110.62;Molecular weight (m/z): 298.71(M+2); Formula of the compound : $C_{14}H_7ClIN_5O$.

2.3.7.4-(5-(6-chloropyrazolo (1,5-a)pyrimidin-3-yl)-1,3,4-oxadiazol-2-yl)benzonitrile(5g): Pale yellow compound; Yield-84%; M.P-228-230^0C; ^{1}HNMR (400MHz, DMSO) δppm: 8.897(s, 1H), 7.884(s, 1H), 7.804(s, 1H), 7.746-7.546(m, 4H, Ar-H); 13CNMR (100 MHz, DMSO) δppm: 167.28, 157.05, 153.16, 142.75, 132.69, 130.06, 129.44, 128.92, 127.46, 119.65, 105.09;Molecular weight (m/z): 324.27(M+2); Formula of the compound : $C_{15}H_7ClN_6O$.

2.3.8.2-(6-chloropyrazolo (1,5-a)pyrimidin-3-yl)-5-(4-nitrophenyl)-1,3,4-oxadiazole(5h): Pale red compound; Yield-85%; M.P-228-230^0C; ^{1}HNMR (400MHz, DMSO) δppm: 8.925(s, 1H), 8.315-8.025(m, 4H), 7.804(s, 1H), 7.614(s,1H); ^{13}CNMR (100 MHz, DMSO) δppm: 165.72, 158.04, 154.32, 146.77, 142.65, 132.11, 130.05, 129.66, 129.04, 128.77, 128.16, 108.08.Molecular weight (m/z): 344.08(M+2); Formula of the compound: $C_{14}H_7ClN_6O_3$.

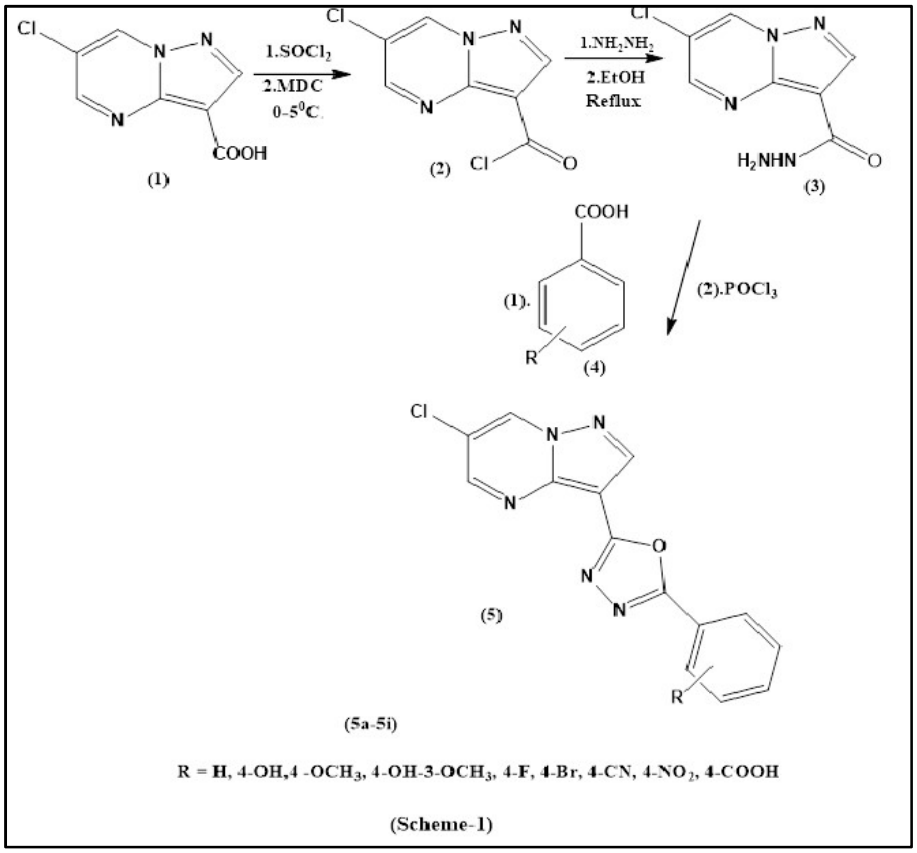

Table. Antimicrobial potent activity of compounds (5a-5i)

Entry	Antibacterial MIC (µg/mL)				Antifungal MIC (µg/mL)	
Strains	B. subtilis	S. aureus	P. aeruginosa	E. coli	A. Niger	C. Albicans
5a	07	09	10	08	06	08
5b	18	19	18	19	15	16
5c	19	20	19	16	14	15
5d	21	22	20	20	17	17
5e	22	21	21	19	17	18
5f	20	19	19	18	16	17
5g	08	07	10	09	08	06
5h	08	09	11	07	04	08
5i	09	04	05	10	08	06
Streptomycin	25	25	25	25	-	-
Ketonozole	-	-	-	-	22	22
DMSO						

2.3.9.4-(5-(6-chloropyrazolo (1,5-a)pyrimidin-3-yl)-1,3,4-oxadiazol-2-yl)benzoic acid(5i): Palered compound; Yield-80%; M.P-236-238$_0$C; ^{1}HNMR (400MHz, DMSO) δppm: 12.166(s,H),8.945(s,1H),8.737(s,1H),8.046-7.895(m,2H), 7.825-7.611(m,2H), 7.736(s,1s), ^{13}CNMR (100 MHz, DMSO) δppm: 175.78, 168.36, 155.25, 152.39, 143.33, 134.05, 130.07, 129.54, 128.94, 128.41, 128.02,108.65; Molecular weight (m/z): 343.65(M+2); Formula of the compound: $C_{15}H_8ClN_5O_3$

RESULTS AND DISCUSSION

A novel procedure for the synthesis of 1, 3, 4-oxidiazole analogous was bearing 6-chloropyrazolo (1, 5-a) pyrimidine-3-carboxylic acid. This moiety was transformed into 2-(6-chloropyrazolo (1, 5-a) pyrimidin-3-yl)-5-phenyl-1, 3, 4-oxadiazole derivatives in three steps. The novel series of 1, 3, 4oxidiazole can be obtained fromcompound (3) treatedwith aryl carboxylic acid and $POCl_3$. The compound (3) can be prepared from compound (2) treated with hydrazine hydrate at reflux in ethanol.

The compound (2) can be obtained by the 6-chloropyrazolo (1, 5-a) pyrimidine-3-carboxylic acid with thionyl chloride. Scheme-1 was represented the examination of the universality of these conditions to the conversion of various aryl carboxylic acid containing electron-donating and withdrawing groups combined compound (3) with to their scaffold required titled products. The proof of the analogous was showed that all of the investigated substituted aryl carboxylic acid was fully transformed into their corresponding titled products with high isolated yields in appropriate time. In particularly, the substituted aryl carboxylic acid are bearing electron-withdrawing groups, such 1,4-benzenedicarboxylic acid , 4-cyanobenzoicacid and 4-nitrobenzoic acid, underwent reactions faster than those with electron releasing groups, like 4-methyl benzoic acid benzaldehyde and 4-hydroxy benzoic acid etc.

Characterization: The structure of the series desired analogous constructed by the evidence of spectral data such as ^{1}HNMR, ^{13}CNMR, LCMS. In this study, proton NMR of titled derivatives was showed by different values of respective

groups viz; hydroxyl proton appears at 9.672-9.452ppm, methoxy protons appears at 3.712-3.626ppm as well as pyrimidine aromatic protons appeared at range between 8.925-8.879 ppm. The various range of values.13CNMR of these derivatives appeared at different values appeared at 169.21ppm.

BIOLOGICAL ACTIVITIES

Antibacterial and antifungal activities: The titled derivatives were examined for their *in-vitro* antibacterial and antifungal active potential following micro broth dilution method. The *invitro* antibacterial activity was evaluated against gram-positive (B.substills and S. aureus) and gram-negative (E. coli and P. aeruginosa) microorganisms. The *invitro* antifungal activity was checked against A.ngier and C.albicans microorganisms. The standard drugs tested for this study were Streptomycin was used for antibacterial screening. Ketonozole was used for antifungal screening. The standard strains used for examination of antibacterial and antifungal activities and there were purchased from the Culture collection and geneank (MTCC), Chandigarh, India. Mueller Hinton Broth was used as a nutrient medium for bacteria and Sabouraud dextrose Broth for fungal growth.

Inoculums size for test strain was adjusted to 108 CFU/mL by comparing the turbidity. The results were recorded in the form of primary and secondary evaluation. In the mainly focused on the preliminary screening 500, 250 and 100 µg/mL concentrations of the derivatives were used. The analogous identified to be active in this primary examination were further examination. In secondary screening, 200, 100, 50 and 25 µg/mL concentrations were used.

The inoculated wells were incubated overnight at 37°C in a humid atmosphere. The majority of the dilutionexhibiting complete inhibition was considered as a minimum inhibition concentration (MIC). The MIC values indicated that the synthesized compounds showed moderate to good inhibition. Compounds 4d, 4e exhibited good to excellent activities against bacterial strains. The MIC values of antifungal activity shown that compound 5e and 5f exhibited good activity against all fungal strain. Antimicrobial activity of compounds (5a-5i) is listed in Table-I.

CONCLUSION

We have successfully enhanced an efficient method for the synthesis of novel Pyrazolo (1, 5-a) pyrimidine analogous (5a-5i) as the catalyst. The method employs readily available reagents and possesses broad scope and effective functional group tolerance. Further efforts to utilize these compounds as versatile building blocks for assembling interesting heterocyclic molecules which can be applied in medicinal chemistry research are currently underway in our laboratories.

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