IJMPR 2025, 9(1), 76-80

International Journal of Modern Pharmaceutical Research
www.ijmpronline.com

ISSN: 2319-5878
IJMPR
Research Article
SJIF Impact Factor: 6.669

LEWIS ACID CATALYSED - MULTICOMPONENT SYNTHESIS OF 1*H*-PYRIDO[2, 1-*B*]QUINAZOLIN-11-ONE AND BIOEVLUATION

Dr. DVL. Sirisha[1], V. Sureshgowd[2], Dr. V. Narasingrao[1], B. V. Durgarao[3], Dr. N. Krishnarao[1] and Dr. Shaik Lakshman[4*]

[1]Department of Chemistry and Biochemistry, PRISM PG. DG. College, Visakhapatnam, India.
[2]Department of Chemistry, Aditya Degree College, Amalapuram, A.P, India.
[3]Department of DFS (Chemistry), ONGC, RJY, AP, India.
[4]*GSS, GITM (Deemed to be University), Visakhapatnam, India.

Article Received on: 08/11/2024
Article Revised on: 29/11/2024
Article Accepted on: 19/12/2024

***Corresponding Author**
Dr. Shaik Lakshman
GSS, GITM (Deemed to be University), Visakhapatnam, India.

ABSTRACT
This method is very suitable and an efficient procedure for preparation of 1H-Pyrido[2, 1-b] quinazolin-11-onederivative can be synthesized by promoted aLewis acidcatalyst which is designed. The preparation of 1H-Pyrido[2,1-b]quinazolin-11-one derivatives fromIsatin, 2-bromopyridine with $KHCO_3$ subjectedby$ZrOCl_2$ in CH_3CNas solvent and the desired compounds were characterized by advanced spectral techniques IR, ^{1}NMR, ^{13}NMR and LCMS. This method is also rate of reaction as well as yield enhancement of desired compound. In addition to study of antimicrobial activity of the titled derivatives.

KEYWORDS: Substituted Isatin, 2-bromopyridine, 1*H*-Pyrido[2,1-*b*]quinazolin-11-one and $ZrOCl_2$, Antimicrobial activity.

INTRODUCTION

Heterocycles that contain nitrogen are significant molecular motifs found in materials, bioactive compounds, and natural products.Nitrogen-containing heterocyclic compounds are the most abundant and integral scaffolds that occur ubiquitously in a variety of synthetic drugs, bioactive natural products, pharmaceuticals and agrochemicals. Owing to their widespread applications, these skeletons have long been a subject of immense interest, and substantial efforts have been made to the development of synthetic strategies which could lead to the discovery of new bioactive compounds in medicinal chemistry.[1-3] Indeed, with particular reference to the pharmaceutical industry, heterocyclic motifs are especially prevalent with over 60% of the top retailing drugs containing at least one heterocyclic nucleus as part of the overall topography of the compound.

Quinazoline and quinazolinones derivatives have attracted significant attention due to their diverse pharmacological activities such as Anti-microbial[4], anti-cancerandanti-tuberculosisactivities[5-7], antitumoragents[8], NF-κbinhibitors[9], antioxidantagents[10], Alzheimer's[11,12], Anti-inflammatory.[13] Quinazoline also exhibit a wide variety of biological functions like cellular phosphorylation inhibition, ligands for benzodiazepine and GABA receptors in the central nervous system, and some of them have acted as DNA binding agents.

We developed desired products $ZrOCl_2$ catalysed cascade cyclization of 1H-Pyrido [2, 1-b] quinazolin-11-one derivatives in good to excellent yields. This novel synthetic approach is followed by the generation of a library of pyridoquinoline-fused quinazolinones analogues. Further, the development of the current strategies was promoted by the effect catalyst.

2. METHODS AND MATERIAL

2.1. EXPERIMENTAL

All melting points newly prepared derivatives were measured by Griffin and Geory melting point apparatus and are uncorrected. IR spectra were recorded on Pye Unicam SP1200 spectrophotometer using KBr Wafer technique. ^{1}H NMR spectra were determined on a Varian Gemini 200 MHz using TMS as internal standard (chemical shifts in δ-scale). LCMS were measured on a Shimadzu-GC-MS operating at 70 eV.[13] C NMR spectra were measured on Jool 100MHz.. The homogeneity of the synthesized compounds was controlled by TLC.

2.2. GENERAL PROCEDURE FOR THE SYNTHESIS OF COMPOUND (3)

The mixture of the starting material such as isatin (1.0 mmol), 2-bromopyridine (1.2 mmol), $ZrOCl_2$ (0.5

mmol), $KHCO_3$(2.0mmol)was dissolved in solvent such as CH_3CN (5 mL taken in four neck 25 ml RBF. The resulting mixture was stirred at80^{0}C for 5 h. After disappearance of the reactant in the reaction and followed by monitored by TLC. The mixture was slowly cooled to room temperature and CH_3CN was removed under reduced pressure. Then water was added to the mixture, and extracted with EtOAc three times. The extract was combined and dried over anhydrous Na_2SO_4 and evaporation. The residue was purified by column chromatography on silica gel (petroleum ether/EtOAc) to anexcellent yield excellent.

2.2.1.1*H*-Pyrido [2,1-*b*]quinazolin-11-one (3a)
Yield -80%; yellow compound; mp 174–176 °C;^{1}HNMR (400 MHz, $CDCl_3$) δ ppm : 8.884 (d, *J* = 6.8 Hz, 1H), 8.451 (d, J=8.0Hz,1H), 7.810−7.679 (m, 2H), 7.584−7.425 (m, 3H), 6.947−6.805 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δppm: 158.25, 147.05, 146.72, 136.71, 133.01, 128.32, 126.59, 126.17, 125.65, 124.28, 117.02, 113.55;LCMS(m/z):196.05 $[M+H]^+$

2.2.2.2-Methoxy-11H-pyrido[2,1-b]quinazolin-11-one (3b).
Yield-89% (215 mg); Pale yellow solid; mp 185–187 °C; 1H NMR (400 MHz, CDCl3) δ ppm: 8.840 (d, J = 10.4 Hz, 1H), 7.713 (d, J = 9.2 Hz, 2H), 7.560−7.407 (m, 3H), 6.855 (d, J=4.6Hz,1H), 3.654 (s, 3H); 13C NMR (100 MHz, CDCl3) δ ppm; 159.47, 155.64, 148.01, 144.78, 132.28, 128.99, 127.09, 126.41, 117.25, 113.06, 105.94, 56.03; LCMS(m/z): 224.90 [M-H]+.

2.2.3.2-Methyl-11*H*-pyrido [2,1-*b*]quinazolin-11-one (3c)
Yield 85% (183 mg); Dark Yellow solid; mp 190–192 °C;^{1}H NMR (400 MHz, $CDCl_3$) δ ppm : 8.947 (d, *J* = 12.4 Hz, 1H), 8.124 (s, 1H), 7.787−7.548 (m, 2H), 7.459−7.381 (m, 2H), 6.882 (d, J=8.0, 1H), 1.847 (s, 3H); ^{13}C NMR (100MHz, $CDCl_3$)δppm: 160.09, 149.21, 145.57, 137.59, 135.45, 132.86, 128.07, 127.45, 126.53, 125.02, 118.81, 114.4, 20.84; LCMS(m/z): *m/z* 210.54 $[M+]^+$.

2.2.4.2-Fluoro-11*H*-pyrido[2,1-*b*]quinazolin-11-one (3d)
Yield-84%; Pale yellow solid; mp 165–167 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 8.784 (d, *J* = 7.6 Hz, 1H), 8.146 (dd, J_1 = 8.0 Hz, J_2 = 2.8 Hz, 1H), 7.734−7.750 (m, 1H), 7.664−7.489 (m, 3H), 6.910-6.867 (m, 1H); ^{13}CNMR (100MHz, $CDCl_3$) δppm: 160.47, 156.24, 148.01, 144.66, 132.89, 128.05, 127.14, 126.03, 124.55, 117.44, 112.11, 110.28; LCMS(*m/z):*215.56 [M+H]+.

2.2.5.4-(Trifluoromethyl)-11H-pyrido[2,1-b]quinazolin-11-one (3e)
Yield-84%; Pale yellow solid; mp - 208–210 °C; IR (KBr) νcm-1; 1630, 1395, 1355, 1128, 760, 510 cm−1; 1H NMR (400 MHz, CDCl3) δppm: 8.877(d, J = 7.8 Hz, 1H), 8.616−8.619(m, 1H), 8.217 (d, J = 7.6 Hz, 1H), 7.672−7.507 (m, 2H), 7.520 (t, J = 9.2 Hz, 1H), 6.978−6.952 (m, 1H); 13C NMR (100 MHz, CDCl3) δ ppm : 160.84, 149.58, 145.52, 136.59, 132.20, 130.76, 127.25, 126.45, 125.49, 124.25, 122.50, 118.02, 113.04; LCMS: (m/z): 265.47 [M+H]+.Molecular Formulae:C13H7F3N2O.

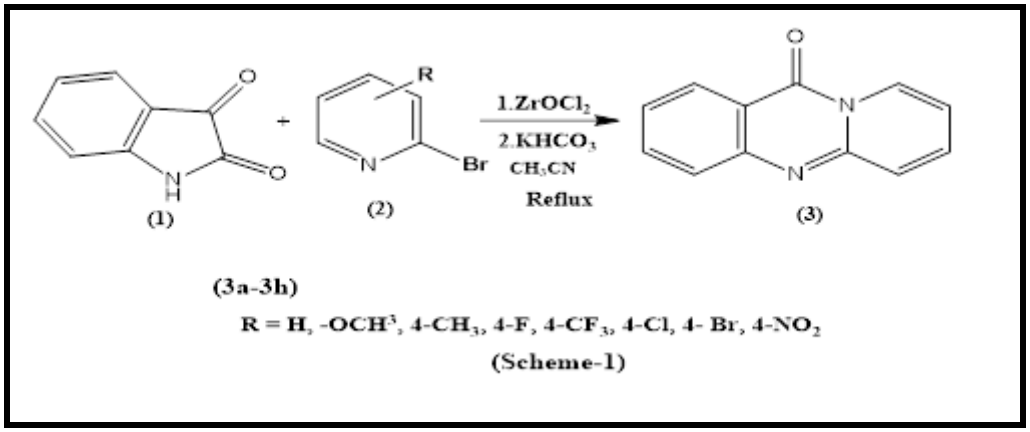
2.2.6.2-Chloro-11*H*-pyrido[2, 1-*b*]quinazolin-11-one (3f).
Yield -83%; Pale yellow solid; mp 191–193 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δppm: 8.745 (d, *J* = 5.6 Hz, 1H), 8.408 (d, *J* = 3.6 Hz, 1H), 7.775−7.687 (m, 2H), 7.455−7.350 (m, 2H), 6.914−6.898 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δppm : 158.78, 148.17, 145.07, 138.16, 134.54, 130.47, 128.57, 127.27, 126.44, 125.72, 118.05, 112.22; LCMS(*m/z):*232.32 [M+2]+.

2.2.7.2-Bromo-11*H*-pyrido [2,1-*b*]quinazolin-11-one (3g).
Yield-84%; Reddishbrown solid; mp 202–204 °C;^{1}H NMR (400 MHz, $CDCl_3$) δ ppm:8.882 (d, *J* = 7.2 Hz, 1H), 8.556 (d, *J* = 8.8 Hz, 1H), 7.848 (dd, *J*1 = 6.8 Hz, *J*2 = 3.2 Hz, 1H), 7.625 (d, *J* = 8.0 Hz, 1H), 7.568−7.448 (m, 2H), 6.902−6.879 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δppm: 157.59, 147.09, 145.24, 138.02, 134.51, 129.55, 128.68, 126.98, 126.14, 118.33, 117.47, 113.50; LCMS(*m/z):*276.25 [M+H]+.

2.2.8.2-Nitro-11*H*-pyrido[2,1-*b*]quinazolin-11-one (3h)
Yield 80%; Dark yellowcompound; mp-217–219°C; IR (KBr) νcm^{-1}; 1715, 1602, 1339, 1154, 1055, 1085, 761, 688 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δppm: 9.245 (d, *J* = 3.8 Hz, 1H), 8.874 (d, *J* = 7.6 Hz, 1H), 8.559 (dd, J_1= 9.6 Hz, J_2= 2.4 Hz, 1H), 7.886−7.560 (m, 3H), 7.026 (t, *J* = 8.0 Hz, 1H); ^{13}C NMR (100MHz, $CDCl_3$) δ ppm: 159.24, 153.02, 148.58, 144.59, 136.57, 128.97, 128.24, 127.51, 126.56, 124.28, 116.38, 113.51; LCMS(*m/z*):242.47$[M+H]^+$; Molecular Formulae:$C_{12}H_7N_3O_3$.

3. RESULTS AND DISCUSSION

Initially, it was developed the synthesis of titled derivatives by using Lew's acid catalyst like ZrOCl2, this catalyst was applied during the reaction due to the effective rate of reaction, enhanced the percentage of product as well as minimized the time factor of the completion of the reaction. In addition to commercially available, easily handling and also workup procedure was simplicity. A effective catalyst was designed and synthesized based on 1H-Pyrido [2,1-b]quinazolin-11-one of $ZrOCl_2$. The preparation of titled derivatives from isatin, 2-bromopyridine with $NaHCO_3$ subjected with $ZrOCl_2$ in CH_3CN as solvent as shown scheme-1.



(Scheme-1)

The various catalysts were used during the completion of the reaction such as $FeCl_3$, $ZnCl_2$, $AlCl_3$, CAN and $ZrOCl_2$. An excellent effective role of the catalyst among the Lew's acid catalyst is $ZrOCl_2$. The percentage of the product as well as reduce the time factor is considered mainly important for the preparation of desired product as shown in Table-1.

Table 1: Effect of the catalyst for synthesis of titled derivative (3b).

Entry	Catalyst	Time (min)	Yield (%)
1	$Fecl_3$	240	74
2	$ZnCl_2$	300	58
3	$AlCl_3$	180	71
4	CAN	150	65
5	$ZrOCl_2$	120	87

The main objective of the preparation of titled compound is an impact of the solvent in the reaction. The key role is an impact of the solventin during the reaction, all the reactants werecompletely soluble above and also effect of the starting materials was finished appropriate time.

Table 2: Effect of solvent for synthesis of titled derivative (3b).

Entry	Catalyst	Time (min)	Yield (%)
1	MeOH	120	70
2	MDC	120	52
3	CH_3CN	120	87
4	EtOH	120	61

The loaded catalyst is another parameter of this reaction, there is no improvement for the reaction if absence of the catalyst. The amount of catalyst was increased gradually, and then the rate of reaction was developed by percentage of the yield up to 87% by using 0.5 moles as shown in table-3.

Table 3: Effect of loaded catalyst for synthesis of titled derivative (3b).

Entry	Loaded catalyst(mole)	Time (min)	Yield (%)
1	0.1	120	Traces
2	0.2	120	45
3	0.4	120	52
4	0.5	120	87

The structures of the desired (3a-3h) compounds were analysed by ^{1}HNMR, ^{13}CNMR, mass spectral. ^{1}H NMR spectrum of the titled derivatives showed in various aromatic protons appears at δ 9.245 to 6.879 ppm. The methoxy protons showed at 3.654 and the methyl protons appeared at 1.847ppm. The mass spectrum of halogen derivatives exhibited molecular ion peak at (m/z)(M+2).

Overall the reaction, we also identified that the highest yield acquired during synthesis, the product analogous bearing electron releasing group (3b-3c) greater than the product of the derivatives having electron attracting group (3h) and the compounds was bearing including the halogen containing group (3d-3g) also got good yield.

4. ANTIMICROBIAL ACTIVITY OF COMPOUNDS

The desired derivatives were examined for their in-vitro antibacterial and antifungal activities following micro broth dilution method. The invitro antibacterial activity was examined against gram-positive (B. subtilis and S.aureus) and gram-negative (E.coli and P.aeruginosa) microorganisms. The invitro antifungal activity was evaluated against A.Niger and C.albicans microorganisms. The standard drugs were used for this study were Streptomycin and Ketonozole for antibacterial as well as antifungal screening. The standard strains used for screening of antibacterial and antifungal activities were commercially 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. The stock solution (2000 µg/mL) of the compounds under investigation and standard drugs were prepared by successive two fold dilution.

Table 4: Antimicrobial activity of compounds (3a-3h).

Entry	Antibacterial MIC (µg/mL)				Antifungal MIC (µg/mL)	
Strains	**B. subtilis**	**S. aureus**	**P. aeruginosa**	**E. coli**	**A. Niger**	**C. Albicans**
3a	05	06	09	07	04	05
3b	20	22	20	18	17	17
3c	18	16	18	14	13	14
3d	18	16	16	15	16	15
3e	19	20	18	20	16	16
3f	20	21	21	22	17	18
3g	10	12	10	13	10	09
3h	08	08	06	06	08	09
Streptomycin	25	25	25	25	-	-
Ketonozole	-	-	-	-	22	22
DMSO						

In the preliminary examination 500, 250 and 100 µg/mL concentrations of the compounds were used. The compounds found to be active in this primary screening 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 highest dilution showing complete inhibition was considered as a minimum inhibition concentration (MIC). The MIC values revealed that the synthesized compounds showed moderate to good inhibition. The compounds "3e and 3f exhibited good excellent activities against bacterial strains. The MIC values of antifungal activity shown that compound 3c and 3b exhibited good activity against all fungal strain. Antimicrobial activity of compounds (3a-3h) is listed in Table-4.

5. CONCLUSIONS

It have been developed a new, easy and an efficient process for synthesis of 1H-Pyrido[2, 1-b]quinazolin-11-one derivatives via one-pot two component condensation of substituted isatin and 2-bromopyridine with $KHCO_3$ subjected by $ZrOCl_2$ in CH_3CN as solvent and also an efficient catalyst. The effective conversion, the experimental simplicity, compatibility with various functional groups, excellent product yields and the easy work-up procedure make this approach attractive for synthesizing a variety of such derivatives.

6. ACKNOWLEDGEMENTS

Authors are very thankful to GITAM management and they were for providing all the necessary facilities.

7. REFERENCES

1. Kevin George, Pavithra Elavarasan, Shanmugam Ponnusamy, annadasan Sathananthan," Facile One-Pot Synthesis of Functionalized Quinoline-Fused Fluorescent Dihydro/Spiro-quinazolinone Derivatives" ACS Omega, 2022; 7: 24, 20605-20618.
2. Mahmoud Refaee Mahmoud, Manal Mohamed El-Shahawi and FatmaSaber Mohamed Abu El-Azm*," Synthesis of novel quinazolinone and fused quinazolinones", European Journal of Chemistry, 2011; 2(3): 404-409.
3. Sulochana Sharma1, Kailash Sharma2, Sakshi Pathak3, Mahendra Kumar3 and Praveen Kumar Sharma4,* Synthesis of Medicinally Important Quinazolines and Their Derivatives: A Review". The Open Medicinal Chemistry Journal, 2020; 14: 109.
4. Yahia Nasser Mabkhot,1,* Munirah S. Al-Har,1,2 Assem Barakat,1,3,* Fahad D. Aldawsari,1,4 Ali Aldalbahi,1 and Zaheer Ul-Haq5"Synthesis, Anti-microbial and Molecular Docking Studies of Quinazolin-4(3H)-one Derivatives", Molecules, 2014 Jul; 19(7): 8725–8739. Published online, 2014 Jun 25. doi: 10.3390/molecules19078725
5. Kamelia M. Amin1 Et Al, "Synthesis, Cytotoxic Evaluation And Molecular Dockingstudy Of Novel Quinazoline Derivatives As Parp-1 Inhibitors", Acta Poloniae Pharmaceutica Ñ Drug Research, 2013; 70(5): 833ñ849.
6. Leila Emami, Soghra Khabnadideh, Zahra Faghih, Farnoosh Farahvasi, Fatemeh Zonobi, Saman Zare Gheshlaghi, Shadi Daili, Ali Ebrahimi & Zeinab Faghih," Synthesis, biological evaluation, and computational studies of some novel quinazoline derivatives as anticancer agents" BMC Chemistry, 2022; 16: Article number: 100.
7. Gourav Kumar, Parveen Kumar, AktaSoni, Venu Sharma, Meena Nemiwa" Efficient synthesis and molecular docking analysis of quinazoline and azole hybrid derivatives as promising agents for anti-cancer and anti-tuberculosis activities", Journal of Molecular Structure, 15 August 2024; 1310: 138289.
8. Adel S. El-Azab a,* et al," Design, synthesis and biological evaluation of novel quinazoline derivativesas potential antitumor agents: Molecular

docking study" European Journal of Medicinal Chemistry, September 2010; 45(9): 4188-4198.
9. Guang-Ming Lu et al Design, synthesis and biological evaluation of novel quinazoline derivatives as potential NF-κb inhibitors Arabian Journal of Chemistry, July 2022; 15(7): 103908.
10. Sara Sadeghian, Raziyeh Razmi, Soghra Khabnadideh, Mehdi Khoshneviszadeh, Pegah Mardaneh, Arman Talashan, Arman Pirouti, Fatemeh Khebre, Zahra Zahmatkesh & Zahra Rezaei," Synthesis, biological evaluation, molecular docking, and MD simulation of novel 2,4-disubstituted quinazoline derivatives as selective butyrylcholinesterase inhibitors and antioxidant agents", Scientific Reports, 2024; 14: 15577.
11. Haghighijoo, Z. et al. Synthesis and biological evaluation of quinazolinone-based hydrazones with potential use in Alzheimer's disease. Bioorgan. Chem, 2017; 74: 126–133.
12. Mohamed, T., Mann, M. K. & Rao, P. P. Application of quinazoline and pyrido [3, 2-d] pyrimidine templates to design multi-targeting agents in Alzheimer's disease. RSC Adv, 2017; 7(36): 22360–22368.
13. Jie Hu, Yali Zhang, Lili Dong, Zhe Wang, Lingfeng Chen, Dandan Liang, Dengjian Shi, Xiaoou Shan, Guang Liang, "Design, Synthesis, and Biological Evaluation of Novel Quinazoline Derivatives as Anti-inflammatory Agents against Lipopolysaccharide-induced Acute Lung Injury in Rats".