Novel One-Pot Three-Component Synthesis of Fused Dihydropyrimido-Thiadiazole Quinozoline Derivatives of Biological Interest

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DOI: https://doi.org/10.51584/IJRIAS.2026.11070117

Received: 24 July 2026; Accepted: 29 July 2026; Published: 08 August 2026

ABSTRACT

Multi-component one-pot reaction is the simplest and the most economical method for the synthesis of biologically important and pharmacologically active compounds. This reaction process allows the certain of several bonds in a single operation and are attracting increasing attention as one of the most powerful emerging synthetic tools for the reaction of molecular diversity and complexity. The multi component process has proved efficient method for one-pot synthesis of dihydro-thiadiazolo-quinazolin derivatives (2a-h) in excellent yields from thiadiazoles, dimedone and aldehydes under thermal condition without using any catalyst. This environmentally benign procedure for the synthesis of dihydro-thiadiazolo-quinazolin derivatives is suitable for library synthesis and it will find application in the synthesis of biologically active molecules. The process presented here is operationally simple, environmentally benign and has excellent yield. Furthermore, the reaction time is very short within an hour under steam bath reflux condition. The new compounds were screened for antimicrobial activity against various gram-positive, gram-negative bacteria and fungi, during which the compounds depicted good to moderate antimicrobial behavior against *S.aureus,B.subti is, P.aeruginosa, E.coi* and *C.freundii.*

Key words: Greener, Drugs, Short time, Antibacterial, Antifungal.

INTRODUCTION

Multi-component reactions (MCRs) are one-pot processes in which three or more reactants come together in a single reaction vessel to give a final product. Currently, multi-component reactions are an important part of numerous research work involved in the drug discoveries to achieve synthetic targets in effective way, because they are easy to carry out and provide rapid access to libraries of organic compounds with diverse substitution patterns [1-3].

In an MCR, a product is assembled according to a cascade of elementary chemical reactions. Thus, there is a network of reaction equilibria, which all finally flow into an irreversible step yielding the product. The challenge is to conduct an MCR in such a way that the network of pre-equilibrated reactions channel into the main product and do not yield side products. The result is clearly dependent on the reaction conditions: solvent, temperature, catalyst, concentration, the kind of starting materials and functional group. Some examples of MCRs are Hantzsch dihydropyridine synthesis [4], Biginelli reaction (3CR) [5], Passerini reaction (3CR) [6].

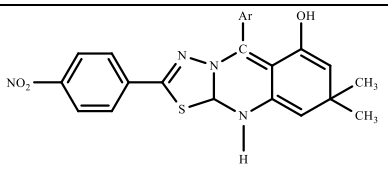
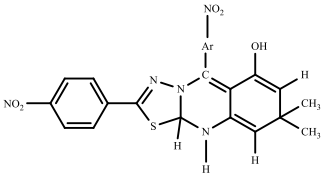
One pot reaction where several reaction sequences are conducted in the same reaction flask are one of the methods that can be used in order to conduct synthesis in a greener fashion. The chemistry is greener due to the reduction of work-up procedures and purification steps required compared to a more stepwise approach. In catalytic reaction it is possible to combine several catalytic processes in the same reaction vessel. The most significant advantage, in the synthetic point of view is that it is less likely to lose material that would otherwise be lost during work up and purification. The second advantage is the economy of utilizing chemicals and solvents. One-flask reaction, multicenter involving multiple steps would only requires final workup at the final step. The third advantage is the minimal amount of work required, instead of working up each step of the synthesis involving, say, three steps, it only need to do one work up at the end.

ISSN No. 2454-6194 | DOI: 10.51584/IJRIAS |Volume XI Issue VII July 2026

In recent years, dihydropyrimidine-2 (1H) one derivative have gained much interest for their biological and pharmaceuticals properties such as HIV gp-120-CD4 inhibitors [7], calcium channel blockers [8], α-adrenergic and neuropeptide Y antagonists [9], as well as antihypertensive, antitumor, antibacterial, anti-inflammatory [10] agent. The scope of this pharmacophore has been further increased by the identification of the Monostrol a novel as a cell-permeable lead compound for the development of the new anticancer drugs [11] bearing the dihydropyrimidones core. It is also involved in the degradation of the chemotherapeutic drugs 5-fluorouracil and tegafur [12]. Dihydropyridine (DHP) calcium channel blockers are derived from the molecule dihydropyrdine and often used to reduce systemic vascular resistance and arterial pressure. Dihydropyridine calcium channel blockers can worsen proteinuria in patients with nephropathy [13]. Dihydropyridines (DHPS) have attracted increasing interest due to their diverse therapeutic and pharmacological properties such as insecticidal, bactericidal and herbicidal effects [14]. DHP drugs, namely nifedipine, nicardipine and amlodipine, are cardiovascular agents for the treatment of hypertension [15] and congestive heart failure [16]. Recently, DHPs are used as organocatalysts for asymmetric reactions. Additionally, dihydropyrimidinones (DHPMs) have exhibited important therapeutic and pharmacological properties as the integral backbone of several calcium channel blockers [17], antihypertensive agents [18], and α1a-antagonists [19]. A broad range of biological effects including antiviral, antitumor, antibacterial and anti-inflammatory activities has been described for these compounds [21-23]. Therefore, their synthesis has been the focus of great interest for organic and medicinal chemists [24].

In chemistry thiadiazoles are a sub-family of azole compounds. During recent years there has been intense investigation of different classes of thiadiazole compounds, many of which known to possess interesting biological properties such as antimicrobial [25-27], anti-inflammatory [28, 29-30], anticonvulsants [31,32-35], antioxidant [36], anticancer [37] and antifungal [38] activities. The activity of 1,3,4- thiadiazoles is possibly due to the presence of the, N–C–S moiety [39]. Derivatives of 1,2,3-thiadiazoles is known to exhibit antiviral [40, 41], analgesic [42,43] and antidepressant activity [44]. Antitubercular activities of thiadiazoles linked with aromatic cycles through the methyleneoxy group have also been reported and compounds of this type have shown inhibition on both cycloxygenase and 5-lipoxygenase activities [45]. More recently, sulfonamide derivatives of 1,3,4-thiadiazoles have been reported to behave as a modulator of anticancer therapies in combination with some cytotoxic compounds [46-49]. In addition, Schiff bases have been the focus of numerous studies due to their wide spectrum of biological activities [50]. Based on all above considerations and as an extension of our studies on the developments of novel azoles antimicrobial agents [51,52], 1,3,4-Thiadiazole derivatives possessed a wide range of therapeutic activities like antimycobacterial [53], antileshmanial [54], analgesic, antipsychotic [55] and anticonvulsant [56,57].

Table -1

M.F of Reactants			Product	M.F of products
$CN_2SNH_2NO_2$	ArCHO		1.	
	4-NO_2ArCHO		2.	

Experimental

1. Synthesis of [5-amino-1,3,4-thiadiazol-2-yl]4-nitro benzene

A mixture of thiosemicarbazide (0.01 mol), para nitrobenzoic acid (0.01 mol) and concentrated sulphuric acid 1 ml in 10 ml ethanol was taken in a round bottomed flux. The flux was then placed on water-bath with constant

ISSN No. 2454-6194 | DOI: 10.51584/IJRIAS |Volume XI Issue VII July 2026

stirring for one and half hour under reflux condition. The progress of the reaction was monitored by TLC. Reaction mixture was then kept on ice bath. The solid product was separated out by filtration. After filtration a white crude product was obtained. The crude product was separated out by filtration. The crude product was then purified by recrystallization from 10% aqueous ethanol to yield 81% as a white solid. The melting point was recorded as 220-222 ºC.

IR (KBr, cm^{-1}): 3394 (N-H, symmetric stretching), 3290 (N-H, asymmetric stretching), 3193 (C-H, aromatic), 1621 (C=N), 1600, 1580, 1536 (C=C, aromatic),719 (C-S-C linkage of thiadiazole).

General procedure:

A mixture of [5-amino-1,3,4-thiadiazol-2-yl] 4-nitro benzene (0.01 mol), dimedone (0.01 mol) and aromatic aldehyde (0.01 mol) **[compound 1-2]** in 5 ml of ethanol was taken in a round bottomed flux. The flux was then placed on water-bath with constant stirring for one hour under reflux condition. The progress of the reaction was monitored by TLC. Reaction mixture was then kept on ice bath. The solid product was separated out by filtration. After filtration many colours like orange, yellow crude product was obtained. The crude product was then purified by recrystallization from absolute ethanol to yield 75% and 73% as solid. The melting point was recorded. Different product show different melting point.

Table 2:

Compound	Melting point	Colour of compounds	Yields%
Product -1	195-198	Orange solid	75%
Product -2	198-200	Yellow solid	73%

RESULTS AND DISCUSSION

2. Characterization of 5-(phenyl)– 8,8-dimethyl-2-(4-nitrophenyl)-10, 10a-dihydro-8H- [1,3,4] thiadiazolo [2,3-b] quinazolin-6-ol. (1)

IR (KBr, cm^{-1}): 3400-3475 (O-H), 3346 (N-H), 3123 (C-H, aromatic), 2975 (C-H, aliphatic), 1600 (C=N), 1572, 1540, 1520 (C=C, aromatic and aliphatic), 693 (C-S-C).

^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 1.051(s, 6H, $2CH_3$), 6.90 (d, 1H, J=8.00 Hz, =CH), 7.18 (bd, s, 1H, SCHN), 7.27 (m, 5H, Ar-H), 7.43 (m ,4H, Ar-H), 7.71 (d, 1H, J=8 Hz, C=CH), 8.120 (s ,1H, O-H), 11.651 (s, 1H, N-H).

^{13}C NMR (100 MHz , DMSO-d_6 , δ ppm) : 176.86 (1C , C=N) , 143.31 , 142.50 (2C, C=C) , 134.57 , 130.46 (2C , C=C) , 129.39 , 129.11 (2C , C=C) , 128.45 (4C , Ar) , 127.33 (2C , Ar) , 126.77 (1C , Ar) , 126.39 (5C , Ar) , 113.79 (1C , S-C-N) , 51.48 (1C , aliphatic) , 32.35 (1C , aliphatic) , 28.31 (1C , aliphatic).

2. Characterization 5-(4-nitrophenyl)–8,8-dimethyl-2-(4-nitrophenyl)-10, 10a-dihydro-8H-[1,3,4] thiadiazolo[2,3-b] quinazolin-6-ol. (2)

IR (KBr, cm^{-1}): 3450-3500 (O-H), 3337 (N-H), 3085 (C-H, Ar), 2963 (C-H, aliphatic), 1607 (C=N), 1604 , 1580 ,1527 ,1510 (C=C, Aromatic and aliphatic), 720 (C-S-C).

^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 1.013 (s, 3H, CH_3), 1.096 (s, 3H, CH_3), 7.49 (d, 1H, J=8.0 Hz, =CH), 8.11 (m, 2H, -CH, O-H), 8.246 (m, 4H, Ar-H), 8.297 (m, 4H, Ar-H), 8.42 (d ,1H, J=8.0 Hz, C=H), 10.185 (s, 1H, N-H).

ISSN No. 2454-6194 | DOI: 10.51584/IJRIAS |Volume XI Issue VII July 2026

Antimicrobial

This test measures the ability of each antibacterial agent to inhibit the *in vitro* bacterial growth. This ability may be estimated by disc diffusion method. * 50 µL dose used & concentration was 300 µg disc-1. The observed zone of inhibition is indicated by diameters (in mm) and (-) represents no activity. *S.a., Staphylococcus aureus* (cars-2), *B.s., Bacillus subtilis,* (carsgp-3), *E.c., Escherichia coli,* (carsgn-2), *P.a., Pseudomonas aeruginosa,* (carsgn-3), *S.t., Salmonella typhimurium,* (JCM-1652), *C.f., Citrobacterfreundii,* (JCM-1657), *T.h., Tricodarmaharzianum,* (carsm-2), *A.n., Aspergillusniger.* (carsm-3) *.Michonazole (Mc)* used as Standard antifungal agent *& Ciprofloxacin (Cp)* as standard antibacterial agent.

Comparatively study of the two compounds

The tested compounds showed activities at a dose of 300 µg disc-1 comparable to Ciprofloxacin for bacteria and Michonazole for fungi (standard) at 300 µg disc-1.

The compound 2 showed bactericidal moderate activity against *S. aureus, B. subtilis, P. aeruginosa.* Noticeably, both the compounds showed the antibacterial activity against *B. subtilis. P. aeruginosa E. coli, S.* aureus, *C. freundii.* Between them compound -1 showed very good activity against *B. subtilis, P. aeruginosa, E. coli, S.* aureus. compound-2.

Table 3:

Comp.	Bacterial species						Fungal Species	
	Gram positive	Gram negative						
	S.a	*B.s*	*E.c*	*P.a*	*S.t*	*C.f*	*T.h*	*A.n*
P – 1	25	23	26	22	18	32	9	7
P – 2	11	15	10	9	13	15	6	13

CONCLUSION

We have synthesized a novel dihydro - thiadiazole quinozoline derivatives. The products were synthesized by multi – component one – pot process in which three reactants come together in a single reaction vessel gave a final product. Multi – component one – pot synthetic method is very easy to carry out and provide rapid access to libraries of organic compounds with diverse substitution patterns. Multi – component one – pot methods eliminate the isolation of intermedials, thereby reduces the reaction time and increases the yield than the normal multistep methods. Multi – component one – pot method is the simplest and most straight forward procedure involves three components one – pot cyclo conduction of aldehydes, thiadiazole and dimedone. The synthesized dihydro – thiadiazole quinozolino showed moderate to good antibacterial and antifungal activity.

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