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SYNTHESIS AND ANTIMICROBIAL ACTIVITY OF NOVEL N-(4-(4-(BENZYLOXY)-3-NITROPHENYL)THIAZOL-2-YL)-1-(3-ARYL-1-PHENYL-1*H*-PYRAZOL-4-YL)METHANIMINE

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ABSTRACT
In this study, the synthesis, characterisation, and biological evaluation of a series of novel N-(4-(4-(benzyloxy)-3-nitrophenyl)thiazol-2-yl)-1-(3-aryl-1-phenyl-1*H*-pyrazol-4-yl)methanimine derivatives have been carried out using 4-(4-(benzyloxy)-3-nitrophenyl)thiazole-2-amine and substituted pyrazole aldehyde. These derivatives were synthesised using a two-step process employing PEG-400 as a green solvent and citric acid as a catalyst. Synthesised compounds were confirmed using ^{1}H-NMR and mass spectra. The method is efficient and eco-friendly with high yield, and the synthesised compounds possess moderate to high antimicrobial activity.
Keywords: Pyrazole Aldehyde, Thiazole, Antimicrobial Activity, PEG-400, Schiff Bases.
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INTRODUCTION

Pyrazoles are five-membered heterocyclic rings that have attracted considerable attention. Because they are easy to synthesise and highly versatile, they are widely used in the development of new medicines and treatments for various diseases. This pyrazolyl moiety with various substituents shows broader pharmacological activities such as antitubercular[1], antioxidant[2], antiinflammatory[3], anticancer[4], anticonvulsant[5], antiheptatoxic[6], antimicrobial[7], antidepressant[8], antimalarial[9], etc. Another important scaffold is thiazole and its derivatives, which contribute to significant biological activities such as anticancer[10], antimicrobial[11], analgesic[12], antioxidant[13], antiinflammatory[14,15], antitubercular[16] and antidepressant[17] activities. Studies have shown that the combination of these privileged structures is highly effective for developing new drugs. These hybrid molecules often show better strength, target specific areas more accurately and offer greater healing potential compared with each part alone, supporting the idea of synergistic effects.[18-19] The rapid rise in microbial infections and the growing threat of multidrug-resistant "superbugs" pose serious global health threats. Conventional antibiotics are becoming less effective as microorganisms develop resistance, leading to more treatment failures and limited therapeutic options[20-21]. To address this need, chemists are developing novel antimicrobial compounds with unique chemical structures and mechanisms of action. Conventional methods in organic synthesis often rely on toxic solvents and hazardous reagents, which generate large amounts of harmful waste and pose environmental and health risks. To address these drawbacks, the field of green chemistry promotes sustainable synthetic methods that reduce or eliminate the use of toxic solvents and catalysts, promote eco-friendly solvents, and develop energy-efficient methods and processes that generate less waste. In recent years, polyethylene glycols (PEGs) have attracted numerous attentions as green solvents in organic synthesis. These low-cost compounds are available in a wide range of molecular weights. PEG 400 is a viscous water-soluble liquid which is biodegradable, non-volatile, non-toxic, odourless, and non-irritating. Recent literature highlights the increasing utility of PEG-400 in promoting various chemical transformations attributed to the simplified workup procedures it facilitates.[22-23] The synthesis of multi-heterocyclic compounds is an important area of organic and medicinal chemistry due to their broad range of biological activities. With more drugs becoming less effective due to resistance and many conventional

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methods having drawbacks such as the use of volatile organic reagents and catalysts, requires harsh reaction conditions, long reaction time and a difficult workup procedure, there is an increasing need for developing new compounds using eco-friendly methods. In continuation of our work in the synthesis of biologically active compounds[24-26], here we describe an environmentally benign protocol for the synthesis of novel N-(4-(4-(benzyloxy)-3-nitrophenyl)thiazol-2-yl)-1-(3-aryl-1-phenyl-1*H*-pyrazol-4-yl)methanimine derivatives using PEG-400.

EXPERIMENTAL

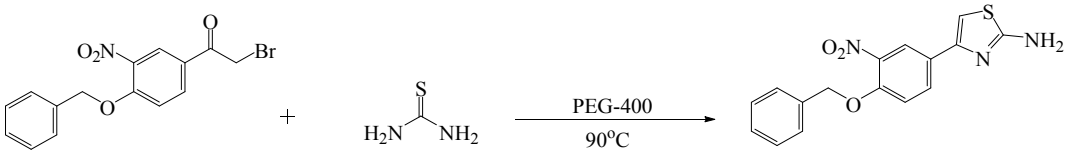
Material and Methods

All the raw chemicals were purchased from BLD Pharma and used without further purification. ^{1}HNMR Spectra were recorded on a Bruker Avance Neo (500 MHz) NMR spectrometer in DMSO using tetramethylsilane (TMS) as an internal standard, and chemical shifts were reported in parts per million relative to TMS. Mass spectra were recorded on a MALDI-TOF Synapt XS HD spectrometer. Melting points were determined in open capillary tubes and are uncorrected.

General Procedure for the Synthesis of Novel Pyrazole-Thiazolyl Schiff Base

Step 1: Synthesis of 4-(4-(benzyloxy)-3-nitrophenyl)thiazole-2-amine (3)

A mixture of 1-(4-benzyloxy-3-nitrophenyl)-2-bromoethanone **(1)** (1 mmol) and thiourea (2) (1 mmol) in PEG-400 (5 ml) was heated at 90°C for 4-5 hours. The progress of the reaction was monitored by TLC. Upon completion, the reaction mixture was cooled to room temperature and poured into ice-cold water. The resulting precipitate was stirred, filtered, and dried. The crude product was recrystallised from ethanol to afford pure 4-(4-(benzyloxy)-3-nitrophenyl)thiazole-2-amine (3) (Scheme-1).

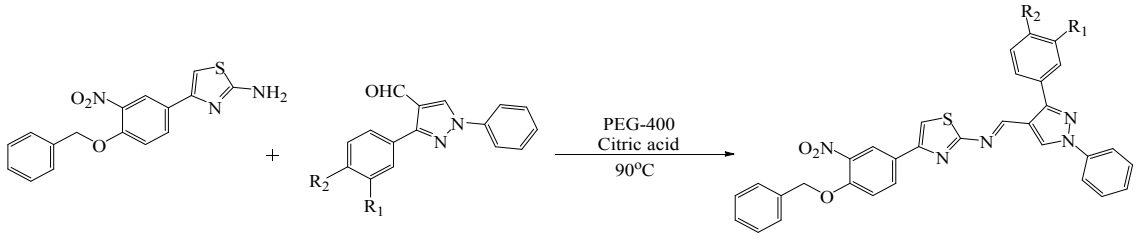


1 2 3

Scheme-1: Synthesis of 4-(4-(benzyloxy)-3-nitrophenyl)thiazole-2-amine, (3)

Step 2: Synthesis of N-(4-(4-(benzyloxy)-3-nitrophenyl)thiazol-2-yl)-1-(3-aryl-1-phenyl-1*H*-pyrazol-4-yl)methanimine (5a-h)

4-(4-(benzyloxy)-3-nitrophenyl)thiazole-2-amine (3) (1 mmol) and substituted pyrazole aldehyde (4) (1 mmol) in PEG-400 (5ml) and citric acid were heated at 90°C as time indicated in Table-2. The reaction progress was monitored by TLC. After completion of the reaction, the reaction mass was poured into ice-cold water and stirred. The solid product was filtered, dried, and recrystallised from ethanol to yield the pure N-(4-(4-(benzyloxy)-3-nitrophenyl)thiazol-2-yl)-1-(3-aryl-1-phenyl-1*H*-pyrazol-4-yl)methanimine Schiff base derivatives (5a-h). (Scheme-2)



3 4 5a-h

Scheme-2: Synthesis of N-(4-(4-(benzyloxy)-3-nitrophenyl)thiazol-2-yl)-1-(3-aryl-1-phenyl-1*H*-pyrazol-4-yl)methanimine, (5a-h)

Spectral Data

5a: 4-(4-(((4-(4-(benzyloxy)-3-nitrophenyl)thiazol-2-yl)imino)methyl)-1-phenyl-1*H*-pyrazol-3-yl)phenol

^{1}H NMR (500MHz, DMSO, δ ppm): 5.5(s, 2H), 5.2(s, 1H), 8.38(s, 1H), 7.5(s, 1H), 8.0(s, 1H), 6.5-8.1(m, 17H), Mass: $[ES]^+$: Calculated-573, Found-574.10

5b:N-(4-(4-(benzyloxy)-3-nitrophenyl)thiazol-2-yl)-1-(3-(3-chlorophenyl)-1-phenyl-1*H*-pyrazol-4-yl)methanimine
^{1}H NMR (500MHz, DMSO, δ ppm): 5.6(s, 2H), 8.5(s, 1H), 7.2(s, 1H), 8.1(s, 1H), 7.0-7.9(m, 17H), Mass: $[ES]^+$: Calculated-591.5, Found-592.16

5c:N-(4-(4-(benzyloxy)-3-nitrophenyl)thiazol-2-yl)-1-(3-(3-nitrophenyl)-1-phenyl-1*H*-pyrazol-4-yl)methanimine
^{1}H NMR (500MHz, DMSO, δ ppm): 5.6(s, 2H), 8.5(s, 1H), 7.7(s, 1H), 7.4(s, 1H), 6.6-8.2(m, 17H), Mass: $[ES]^+$: Calculated-602, Found-603.14

5d:N-(4-(4-(benzyloxy)-3-nitrophenyl)thiazol-2-yl)-1-(3-(3-bromophenyl)-1-phenyl-1*H*-pyrazol-4-yl)methanimine
^{1}H NMR (500MHz, DMSO, δ ppm): 5.5(s, 2H), 8.5(s, 1H), 8.4(s, 1H), 7.7(s, 1H), 7.0-8.6(m, 17H), Mass: $[ES]^+$: Calculated-635.90, Found-636.12

5e:N-(4-(4-(benzyloxy)-3-nitrophenyl)thiazol-2-yl)-1-(1-phenyl-3-(p-tolyl)-1*H*-pyrazol-4-yl)methanimine
^{1}H NMR (500MHz, DMSO, δ ppm): 2.3(s, 3H), 5.5(s, 2H), 8.4(s, 1H), 7.8(s, 1H), 7.2(s, 1H,), 6.8-8.1(m, 17H), Mass: $[ES]^+$: Calculated-571, Found-572.22

5f:N-(4-(4-(benzyloxy)-3-nitrophenyl)thiazol-2-yl)-1-(3-(4-fluorophenyl)-1-phenyl-1*H*-pyrazol-4-yl)methanimine
^{1}H NMR (500MHz, DMSO, δ ppm): 5.5(s, 2H), 8.5(s, 1H), 7.0(s, 1H), 7.9(s, 1H), 6.9-8.1(m, 17H), Mass: $[ES]^+$: Calculated-574.99, Found-575.13

5g:N-(4-(4-(benzyloxy)-3-nitrophenyl)thiazol-2-yl)-1-(3-(4-bromophenyl)-1-phenyl-1*H*-pyrazol-4-yl)methanimine
^{1}H NMR (500MHz, DMSO, δ ppm): 5.5(s, 2H), 8.4(s, 1H), 7.8(s, 1H), 8.0(s, 1H), 7.0-8.1(m, 17H), Mass: $[ES]^+$: Calculated-635.9, Found-636.06

5h:4-(4-(((4-(4-(benzyloxy)-3-nitrophenyl)thiazol-2-yl)imino)methyl)-1-phenyl-1*H*-pyrazol-3-yl)-2-methylphenol
^{1}H NMR (500MHz, DMSO, δ ppm): 2.5 (s, 3H), 5.2 (s, 1H), 5.7(s, 2H), 8.5(s, 1H), 7.1(s, 1H), 7.3 (s, 1H), 6.8-8.1(m, 16H), Mass: $[ES]^+$: Calculated-587.65, Found-588.18

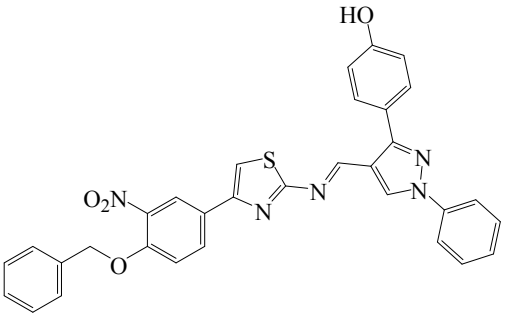
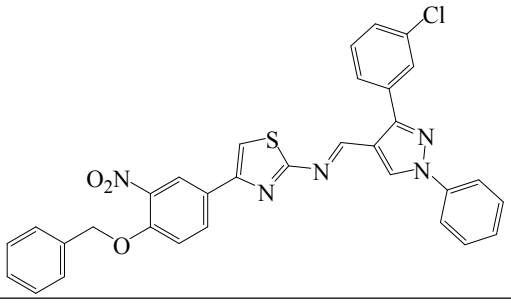
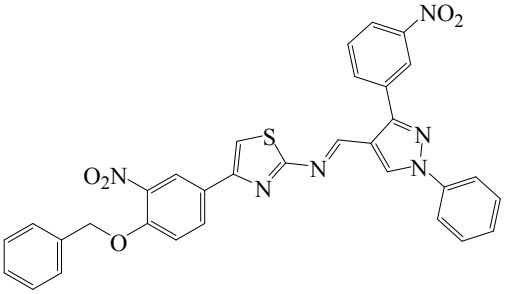
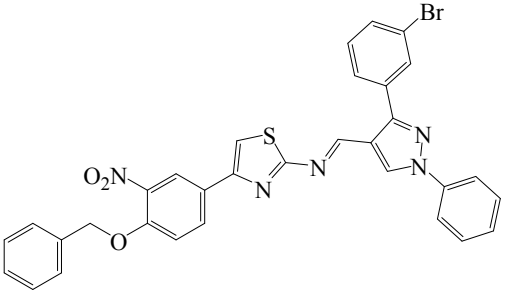
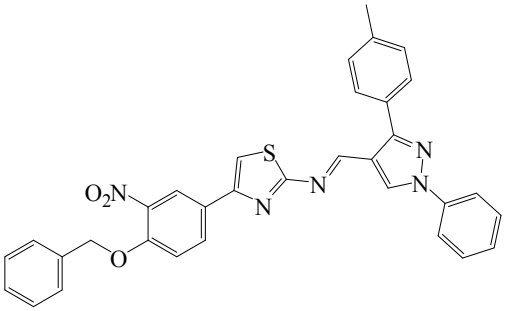
RESULTS AND DISCUSSION

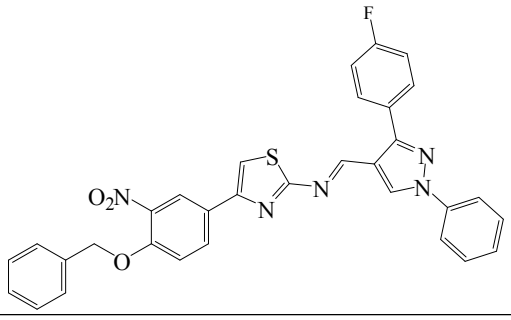
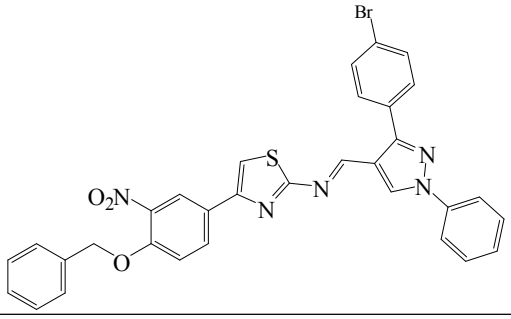
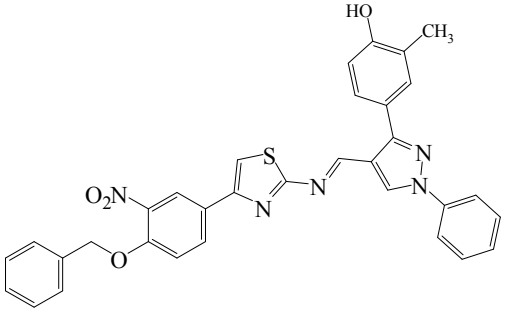
Polyethylene glycol-400 (PEG-400) has emerged as a versatile and sustainable medium in chemistry due to its low toxicity, high solvency power and biodegradability. As a water-soluble and hygroscopic polymer, PEG-400 serves as an efficient alternative to volatile organic solvents, aligning with the principles of Green Chemistry. Owing to the importance of biologically active multi-heterocyclic compounds and the advantages of PEG-400, we have reported a two-step protocol for the synthesis of novel pyrazole-thiazolyl Schiff base derivatives using PEG-400 as an eco-friendly reaction medium. In the first step, 4-(4-(benzyloxy)-3-nitrophenyl)thiazole-2-amine (3) was synthesized by the reaction between 1-(4-benzyloxy-3-nitrophenyl)-2-bromoethanone and thiourea in PEG-400 at 90^{o}C for 4-5 hours. The reaction completed smoothly, and the obtained products were collected and used in the second step. This synthesised 4-(4-(benzyloxy)-3-nitrophenyl)thiazole-2-amine (3) was then heated with various substituted pyrazole aldehydes in PEG-400 with a little amount of citric acid as a catalyst and obtained the N-(4-(4-(benzyloxy)-3-nitrophenyl)thiazol-2-yl)-1-(3-aryl-1-phenyl-1*H*-pyrazol-4-yl)methanimine Schiff base derivatives in higher yields. Various substituents also affected the yields of the products. Electron-withdrawing and donating groups do not affect the yield of the products (Table-1).

Antimicrobial activity of the synthesised compounds was also screened against Gram-positive bacteria (*Staphylococcus aureus* and *Bacillus acne*), Gram-negative bacteria (*Pseudomonas fluorescens* and

Escherichia coli), using ofloxacin (2 mcg) as a standard drug and fungi (*Trichophyton rubrum* and *Candida albicans*), using fluconazole (25 mcg) as a standard drug.

Table-1: Physical Data of the Synthesised Compounds

Entry	Compound	Yield	Time (hrs)	MP (°C)
5a		86	4.4	165
5b		84	4.3	153
5c		87	4.4	173
5d		89	4.2	144
5e		82	4	160

5f		85	4.1	148
5g		81	4.2	160
5h		84	4.5	175

All the compounds show good activity against Gram-positive bacteria, *Staphylococcus aureus* (Table-2). Compounds 5c and 5d showed excellent antimicrobial activity with a zone of inhibition of 20mm. Compound 5a shows moderate activity against the fungus *Trichophyton rubrum*. All the synthesised compounds are characterised by ^{1}HNMR and mass spectroscopic techniques.

CONCLUSION

In this study, we have reported an environmentally benign protocol for the synthesis of novel N-(4-(4-(benzyloxy)-3-nitrophenyl)thiazol-2-yl)-1-(3-aryl-1-phenyl-1*H*-pyrazol-4-yl)methanimine derivatives using PEG-400 as a solvent and citric acid as a catalyst. The reactions proceeded smoothly under mild conditions, affording the products in higher yields while avoiding tedious workup procedures. Antimicrobial activity of all the synthesised compounds was also evaluated. This study not only contributes to the search for new molecules but also illustrates the importance of green methodologies in modern drug discovery.

Table-2: Antimicrobial Activity of Synthesised Compounds

S. No.	Compound	Antimicrobial Sensitivity Test Against Bacteria & Fungi (After 24 hours at 37°C & Fungus at Room Temperature) (*Zone of Inhibition in mm*)					
		Gram -ve Bacteria		Gram +ve Bacteria		Fungi	
		Pseudomonas fluorescens	*Escherichia coli*	*Staphylococcus aureus*	*Bacillus acne*	*Trichophyton rubrum*	*Candida albicans*
1	5a	-	-	18 mm	-	10 mm	-
2	5b	-	-	16 mm	-	-	-
3	5c	-	-	20 mm	-	-	-
4	5d	-	-	20 mm	-	-	-

5	5e	-	-	20 mm	-	-	-
6	5f	-	-	18 mm	-	-	-
7	5g	-	-	16 mm	-	-	-
8	5h	-	-	14 mm	-	-	-
9	Control	-	-	10 mm	-	-	-
10	Standard Drug Ofloxacin (2 Mcg) for Bacteria & Fluconazole (25 Mcg) for Fungi	20 mm	11mm	22 mm	18 mm	23 mm	14 mm

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CONFLICT OF INTERESTS

The authors declare that there is no conflict of interest.

AUTHOR CONTRIBUTIONS

The present work is related to *SDG-9: Industry, Innovation and Infrastructure*. All the authors contributed significantly to this manuscript, participated in reviewing/editing and approved the final draft for publication. The research profile of the authors can be verified from their ORCID ids, given below:

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