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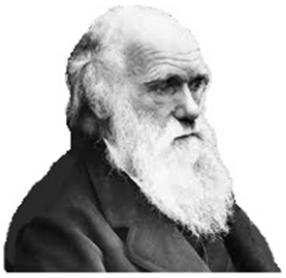

World News of Natural Sciences

An International Scientific Journal

WNOFNS 54 (2024) 159-169 EISSN 2543-5426

Synthesis, sprectral analysis and antimicrobial activity of 1,2,3-triazole and arylamide derivatives using 4-aminoantipyrine nucleus

Priyanka Pankhaniya[1,a], Nikhil P. Savaniya[2], Dipak M. Purohit[1,b]

[1]Department of Chemistry, Shree M. & N. Virani Science College, Rajkot - 360005, India

[2]Department of Chemistry, Government Science College, Ahwa, Dist. Dang - 394710, India

[a,b]E-mail address: priyankapankahniya16@gmail.com , dmpurohit@vsc.edu.in

ABSTRACT

Pyrazole derivatives shows remarkable antibacterial activity, antifungal activity, anti-oxidant activity, anti-inflammatory activity, anticancer activity etc. In view of getting to synthesize 2-{4'-[1',5'-Dimethyl-3'-oxo-2'-phenyl-pyrazol-4'-yl]aminomethyl-1H-1,2,3-triazol-1-yl}-N-arylethanamide derivatives (8a-8j) and 2-[(1',5'-dimethyl-3'-oxo-2'-phenyl-pyrazol-4'-yl)amino]-N-arylethanamide derivatives (9a-9j). The structures of the compounds were analyzed by IR, ^{1}H NMR, mass spectral data and TLC. The synthesized compounds were evaluated their antimicrobial activity with Gram-positive, Gram-negative bacteria and fungi.

***Keywords*:** 4-aminoantipyrine, 1-2-3-traizole, Click chemistry, CuAAC, Arylamide, Antibacterial Activity, Anti-fungal Activity

1. INTRODUCTION

Now a days synthetic research communities are majorly focuses on the development of efficient heterocyclic frameworks [1], which are easy to synthesize with high yield and will show greater pharmacological activity [2]. For such aim, most common choice of heterocycles are of nitrogen [3] containing heterocycles. Five membered heterocycle containing nitrogen atom at 1st and 2nd position called pyrazolone [4-6] attracted most scientific communities for

(Received 15 April 2024; Accepted 15 May 2024; Date of Publication 17 May 2024)

its diverse reactivity and exceptionally high biological activity [7]. One of the significantly studied scaffold containing pyrazolone is 4-aminoantipyrine [8-10]. 4-aminoantipyrine derivatives possess efficient biological activity such as analgesic [11], anti-inflammatory [12], anticancer [13-15], antibacterial [16-17], antifungal [18], antiviral [19], etc. These are also strong inhibitors of cycloxygenase isoenzymes [20], platelet tromboxane synthesis [21], and prostanoids synthesis [22], which catalyze the rate-limiting step of prostaglandin synthesis [23]. Some of the famous examples of 4-aminoantipyrine contacting drugs are metamizole and aminophenazone.

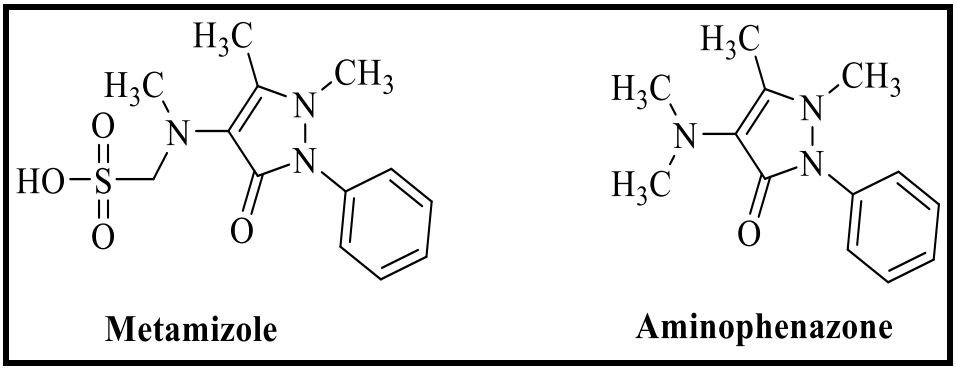

Figure 1. Drug molecules containing 4-aminoantipyrine nucleus

In the current scenario, synthesis of 1,2,3-triazole [24] derivatives using CuAAC approach [25] have been developed as an efficient tool of click chemistry [26] methodology. A safer and significant reaction conditions provide quicker way to get desired product without any side reaction and side product. Further, 1,2,3-triazole scaffold possess tremendous pharmaceutical ingredient for many drug molecules such as Tazobactam/Ceftolozane, Radezolid, Cefatrizine etc.

The current research article insight into synthesis of 1,2,3-traizole derivatives from 4-aminoantipyrine derivatives and 2-azidoaryamide derivatives via click chemistry approach using DMF: water: n-BuOH solvent system. Here in this work, synthesis of arylamide [27] derivatives using 4-aminoantipyrine and 2-chloroaryamide derivatives have displayed too. Both types of derivatives were evaluated for their molecular structure as well as antimicrobial activity.

2. MATERIALS AND METHODS

All the chemicals were purchased from Loba chemie and Avra chemicals are of AR grade and used directly without purification. Melting points were determined using open glass capillaries, and are uncorrected. To check the course of reaction, thin-layer chromatography was performed using a 0.2 mm pre-coated silica gel plate and visualization have been made using UV light (254 nm and 365 nm) of Shimadzu UV spectrophotometer. For the determination of NMR spectra, Bruker Advance II (400 MHz) spectrometer were used by employing solvent DMSO-d^6. All chemical shifts are expressed as δ ppm with respect to

downfield from the signal of tetramethylsilane (TMS), which used as an internal standard. The FT-IR spectra were recorded in Bruker Alpha II IR spectroscope. GC-MS QP-2010 mass spectrometer was used to record mass spectroscopy data.

2. 1. Experimental Section

2. 1. 1. Synthesis of 2-chloro-N-phenylethanamide (3a)

A round bottom flask containing aniline (1a) (1 mmol) and acetone (20 mL) are allowed to react with solution of 2-chloroacetyl chloride (2) (1.5 mmol) in acetone at ambient temperature for 30 minutes. Catalytical amount of K_2CO_3 were added and stirred for 3-4 h. The course of reaction was determined using TLC by employing solvent system ethyl acetate: n-hexane (1:4).

Further the product was discharged into chilled water, filtered, dried and re-crystallized using methanol. M.P.: 138 °C, Yield: 86%, C: 57.65%, H: 4.43%, N: 7.75%, O: 10.26%, Cl: 20.80%, Mol. Formula: C_8H_8NOCl, Calculated: C: 56.65%, H: 4.75%, N: 8.26%, O: 9.43%, Cl: 20.90%

Subsequently other derivatives (3a-3j) were synthesized using same process as reported in *Journal of Chemical Research* volume 38, Article number: 10(2014) DOI: https://doi.org/10.3184/174751914X14116443659287

2. 1. 2. Synthesis of 2-azido-N-phenylethanamide (4a)

2-chloro-N-phenylethanamide **(3a)** (1 mmol) were dissolved in acetone and proceed to react with sodium azide (NaN_3) (3 mmol) for 20-24 h at room temperature. The development of product has been monitored using TLC by employing solvent system ethyl acetate: n-hexane (2:3). The product was obtained by adding reaction mass in to crush ice. The solid product so formed was filtered, dried and purified from methanol to get white crystals. M.P.: 160 °C, Yield: 75%, C: 54.54%, H: 4.58%, N: 31.80%, O: 9.08%, Mol. Formula: $C_8H_8N_4O$, Calculated: C: 55.00%, H: 4.10%, N: 31.30%, O: 9.40%

Similarly other compounds **(4a-4j)** were synthesized using same process as reported in *European Chemical Bulletin* volume 11, Issue 10 Article number: 99 (2022) DOI: 10.53555/ecb/2022.11.10.106

2. 1. 3. Synthesis of 1,5-Dimethyl-2-phenyl-4-(prop-2'-yne-1'-ylamino)-pyrazol-3-one (7)

A two neck round bottom flask containing a solution of 4-amino-1,5-dimethyl-2-phenyl-pyrazol-3-one **(5)** (1 mmol) in acetone were stirred with small amount of potassium carbonate (K_2CO_3) for 30. To this reaction mixture solution of propargyl bromide **(6)** (1.2 mmol) in acetone was added gradually with constant stirring for next 1 h. Whole reaction mass was then refluxed at 60 °C for 12-13 h.

Monitoring of progress of reaction was done using TLC. Upon completion of reaction, reaction mass was allowed to cool and discharge in cold water to get crude product, which was filtered and dried. The purification of product was made using methanol. M.P.: 148 °C, Yield: 75%, C: 68.54%, H: 5.58%, N: 18.80%, O: 7.08%, Mol. Formula: $C_{13}H_{13}N_3O$, Calculated: C: 68.70%, H: 5.77%, N: 18.49%, O: 7.04%

The synthesis process is reported in *Journal of Molecular Structure* volume 1250, Issue 10 Article number: 2 (2022) DOI: https://doi.org/10.1016/j.molstruc.2021.131766

2. 1. 4. Synthesis of 2-{4'-[1',5'-dimethyl-3'-oxo-2'-phenyl-pyrazol-4'-yl]aminomethyl-1H-1,2,3-triazol-1-yl}-N-phenylethanamide (8a)

Three neck round bottom flask containing solvent system DMF: Water: n-Butanol (1:1:1) was allowed to dissolve 1,5-Dimethyl-2-phenyl-4-(prop-2'-yne-1'-ylamino)-pyrazol-3-one **(7)** (1 mmol). To this reaction mass small amount of copper sulphate pentahydrate and sodium ascorbate was added as a catalyst. Subsequently, addition of 2-azido-N-phenylethanamide **(4a)** (1 mmol) was carried out at room temperature. The reaction mixture was stirred at 90 °C for 4 hrs. After completion of reaction, which was monitored by TLC, the mixture was poured into crushed ice and separated crude product were washed with ammonia. Recrystallization was carried out from ethanol M.P.: 218-220 °C, Yield: 80 %

Similarly other compounds **(8a-8j)** were synthesized using above mentioned method.

Spectral Data

White solid, IR (KBr) cm^{-1}: 3055 (-N=N-), 3263 (-N-H str.), 3194, 2990 (C-H str.), 1697 (C=O str. -$CONH_2$), 1604, 1496 (Ar C=C bend.), 1450, 1311 (Ali. C-H bend.), 1249 (C=N, Pyrazolone). ^{1}H NMR (DMSO-d^6) δ ppm: 10.43 (s, 2H), 7.27-7.93 (m, 10H), 7.07-7.08 (t, 1H), 5.29 (s, 2H), 4.29 (s, 2H), 3.33 (s, 3H), 2.51 (s, 3H), MS: m/z; 417.00.

2. 1. 5. Synthesis of 2-[(1',5'-dimethyl-3'-oxo-2'-phenyl-pyrazol-4'-yl)amino]-N-phenylethanamide (9a)

To the solution of 4-amino-1,5-dimethyl-2-phenyl-pyrazol-3-one **(5)** (1 mmol) in tetrahydrofuran, pinch of K_2CO_3 was added and left for stirring for 40 min. To this reaction mass, solution of 2-chloro-N-phenylethanamide **(3a)** (1.3 mmol) was added in drop-wise manner and refluxed for 5 h. TLC was performed to track the reaction progress. At the completion stage, ice cold water was added. The crude product was separated by filtration and dried, recrystallized using ethyl acetate. M.P: 190-192 °C, Yield: 61 %.

Similarly other compounds **(8a-8j)** were synthesized using above mentioned method.

Spectral Data

Yellow solid, IR (KBr) cm^{-1}: 3294 (N-H str.), 3055 (C-H str. Ar-H), 2970-2870 (C-H str.), 1651 (C=O str. -$CONH_2$), 1550-1604 (Ar C=C bend.), 1442, 1396 (Ali. C-H bend.). ^{1}H NMR (DMSO-d^6) δ ppm: 10.58 (s, 1H), 6.93-7.87 (m, 10H), 6.59 (s, 1H), 4.10 (s, 2H), 3.17 (s, 3H), 2.30 (s, 3H) MS: m/z; 337.10;

Table 1. Characteristic physical data of 2-{4'-[1',5'-dimethyl-3'-oxo-2'-phenyl-pyrazol-4'-yl]aminomethyl-1H-1,2,3-triazol-1-yl}-N-arylethanamides (8a-8j)

Code	Ar	M.F.	M.W.	M.P.	% Yield
8a	C_6H_5-	$C_{22}H_{23}N_7O_2$	417.0	218-220	80
8b	2-CH_3-C_6H_4-	$C_{23}H_{25}N_7O_2$	431.0	260-262	78

8c	4-CH_3-C_6H_4-	$C_{23}H_{25}N_7O_2$	431.0	246-248	79
8d	4-OCH_3-C_6H_4-	$C_{23}H_{25}N_7O_3$	447.0	270-272	81
8e	2-Cl-C_6H_4-	$C_{22}H_{22}ClN_7O_2$	451.15	232-234	76
8f	3-Cl-C_6H_4-	$C_{22}H_{22}ClN_7O_2$	451.2	236-238	71
8g	4-Cl-C_6H_4-	$C_{22}H_{22}ClN_7O_2$	451.4	240-242	78
8h	3-Br-C_6H_4-	$C_{22}H_{22}BrN_7O_2$	496.0	262-264	80
8i	4-F-C_6H_4-	$C_{22}H_{22}FN_7O_2$	434.0	244-246	79
8j	2-NO_2-C_6H_4-	$C_{22}H_{22}N_8O_4$	462.0	242-244	72

Table 2. Characteristic physical data of 2-[(1',5'-Dimethyl-3'-oxo-2'-phenyl-pyrazol-4'-yl)amino]-N-arylethanamides (9a-9j)

Code	**Ar**	**M.F.**	**M.W.**	**M.P**	**% Yield**
9a	C_6H_5-	$C_{18}H_{18}N_4O_2$	337.10	190-192	61
9b	2-CH_3-C_6H_4-	$C_{20}H_{20}N_4O_2$	350.17	200-202	56
9c	4-CH_3-C_6H_4-	$C_{20}H_{22}N_4O_2$	350.42	198-200	58
9d	4-OCH_3-C_6H_4-	$C_{19}H_{20}N_4O_3$	366.1	210-212	59
9e	2-Cl-C_6H_4-	$C_{19}H_{19}ClN_4O_2$	370.2	224-226	70
9f	3-Cl-C_6H_4-	$C_{19}H_{19}ClN_4O_2$	370.0	252-254	65
9g	4-Cl-C_6H_4-	$C_{19}H_{19}ClN_4O_2$	370.4	278-280	56
9h	3-Br-C_6H_4-	$C_{19}H_{19}BrN_4O_2$	414.0	250-252	55
9i	4-F-C_6H_4-	$C_{19}H_{19}FN_4O_2$	354.1	200-202	60
9j	2-NO_2-C_6H_4-	$C_{19}H_{19}N_5O_4$	381.14	214-216	62

2. 2. Reaction Scheme

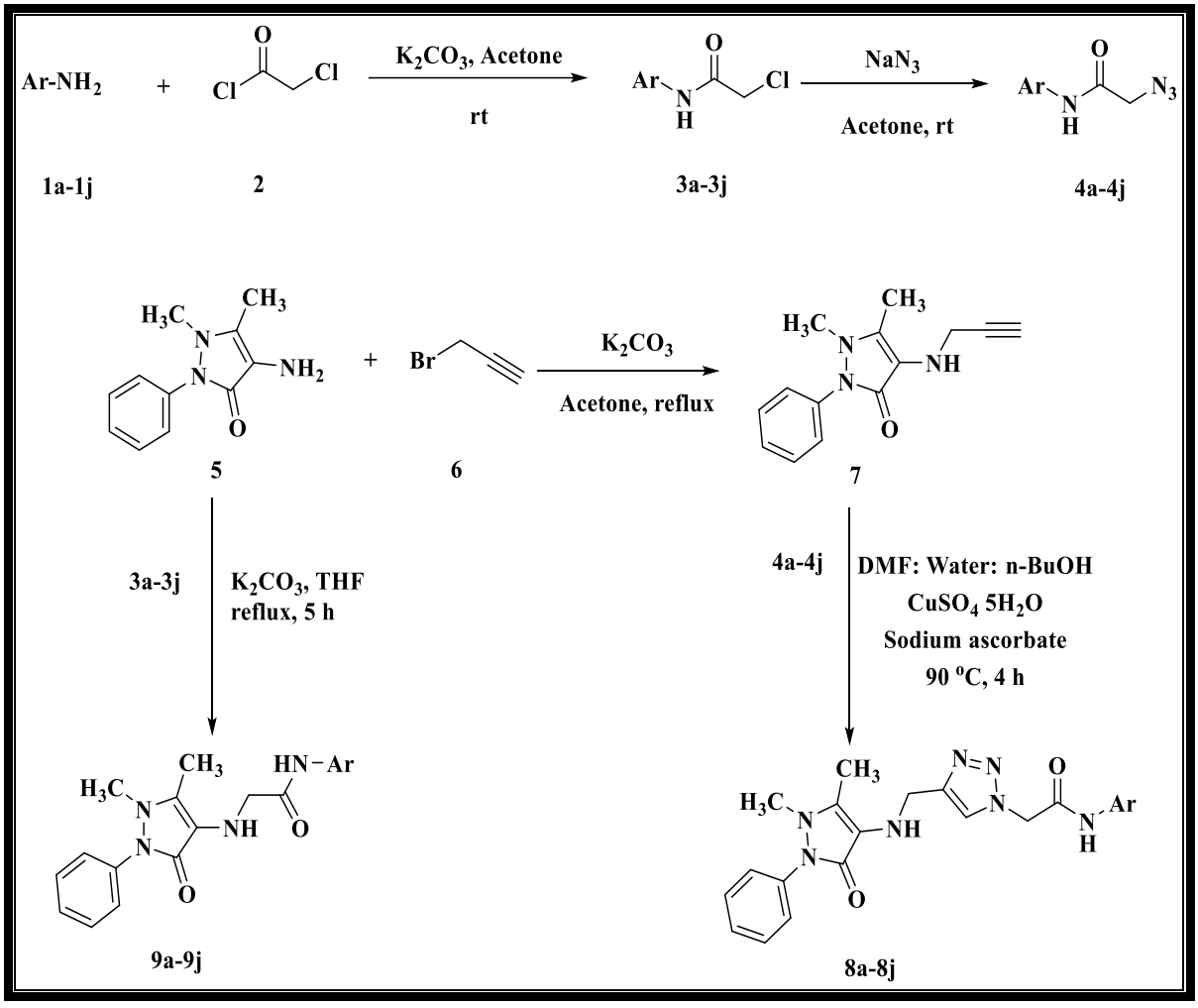

Figure 2. Reaction scheme for the synthesis of targeted compounds (8a-8j) and (9a-9j)

3. RESULTS AND DISCUSSION

3. 1. Antimicrobial Activity

All the synthesized compounds were employed for antimicrobial activity study using cup plate [28] method to assess the zone of inhibition. The concentration of the sample was kept at 100 µg/ml and standard drug concentration was kept as 50 µg/ml, in DMSO serving as the solvent. The anti-bacterial activity study was tested using G ram-positive bacteria such as *Bacillus subtilis* & *Staphylococcus epidermidis*, while Gram-negative bacteria such as *Proteus vulgaris* &, *Pseudomonas aeruginosa*. The antifungal activity was carried out using fungi *Aspergillus niger*. Here the standard drugs were used for antimicrobial activity comparison are streptomycin as broad spectrum and nystatin as an anti-fungal. The findings of antimicrobial activity study in terms of clearance of bacterial and fungi colony (Zone of inhibition) is displayed in Table no. 3 and 4.

Table 3. Antimicrobial activity data of 2-{4'-[1',5'-dimethyl-3'-oxo-2'-phenyl-pyrazol-4'-yl]aminomethyl-1H-1,2,3-triazol-1-yl}-N-arylethanamides (8a-8j)

Compound ID	Antibacterial activity				Antifungal Activity
	Gram positive bacteria		Gram negative bacteria		Fungus
	Bacillus subtilis	*Staphylococcus epidermidis*	*Proteus vulgaris*	*Pseudomonas aeruginosa*	*Aspergillus niger*
8a	18	13	13	8	9
8b	16	17	12	7	10
8c	17	17	14	6	8
8d	16	16	15	7	8
8e	17	17	16	5	9
8f	17	09	16	11	10
8g	13	14	12	4	3
8h	22	15	12	6	5
8i	19	08	17	6	11
8j	15	10	11	16	12
Zone of inhibition in mm					

Table 4. Antimicrobial activity data of 2-[(1',5'-dimethyl-3'-oxo-2'-phenyl-pyrazol-4'-yl)amino]-N-arylethanamides (9a-9j)

Compound ID	Antibacterial activity				Antifungal Activity
	Gram positive bacteria		Gram negative bacteria		Fungus
	Bacillus subtilis	*Staphylococcus epidermidis*	*Proteus vulgaris*	*Pseudomonas aeruginosa*	*Aspergillus niger*
9a	15	10	16	11	8
9b	14	15	11	10	7
9c	12	16	10	10	8

9d	12	12	13	10	7
9e	11	15	18	8	6
9f	9	11	12	7	5
9g	5	14	10	5	7
9h	13	15	12	5	4
9i	14	8	9	8	15
9j	20	12	16	11	10
Zone of inhibition in mm					

Table 5. Compounds (8a-8j) & (9a-9j) showing antibacterial & antifungal activity compared with known standard drugs

Compound	**Antibacterial activity**				**Antifungal Activity**
	Gram positive bacteria		Gram negative bacteria		Fungus
	B. subtilis	*S. epidermidis*	*P. vulgaris*	*P. aeruginosa*	*A. niger*
8a-8j	8h, 8i	8e	-	8j	-
9a-9j	9j	-	9e	-	9i
Activity of Known Standard Drugs:					
Streptomycin	25	25	26	19	-
Nystatin	-	-	-	-	22
Zone of inhibition in mm					

4. CONCLUSIONS

In the present study, we have successfully synthesized and characterized two different series of heterocycles from an active pharmacological scaffold 4-aminoantipyrine. One of the series contains 1,2,3-triazole derivatives **(8a-8j)** synthesized using click chemistry (CuACC) approach from 4-aminoantipyrine nucleus and various substituted 2-azido-N-phenylethanamide derivatives. Another approach was the synthesis of arylamide derivatives **(9a-9j)** via reaction of 4-aminoantipyrine and 2-chloro-N-phenylethanamide derivatives. All the synthesized compounds were employed for antimicrobial activity study using various bacterial and fungal

strains against the standard drug streptomycin as an anti-bacterial agent, while nystatin as an anti-fungal agent respectively. The findings of antimicrobial activity of 1,2,3-triazole derivatives reveals that, compounds **8e, 8h, 8i** and **8j** are moderately active against bacterial strains, while none of the synthesized compound possessing 1,2,3-triazole derivative were active against fungus. Further, antimicrobial screening of arylamide derivatives shows that derivatives **9e** and **9j** are active against bacteria, while compound **9i** is moderately active against fungi.

Acknowledgement

The authors would like to thank Management and Principal of Shri M. & N. Virani Science College, Rajkot and Department of Chemistry, Saurashtra University, Rajkot for providing spectral data facilities.

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