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6-Bromo-1H-Indazole Bearing 1,2,3-Triazole Analogues: Synthesis, Characterization and Antimicrobial Evaluation

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Abstract

This research paper covers the synthesis of novel pharmaceutically active and high yield scaffolds with easier pathway. A series of novel 1,2,3-traizole derivatives tethered with 6-bromo-1H-indazole were synthesized using various 2-azido-N-arylacetamide derivatives via 1,3-dipolar cycloaddition reaction. Structural evaluation was carried out using different analytical techniques such as IR, Mass and ^{1}H-NMR spectroscopy. Further, newly synthesized molecules were evaluated for their antimicrobial efficacy using different bacterial and fungal strains. Several of these synthesized derivatives expressed moderate to good inhibition in comparison with standard drugs.

Keywords: 6-Bromo-1H-indazole; 1,2,3-traizole; Click chemistry; CuAAC; Antimicrobial evaluation.

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1. Introduction

In the domain of organic chemistry, heterocyclic compounds [1,2] exhibit an indispensable role, showcasing vast implications in the field of medicinal chemistry and pharmaceuticals. Among various nitrogen [3,4] containing compounds, indazoles [5] have emerged as versatile scaffolds, demonstrating remarkable therapeutic potential and biological activities. Within family of benzo fused [6] nitrogen containing compounds, 6-bromo-1H-indazole [7] has recently garnered significant attention for its promising biological properties and synthetic accessibility. This paper endeavors to provide a comprehensive overview of the attributes of new 6-bromo 1H-indazole containing triazoles, encompassing their synthetic aspects, structural characteristics, therapeutic potential, and pharmacological applications [8].

6-bromo-1H-indazole is chemically represented as $C_7H_5BrN_2$, is a heterocyclic compound comprises of a bicyclic ring system composed of a five-membered pyrazole ring fused with benzene ring. The strategic presence of a bromine atom at the sixth position enhances its unique reactivity and amplifies the compound's chemical properties. Indazole

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exhibits distinctive structural properties, giving it docile to diverse synthesis strategies, thereby enhancing its synthetic utility and enabling the study of structure-activity relationships [9].

The pharmacological data of 6-bromo-1H-indazole is described by plethora of bioactivities with various therapeutic properties [10]. Notably, research attempts have characterized its potent anticancer activity [11,12] with compelling evidence of inhibition across a spectrum of cancer cell lines. Its anti-proliferative [13] effects have contributed to the inhibition of key cellular pathways responsible for cell cycle progression and apoptosis. Furthermore, 6-bromo-1H-indazole has demonstrated notable antimicrobial [14,15] efficacy against both gram-positive and gram-negative bacteria as well as fungi. This antimicrobial potential underscores its relevance in combating infectious diseases. Beyond its anticancer and antimicrobial activities, 6-bromo-1H-indazole has exhibited interesting pharmacological activities across various therapeutic aspects. It's a potent neuroprotective [16] agent, significant cardiovascular [17,18] agent and also possesses good anti-inflammatory[19,20] properties. Triazoles [21,22] are identified by a five-membered heterocyclic ring containing three nitrogen atoms synthesized via click chemistry [23,24] approach. In the pursuit of molecular synthesis, the triazoles have emerged as a classic antibacterial [25], antifungal [26], anticancer [27], antioxidant [28] and anti-inflammatory [29,30] agent.

This paper aims to explore the symbiotic relationship between 6-bromo-1H-indazole and 1,2,3-triazole via click chemistry, highlighting their synergistic roles in the synthesis of various biologically active molecules and their extensive applications across various pharmaceutical domains. In this study, we report the synthesis of ten novel indazole-triazoles containing compounds synthesized using copper(I) catalyzed azide-alkyne cycloaddition (CuAAC) reaction, involving a terminal alkyne attached to nitrogen at the 1st position of 6-bromo-1H-indazole with various 2-azido-N arylacetamide derivatives. All these compounds were analyzed and confirmed using various analytical techniques including mass, ^{1}H NMR and IR spectroscopy. Our findings add to the growing collection of heterocyclic compounds, opening up new opportunities for research and development.

2. Materials and Methods

The chemicals utilized in the experiments such as 6-bromo-1H-indazole, propargyl bromide, sodium ascorbate and copper sulphate were procured from supplier, namely Actylis Chemicals Pvt. Ltd., India (Formerly known as Finar Ltd.) and solvents like acetone, n-Butanol and DMF were purchased from SRL chemicals Pvt. Ltd., India, with purity of analytical reagent (AR) grade. They were utilized directly without undergoing additional purification steps. The melting points was measured using open glass capillaries, and were used uncorrected. To monitor the advancement of reactions, thin-layer chromatography (TLC) was used, utilizing Silica Gel 60 F254 from Sigma-Aldrich, India with 0.2 mm thickness. Visualization under UV light was facilitated by a JSI UV Inspection Cabinet Single Tubes. Nuclear Magnetic Resonance (NMR) spectra were recorded using Bruker Advance II NMR spectrometer, USA operated at 400 MHz using deuterated dimethyl sulfoxide (DMSO-d^{6}). Chemical shifts were documented using tetramethylsilane (TMS) as an internal standard in δ

ppm. IR was recorded using Bruker Alpha II IR spectrometer, USA. Mass spectrometry data and fragmentation patterns were recorded using Shimadzu GC-MS QP-2010, Japan mass spectrometer.

2.1. *Experimental section*

2.1.1. *General synthesis of 2-chloro-N-arylacetamide derivatives (3a-3j)*

Solution of various substituted aniline derivatives (1a-1j) (1 equiv.) were prepared in acetone and were allowed to react with potassium carbonate for 30 min. To the following solution 2-chloroacetyl chloride (2) (1.5 equiv.) was added at room temperature and stirred for 3-4 h. Reaction progress was tracked using TLC, upon completion the product was gushed into ice water, filtered, dried and purified using methanol.

2.1.2. *General synthesis of 2-azido-N-arylacetamide derivatives (4a-4j)*

To the solution of 2-chloro-N-Arylacetamide derivatives (3a-3j) (1 equiv.) in DMF, excess amount of sodium azide (NaN_3) (3 equiv.) was added, reaction was stirred at room temperature for 20 h. Progress of the reaction was traced using TLC. At the end it was poured in to chilled water to get crystalline product, filtered, dried and directly used without purification for further step.

2.1.3. *Synthesis of 6-bromo-1-(prop-2-yn-1-yl)-1H-indazole (7)*

Two necked round bottom flask containing, solution of 6-bromo-1H-indazole (5) (1 mmol) in acetone at room temperature was allowed to react with excess amount of potassium carbonate (K_2CO_3) and was stirred for 2 h. Propargyl bromide (6) (1.5 mmol) was added into above mentioned reaction mixture gradually and refluxed for 15-16 h. The course of the reaction was monitored using TLC, cooled to ambient temperature and dumped in to ice cold water, filtered, dried and recrystallized using methanol. M.P.: 180-182 °C, Yield: 64 %.

2.1.4. *General synthesis of substituted 2-(4-((6-bromo-1H-indazol-1-yl)methyl)-1H-1,2,3-triazol-1-yl)-N-arylacetamide derivatives (8a-8j)*

Three necked round bottom flask equipped with reflux assembly containing solution of 6-bromo-1-(prop-2-yn-1-yl)-1H-indazole (7) (1 equiv.) in mixture of solvents DMF: water: n-BuOH (1:1:1), was allowed to react with different substituted 2-azido-N-Arylacetamide derivatives (4a-4j) (1 equiv.). The reaction mass was refluxed at 80 °C, for 10 h. Progression of reaction was investigated using TLC, reaction mass was cooled to room temperature and poured in to crushed ice to yield crude product, washed with ammonia and further with hot water, filtered, dried and recrystallized using methanol.

2.2. *Spectral data analysis*

6-bromo-1-(prop-2-yn-1-yl)-1H-indazole (7)
Yellow solid, IR (KBr) cm^{-1}: 3310 (C-H str. Terminal alkyne), 3110 (C-H str. Ar-H), 3003 (C-H str.), 1610, 1498, 1480 (Ar, C=C bend.), 1250 (Ali. C-H bend.), 1048(C=N, indazole), 675 (C-Br str.); ^{1}H NMR (DMSO-d^6) δ ppm: 3.403-3.416 (t, 1H), 5.347-5.353 (s, 2H), 7.304-7.308 (d, 1H), 7.325-7.329 (d, 1H), 7.747- 7.768 (d, 1H), 8.066-8.145 (d, 1H); MS: m/z 233.90 $(M-H)^+$

2-(4-((6-bromo-1H-indazol-1-yl)methyl)-1H-1,2,3-triazol-1-yl)-N-phenylacetamide (8a): Off white solid, IR (KBr) cm^{-1}: 3037 (triazole str.), 1672 (C=O str. -$CONH_2$), 1612, 1535, 1510 (Ar C=C bend.), 1203 (Ali. C-H bend.), 1043 (C=N, indazole), 680 (C-Br str.); ^{1}H NMR (DMSO-d^6) δ ppm: 5.282 (s, 2H), 5.755 (s, 2H), 7.054-7.091 (t, 1H), 7.277-7.336 (m, 3H), 7.539-8.175 (m, 6H), 10.438 (s, 1H); MS: m/z 412.10 $(M+H)^+$

2-(4-((6-bromo-1H-indazol-1-yl)methyl)-1H-1,2,3-triazol-1-yl)-N-(4-methoxyphenyl) acetamide (8b): Off white solid, IR (KBr) cm^{-1}: 3435 (C-O str., -Ome group) 3137 (C-H str. Ar-H), 3078 (triazole str.), 1675 (C=O str. -$CONH_2$), 1610, 1555, 1512, 1462 (Ar C=C bend.), 1248 (Ali. C-H bend.), 1052 (C=N, indazole), 654 (C-Br str.); ^{1}H NMR (DMSO-d^6) δ ppm: 3.710 (s, 3H), 5.242 (s, 2H), 5.749 (s, 2H), 6.875-6.903 (d, 3H), 7.130-7.298 (m, 1H), 7.434-7.743 (m, 3H), 8.083-8.197 (m, 2H), 10.302 (s, 1H); MS: m/z 440.50 $(M)^+$

2-(4-((6-bromo-1H-indazol-1-yl)methyl)-1H-1,2,3-triazol-1-yl)-N-(3-bromophenyl) acetamide (8c): Brown solid, IR (KBr) cm^{-1}: 3250 (C-H str. Ar-H), 3073 (triazole str.), 2943 (C-H str.), 1685 (C=O str. -$CONH_2$), 1657, 1612, 1595, 1551 (Ar C=C bend.), 1271 (Ali. C-H bend.), 1076 (C=N, indazole), 810, 679 (C-Br str.); ^{1}H NMR (DMSO-d^6) δ ppm: 5.301 (s, 2H), 5.757 (s, 2H), 7.134-7.154 (d, 1H), 7.277-7.419 (m, 3H), 7.724-7.745 (m, 2H), 8.087-8.190 (m, 3H), 10.641 (s, 1H); MS: m/z 489.10 $(M-H)^+$

2-(4-((6-bromo-1H-indazol-1-yl)methyl)-1H-1,2,3-triazol-1-yl)-N-(4-fluorophenyl) acetamide (8d): Brown solid, IR (KBr) cm^{-1}: 3254 (C-H str. Ar-H), 3068 (triazole str.), 1685 (C=O str. -$CONH_2$), 1657, 1612, 1595, 1551, 1480 (Ar C=C bend.), 1357 (Ali. C-H bend.), 1051 (C=N, indazole), 1037 (C-F str.), 625, 515 (C-Br str.); ^{1}H NMR (DMSO-d^6) δ ppm: 5.274 (s, 2H), 5.752 (s, 2H), 7.140-7.184 (d, 2H), 7.296 (s, 1H), 7.550-7.743 (m, 3H), 8.112-8.193 (m, 3H), 10.501 (s, 1H); MS: m/z 430.20 $(M+H)^+$

2.3. *Antimicrobial activity*

All the synthesized compounds were assessed for *in vitro* antimicrobial activity. The anti-bacterial assessment was carried out using gram-positive bacteria such as *Bacillus subtilis & Staphylococcus aureus,* while gram-negative bacteria such as *Escherichia coli & Pseudomonas aeruginosa*. For antifungal activity *Aspergillus niger* and *Candida albicans* were chosen. The broth used for characterizing antibacterial activity was Muller-

Table 1. Characteristic physical data of 2-(4-((6-bromo-1H-indazol-1-yl)methyl)-1H-1,2,3-triazol-1-yl)-N-Arylacetamide derivatives (8a-8j).

Code	-R	Molecular formula	Molecular weight (m/z)	M.P. (°C)	Yield (%)
8a	4-H	$C_{18}H_{15}BrN_6O$	410.05	310-312	76
8b	4-Ome	$C_{19}H_{17}BrN_6O_2$	440.06	290-292	62
8c	3-Br	$C_{18}H_{14}Br_2N_6O$	489.96	280-282	58
8d	4-F	$C_{18}H_{14}FBrN_6O$	428.04	296-298	65
8e	4-Me	$C_{19}H_{17}BrN_6O$	424.06	290-292	75
8f	3-Cl	$C_{18}H_{14}BrClN_6O$	444.01	286-288	66
8g	4-Cl	$C_{18}H_{14}BrClN_6O$	444.01	294-296	67
8h	3-NO_2	$C_{18}H_{14}BrN_7O_3$	455.03	316-318	53
8i	4-NO_2	$C_{18}H_{14}BrN_7O_3$	455.03	314-316	75
8j	2-Me-5-NO_2	$C_{19}H_{16}BrN_7O_3$	469.05	294-296	65

Hinton broth and potato dextrose broth was used as media for fungi. The turbidity of the microbial suspension was adjusted to 10^8 CFU/mL and for fungi it was adjusted as 10^6 CFU/mL. Various concentration of the compounds was made for primary and secondary screening of compounds for their antifungal and antibacterial activity. The stock solutions (2000 µg/mL) were prepared for compounds and standard drugs. The turbidity was examined by setting up first 1000, 500, 250, and 125 µg/mL concentrations for primary screening. To observe antimicrobial study on the samples which remained ineffective in first analysis, various other dilutions were used for secondary analysis using six different concentrations ranging from 6.5 to 200 µg/mL.

2.4. *Reaction scheme*

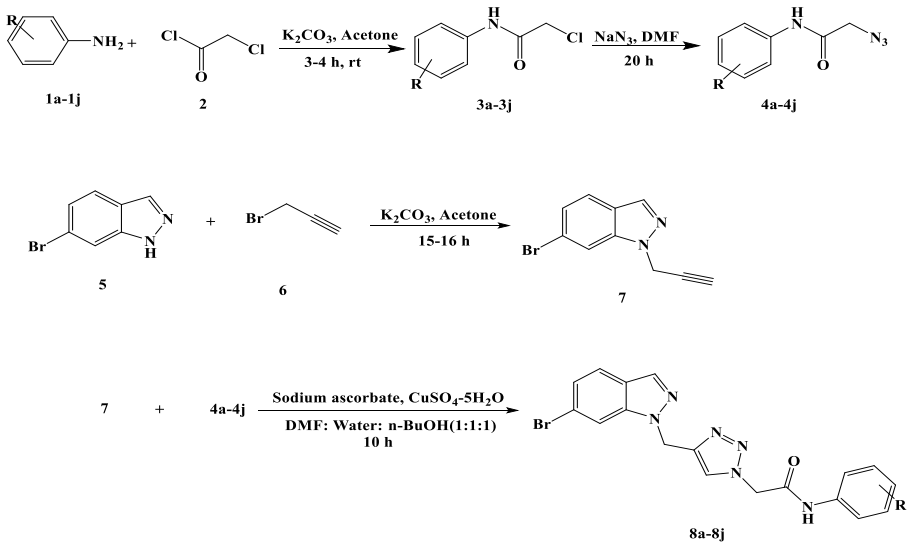

Fig. 1. Reaction scheme for the synthesis of targeted molecules 8a-8j.

3. Results and Discussion

3.1. *Chemistry*

The reaction was carried out in multiple steps. Initially, 2-chloro-N-arylacetamide derivatives (3a-3j) were prepared from various substituted aniline derivatives (1a-1j) and 2-chloroacetyl chloride (2) in the presence of potassium carbonate using acetone as a solvent at room temperature. Further, these 2-chloro-N-arylacetamide (3a-3j) derivatives were reacted with excess amount of sodium azide to yield 2-azido-N-arylacetamides (4a-4j) in DMF at room temperature. Simultaneously, propargylation reaction of 6-Bromo-1H-indazole (5) was carried out by dissolving in acetone containing and drop wise addition of propargyl bromide (6) to afford 6-bromo-1-(prop-2-yn-1-yl)-1H-indazole (7) at refluxed temperature. In order to synthesize final targeted molecules 2-(4-((6-bromo-1H-indazol-1-yl)methyl)-1H-1,2,3-triazol-1-yl)-N-Arylacetamide derivatives (8a-8j), solution of 6-bromo-1-(prop-2-yn-1-yl)-1H-indazole (7) was prepared in mixture of solvents namely DMF: Water: n-BuOH and subsequent addition of differently substituted 2-azido-N-arylacetamide derivatives (3a-3j) were carried out at 80 °C. Hence final step for the synthesis of targeted molecules involves Cu (I) and ascorbate salt catalyzed click chemistry (CuAAC) approach, which provide high yield, efficient pathway and affordable pure synthetic route for the synthesis. This reaction is also an example of 1, 3-dipolar cyclo addition reaction which is recognized as a most powerful synthesis tool for so many different scaffolds.

The spectral data study of the designed compounds was carried out by performing IR, ^{1}H-NMR and mass spectrometry. As per IR, 3310 cm^{-1} (terminal alkyne) was observed for intermediate 6-bromo-1-(prop-2-yn-1-yl)-1H-indazole **(7)**. The IR spectra study of all the designed compounds does not show frequency near 3300 cm^{-1}, which shows formation of product. Further, 2098 cm^{-1} (azide) frequency is also not observed in IR spectra of products. Notably, a strong absorption peak near 3075 cm^{-1} shows the presence of 1,2,3-triazole ring in the product. Additionally, absorption peak near to 1675 cm^{-1} confirmed the presence of $–CONH_2$ (Amide) group in the product. Here presence of bromine present at 6th position in both intermediate and product was characterized by absorption frequency near 680 cm^{-1} (C-Br). Different substitutions present in the product were evaluated based on IR frequency. In the compound 8b, the presence of methoxy ($O-CH_3$) group was assessed by appearance of 3435 cm^{-1} absorption peak in IR. In compounds 8c and 8d characteristic frequency of absorption for C-Br and C-F is observed at 810 – 679 cm^{-1} and 1037 cm^{-1} respectively. Here absorption near 1050 cm^{-1} shows the presence of C=N stretching frequency for 6-bromo-1H-indazole (5). 6-bromo-1H-indaozle and N-substituted phenylacetamide derivatives are key component of the product molecules. Subsequently to confirm the structure ^{1}H-NMR spectral study was performed. We find singlet peak above 10 ppm (-N-H), which confirmed the presence of -N-H. From NMR we didn't find triplet at 3.403-3.416 ppm, which proves the absence of terminal alkyne in the product molecules. Singlet peak near 5.2 ppm shows the presence of $–CH_2$- group linking indazole and triazole scaffolds. Additionally, one more singlet peak at 5.7 ppm shows the existence of $–CH_2$- comes from 2-azido-arylacetamide

derivatives. Normally, aromatic protons are observed at 7.1-7.7 ppm as multiplet. Mass spectrometry was also employed to confirm the m/z values of synthesized intermediate and final products. Intermediate was confirmed by m/z 233.90 $(M-H)^+$ as molecular ion peak in mass spectra. Various substituted final molecules were further confirmed with their m/z values as $(M+H)^+$ and $(M-H)^+$. Overall, advanced spectral analysis techniques provide wide evidence for elucidation of correct structures with high accuracy. The molecular structure and interactions of precursors to yield target compounds were characterized through advanced spectral techniques. These techniques helped to elucidate the compounds and paved the way for further research in pharmaceutical chemistry and related disciplines. These experiments show strong agreement with the proposed structure of the compounds.

3.2. *Biological evaluation*

Like other indazole derivatives, 6-bromo-1H-indazole may inhibit key bacterial enzymes involved in cell wall synthesis or DNA replication. The compound might disrupt bacterial cell membranes, leading to increased permeability and ultimately cell death. The incorporation of bromine could enhance the compound's ability to penetrate bacterial cells due to changes in hydrophobicity. The presence of the bromine atom at the 6-position can affect the compound's lipophilicity and electronic properties, potentially enhancing its interaction with bacterial membranes and targets. The indazole moiety may contribute to the overall stability and reactivity of the compound, providing sites for further modifications.

Modifying other positions on the 6-bromo-1H-indazole ring or the addition of functional groups could lead to different activity profiles, emphasizing the importance of structure-activity relationships. The antibacterial activity of 6-bromo-1H-indazole is promising, and its structure provides a foundation for further exploration of its potential as an antibacterial agent. Continued research could yield new derivatives with enhanced activity and specificity.

The synthesized entitled compounds were subjected to *in vitro* anti-microbial analysis. The findings of the biological activity suggested that compound 8f and 8g are potentially active, while compound 8a and 8b are moderately active against gram positive bacteria *Bacillus subtilis*. Compound 8e is only active derivative against fungi *Candida albicans*. Remaining gram-positive bacteria *Staphylococcus aureus*, gram negative bacteria *Escherichia coli* & *Pseudomonas aeruginosa*, fungi *Aspergillus niger* remained unaffected from the inhibition effect of synthesized molecules.

Table 2. Antimicrobial Evaluation of 2-(4-((6-bromo-1H-indazol-1-yl) methyl)-1H-1,2,3-triazol-1-yl)-N-Arylacetamide derivatives (8a-8j).

Compound	Minimum Inhibition Concentration (µg/mL)					
	Antibacterial activity				Antifungal Activity	
	Gram positive bacteria		Gram negative bacteria		Fungus	
	B. subtilis	*S. aureus*	*E. Coli*	*P. aeruginosa*	*C. albicans*	*A. niger*
Streptomycin			50	50		
Ampicillin	100	100				
Nystatin					100	100
8a	500	1000	1000	1000	1000	1000
8b	500	1000	1000	1000	1000	1000
8c	1000	1000	1000	1000	1000	1000
8d	1000	1000	1000	1000	1000	1000
8e	500	1000	1000	1000	500	1000
8f	250	1000	1000	1000	1000	1000
8g	250	1000	1000	1000	1000	1000
8h	1000	1000	1000	1000	1000	1000
8i	1000	1000	1000	1000	1000	1000
8j	1000	1000	1000	1000	1000	1000

Table 3. Compounds (8a-8j) showing antibacterial and antifungal activity.

Compounds	Minimum Inhibition Concentration (µg/mL)					
	Antibacterial activity				Antifungal Activity	
	Gram positive bacteria		Gram negative bacteria		Fungus	
	B. subtilis	*S. aureus*	*E. Coli*	*P. aeruginosa*	*C. albicans*	*A. niger*
(8a-8j)	8a, 8b, 8e, 8f, 8g	-	-	-	8e	-

4. Conclusion

In summary, we aimed to design and synthesize novel series of 6-bromo-1H-indazole possessing 1,2,3-triazole using click chemistry. The reaction was executed via Cu(I) catalyzed aryl-alkyne 1,3-dipolar cycloaddition reaction. The aspect of the synthesis was to develop efficient anti-microbial agents using reaction which provides product with high purity and lesser by-product formation. Among these derivatives few molecules exhibited moderate to good anti-microbial activity.

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