Received: 13 October 2019 | Revised: 6 December 2019 | Accepted: 7 December 2019

DOI: 10.1002/jhet.3866

WILEY

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The efficient synthesis of 3-[6-(substituted)-[1,2,4]triazolo [3,4-*b*][1,3,4]thiadiazol-3-yl]-1H-indazole

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Abstract

This study presents an efficient synthesis of 3-[6-(substituted-phenyl)-[1,2,4]triazolo [3,4-*b*][1,3,4] thiadiazol-3-yl]-1*H*-indazole via dehydrative condensation with cyclization of 4-amino-5-(1*H*-indazol-3-yl)-4*H*-[1,2,4]triazole-3-thiol and fluorinated or nonfluorinated carboxylic acids in presence of phosphorous oxychloride. The multistep reaction pathway proceeds through different compounds. Present synthesis has the advantages of easily accessible starting materials, convenient synthesis, simple reaction condition, wider substrate scope, and higher yield (75% to 90% isolated).

1 | INTRODUCTION

A large number of fluorinated and nonfluorinated heterocyclic compounds show various pharmacological activities. Because of this, organic chemists work day and night to synthesize more active pharmacophores. A literature survey revealed that indazole derivatives are the least studied among all the heterocycles studied for their medicinal activities, although natural products containing indazole moieties are rare.[1]

The literature survey shows that synthetic indazole derivatives give biological activities like anti-inflammatory,[2] antimicrobial,[3] anti-HIV,[4] antitumor,[5] and contraceptive properties,[6] high binding affinity for estrogen receptor, inhibition of protein kinase,[7] and 5-HT-2 and HT-3 receptor antagonism[8]; selective compound 3-aminoindazole is a nonsteroidal anti-inflammatory candidate with analgesic properties.[9] It is also reported as a dopamine receptor antagonist used for antipsychotic treatment.[10] Fluorinated 3-aminoindazoles have been used in psychiatric disorders such attention deficit disorder.[11] Not only indazole derivatives are biologically active; a combination of triazolo with thiadiazoles is also a potent active antimicrobial agent.[12,13]

The compounds having 1,2,4-triazolo[3,4-*b*]-1,3,4-thiadiazole nucleus also exhibit various biological activities like analgesic, anti-inflammatory, ulcerogenic,[14,15] and antibacterial.[16]

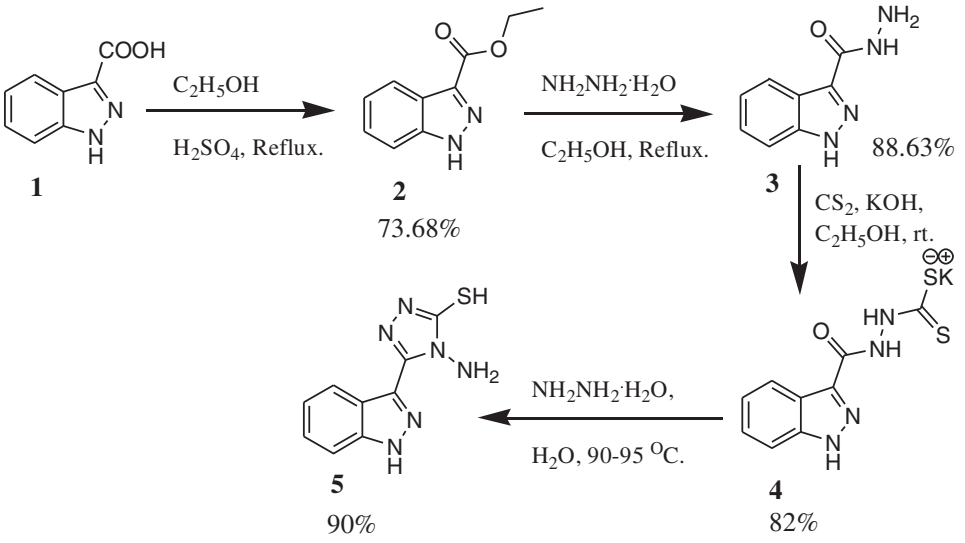
The precedent literature shows that various catalyses and methods have been reported by different researchers for the synthesis of indazoles and its derivatives. The frequently used procedures involve chromium tricarbonyl complex,[17] 3-carboxyindazole,[18] trimethylsilylindazole/CSF,[19] polyphosphoric acid–catalyzed cyclization of 2,6-dihydroxyacetophenone hydrazones,[20] using $NaHSO_3$/DMF,[21] palladium-catalyzed intramolecular amination reaction of *N*-tosyl hydrazones trimethylsilylindazole[22] as well as aryl halides,[23] and copper metal complex–catalyzed synthesis of indazole.[24] Condensation of *o*-fluorobenzaldehydes and their oximes with hydrazine yield indazoles,[25] while 3-substituted indazole and benzoisoxazoles synthesis via palladium catalyzed cyclization reactions[26] indazole *N*-oxide through 1,7-electrocyclization of azomethine ylides[27] cyclization of *o*-substituted aryl hydrazones with halogens, nitro and methoxy[28] group as substituent are already reported in the literature. A similar type of simple derivatives is also synthesized by various researchers[29–31] using $POCl_3$.

Keeping the importance of indazole and combination of triazolo with thiadiazoles derivatives, the research group decided to synthesize 3-[6-(substituted-phenyl)-[1,2,4]triazo-lo[3,4-*b*][1,3,4]thiadiazol-3-yl]-1*H*-indazole using simple, efficient, and convenient method.

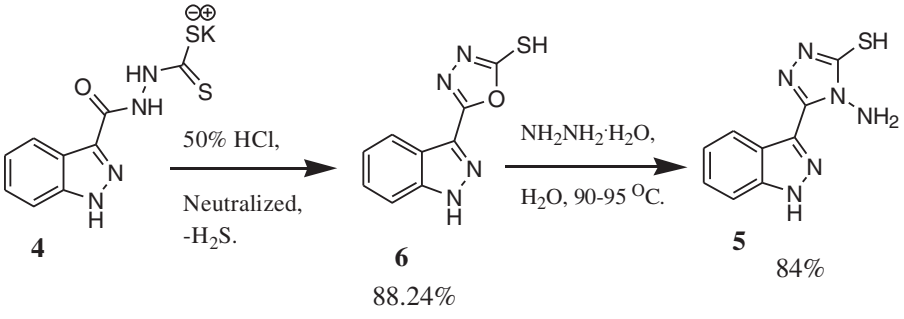
2 | RESULTS AND DISCUSSION

The method used for the multistep synthesis of fluorinated and nonfluorinated 3-[6-(substituted-phenyl)-[1,2,4]triazolo[3,4-*b*][1, 3, 4] thiadiazol-3-yl]-1*H*-indazole **8**(**a**-**v**) was based on the commercial availability of raw material, conventionality, and handling simplicity, thus for the synthesis of the aimed products, condensation and cyclization reaction appeared to be the best and most precise in presence of phosphorous oxychloride. The well-known and simple esterification reaction was performed for the synthesis of 1*H*-indazole-3-carboxylic acid ethyl ester **2**. 1*H*-indazole-3-carboxylic acid ethyl ester then reacted with excess amount of hydrazine hydrate under reflux in ethanol solvent to selectively afford 1*H*-indazole-3-carboxylic acid hydrazide **3** (Scheme 1). The 1*H*-indazole-3-carboxylic acid hydrazide obtained in the second step were reacted with carbon disulfide and potassium hydroxide in presence of absolute alcohol, and the reaction mass was stirred for 12 hours to obtain potassium salt of 1*H*-indazole-3-carboxylic acid hydrazide dithiocarbamate **4**. If the potassium salt of 1*H*-indazole-3-carboxylic acid hydrazide dithiocarbamate is neutralized with 50% hydrochloric acid, it gives 5-(1*H*-indazol-3-yl)-[1,3,4]oxadiazole-2-thiol **6**[32,33] with strong smell of H_2S gas; then, the obtained product was refluxed in excess of hydrazine hydrate to form 4-amino-5-(1*H*-indazol-3-yl)-4*H*-[1,2,4]triazole-3-thiol **5** (Scheme 3). But in the present work, 1 Eq potassium salt of 1*H*-indazole-3-carboxylic acid hydrazide dithiocarbamate **4** is directly reacted with 2 Eq of hydrazine hydrate in water as solvent at 90°C to 95°C to form **5** with 92% of isolated yield (Scheme 2).

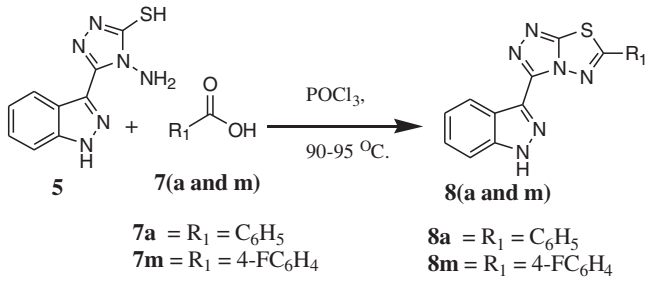
Spectroscopic methods like infrared (IR) spectroscopy, mass spectroscopy, and ^{1}H NMR confirmed the formation of intermediate **6** from neutralization of **4** with 50% hydrochloric acid. IR spectroscopic values were at 660 to 782 cm^{-1} for aromatic protons ArH, 1248 cm^{-1} for cyclic C—N bond vibrations, 1615 cm^{-1} for the C═N vibrations, 1360 cm^{-1} for cyclic ether (C—O), and 3066 cm^{-1} for cyclic amines (N—H). Mass spectra at 218.81 also support the intermediate **6** formation. For the ^{1}H NMR study, δ 7.25-8.53 multiplates for aromatic protons were present on indazole-fused benzene ring, singlet



SCHEME 1 Synthesis of 4-Amino-5-(1H-indazol-3-yl)-4H-[1,2,4] triazole-3-thiol 5 from 4



SCHEME 2 Synthesis of 4-Amino-5-(1H-indazol-3-yl)-4H-[1,2,4]triazole-3-thiol 5 from 5-(1H-Indazol-3-yl)-[1,3,4] oxadiazole-2-thiol 6



SCHEME 3 Cyclization of 5 and 7(a-v) to form 8(a-v)

was at δ 3.36 for S—H proton, and highly deshielded proton from indazole N—H gives singlet chemical shift at δ 13.48.

Finally, the intermolecular condensation or cyclization of 4-amino-5-(1*H*-indazol-3-yl)-4*H*-[1,2,4]triazole-3-thiol **5** with substituted-carboxylic acid **7**(**a**-**v**) gives desired products 3-[6-(substituted-phenyl)-[1,2,4]triazolo [3,4-b][1,3,4]thiadiazol-3-yl]-1*H*-indazole **8**(**a**-**v**) in 75% to 90% yield shown in Table 1 (Scheme 4). In the present synthesis, we used 0.01 mol of **5** and 0.02 mol of **7**(**a**-**v**) to shift the equilibrium fast towards product formation; excess amounts of substituted-carboxylic acid **7**(**a**-**v**) were easily separated from the reaction mass by simple neutralization using saturated solution of sodium bicarbonate.

We optimize the standard reaction condition for the synthesis of the final product, ie, substituted-carboxylic acid 7(**a**-**v**) (0.02 mol) and 4-amino-5-(1*H*-indazol-3-yl)-4*H*-[1,2,4]triazole-3-thiol **5** (0.01 mol) in $POCl_3$ (15 mL) was heated at 90°C to 95°C for a time as mentioned in Table 1. The excess of carboxylic acid shift equilibrium fast towards the product formation, and after completion of the reaction, the excess amount of carboxylic acid is neutralized with aqueous concentrated sodium bicarbonate solution to afford a pure product. We also studied the effect of combined solvents like ethanol and $POCl_3$ with different proportions as reported in Table 2 for compounds **8a** and **8 m**. We observed that 5 mL of $POCl_3$ and 10 mL of ethanol give good results, but changing the proportion of $POCl_3$ and ethanol or vise versa gives unacceptable results with more fluctuation on both products. We also found that an amount of $POCl_3$ in excess of or less than 10 mL adversely affects the percent yield as well as the time required for completion. So, finally, we decided to synthesize the aimed products using 10 mL of $POCl_3$ at 90°C to 95°C and make it a standard procedure for further synthesis of other derivatives.

Secondly, we are reporting the synthesis of products containing C═C (from cinnamic group) bond by using substituted cinnamic acid **7i** and **7u** and 4-amino-5-(1*H*-indazol-3-yl)-4*H*-[1,2,4]tria-zole-3-thiol **5**. From the ^{1}H NMR spectroscopic data, J = 16.0 to 16.8 values of two protons on the double bond in both compounds **8i** and **8u** respectively have trans (E) geometry as given in (Scheme 1).

Similarly, 3-[6-(2-trifluoromethyl-pyridin-3-yl)-[1,2,4] triazolo[3,4-*b*][1,3,4]thiadiazol-3-yl]-1*H*-indazole **8t** is successively synthesized from 2-trifluoromethyl-nicotinic acid **7t**. Under the standard reaction condition, the condensation of **5** and **7t** gives **8t** with 86% of yield in 4 hours (Scheme 5). A similar type of molecules possesses pyridine ring without trifluoromethyl group, and the indazole part shows various biological activities.[14,15] In the present study, the compound bearing the trifluoromethyl group and indazole nucleus was synthesized, which may have enhance the biological activity of compound **8t**.

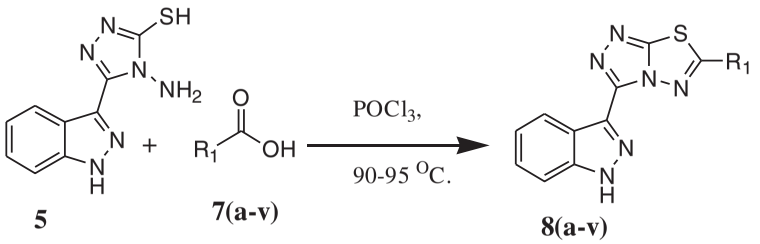
When aliphatic carboxylic acid ie. trifluoro acetic acid is reacted with 4-amino-5-(1*H*-indazol-3-yl)-4*H*-[1,2,4]triazole-3-thiol **5** under standard reaction condition to afford 3-(6-trifluoromethyl-[1,2,4]triazolo[3,4-*b*][1,3,4] thiadiazol-3-yl)-1*H*-indazole **8v** with 80% yield within 5 hours of reaction time.

If the reverse synthesis is carried out by the preparation of 4-amino-5-(4-methoxy-phenyl)-4*H*-[1,2,4]triazole-3-thiol **9** from 4-methoxy-benzoic acid, then 1*H*-indazole-3-carboxylic acid **1** is reacted with 4-methoxy-benzoic acid **9** to afford 3-[3-(4-methoxy-phenyl)-[1,2,4]triazolo[3,4-*b*] [1,3,4] thiadiazol-6-yl]-1*H*-indazole **10** (Scheme 7) instead of 3-[6-(4-methoxy-phenyl)-[1,2,4]triazolo[3,4-*b*][1,3,4] thiadiazol-3-yl]-1*H*-indazole **8k**.

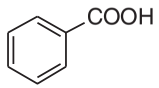
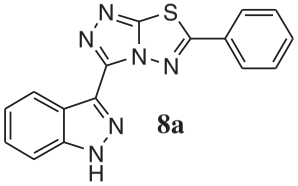
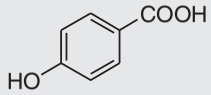
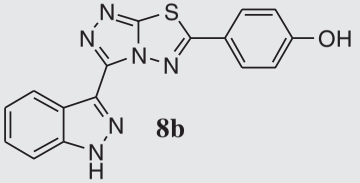
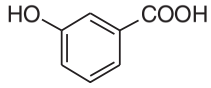
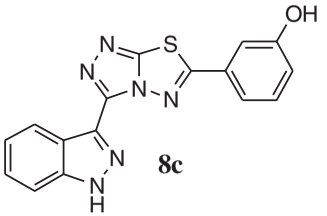
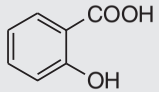
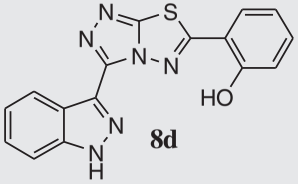
The spectroscopic data of all synthesized compounds show the formation of particular products, ie, compound **8a** has IR band at 747 to 846 cm^{-1} for indazole ring C—H vibrations, 1248 cm^{-1} for cyclic C—N bond vibrations, 1549 cm^{-1} for the C═N vibrations, 1694 cm^{-1} for aromatic protons ArH, and cyclic amines (N—H) at 2913 cm^{-1}. Mass spectra at 319 also confirm the product formation. For the ^{1}H NMR study, δ 7.45 to 7.76 is for aromatic protons present on phenyl ring (m, 5H, ArH), for δ 8.29 to 8.73, these chemical shift values for aromatic protons present on indazole fused benzene ring, and highly deshielded proton from indazole N—H gives singlet at 14.26. Fourteen different carbons associated with **8a** also give 14 ^{13}C NMR signals, and these confirm the product.

The indazoles shows various biological activities, and their combination with two fused five-member heterocyclic rings containing nitrogen and sulfur atoms enhances the biological activities. Similarly synthesized compounds having fluorine atoms may also show good biological activities to the nonfluorinated compounds. Recently,

TABLE 1 Substrate scope for the synthesis of **8(a-v)** from **5** and **7(a-v)**

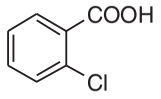
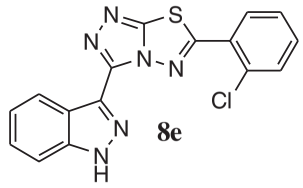
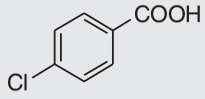
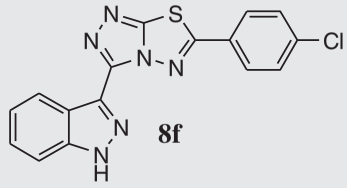
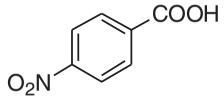
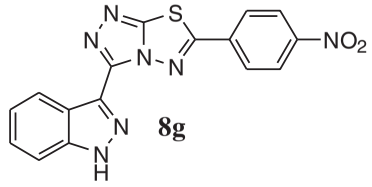
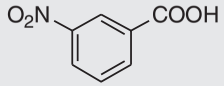
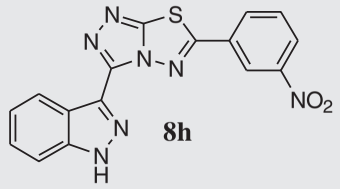
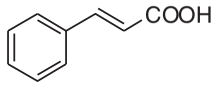
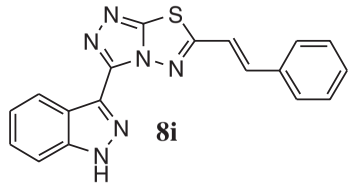


5 **7(a-v)** **8(a-v)**

Starting Material 7(a-v)	Reaction Time, h[a]	Product 8(a-v)	Yield,[b] %
 **7a**	4.5	 **8a**	86
 **7b**	4	 **8b**	79
 **7c**	4.5	 **8c**	75
 **7d**	5.5	 **8d**	75

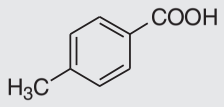
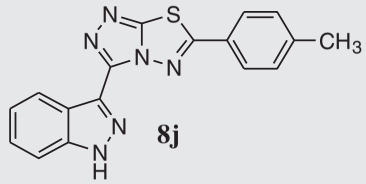
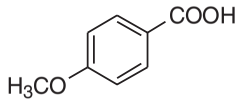
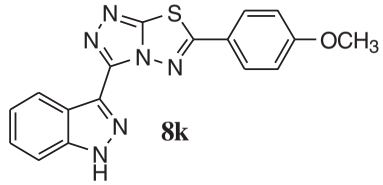
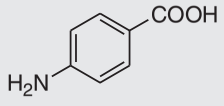
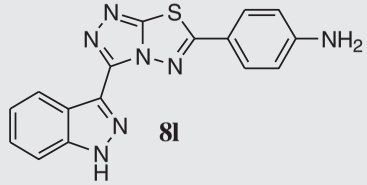
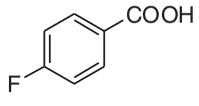
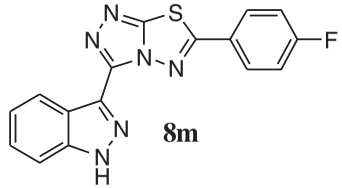
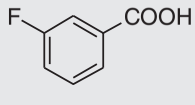
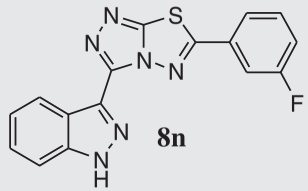
(Continues)

TABLE 1 (Continued)

Starting Material 7(a-v)	Reaction Time, h[a]	Product 8(a-v)	Yield,[b] %
 **7e**	6	 **8e**	82
 **7f**	4	 **8f**	88
 **7g**	6	 **8g**	76
 **7h**	6	 **8h**	75
 **7i**	4.5	 **8i**	78

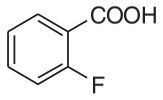
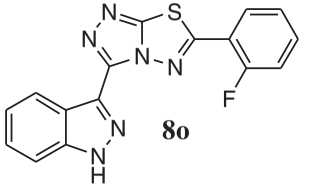
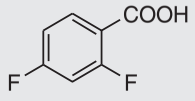
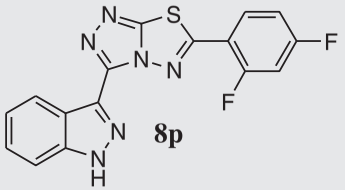
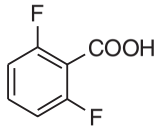
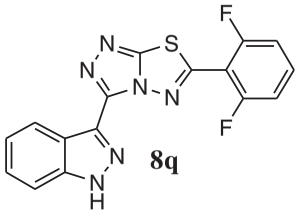
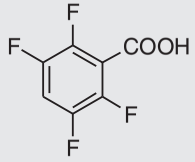
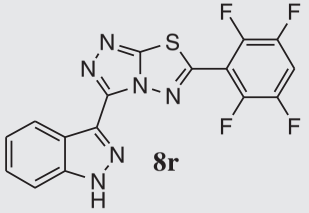
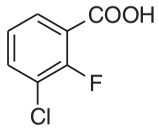
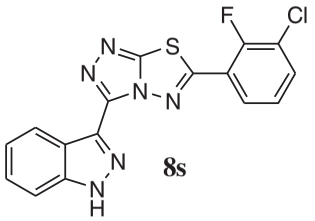
(Continues)

TABLE 1 (Continued)

Starting Material 7(a-v)	Reaction Time, h[a]	Product 8(a-v)	Yield,[b] %
 **7j**	4	 **8j**	88
 **7k**	4	 **8k**	90
 **7l**	4.5	 **8l**	83
 **7m**	5.5	 **8m**	90
 **7n**	4	 **8n**	81

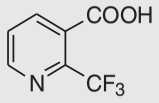
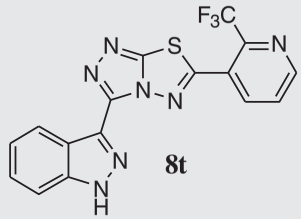
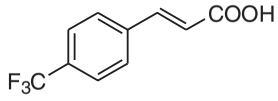
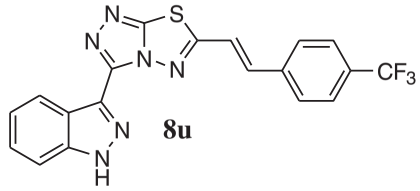
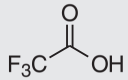
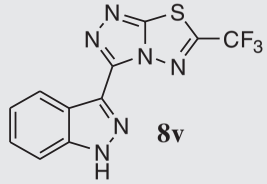
(Continues)

TABLE 1 (Continued)

Starting Material 7(a-v)	Reaction Time, h[a]	Product 8(a-v)	Yield,[b] %
 **7o**	6	 **8o**	79
 **7p**	4.5	 **8p**	76
 **7q**	6	 **8q**	75
 **7r**	5.5	 **8r**	75
 **7s**	4	 **8s**	80

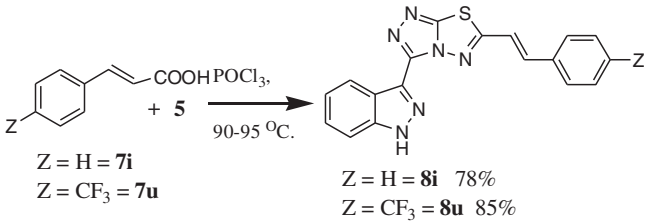
(Continues)

TABLE 1 (Continued)

Starting Material 7(a-v)	Reaction Time, h[a]	Product 8(a-v)	Yield,[b] %
 **7t**	4	 **8t**	86
 **7u**	6	 **8u**	85
 **7v**	5	 **8v**	80

[a]Time required for complete conversion of **7**(**a**-**v**) to **8**(**a**-**v**).
[b]Isolated yields of product.

researchers are focus on the synthesis of fluorinated compounds; fluorine gives a hydrophilic and lipophilic nature to compound, and because of these properties, its compounds are more biologically active. Hence, here, we are reporting the synthesis of heterocyclic compounds having indazole bearing fused five-member heterocyclic rings with fluorinated and nonfluorinated phenyl groups.



SCHEME 4 Cyclization of 7i or 7u with 5 to form 8i or 8u

3 | CONCLUSION

In summary, we disclosed a series of efficient synthesis of 3-[6-(substituted-phenyl)-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazol-3-yl]-1*H*-indazole via dehydrative condensation with cyclization of 4-amino-5-(1*H*-indazol-3-yl)-4*H*-[1,2,4]triazole-3-thiol and fluorinated or nonfluorinated carboxylic acids in presence of phosphorous oxychloride. The multistep reaction pathway proceeds through a number of different compounds. The advantages of the present synthesis were convenient synthesis, simple reaction condition, easily accessible starting materials, 75% to 90% of isolated yield, and wider substrate scope.

4 | EXPERIMENTAL SECTION

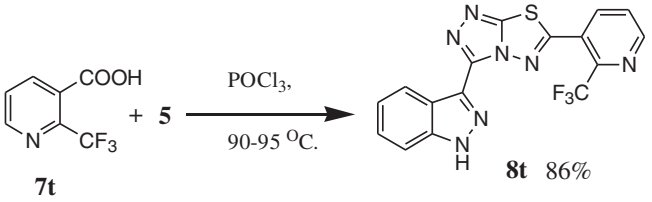
4.1 | General

All condensation/cyclization reactions were performed in electric oven–dried glassware under atmospheric pressure. All the starting chemical material, reagents, and solvents

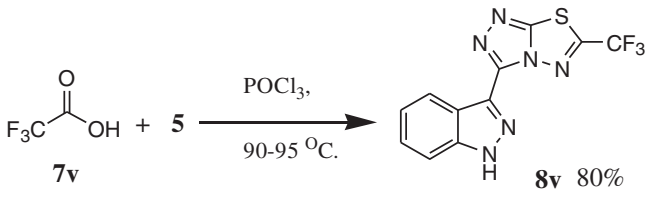
TABLE 2 Optimization of reaction condition at different concentrations of solvent

Entry	$POCl_3$ in mL	Ethanol in mL	Time, h	Compound, % Yield[a]
1	15	--	7	8a (65)
2	5	--	10	8a (62)
3	**10**	--	**4.5**	**8a (86)**
4	5	10	9	8a (21)
5	10	15	13.5	8a (35)
6	5	15	16	8a (18)
7	15	--	8.5	8m (68)
8	5	--	9	8m (52)
9	**10**	--	**5.5**	**8m (90)**
10	5	10	8	8m (24)
11	10	15	11.5	8m (32)
12	5	15	18.5	8m (18)

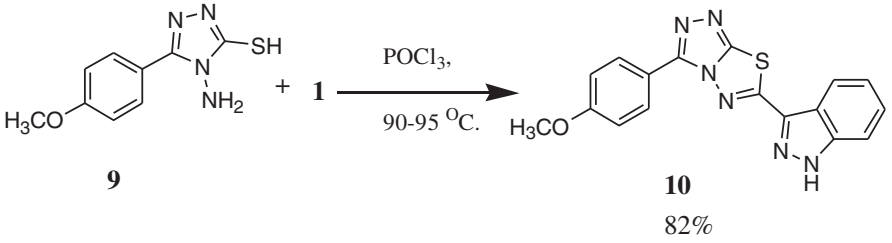
Bold values represents optimum condition at which maximum yield is achieved.
[a]Isolated yields of product.



SCHEME 5 Cyclization of **5** and **7t** to form **8t**



SCHEME 6 Cyclization of **7v** and **5** to form **8v**



SCHEME 7 Cyclization of **1** and **9** to form **10**

used were of analytical grade (AR) and used without further purification. Melting point of all the synthesized compounds was taken on a precision melting point apparatus (DBK instrument), and all are uncorrected. IR spectra of the compounds are obtained in potassium bromide (KBr) disks on a Bruker IR spectrometer, and ^{1}H NMR and ^{13}C spectra were recorded in $CDCl_3$ or DMSO solvent on a Bruker Avance-II 400 MHz spectrometer. A mass spectrum was recorded on a Waters ZQ-4000 spectrometer. The yield of the synthesized compounds mentioned is for isolated product.

4.2 | Synthesis of 1*H*-indazole-3-carboxylic acid ethyl ester (2)

The lotwise addition of 1*H*-indazole-3-carboxylic acid (**1**) 16.2 g (0.1 mol) in the previously taken mixture of ethanol 162 mL (10vol.) and catalytic amount of sulfuric acid 5 g (0.051 mol) were completed in 20 minutes at the room temperature (25°C to 28°C) in 500 mL RBF. The suspension was stirred to form a clear solution. Then, the reaction mixture was heated to reflux (78°C) for 3 to 4 hours. Progress of reaction was checked by using TLC plate in the mobile phase *N*-hexane: ethyl acetate (8:2). After completion of reaction, reaction mass was cooled to rt and poured in 200 mL of water and 100 mL of ethyl acetate and neutralized with saturated solution of sodium bicarbonate, and the organic layer was separated. The aqueous layer was extracted with (50 mL × 2) ethyl acetate. All organic layer was collected and washed with 100 mL water, dried over anhydrous sodium sulfate, and filtered and concentrated on Rota-vapor, and the solid obtained was filtered, washed with chilled ethyl acetate (10 mL), and recrystallized using ethanol.

Weight of dry product 14 g, mp 137°C, Yield 73.68%.

IR (cm^{-1}): 1525-1600 (C═C), 1670 (C═N), 1710 (ester) 3281 (N—H). Mass (m/z) ES^+: Expected 191.08, observed 191.10. ^{1}H NMR ($CDCl_3$) δ (ppm): 1.48 (t, J = 14.4 Hz, 3H), 4.57 (q, J = 14 Hz, 2H), 7.32 (d, J = 8.0 Hz, 1H), 7.44 (dd, J = 8.0, 7.8 Hz, 1H), 7.65 (dd, J = 7.8, 8.2 Hz, 1H), 8.21 (d, J = 8.2 Hz, 1H), 12.46 (s, 1H, NH). ^{13}C NMR ($CDCl_3$) δ (ppm): 14.20, 61.16, 111.6, 121.4, 121.6, 123.1, 126.5, 139.7, 141.3, and 163.3.

4.3 | Synthesis of 1*H*-indazole-3-carboxylic acid hydrazide (3)

In a clean and dry 250 mL RBF charged 9.5 g (0.05 mol) of 1*H*-indazole-3-carboxylic acid ethyl ester (**2**) and 95 mL (10vol.) of ethyl alcohol, stirred the reaction mass well. Dropwise addition of 5 g (0.1 mol) of Hydrazine hydrate was completed in 10 minutes at rt. The reaction mixture is heated to reflux temperature (78°C) for 3 hours. Progress of reaction was monitored on TLC plate. After completion of reaction concentrate the reaction mass to obtain a solid, cooled and filtered out. The products are recrystallized in methanol as solvent.

Weight of dry product 7.8 g, mp 200°C to 202°C, Yield 88.63%.

IR (cm^{-1}): 1525-1600 (C═C), 1339 (—CH_3), 1674 (C═N), 1596 (amide) 3181 (N—H). Mass (m/z) ES^+: Expected 177.07, observed 177.00. ^{1}H NMR ($CDCl_3$) δ (ppm): 4.49 (s, 2H, —NH_2), 9.56 (s, 1H, —NH), 7.23 (d, J = 8.2 Hz, 1H), 7.41 (dd, J = 8.2, 8.5 Hz, 1H), 7.68 (dd, J = 8.5, 8.1 Hz, 1H), 8.08 (d, J = 8.1 Hz, 1H), 13.47 (s, 1H, —NH). ^{13}C NMR ($CDCl_3$) δ (ppm): 111.0, 121.8, 122.0, 122.3, 126.9, 138.1, 141.3, and 162.4.

4.4 | General procedure for the synthesis of potassium-1*H*-indazole-3-carboxylic acid hydrazide dithiocarbamate 4

A mixture of substituted carboxylic acid hydrazide **3** (0.01 mol), KOH (0.84 g, 0.015 mol), and 2 mL CS_2 in absolute alcohol 30 mL was stirred for 14 hours at room temperature (24°C to 30°C), and the product was isolated by simple evaporation of solvent on Petri dish.

4.5 | General procedure for the synthesis of 4-amino-5-(1*H*-indazol-3-yl)-4*H*-[1,2,4] triazole-3-thiol 5

Potassium salt (0.01 mol) **4** was taken in excess of hydrazine hydrate and 25 mL of water then heated (90°C to 95°C) up to the evolution of H_2S gas completed nearly 3 to 5 hours in oil bath. After completion reaction monitored by TLC, mixture was cooled and poured into

crushed ice and neutralized with glacial acetic acid. The white precipitate obtained was filtered and purified by crystallization from 50% ethanol.

Mass (m/z) ES^+: Expected 233.06, observed 233.20. ^1H NMR ($CDCl_3$) δ (ppm): 3.02 (s, 1H, S—H), 4.29 (s, 2H, NH_2), 7.33 (d, J = 8.0 Hz, 1H), 7.41 (dd, J = 8.0, 8.3 Hz, 1H), 7.66 (dd, J = 8.3, 8.2 Hz, 1H), 8.46 (d, J = 8.2 Hz, 1H), 13.48 (s, 1H, —NH).

4.6 | General procedure for the synthesis of 3-[6-(substituted-phenyl)-[1,2,4]triazolo [3,4-*b*][1,3,4]thiadiazol-3-yl]-1*H*-indazole 8 (a-v)

A mixture of substituted carboxylic acid (0.02 mol) **7**(**a-v**) and 4-amino-5-(1*H*-indazol-3-yl)-4*H*-[1,2,4]triazole-3-thiol 5 (0.01 mol) in $POCl_3$ (10 mL) was heated at 90°C to 95°C for 4 to 6 hours. After completion of reaction observed by TLC, the reaction mixture was cooled to room temperature and poured into crushed ice, neutralized with concentrated sodium bicarbonate solution, and the precipitate that separates out was filtered, washed with chilled water, and crystallized from 1:1 solution of ethanol and ethyl acetate.

Secondly, similar synthesis was carried out as the above procedure with changing 10 mL of $POCl_3$ by 10 mL of ethanol containing 5 mL of $POCl_3$ as solvent at reflux temperature (77°C to 79°C).

4.6.1 | 3-(6-Phenyl-[1,2,4]triazolo[3,4-*b*] [1,3,4]thiadiazol-3-yl)-1*H*-indazole (8a)

mp 247°C to 249°C, IR (cm^{-1}): 747-846 (indazole C—H), 1694 (ArH), 1248 (C—N), 1549 (C═N), 2913 (N—H). Mass (m/z) ES^+: Expected 319.07, observed 319.00. ^1H NMR: δ 7.45-7.76 (m, 5H, ArH), 8.73 (d, J = 8.0 Hz, 1H, ArH), 8.29 (dd, J = 8.0, 7.5 Hz 1H, ArH), 8.33 (dd, J = 7.5, 7.9 Hz, 1H, ArH), 8.86 (d, J = 7.9 Hz, 1H, ArH), 14.26 (s, 1H, NH). ^{13}C NMR: δ 112.02, 119.99, 120.98, 124.21, 126.14, 126.36, 128.33, 129.78, 130.80, 135.28, 142.12, 146.06, 153.79, 162.20.

4.6.2 | 4-[3-(1*H*-Indazol-3-yl)-[1,2,4] triazolo[3,4-*b*][1,3,4]thiadiazol-6-yl]- phenol (8b)

mp 256°C to 258°C, Mass (m/z) ES^+: Expected 335.06, observed 335.19. ^1H NMR: δ 3.37 (s, 1H, OH), 7.35 (d, J = 8.4 Hz, 2H, ArH), 7.70 (d, J = 8.4 Hz, 2H, ArH), 8.30 (d, J = 8.0 Hz, 1H, ArH), 7.32 (dd, J = 8.0, 8.3 Hz, 1H, ArH), 7.46 (dd, J = 8.3, 8.2 Hz, 1H, ArH), 7.55 (d, J = 8.2 Hz, 1H, ArH), 13.98 (s, 1H, NH). ^{13}C NMR: δ 108.00, 110.19, 112.89, 116.61, 118.09, 121.94, 122.49, 128.27, 131.94, 136.94, 138.59, 142.81, 148.73, 152.36.

4.6.3 | 3-[3-(1*H*-Indazol-3-yl)-[1,2,4] triazolo[3,4-*b*][1,3,4]thiadiazol-6-yl]- phenol (8c)

mp 132°C to 134°C, Mass (m/z) ES^+: Expected 335.06, observed 335.07. ^1H NMR: δ 3.35 (s, 1H, OH), 7.43 (s, 1H, ArH), 7.63 (d, J = 7.8 Hz, 1H, ArH), 7.79 (dd, J = 7.8, 8.0 Hz, 1H, ArH), 8.07 (d, J = 8.0 Hz, 1H, ArH), 8.50 (d, J = 7.9 Hz, 1H, ArH), 7.28 (dd, J = 7.9, 8.3 Hz, 1H, ArH), 7.60 (dd, J = 8.3, 8.2 Hz, 1H, ArH), 7.65 (d, J = 8.2 Hz, 1H, ArH), 13.02 (s, 1H, NH).

4.6.4 | 2-[3-(1*H*-Indazol-3-yl)-[1,2,4] triazolo[3,4-*b*][1,3,4]thiadiazol-6-yl]- phenol (8d)

mp 142°C to 144°C, Mass (m/z) ES^+: Expected 335.06, observed 335.12. ^1H NMR: δ 7.21 (d, J = 8.1 Hz, 1H, ArH), 7.42 (dd, J = 8.1, 7.6 Hz, 1H, ArH), 7.52 (dd, J = 7.6, 7.5 Hz, 1H, ArH), 7.59 (d, J = 7.5 Hz, 1H, ArH), 7.61 (d, J = 8.0 Hz, 1H, ArH), 7.94 (dd, J = 8.0, 8.2 Hz, 1H, ArH), 8.00 (dd, J = 8.2, 8.6 Hz, 1H, ArH), 8.13 (d, J = 8.6 Hz, 1H, ArH), 14.02 (s, 1H, NH).

4.6.5 | 3-[6-(2-Chloro-phenyl)-[1,2,4] triazolo[3,4-*b*][1,3,4]thiadiazol-3-yl]-1*H*- indazole (8e)

mp 238°C to 240°C, Mass (m/z) ES^+: Expected 353.03, observed 353.03. ^1H NMR: δ 7.52 (d, J = 7.6 Hz, 1H, ArH), 7.41 (dd, J = 7.6, 7.9 Hz, 1H, ArH), 7.65 (dd, J = 7.9, 8.0 Hz, 1H, ArH), 7.72 (d, J = 8.0 Hz, 1H, ArH), 8.02 (d, J = 7.9 Hz, 1H, ArH), 7.37 (dd, J = 7.9, 8.1 Hz, 1H, ArH), 7.58 (dd, J = 8.1, 7.6 Hz, 1H, ArH), 7.69 (d, J = 7.6 Hz, 1H, ArH), 14.34 (s, 1H, NH). ^{13}C NMR: δ 112.59, 116.23, 120.01, 122.89, 122.98, 124.56, 126.06, 126.79, 128.19, 132.02, 134.49, 138.63, 142.47, 144.94, 158.52, 161.71.

4.6.6 | 3-[6-(4-Chloro-phenyl)-[1,2,4] triazolo[3,4-*b*][1,3,4]thiadiazol-3-yl]-1*H*- indazole (8f)

mp 170°C, Mass (m/z) ES^+: Expected 353.03, observed 353.09. ^1H NMR: δ 6.39 (d, J = 7.8 Hz, 2H, ArH), 7.58 (d, J = 7.8 Hz, 2H, ArH), 8.29 (d, J = 8.2 Hz, 1H, ArH), 7.45 (dd, J = 8.2, 8.4 Hz, 1H, ArH), 7.56 (dd, J = 8.2, 7.9 Hz, 1H,

ArH), 7.61 (d, J = 7.9 Hz, 1H, ArH), 14.24 (s, 1H, NH). ^{13}C NMR: δ 111.99, 119.95, 121.16, 124.21, 126.33, 127.17, 128.13, 130.69, 131.24, 135.40, 142.09, 145.18, 150.84, 162.43.

4.6.7 | 3-[6-(4-Nitro-phenyl)-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazol-3-yl]-1*H*-indazole (8g)

mp 180°C to 182°C, Mass (m/z) ES$^+$: Expected 364.06, observed 364.06. ^{1}H NMR: δ 8.07 (d, J = 8.7 Hz, 2H, ArH), 7.65 (d, J = 8.7 Hz, 2H, ArH), 8.09 (d, J = 8.0 Hz, 1H, ArH), 7.27 (dd, J = 8.0, 8.2 Hz, 1H, ArH), 7.30 (dd, J = 8.2, 8.0 Hz, 1H, ArH), 7.65 (d, J = 8.0 Hz, 1H, ArH), 14.01 (s, 1H, NH). ^{13}C NMR: δ 110.00, 112.26, 114.50, 118.71, 121.67, 122.77, 123.02, 126.94, 128.23, 142.94, 144.18, 148.59, 152.10, 159.31.

4.6.8 | 3-[6-(3-Nitro-phenyl)-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazol-3-yl]-1*H*-indazole (8h)

mp 210°C to 212°C, Mass (m/z) ES$^+$: Expected 364.06, observed 364.09. ^{1}H NMR: δ 8.41 (s, 1H, ArH), 8.44 (d, J = 8.2 Hz, 1H, ArH), 8.22 (dd, J = 8.2, 7.6 Hz, 1H, ArH), 8.31 (d, J = 7.6 Hz, 1H, ArH), 8.53 (d, J = 8.4 Hz, 1H, ArH), 7.72 (dd, J = 8.4, 8.1 Hz, 1H, ArH), 8.29 (dd, J = 8.1, 7.6 Hz, 1H, ArH), 8.35 (d, J = 7.6 Hz, 1H, ArH), 14.38 (s, 1H, NH). ^{13}C NMR: δ 112.92, 117.99, 118.98, 121.01, 124.21, 126.14, 126.30, 128.68, 129.70, 130.80, 135.28, 142.12, 146.06, 153.79, 160.03, 162.20.

4.6.9 | 3-(6-Styryl-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazol-3-yl)-1*H*-indazole (8i)

mp 142°C to 144°C, ES$^+$: Expected 345.09, observed 345.17. ^{1}H NMR: δ 2.50 (d, J = 16.2, 1H, CH═CH), 3.41 (d, J = 16.2, 1H, CH═CH), 7.28-7.47 (m, 5H, ArH), 8.09 (d, J = 8.0 Hz, 1H, ArH), 7.26 (dd, J = 8.0, 8.6 Hz, 1H, ArH), 7.50 (dd, J = 8.6, 8.2 Hz, 1H, ArH), 7.60 (d, J = 8.2 Hz, 1H, ArH), 14.36 (s, 1H, NH). ^{13}C NMR: δ 112.18, 120.13, 120.98, 123.18, 124.08, 126.23, 126.29, 127.70, 128.49, 130.08, 132.48, 133.52, 134.94, 140.28, 147.00, 148.12.

4.6.10 | 3-(6-*p*-Tolyl-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazol-3-yl)-1*H*-indazole (8j)

mp 287°C to 289°C, Mass (m/z) ES$^+$: Expected 333.09, observed 333.08. ^{1}H NMR: δ 2.50 (s, 3H, CH_3), 7.50 (d, J = 7.7 Hz, 2H, ArH), 7.58 (d, J = 7.7 Hz, 2H, ArH), 8.01 (d, J = 8.1 Hz, 1H, ArH), 7.43 (dd, J = 8.1, 8.3 Hz, 1H, ArH), 7.52 (dd, J = 8.3, 8.0 Hz, 1H, ArH), 7.65 (d, J = 8.0 Hz, 1H, ArH), 14.23 (s, 1H, NH). ^{13}C NMR: δ 21.55, 112.03, 121.08, 121.17, 121.67, 123.02, 124.21, 126.31, 126.94, 127.01, 128.36, 130.34, 130.69, 131.25, 150.35.

4.6.11 | 3-[6-(4-Methoxy-phenyl)-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazol-3-yl]-1*H*-indazole (8k)

mp 208°C to 210°C, Mass (m/z) ES$^+$: Expected 349.08, observed 349.09. ^{1}H NMR: δ 3.84 (s, 3H, OCH_3), 7.20 (d, J = 8.0 Hz, 2H, ArH), 7.51 (d, J = 8.0 Hz, 2H, ArH), 8.35 (d, J = 8.2 Hz, 1H, ArH), 7.00 (dd, J = 8.2, 8.6 Hz, 1H, ArH), 7.20 (dd, J = 8.6, 8.0 Hz, 1H, ArH), 7.88 (d, J = 8.0 Hz, 1H, ArH), 13.99 (s, 1H, NH). ^{13}C NMR: δ 56.15, 111.25, 114.15, 115.30, 121.23, 122.52, 124.15, 127.50, 131.75, 141.22, 142.78, 154.19, 162.43, 163.22, 167.70.

4.6.12 | 4-[3-(1*H*-Indazol-3-yl)-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazol-6-yl]-phenylamine (8l)

mp 188°C to 190°C, Mass (m/z) ES$^+$: Expected 334.08, observed 334.08. ^{1}H NMR: δ 3.42 (s, 2H, NH_2), 6.20 (d, J = 8.7 Hz, 2H, ArH), 6.71 (d, J = 8.7 Hz, 2H, ArH), 7.32 (d, J = 8.1 Hz, 1H, ArH), 7.50 (dd, J = 8.1, 8.2 Hz, 1H, ArH), 7.72 (dd, J = 8.2, 8.0 Hz, 1H, ArH), 8.29 (d, J = 8.0 Hz, 1H, ArH), 13.75 (s, 1H, NH). ^{13}C NMR: δ 111.21, 113.03, 114.11, 121.09, 121.77, 122.53, 127.52, 129.27, 130.07, 131.90, 141.20, 143.28, 148.00, 150.35.

4.6.13 | 3-[6-(4-Fluoro-phenyl)-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazol-3-yl]-1*H*-indazole (8m)

mp 168°C, Mass (m/z) ES$^+$: Expected 337.06, observed 337.23. ^{1}H NMR: δ 7.42 (d, J = 8.1 Hz, 2H, ArH), 7.58 (d, J = 8.1 Hz, 2H, ArH), 8.13 (d, J = 7.5 Hz, 1H, ArH), 7.55 (dd, J = 7.5, 8.0 Hz, 1H, ArH), 7.60 (dd, J = 8.0, 7.8 Hz, 1H, ArH), 8.07 (d, J = 7.8 Hz, 1H, ArH), 12.16 (s, 1H, NH). ^{13}C NMR: δ 117.07, 118.09, 121.08, 121.17, 125.06, 127.20, 130.69, 131.25, 146.12, 150.85, 158.01, 164.23, 166.06, 168.14.

4.6.14 | 3-[6-(3-Fluoro-phenyl)-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazol-3-yl]-1*H*-indazole (8n)

mp 288°C to 290°C, Mass (m/z) ES$^+$: Expected 337.06, observed 337.49. ^{1}H NMR: δ 7.32 (s, 1H, ArH), 7.47

(d, J = 7.5 Hz, 1H, ArH), 7.49 (dd, J = 7.5, 8.0, 1H, ArH), 7.99 (d, J = 8.0 Hz, 1H, ArH), 8.00 (d, J = 7.9 Hz, 1H, ArH), 7.50 (dd, J = 7.9, 7.4 Hz, 1H, ArH), 7.53 (dd, J = 7.9, 7.4 Hz, 1H, ArH), 8.10 (d, J = 7.4 Hz, 1H, ArH), 13.08 (s, 1H, NH). ^{13}C NMR: δ 112.20, 116.18, 117.25, 120.18, 121.80, 122.59, 124.15, 127.79, 129.94, 130.42, 132.61, 163.80, 164.38, 165.89, 166.37, 167.21.

4.6.15 | 3-[6-(2-Fluoro-phenyl)-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazol-3-yl]-1*H*-indazole (8o)

mp 162°C to 164°C, Mass (m/z) ES$^+$: Expected 337.06, observed 337.02. ^{1}H NMR: δ 7.31 (d, J = 7.9 Hz, 1H, ArH), 7.34 (dd, J = 7.9, 7.5 Hz, 1H, ArH), 7.51 (dd, J = 7.5, 7.8 Hz, 1H, ArH), 7.53 (d, J = 7.8 Hz, 1H, ArH), 8.21 (d, J = 8.2 Hz, 1H, ArH), 7.47 (dd, J = 8.2, 7.9 Hz, 1H, ArH), 7.99 (dd, J = 7.9, 7.3 Hz, 1H, ArH), 8.01 (d, J = 7.3 Hz, 1H, ArH), 13.98 (s, 1H, NH). ^{13}C NMR: δ 111.25, 116.01, 117.07, 117.33, 120.45, 121.22, 122.59, 127.55, 129.87, 130.35, 132.53, 132.61, 141.21, 163.66, 164.28, 166.83.

4.6.16 | 3-[6-(2,4-Difluoro-phenyl)-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazol-3-yl]-1*H*-indazole (8p)

mp 132°C to 134°C, Mass (m/z) ES$^+$: Expected 355.05, observed 355.05. ^{1}H NMR: δ 7.72 (s, 1H, ArH), 7.34 (d, J = 7.8 Hz, 1H, ArH), 7.50 (d, J = 7.8 Hz, 1H, ArH), 7.82 (d, J = 8.1 Hz, 1H, ArH), 7.32 (dd, J = 8.1, 8.3 Hz, 1H, ArH), 7.34 (dd, J = 8.3, 8.0 Hz, 1H, ArH), 7.72 (d, J = 8.0 Hz, 1H, ArH), 13.81 (s, 1H, NH). ^{13}C NMR: δ 107.68, 111.26, 113.35, 113.52, 113.55, 121.14, 122.60, 127.56, 131.73, 135.48, 135.66, 141.22, 142.83, 155.82, 159.10, 161.13.

4.6.17 | 3-[6-(2,6-Difluoro-phenyl)-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazol-3-yl]-1*H*-indazole (8q)

mp 158°C to 160°C, Mass (m/z) ES$^+$: Expected 355.05, observed 355.07. ^{1}H NMR: δ 8.09 (d, J = 8.0 Hz, 2H, ArH), 7.43 (dd, J = 8.0, 8.0 Hz, 1H, ArH), 7.65 (d, J = 8.2 Hz, 1H, ArH), 7.28 (dd, J = 8.2, 8.0 Hz, 1H, ArH), 7.30 (dd, J = 8.0, 7.8 Hz, 1H, ArH), 7.60 (d, J = 7.8 Hz, 1H, ArH), 14.02 (s, 1H, NH). ^{13}C NMR: δ 112.18, 118.05, 121.67, 123.29, 126.95, 127.19, 134.02, 156.12, 158.39, 161.23, 162.79, 164.08, 166.79, 168.00.

4.6.18 | 3-[6-(2,3,5,6-Tetrafluoro-phenyl)-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazol-3-yl]-1*H*-indazole (8r)

mp 118°C to 120°C, Mass (m/z) ES$^+$: Expected 391.03, observed 391.00. ^{1}H NMR: δ 6.31 (s, 1H, ArH), 8.21 (d, J = 7.7 Hz, 1H, ArH), 7.32 (dd, J = 7.7, 8.0 Hz, 1H, ArH), 7.48 (dd, J = 8.0, 8.2 Hz, 1H), 7.66 (dd, J = 8.2 Hz, 1H, ArH), 13.79 (s, 1H, NH). ^{13}C NMR: δ 109.41, 110.18, 114.48, 116.18, 118.62, 121.33, 127.51, 131.74, 140.88, 141.23, 144.91, 152.41, 157.77, 160.78.

4.6.19 | 3-[6-(3-Chloro-2-fluoro-phenyl)-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazol-3-yl]-1*H*-indazole (8s)

mp 172°C, Mass (m/z) ES$^+$: Expected 371.02, observed 371.02. ^{1}H NMR: δ 6.70 (d, J = 7.6 Hz, 1H, ArH), 7.65 (dd, J = 7.6, 8.0 Hz, 1H, ArH), 8.07 (d, J = 8.0 Hz, 1H, ArH), 8.31 (d, J = 7.6 Hz, 1H, ArH), 6.73 (dd, J = 7.6, 8.1 Hz, 1H, ArH), 7.67 (dd, J = 8.1, 8.0 Hz, 1H, ArH), 7.83 (d, J = 8.0 Hz, 1H, ArH), 13.67 (s, 1H, NH). ^{13}C NMR: δ 111.24, 121.12, 121.90, 122.60, 125.38, 126.90, 127.53, 130.43, 131.70, 132.02, 135.88, 136.08, 139.58, 141.23, 142.63, 166.48.

4.6.20 | 3-[6-(2-Trifluoromethyl-pyridin-3-yl)-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazol-3-yl]-1*H*-indazole (8t)

mp 188°C to 190°C, ES$^+$: Expected 388.05, observed 388.00. ^{1}H NMR: δ 7.33 (d, J = 7.7 Hz, 1H, ArH), 7.36 (dd, J = 7.7, 8.3 Hz, 1H, ArH)), 7.71 (d, J = 8.3 Hz, 1H, ArH), 8.33 (d, J = 7.8 Hz, 1H, ArH), 7.31 (dd, J = 7.8, 7.7 Hz, 1H, ArH), 7.36 (dd, J = 7.7, 8.1 Hz, 1H, ArH), 7.81 (d, J = 8.3, 1.9 Hz, 1H, ArH), 12.29 (s, 1H, NH). ^{13}C NMR: δ 111.27, 121.21, 121.86, 122.63, 125.76, 127.00, 127.58, 128.46, 131.12, 134.49, 135.10, 141.23, 142.81, 155.68, 157.74, 164.64.

4.6.21 | 3-{6-[2-(4-Trifluoromethyl-phenyl)-vinyl]-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazol-3-yl}-1*H*-indazole (8u)

mp 130°C, Mass (m/z) ES$^+$: Expected 413.08, observed 413.06. ^{1}H NMR: δ 2.50 (d, J = 16.4 Hz, 1H, CH═CH), 3.34 (d, J = 16.4 Hz, 1H, CH═CH), 7.60 (7.47 (d, J = 8.7 Hz, 2H, ArH), 8.14 (d, J = 8.7 Hz, 2H, ArH), 8.16 (d, J = 8.2 Hz, 1H, ArH), 7.58 (dd, J = 8.2, 8.0 Hz, 1H, ArH), 7.62 (dd, J = 8.0, 7.6 Hz, 1H, ArH), 8.02 (d, J = 7.6 Hz, 1H, ArH), 12.64 (s, 1H, NH). ^{13}C NMR: δ 110.89, 114.12, 118.21, 119.30, 120.12,

120.59, 120.91, 123.46, 123.86, 126.56, 125.51, 133.46, 133.73, 140.84, 144.23, 148.85, 154.00.

4.6.22 | 3-(6-Trifluoromethyl-[1,2,4] triazolo[3,4-*b*][1,3,4]thiadiazol-3-yl)-1*H*-indazole (8v)

mp 156°C, Mass (*m*/*z*) ES^+: Expected 311.03, observed 311.03. ^{1}H NMR: δ 8.30 (d, J = 7.9 Hz, 1H, ArH), 7.18 (dd, J = 7.9, 8.2 Hz, 1H, ArH), 7.32 (dd, J = 8.2, 8.0 Hz, 1H, ArH), 7.66 (dd, J = 8.2 Hz, 1H, ArH), 13.59 (s, 1H, NH). ^{13}C NMR: δ 110.01, 112.94, 118.26, 124.79, 126.91, 132.07, 136.12, 138.00, 152.23, 152.69, 154.49.

4.7 | 5-(1*H*-Indazol-3-yl)-[1,3,4] oxadiazole-2-thiol (6)

mp 159°C, IR (cm^{-1}): 660-782 (indazole C—H), 1248 (C—N), 1615 (C═N), 2729 (S—H), 3066 (N—H). Mass (*m*/*z*) ES^+: Expected 219.03, observed 218.81. ^{1}H NMR ($CDCl_3$) δ (ppm): 3.36 (s, 1H, S—H), 7.25 (d, J = 8.2 Hz, 1H), 7.47 (dd, J = 8.2, 8.3 Hz, 1H), 7.54 (dd, J = 8.3, 8.0 Hz, 1H), 8.23 (d, J = 8.0 Hz, 1H), 13.48 (s, 1H, —NH). ^{13}C NMR: δ 111.46, 118.13, 120.00, 122.32, 126.23, 132.08, 138.01, 140.12, 143.04.

4.8 | 3-[3-(4-Methoxy-phenyl)-[1,2,4] triazolo[3,4-*b*][1,3,4] thiadiazol-6-yl]-1*H*-indazole (10)

mp 190°C to 192°C, Mass (*m*/*z*) ES^+: Expected 349.08, observed 349.28. ^{1}H NMR: δ 3.86 (s, 3H, OCH_3), 7.24 (d, J = 8.7 Hz, 2H, ArH), 7.58 (d, J = 8.7 Hz, 2H, ArH), 8.13 (d, J = 8.0 Hz, 1H, ArH), 7.10 (dd, J = 8.0, 8.9 Hz, 1H, ArH), 7.26 (dd, J = 8.9, 8.4 Hz, 1H, ArH), 7.61 (d, J = 8.4 Hz, 1H, ArH), 14.22 (s, 1H, NH). ^{13}C NMR: δ 55.88, 115.41, 117.26, 119.46, 121.08, 121.17, 125.06, 130.69, 131.25, 142.32, 144.94, 147.38, 148.09, 149.82, 150.84.

ACKNOWLEDGMENTS

One of the authors, Raut S.V., is thankful to CSIR for providing SRF fellowship for this work. The authors are thankful to Principal, Maulana Azad Collage, Aurangabad for providing library and laboratory facilities.

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How to cite this article: Raut S, Hadi A, Pathan MA. The efficient synthesis of 3-[6-(substituted)-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazol-3-yl]-1H-indazole. *J Heterocycl Chem*. 2020;1–15. https://doi.org/10.1002/jhet.3866