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An efficient one-pot expeditious synthesis of 3-phenyl-1-(6-phenyl-7H-[1,2,4] triazolo[3,4-b] [1,3,4] thiadiazin-3-yl)-1H-pyrazol-5-amines via multicomponent approach

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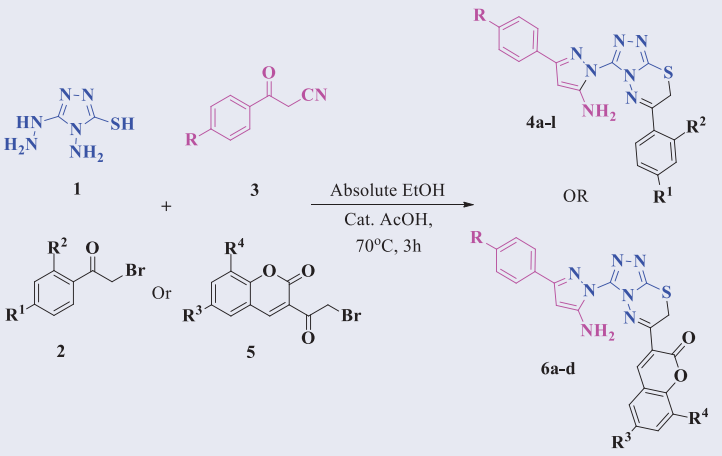
ABSTRACT

An efficient synthesis of 3-phenyl-1-(6-phenyl-7*H*-[1,2,4] triazolo[3,4-b][1,3,4]thiadiazin-3-yl)-1*H*-pyrazol-5-amines was accomplished by a simple, atom-economical, and multicomponent approach. Reaction of 4-amino-5-hydrazinyl-*4H*-1,2,4-triazole-3-thiol with various phenacyl bromides and benzoylacetonitriles in ethanol and catalytic amount of acetic acid afforded the titled compounds. The structures of newly synthesized compounds were confirmed by their analytical and spectral (IR, ^{1}H-NMR, ^{13}C-NMR, and Mass) data.

GRAPHICAL ABSTRACT



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KEYWORDS
Multicomponent reaction; phenacyl bromide; 3-(2-bromoacetyl)-2H-chromen-2-one; triazolothiadiazine

Introduction

Triazoles are important class of heterocyclic compounds for organic chemists on account of their implications in the biological, pharmacological, medicinal, agricultural,

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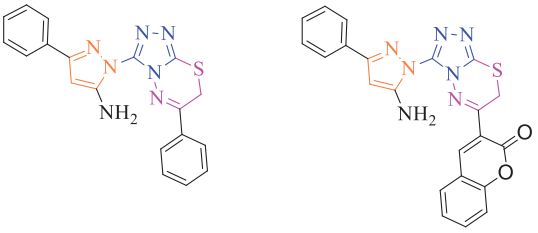
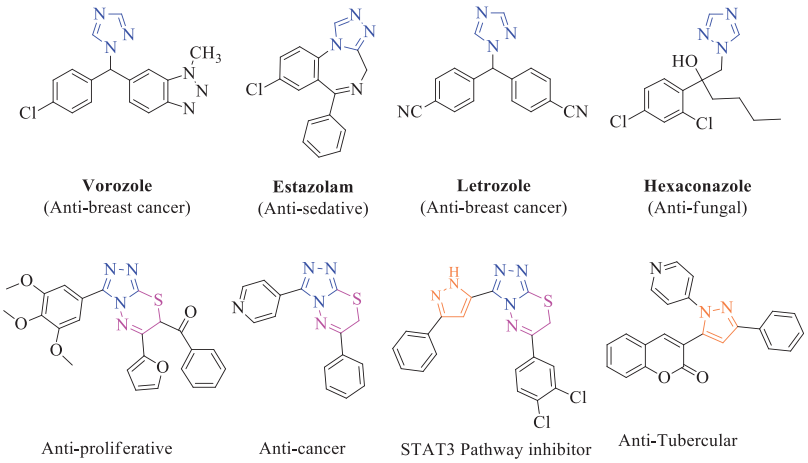


Figure 1. Design strategy of synthesized molecules.

and industry.[1,2] When triazole ring is fused with a 5-membered or with a 6-membered heterocyclic ring its enhance the biological activity of the lead molecule[3,4] and triazolothiadiazines were associated with different biological activities such as anti-cancer,[5,6] anti-tubercular,[7] anti-candidal,[8] and anti-microbial activity.[9] Triazolothiadiazines having substituent's such as substituted aryl, coumarin moieties are reported with better biological activity.[10,11]

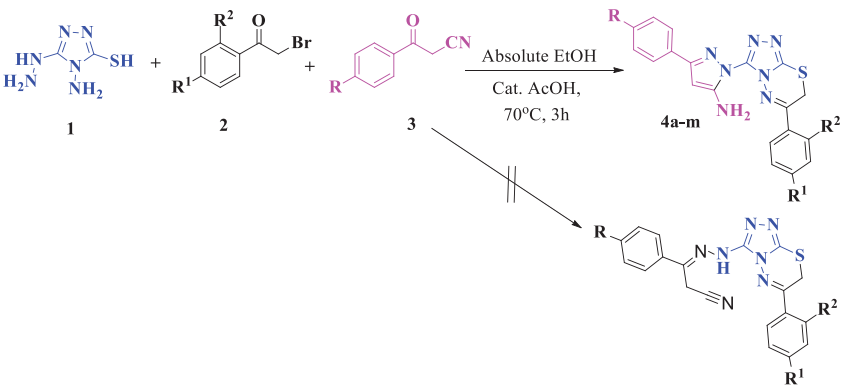
Pyrazoles are also important heterocyclic molecules.[12,13] Pyrazoles and their derivatives are having predominant biological and pharmacological activities,[14–17] such as anti-hyperglycaemic,[18] anticonvulsant, anti-depressant,[19] anti-tubercular, anti-bacterial,[20] anti-viral,[21,22] anti-fungal,[23,24] anti-histaminic,[25] anti-inflammatory,[26] anti-diabetic[27] and anti-leukaemia agent.[28] The existing literature revealed that pyrazole ring directly linked to the 1,2,4-triazolo-[3,4-b]thiadiazines showed human (h) A_3 adenosine receptor[29] and better anti-proliferative activity (Figure 1).[30,31]

Multicomponent reactions are widely used in organic synthesis due to advantages such as high efficiency, atom economy, high yields, clear reactions, and simple procedures resulting in the formation of new structures.[32]



Some of the reported biologically active molecules with triazolothiadiazine, pyrazolotriazolothiadiazines, and pyrazolocoumarin scaffolds.

Keeping the importance of triazoles, pyrazoles, and triazolothiadiazines, our present study is focused on the development of new methodologies for the synthesis of thiadiazine fused to triazole and having pyrazole.



Scheme 1. Synthesis of compounds **4a–4m**.

In continuation of our earlier work on MCR,[33,34] we have developed a one-pot multicomponent reaction for the synthesis of title compounds intending that these compounds may have good biological activities (Schemes 1 and 2).

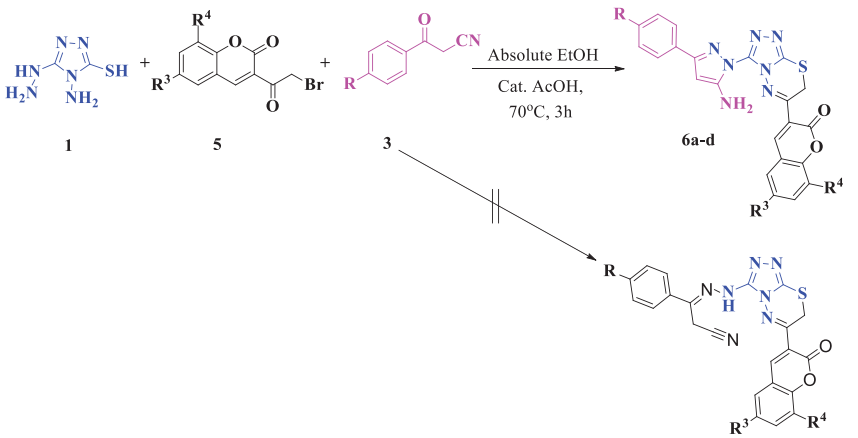
Results and discussion

4-Amino-5-hydrazinyl-*4H*-1,2,4-triazole-3-thiol can be taken as useful tool in building triazolothiadiazinylpyrazoles. It is prepared by reaction of thiourea with hydrazine hydrate under reflux conditions on water bath.[35] Condensation of 4-amino-5-hydrazinyl-*4H*-1,2,4-triazole-3-thiol (**1**), various phenacyl bromides or 3-(2-bromoacetyl)-2*H*-chromen-2-ones (**2**), and benzoylacetonitriles (**3**) resulted in the formation of **4** and **6**.

Reaction between compound **1**, phenacyl bromide or 3-(2-bromoacetyl)-2*H*-chromen-2-one and phenacyl cyanide is expected to produce compound **7** and **8** depending on the mode of cyclization. The formation of compound **7** and **8** can be ruled on the basis of spectral studies. In the present investigation, both NH_2 and SH of **1** at a time undergoes condensation with either **2** or **5** leading to first hetero cyclization. Then, the hydrazino group of **1** reacts with phenacyl cyanide to give the title compound. The desired product was achieved in each case good to excellent yield. The work may trigger an interesting chemistry involving new methodology. The very noticeable feature of the synthesis is that different hetero atom bonds like C–S, 2N = C, and N–C (compounds **4** and **6**) are formed concomitantly in one pot leading to selective new hetero cyclization without formation of any other products (Table 1).

In the formation of fused thiadiazine ring on triazole, the highly nucleophilic sulfur atom of mercapto group of 1 attacks on the carbon atom of the (CH_2-Br) of phenacyl bromide or 3-(2-bromoacetyl)-2*H*-chromen-2-one to give an open chain α-thioketone. Then, it undergoes intra molecular cyclization, leading to the formation of thiadiazine ring. The hydrazino group of triazolothiadiazine undergoes cyclocondensation reaction with benzoylacetonitrile leading to the formation of title compounds with better yields.

The structures of all the newly synthesized compounds were confirmed by their analytical and spectral data and are summarized in supporting information. The IR spectrum of Compound **4a** shows prominent peaks at 3411 cm^{-1} (NH_2 Stretching), 1618 cm^{-1} (–C = N– stretching). The ^{1}H-NMR spectrum of the compound **4a** showed a



Scheme 2. Synthesis of compounds **6a–6d**.

characteristic peak at δ 4.49 ppm corresponds to CH_2 of thiadiazine and δ 5.90 ppm corresponds to pyrazole proton. The 13C NMR of the **4a** exhibits a characteristic peak at δ 23.5 ppm. This is due to carbon atom of CH_2 of thiadiazine. The compound **4a** exhibited the molecular ion peak at m/z 407.

Experimental

All the chemicals which were used in the present study were purchased from commercial sources and used further without any purification. Melting points were determined in open capillaries with a Stuart melting point apparatus Mumbai, India and were uncorrected. IR spectra were recorded on Perkin Elmer Spectrum 100 s. ^{1}H-NMR spectra were recorded on Bruker WM-400 spectrometer in δ ppm using TMS as the standard, ESI-MS spectra were recorded on Jeol JMSD-300 spectrometer. Elemental analyses were performed on a Carlo Erba EA 1108 automatic elemental analyzer, compounds purity was checked by TLC plates (E Merck, Mumbai, India). The Supplemental Materials contain ^{1}H and ^{13}C NMR spectra of products **4**, **6**.

General procedure for the synthesis of compounds (4a–m and 6a–d)

An equimolar amount of 4-amino-5-hydrazinyl-*4H*-1,2,4-triazole-3-thiol (1 mmol) and phenacyl bromide (1 mmol) or 3-(2-bromoacetyl)-2*H*-chromen-2-one (1 mmol) in ethanol (5 ml) and catalytic amount of acetic acid (2 drops) was refluxed for 1 h. Then, the reaction mixture was treated with benzoylacetonitrile (1 mmol) and further refluxed for 1 h. The reaction mixture was cooled to room temperature. The solid separated was filtered and recrystallized from methanol to give final product.

Table1. Different substitutions of the compounds **4a–4m** and **6a–6d**.

Entry	Product	R	R^1	R^2	R^3	R^4	Yields (%)
1	**4a**	Cl	H	H	–	–	92
2	**4b**	Cl	CH_3	H	–	–	96
3	**4c**	Cl	Cl	H	–	–	90
4	**4d**	Cl	F	H	–	–	95
5	**4e**	Cl	OCH_3	H	–	–	95
6	**4f**	H	H	H	–	–	93
7	**4g**	H	Br	H	–	–	91
8	**4h**	H	CH_3	H	–	–	95
9	**4i**	H	Cl	Cl	–	–	89
10	**4j**	H	F	H	–	–	97
11	**4k**	H	OCH_3	H	–	–	92
12	**4l**	Cl	Ph	H	–	–	90
13	**4m**	H	H	CH_3	–	–	85
14	**6a**	H	–	–	H	OEt	96
15	**6b**	Cl	–	–	Cl	–	92
16	**6c**	Cl	–	–	H	OEt	97
17	**6d**	Cl	–	–	Br	OCH_3	93

3 -(4-Chlorophenyl)-1-(6-phenyl-7H-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazin-3-yl)-1H-pyrazol-5-amine (4a)

Pale yellow solid; mp 240–241 °C; Yield (92%); IR (KBr, ν_{max}, cm^{-1}): 3411 (NH_2 Stretching), 1618 (–C = N– stretching); ^{1}H NMR (400 MHz, DMSO-d_6, ppm): δ 4.49 (s, 2 H, CH_2), 5.90 (s, 1H), 7.46 (d, J = 8.4 Hz, 2H), 7.51–7.60 (m, 3 H ArH and 2 H NH_2), 7.79 (d, J = 8.8 Hz, 2H), 7.93 (d, J = 7.2 Hz, 2H); 13C NMR (100 MHz, DMSO-d_6, ppm): δ 23.5, 84.9, 127.5, 128.0, 129.1, 129.5, 130.7, 132.6, 133.1, 133.6, 142.8, 146.3, 151.9, 152.3, 156.6. ESI-MS, *m/z* (%): 408 $(M + H)^+$; anal. calcd. for $C_{19}H_{14}ClN_7S$: C, 55.95; H, 3.46; Cl, 8.69; N, 24.04; S, 7.86. Found: C, 55.90; H, 3.41; Cl, 8.62; N, 24.10; S, 7.82.

3 -(3-(5-Amino-3-phenyl-1H-pyrazol-1-yl)-7H-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazin-6-yl)-8-ethoxy-2H-chromen-2-one (6a)

Brown solid; mp 219–220 °C; Yield (96%); IR (KBr, ν_{max}, cm^{-1}): 3467 (NH_2 Stretching), 1722 (lactone C = O stretching), 1614 (–C = N– stretching); ^{1}H NMR (400 MHz, DMSO-d_6, ppm): δ 1.40 (t, J = 6.8 Hz, 3H), 4.19 (d, J = 6.8 Hz, 2H), 4.35 (s, 2H), 5.85 (s, 1H), 6.02 (s, 2H), 7.31–7.35 (m, 3H), 7.39 (t, J = 6.0 Hz, 3H), 7.75 (d, J = 7.2 Hz, 1H), 8.32 (s, 1H), 8.43 (s, 1H). ESI-MS, *m/z* (%): 486 $(M + H)^+$; anal. calcd. for $C_{24}H_{19}N_7O_3S$: C, 59.37; H, 3.94; N, 20.19; S, 6.60. Found: C, 59.32; H, 3.93; N, 20.15; S, 6.65.

Conclusion

In conclusion, we report a novel one-pot multicomponent synthesis of some 3-phenyl-1-(6-phenyl-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazin-3-yl)-1*H*-pyrazol-5-amines by using readily available starting materials. This synthetic method has more advantages such as shorter reaction time, no use of harsh reaction conditions, easy work-up procedure, and good to excellent yields of the products.

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