One-pot, Multicomponent Cascade Reaction for the Synthesis of Various Aralkyl/alkylthio-3,5-dimethyl-1*H*-pyrazolyl-4*H*-1,2,4-triazol-4-amine and Their Docking Studies

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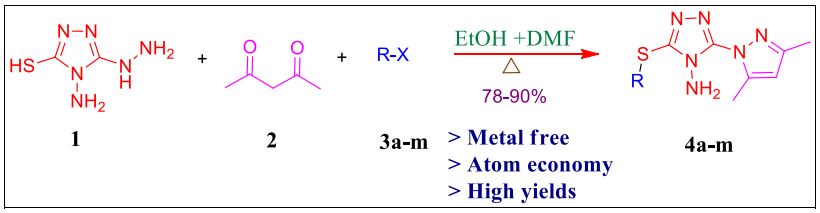

A facile and simple one-pot procedure for the synthesis of various aralkyl/alkylthio-3,5-dimethyl-1*H*-pyrazolyl-4*H*-1,2,4-triazol-4-amines has been described *via* a multicomponent reaction of 4-amino-5-hydrazinyl-4*H*-1,2,4-triazole-3-thiol, acetylacetone, and various aryl/alkyl halides in good yields. All the newly synthesized compounds were characterized by using analytical and spectral studies. Our in silico studies confirmed that **4e**, **4f**, **4g**, and **4j** have the best inhibition activity among the synthesized compounds with a high selective index against the Tubulin protein and showed best interactions with receptor structure. The present study provides a novel series of compounds with a promising inhibitor to prevent on Tubulin protein.

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INTRODUCTION

Chemical reactions that use three or more different starting materials as chemical structures and yields the final product in a one-pot procedure are usually called as multicomponent reactions. In multi component reaction (MCR), a product is accomplished according to a cascade of elementary chemical reactions. MCRs play an insignia part in organic chemistry because they produce the maximum yield of product and selectivity. They produce very less by-products compared with stepwise synthesis. Additionally, MCRs are operationally simple, cost-effective, rapid, and involve easy experimental procedures [1].

Triazole heterocyclic compounds is having a wide range of biological activities [2], like antifungal, CNS-stimulatory, antimicrobial, anticancer, antivirus, anti-HIV, and analgesic activities [3–6]. Likewise, there are known drugs consisting the triazole core ring, for example, etizolam, triazolam, furacilin, and alprazolam [7–10]. Pyrazole, which is a five-membered heterocyclic compound consisting of two nitrogen atoms at adjacent positions, and synthesis of pyrazoles were reported using various procedures in the literature [11]. Pyrazole motifs have been exhibiting interesting biological activities such as anticancer, analgesic, antimicrobial, antidiabetic, anti-inflammatory, and immunosuppressive activity [12–17].

Organosulfur chemistry is one of the most useful and important branch in organic synthesis. Compounds possessing C—S bonds are important in organic chemistry [18–21]. Thioethers are beneficial and important compounds in different branches such as materials, agriculture, industry, pharmaceutical, medicine, heterocyclic chemistry, and biological processes [22–30]. In the field of medicine, organosulfur compounds are broadly used for treatment of different types of diseases such as Alzheimer's, cancer, tuberculosis, and Parkinson [31–34].

RESULTS AND DISCUSSION

In view of the importance of triazoles, pyrazoles, and thioethers, we would like to incorporate all these units in single heterocyclic system so that the resulting molecule may exhibit good biological activity. In continuation of earlier work on MCR [35–37], in the present work, we are reporting the one-pot, multicomponent cascade reaction for the synthesis of various aralkyl/alkylthio-3,5-dimethyl-1*H*-pyrazolyl-4*H*-1,2,4-triazol-4-amines and their docking studies.

For the optimization of reaction conditions, the reaction was conducted with 4-amino-5-hydrazino-4*H*-[1,2,4] triazole-3-thiol (**1**), acetylacetone (**2**), and aralkyl/alkyl halides (**3**) in the water under reflux condition, and no product was formed. On the other hand, when the same reaction was carried out in a mixture of equal amount of

Table 1

Optimization conditions for the reaction **4a**.

Entry	Solvent	Base	Yield (%) of **4a**
1	H_2O	–	0
2	**EtoH**	**DMF**	**90**
3	EtoH	Et_3N	40
4	MeOH	Et_3N	25

Reaction conditions: **1** (1 mmol), **2** (1 mmol), and **3** (1 mmol) and base in the solvents.
DMF, dimethylformamide.
Bold text indicates good optimized condition.

dry ethanol and dimethylformamide (DMF) (1:1) under reflux produced the final compound in 90% yield. Additionally, when the same reaction was examined by using EtOH/Et_3N or MeOH/Et_3N produced lower yields of the product when compared with a mixture of dry ethanol and DMF. The optimized conditions for the heterocyclization and alkylation are a mixture of dry ethanol and DMF under reflux condition (Table 1).

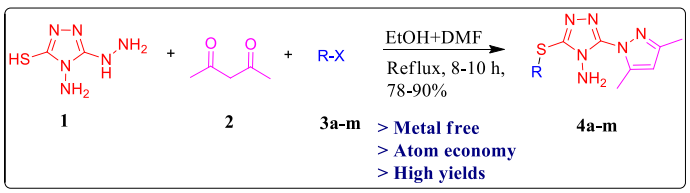
When the reaction is carried out between **1**, **2**, and **3**, there is a possibility of formation of mixture of products like **4**, **5**, or **6** or all of them. But in our case, only one product [*via* thin-layer chromatography (TLC)] formation is observed, that is, **4** only (Scheme 1). The alternative products such as **5** and **6** from the reaction can be rejected on the basis of spectral studies (Scheme 2).

In the present case, the reaction proceeds in such a way that only the hydrazino part of compound **1** undergoes condensation with **2** during heterocyclization followed by aralkylation/alkylation of the —SH group of compound **1** that lead to the formation of title compounds. The formation of S-aralkylated/S-alkylated products can be explained due to high nucleophilicity of thiol group compared with the amino group (Scheme 3). The yields of products obtained were 78–90%.

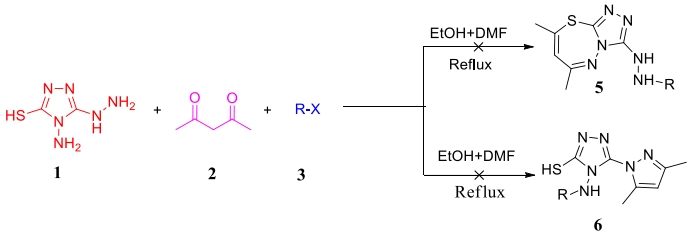
The structures of the products were confirmed by their spectral studies. For example, in the IR spectrum of compound **4a** displayed a peak at 3323 cm^{-1} (—NH_2) and 1584 cm^{-1}(—C═C—). In the ^{1}H-NMR ($CDCl_3$) spectrum of compound **4a** gave characteristic singlets for two —CH_3 groups of pyrazole at δ 2.26 and 2.53, a singlet for —SCH_2— at δ 4.46, —NH_2 two protons showed as a singlet at δ 5.22, and the pyrazole ring proton appeared as singlet at δ 6.02. The ^{13}C-NMR spectrum of compound **4a** displayed the peaks at δ 12.3 and 13.6 for two methyl group carbons of pyrazole. The benzylic (—S—CH_2—) carbon appeared at δ 35.9, and pyrazole carbon showed at δ 108.1. In mass spectrum, the compound **4a** appeared at *m/z* 301 $[M + H]^+$.

In the present one-pot, multicomponent cascade reaction conditions, the relative reactivities of various aralkyl and alkyl halides were examined. When the benzyl bromide (**3a**) and 4-nitrobenzyl bromide (**3b**) were reacted with **1** and **2**, they easily produced the corresponding thioether derivatives (**4a** and **4b**) in 90% and 88% yields, respectively (Table 2). Similarly, when the allyl halides such as propargyl bromide (**3c**) and allyl bromide (**3d**) were used, the expected products (**4c** and **4d**) were formed in 86% and 82% yields, respectively. When the reaction was carried out with bromo ethyl acetate (**3e**) and chloro acetic acid (**3f**), the expected products (**4e** and **4f**) were obtained in 80% and 84% yields, respectively. Furthermore, various alkyl halides (**3g–m**) were also utilized in the present reaction conditions, to give corresponding derivatives in good

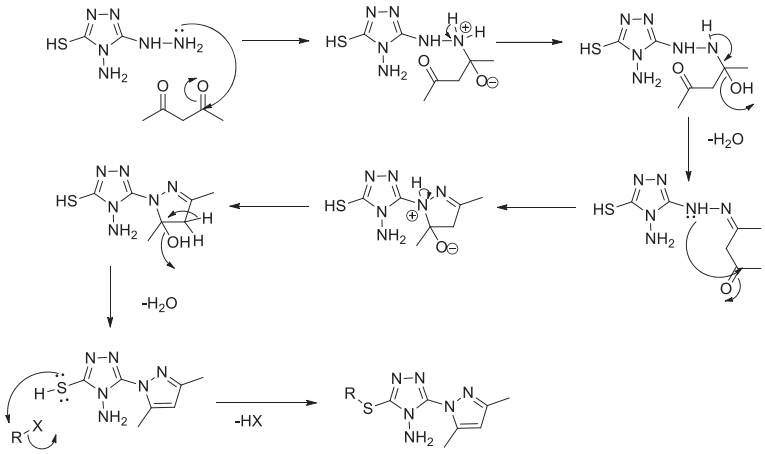
Scheme 1. Synthesis of various aralkyl/alkylthio-3,5-dimethyl-1*H*-pyrazolyl-4*H*-1,2,4-triazol-4-amines (**4a–m**). [Color figure can be viewed at wileyonlinelibrary.com]



Scheme 2. Alternative possible products of the reaction of **2** and **3** with **1**. [Color figure can be viewed at wileyonlinelibrary.com]



Scheme 3. Plausible mechanism for the one-pot, multicomponent cascade reaction for the synthesis of various aralkyl/alkylthio-3,5-dimethyl-1*H*-pyrazolyl-4*H*-1,2,4-triazol-4-amine (**4a**–**m**).



yields (**4g**–**m**; 82–78%). From this investigation, we have observed that the time required for the formation of the products **4a**–**m** depends on the type of aralkyl and alkyl halides. When compared with the alkyl halides, the aralkyl halides require less time and gave high yields of products.

MOLECULAR MODELING STUDIES

Molecular docking tool is helpful to investigate and to gain a profound insight into the mode of binding interactions of each ligand molecules (**4a**–**m**) with receptor structure. All chemical structures were drawn by using ChemDraw Ultra 12.0 and 2D structures drawn and converted to mol2 format by using Open Babel GUI version 2.3.2 (OpenBableGUI; Chris Morley, USA). Molecular energy was minimized using the Energy Minimization module of Discovery Studio version 4.1 (Accelrys Inc., San Diego, CA) under the chemistry at Harvard Macromolecular Mechanics (CHARMM) force field.

The three-dimensional structure of Tubulin protein was retrieved from Protein Data Bank (PDB ID:1SAO) [38]. Molecular docking studies for the synthesized compounds of **4a** to **4m** were performed. The structure preparation and correction protein were performed using Discovery Studio 4.1 suite. The target protein file was prepared by removing the structural water molecule, hetero atoms, and co-factors by leaving only the residues associated with protein by using Accelerys Discovery Studio 4.1 (ADS) tool, which was used to prepare target protein file addition of polar hydrogens to the macromolecule, an essential step to correct the calculation of partial charge by keeping all other values as default. The molecular docking was performed using Ligand Fit module, and obtained results were scrutinized based on highest dock score and number of H-bonds by SS Viewer [39]. The docking studies revealed that all the synthesized molecules exhibited excellent binding energies towards the receptor active sites.

RESULTS

We have carried out the docking studies and found the binding site of the receptor that makes the synthesized compounds easy to fit into the binding site, and it gives supporting evidence in the results. Microtubules are cytoskeletal polymers of Tubulin involved in numerous cellular functions. Their dynamic instability is controlled by several compounds and proteins, including Colchicine. Molecular docking studies suggested the best-interacted ligands at receptor site based on maximum possible interactions with low binding energy and high docking score. Table 3 represents the docking score and binding energies of **4a**–**4m**.

Docking analysis of most excellent active products in the active site of 1SAO receptor of Tubulin-Colchicine discovered that the hydrophobic interactions are significant for the activity. All these compounds showed good binding interactions with the receptor. The most potent compounds of **4e**, **4f**, **4g**, and **4j** showed maximum dock score good H-bond interactions with receptor, and these compounds are tabularized in Table 3. **4e**, **4f**, **4g**, and **4j** show the superior docking score in both open (PDB-1SAO) and closed conformations of the protein, which confirms its high binding affinity. In

addition, the high affinity of compounds can be further testified by its optimal potential energy, columbic and Van der Waals forces, interaction profile as well as excellent hydrogen bonding efficiency in the active site of the protein. The docking images of best compounds of **4e**, **4f**, **4g**, and **4j** were shown in Figure 1 receptor structure (amino acids). Are shown in wireframe representation and ligand structure as shown in sticks representation, and H-bonds are visualized by dotted lines.

Table 2

Synthesis of various aralkyl/alkylthio-3,5-dimethyl-1*H*-pyrazolyl-4*H*-1,2,4-triazol-4-amines (**4a**–**m**).

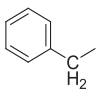
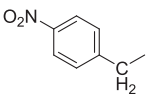
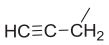
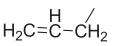
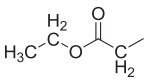
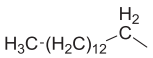
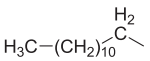
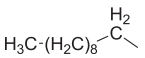
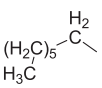
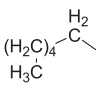
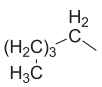
Compound 4	R–	M.F.	M.W.	Time (h)	Yield (%)
4a		$C_{14}H_{16}N_6S$	300	8.00	90
4b		$C_{14}H_{15}N_7O_2S$	345	8.30	88
4c		$C_{10}H_{12}N_6S$	248	8.20	86
4d		$C_{10}H_{14}N_6S$	250	8.40	82
4e		$C_{11}H_{16}N_6O_2S$	296	8.50	80
4f		$C_9H_{12}N_6O_2S$	268	9.00	84
4g		$C_{21}H_{38}N_6S$	406	9.20	82
4h		$C_{19}H_{34}N_6S$	378	9.20	83
4i		$C_{17}H_{30}N_6S$	350	9.30	81
4j		$C_{15}H_{26}N_6S$	322	9.30	85
4k		$C_{14}H_{24}N_6S$	308	9.40	88
4l		$C_{13}H_{22}N_6S$	294	9.40	84
4m		$C_{12}H_{20}N_6S$	280	9.50	78

Table 3

The docking interactions of **4a**–**m** compounds with active site of TUBULIN-COLCHICINE (1SAO).

Ligand name	Interacting residues		Distance (A°)	Docking energy (kcal)
	Ligand	Receptor (1SAO)		
4a	NH	OD1-ASP98	2.69	−88.2354
	NH	OD2-ASP69	2.86	
	NH	OE2-GLU71	2.97	
4b	NH	OG-SER140	2.74	−86.8753
4c	NH	OG-SER140	2.72	−88.1245
4d	NH	OD1-ASN228	2.60	−88.4578
4e	**NH**	**OG-SER140**	**2.55**	−89.2546
4f	**O**	**NH-THR145**	**2.60**	−88.1124
	O	**NH-GLY146**	**2.95**	
4g	**NH**	**O-SER178**	**2.59**	−89.9887
	NH	**O-VAL177**	**2.97**	
4h	NH	O-SER178	2.75	−79.2456
	NH	OE2-GLU183	2.78	
4i	NH	OG-SER140	2.69	−80.2013
4j	**NH**	**O-SER178**	**2.60**	−79.2451
	NH	**O-VAL177**	**2.72**	
4k	NH	OG-SER140	2.60	−79.2456
4l	NH	OD1-ASN228	2.77	−79.2345
4m	Not good interactions	–	–	–

Bold text signifies good interactions with receptors.

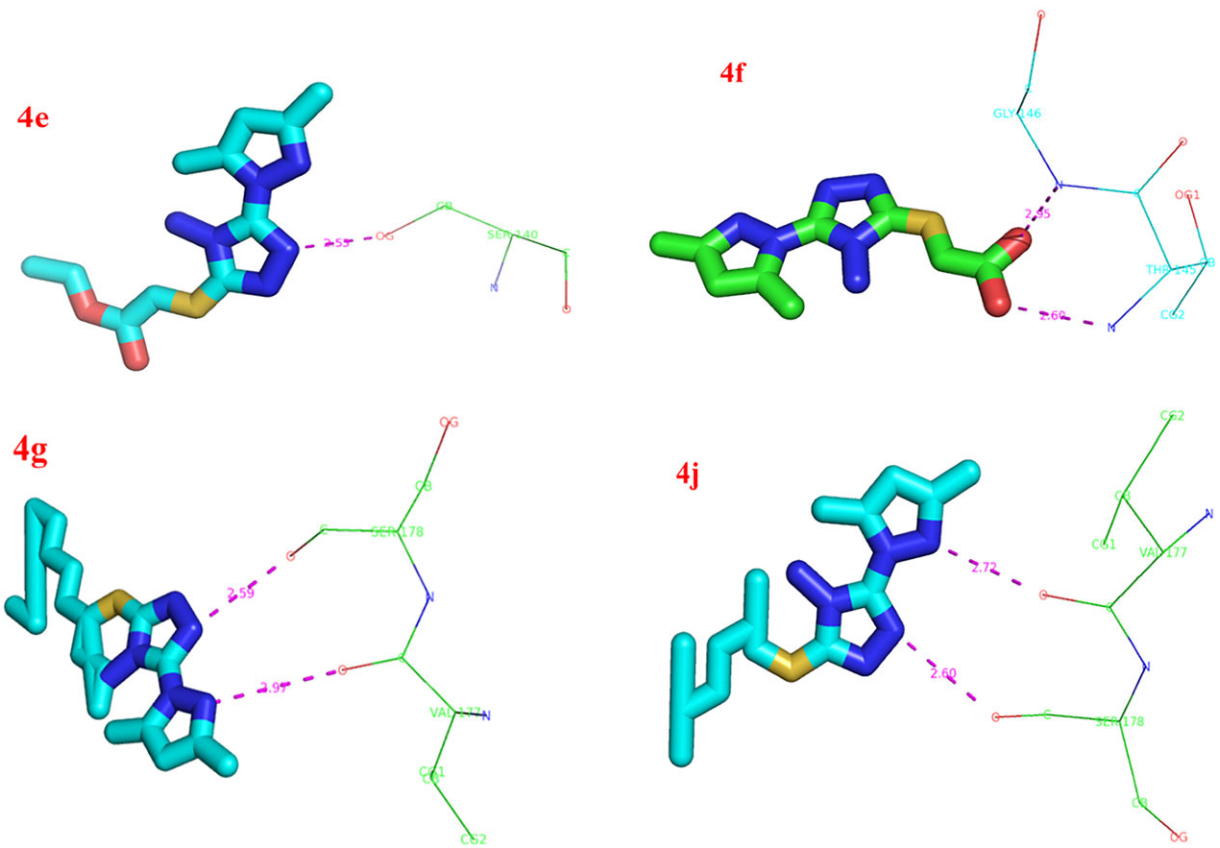


Figure 1. H-bonding interactions between amino acid residues at the active site of the TUBULIN and compounds **4e**, **4f**, **4g**, and **4j**. [Color figure can be viewed at wileyonlinelibrary.com]

CONCLUSION

In summary, a facile and simple procedure for the synthesis of various aralkyl/alkylthio-3,5-dimethyl-1*H*-pyrazolyl-4*H*-1,2,4-triazol-4-amines **4a**–**m** has been achieved *via* a multicomponent approach using readily available chemicals. The attractive and notable features of this approach is as good yields, neat reaction conditions, easy of product purification, metal free, atom economy, and avoiding toxic catalyst. The synthesized compounds could be useful for the medicinal chemistry applications. The biological activity of these compounds is in progress.

EXPERIMENTAL

All the reagents and chemicals were pure, procured commercially, and were used without further purification unless otherwise stated. 4-Amino-5-hydrazinyl-4*H*-1,2,4-triazole-3-thiol (**1**) was synthesized by the following literature procedure [40]. A mixture of thiourea (0.5 mol, 38 g) and 98% hydrazine hydrate (100 mL) were refluxed on water bath for 3 h. The reaction mixture was cooled, diluted with 150-mL distilled water, neutralized (pH 6.5) by adding approximately 10-mL Conc. HCl, and refrigerated at 0°C for 30 min. The crude product was filtered, washed with cold water, and digested in 75-mL 2 M HCl for 15 min. After removal of acid insoluble impurities, the filtrate was neutralized to pH 6.5 with NaOH and refrigerated at 0°C for 30 min. The solid was formed gradually. It was filtered, washed several times with water, dried, and recrystallized from water to give 4-amino-5-hydrazinyl-4*H*-1,2,4-triazole-3-thiol (**1**) as white solid.

All the synthesized compounds purity was checked by TLC (TLC plate) (E. Merck, Mumbai, India). Melting points were recorded by using "VEEGO" programmable melting point apparatus. IR spectra in KBr pellets were determined on a PerkinElmer 100S FTIR spectrophotometer. ^{1}H-NMR and ^{13}C-NMR spectra were recorded on a Bruker WM-400 spectrometer in δ ppm using tetramethylsilane as the reference standard. Dimethyl sulfoxide (DMSO-d_6) and $CDCl_3$ solvents were used for recording ^{1}H-NMR and ^{13}C-NMR. ESI-MS spectra of compounds were recorded on a PerkinElmer spectrometer operating at 12.5 eV. Carbon, Hydrogen, Nitrogen, Sulphur (CHNS) analysis was done on a Carlo Erba EA 1108 CHNS-O Elemental Analyzer.

General procedure for the one-pot, multicomponent cascade reaction for the synthesis of various aralkyl/alkylthio-3,5-dimethyl-1*H*-pyrazolyl-4*H*-1,2,4-triazol-4-amine (4a-m). A mixture of 4-amino-5-hydrazino-4*H*-[1,2,4]triazole-3-thiol (0.001 mol) and pentane-2,4-dione (0.001 mol) was refluxed for 3 h in dry ethanol (2 mL) in a 25-mL round bottom flask. Then to the reaction mixture, appropriate aralkyl/alkyl halides (0.001 mol) and DMF (2 mL) were added. The reaction mixture was refluxed for 8–10 h at 80–90°C by monitoring TLC. After completion of reaction, the resulting mixture was cooled, and the separated solid was filtered and recrystallized from 6- to 8-mL ethanol.

4-Amino-5-hydrazinyl-4H-1,2,4-triazole-3-thiol (1). White color solid; yield 72%; mp 236–238°C; IR (KBr, υ_{max}, cm^{-1}): 3440, 3268, 3215, 3075, 2915, 2792. ^{1}H-NMR (400 MHz, DMSO-d_6, δ ppm): 4.10 (s, 2H, hydrazino —NH_2), 5.27 (s, 2H, —NH_2), 7.15 (s, 1H, —NH—), 12.70 (s,1H, —SH). ^{13}C-NMR (100 MHz, DMSO-d_6, δ ppm): 155.1, 164.9. ESI-MS *m/z* 147 $[M + H]^+$.

3-(Benzylthio)-5-(3,5-dimethyl-1H-pyrazol-1-yl)-4H-1,2,4-triazol-4-amine (4a). White color solid; yield 90%; mp 140–142°C; IR (KBr, υ_{max}, cm^{-1}): 3323 (—NH_2). ^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm): 2.26 (s, 3H, —CH_3), 2.53 (s, 3H, —CH_3), 4.46 (s, 2H, —SCH_2—), 5.22 (s, 2H, —NH_2), 6.02 (s, 1H, —CH— of pyrazole ring), 7.31 (m, 3H, Ar-H), 7.43 (d, 2H, J = 8 Hz, Ar-H). ^{13}C-NMR (100 MHz, $CDCl_3$, δ ppm): 12.34, 13.57, 35.89, 108.11, 127.74, 128.68, 129.18, 136.75, 143.20, 147.66, 151.31, 151.83. ESI-MS *m/z* 301 $[M + H]^+$. Analytical calculated formulae $C_{14}H_{16}N_6S$: C, 55.98; H, 5.37; N, 27.98; S, 10.67. Found: C, 55.95; H, 5.40; N, 27.93; S, 10.71.

3-(3,5-Dimethyl-1H-pyrazol-1-yl)-5-((4-nitrobenzyl)thio)-4H-1,2,4-triazol-4-amine (4b). White color solid; yield 88%; mp 168–170°C; IR (KBr, υ_{max}, cm^{-1}): 3312 (—NH_2). ^{1}H-NMR (400 MHz, DMSO-d_6, δ ppm): 2.24 (s, 3H, —CH_3), 2.35 (s, 3H, —CH_3), 4.56 (s, 2H, —SCH_2—), 5.92 (s, 2H, —NH_2), 6.10 (s, 1H, —CH— of pyrazole ring), 7.73 (d, 2H, J = 8 Hz, Ar-H), 8.16 (d, 2H, J = 8 Hz, Ar-H). ^{13}C-NMR (100 MHz, DMSO-d_6, δ ppm): 11.6, 13.8, 33.9, 107.8, 123.9, 130.8, 143.1, 146.4, 147.1, 149.2, 151.1, 151.9. ESI-MS *m/z* 446 $[M + H]^+$. Analytical calculated formulae $C_{14}H_{15}N_7O_2S$: C, 48.69; H, 4.38; N, 28.39; S, 9.28. Found: C, 48.65; H, 4.33; N, 28.42; S, 9.25.

3-(3,5-Dimethyl-1H-pyrazol-1-yl)-5-(prop-2-yn-1-ylthio)-4H-1,2,4-triazol-4-amine (4c). White color solid; yield 86%; mp 165–167°C; IR (KBr, υ_{max}, cm^{-1}): 3434 (—NH_2). ^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm): 1.26 (s, 1H, —C≡C—H), 2.29 (s, 3H, —CH_3), 2.56 (s, 3H, —CH_3), 4.02 (s, 2H, —SCH_2—), 5.44 (s, 2H, —NH_2), 6.05 (s, 1H, —CH— of pyrazole ring). ^{13}C-NMR (100 MHz, $CDCl_3$ + DMSO-d_6, δ ppm): 12.1, 13.6, 19.7, 72.6, 78.7, 107.9, 142.9, 148.4, 150.4, 151.7. ESI-MS *m/z* 249 $[M + H]^+$. Analytical calculated formulae $C_{10}H_{12}N_6S$: C, 48.37; H, 4.87; N, 33.85; S, 12.91. Found: C, 48.34; H, 4.84; N, 33.89; S, 12.95.

3-(Allylthio)-5-(3,5-dimethyl-1H-pyrazol-1-yl)-4H-1,2,4-triazol-4-amine (4d). White color solid; yield 82%; mp 93–95°C; IR (KBr, υ_{max}, cm^{-1}): 3319 (—NH_2). ^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm): 2.29 (s, 3H, —CH_3), 2.55

(s, 3H, —CH_3), 3.91 (d, 2H, *J* = 8 Hz, —SCH_2—), 5.19 (d, 1H_A, H_X H_A, *J* = 8 Hz), 5.33 (s, 1H_B,), 5.38 (s, 2H, —NH_2), 6.03 (m, 1H_X, =CH—), 6.04 (s, 1H, —CH— of pyrazole ring). ^{13}C-NMR (100 MHz, $CDCl_3$, δ ppm): 12.3, 13.6, 34.1, 108.1, 119.0, 132.7, 143.2, 147.6, 151.2, 151.8. ESI-MS *m/z* 251 $[M + H]^+$. Analytical calculated formulae $C_{10}H_{14}N_6S$: C, 47.98; H, 5.64; N, 33.57; S, 12.81. Found: C, 47.95; H, 5.60; N, 33.60; S, 12.85.

Ethyl-2-((4-amino-5-(3,5-dimethyl-1H-pyrazol-1-yl)-4H-1,2,4-triazol-3-yl)thio) acetate (4e). White color solid; yield 80%; mp 100–102°C; IR (KBr, υ_{max}, cm^{-1}): 3304 (—NH_2). ^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm): 1.30 (t, 3H, *J* = 8 Hz, —CH_3), 2.29 (s, 3H, —CH_3), 2.54 (s, 3H, —CH_3), 4.05 (s, 2H, —SCH_2—), 4.24 (q, 2H, —CH_2O—), 5.49 (s, 2H, —NH_2) 6.04 (s, 1H, —CH— of pyrazole ring). ^{13}C-NMR (100 MHz, $CDCl_3$, δ ppm): 12.3, 13.6, 14.1, 33.6, 62.1, 108.1, 143.2, 147.9, 150.4, 151.9, 158.6. ESI-MS *m/z* 297 $[M + H]^+$. Analytical calculated formulae $C_{11}H_{16}N_6O_2S$: C, 44.58; H, 5.44; N, 28.36; S, 10.82. Found: C, 44.62; H, 5.47; N, 28.39; S, 10.87.

2-((4-Amino-5-(3,5-dimethyl-1H-pyrazol-1-yl)-4H-1,2,4-triazol-3-yl)thio) acetic acid (4f). White color solid; yield 84%; mp 202–204°C; IR (KBr, υ_{max}, cm^{-1}): 3293 (—NH_2). ^{1}H-NMR (400 MHz, DMSO-d_6, δ ppm): 2.21 (s, 3H, —CH_3), 2.25 (s, —NH_2), 2.34 (s, 3H, —CH_3), 3.93 (s, 2H, —SCH_2—), 6.03 (s, 1H, —CH— of pyrazole ring), 7.93 (s, 1H, —OH). ^{13}C-NMR (100 MHz, DMSO-d_6, δ ppm): 11.6, 13.8, 33.3, 107.7, 143.1, 149.0, 151.1, 152.4, 170.0. ESI-MS *m/z* 269 $[M + H]^+$. Analytical calculated formulae $C_9H_{12}N_6O_2S$: C, 40.29; H, 4.51; N, 31.32; S, 11.95. Found: C, 40.33; H, 4.55; N, 31.35; S, 11.99.

3-(3,5-Dimethyl-1H-pyrazol-1-yl)-5-(tetradecylthio)-4H-1,2,4-triazol-4-amine (4g). White color solid; yield 82%; mp 96–98°C; IR (KBr, υ_{max}, cm^{-1}): 3340 (—NH_2). ^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm): 0.88 (t, 3H, *J* = 8 Hz, —CH_3), 1.26 (unresolved m, 20H, —$(CH_2)_{10}$—), 1.45(m, 2H, —CH_2—), 2.28 (s, 3H, —CH_3), 2.54 (s, 3H, —CH_3), 3.26 (t, 2H, *J* = 8 Hz, —SCH_2—), 5.32 (s, 2H, —NH_2), 6.03 (s, 1H, —CH— of pyrazole ring). ^{13}C-NMR (100 MHz, DMSO-d_6, δ ppm): 11.6, 13.8, 22.6, 28.5, 29.0, 29.2, 29.4, 29.5, 30.9, 31.8, 107.6, 143.0, 148.9, 151.0, 152.9. ESI-MS *m/z* 407 $[M + H]^+$. Analytical calculated formulae $C_{21}H_{38}N_6S$; C, 62.03: H, 9.42; N, 20.67; S, 7.89. Found: C, 61.97; H, 9.38; N, 20.62; S, 7.93.

3-(3,5-Dimethyl-1H-pyrazol-1-yl)-5-(dodecylthio)-4H-1,2,4-triazol-4-amine (4h). White color solid; yield 83%; mp 73–75°C; IR (KBr, υ_{max}, cm^{-1}): 3340 (—NH_2). ^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm): 0.89 (t, 3H, *J* = 8 Hz, —CH_3), 1.29 (unresolved m, 16H, —$(CH_2)_8$—), 1.47 (m, 2H, —CH_2—), 1.81 (m, 2H, —CH_2—), 2.26 (s, 3H, —CH_3), 2.56 (s, 3H, —CH_3), 3.29 (t, 2H, *J* = 8 Hz, —SCH_2—), 5.27 (s, 2H, —NH_2), 6.04 (s, 1H, —CH— of pyrazole ring). ^{13}C-NMR (100 MHz, DMSO-d_6, δ ppm): 11.5, 13.8, 14.4, 22.6, 28.5, 29.0, 29.1, 29.4, 29.6, 30.9, 31.8, 107.7, 143.1, 148.9, 151.0, 152.9. ESI-MS *m/z* 351 $[M + H]^+$. Analytical calculated formulae $C_{19}H_{34}N_6S$: C, 60.28; H, 9.05; N, 22.20; S, 8.47. Found: C, 60.23; H, 9.11; N, 22.25; S, 8.43.

3-(Decylthio)-5-(3,5-dimethyl-1H-pyrazol-1-yl)-4H-1,2,4-triazol-4-amine (4i). White color solid; yield 81%; mp 78–80°C; IR (KBr, υ_{max}, cm^{-1}): 3341 (—NH_2). ^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm): 0.89 (t, 3H, *J* = 8 Hz, —CH_3), 1.28 (unresolved m, 12H, —$(CH_2)_6$—), 1.47(m, 2H, —CH_2—), 1.82 (m, 2H, —CH_2—), 2.29 (s, 3H, —CH_3), 2.55 (s, 3H, —CH_3), 3.27 (t, 2H, *J* = 8 Hz, —SCH_2—), 5.35 (s, 2H, —NH_2), 6.04 (s, 1H, —CH— of pyrazole ring). ^{13}C-NMR (100 MHz, $CDCl_3$, δ ppm): 12.3, 13.6, 14.1, 22.7, 28.8, 29.1, 29.3 29.4, 29.5, 31.2, 31.9, 108.1, 143.2, 147.6, 151.8, 152.2. ESI-MS *m/z* 351 $[M + H]^+$. Analytical calculated formulae $C_{17}H_{30}N_6S$: C, 58.25; H, 8.63; N, 23.98; S, 9.15. Found: C, 58.20; H, 8.68; N, 23.95; S, 9.19.

3-(3,5-Dimethyl-1H-pyrazol-1-yl)-5-(octylthio)-4H-1,2,4-triazol-4-amine (4j). White color solid; yield 85%; mp 95–97°C; IR (KBr, υ_{max}, cm^{-1}): 3325 (—NH_2). ^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm): 0.88 (t, 3H, *J* = 8 Hz, —CH_3), 1.27 (unresolved m, 8H, —$(CH_2)_4$—), 1.45 (m, 2H, —CH_2—), 1.80 (m, 2H, —CH_2—), 2.27 (s, 3H, —CH_3), 2.53 (s, 3H, —CH_3), 3.25 (t, 2H, *J* = 8 Hz, —SCH_2—), 5.34 (s, 2H, —NH_2), 6.02 (s, 1H, —CH— of pyrazole ring). ^{13}C-NMR (100 MHz, $CDCl_3$, δ ppm): 12.4, 13.6, 14.1, 22.6, 28.8, 29.1, 29.2, 29.5, 31.3, 31.8, 108.1, 143.2, 147.5, 151.8, 152.2. ESI-MS *m/z* 323 $[M + H]^+$. Analytical calculated formulae $C_{15}H_{26}N_6S$: C, 55.87; H, 8.13; N, 26.06; S, 9.94. Found: C, 55.83; H, 8.10; N, 26.12; S, 9.90.

3-(3,5-Dimethyl-1H-pyrazol-1-yl)-5-(heptylthio)-4H-1,2,4-triazol-4-amine (4k). White color solid; yield 90%; mp 90–92°C; IR (KBr, υ_{max}, cm^{-1}): 3296 (—NH_2). ^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm): 0.88 (t, 3H, *J* = 8 Hz,—CH_3), 1.29 (m, 6H, —$(CH_2)_3$—), 1.45 (m, 2H, —CH_2—), 1.80 (m, 2H, —CH_2—), 2.27 (s, 3H, —CH_3), 2.53 (s, 3H, —CH_3), 3.25 (t, 2H, *J* = 8 Hz, —SCH_2—), 5.33 (s, 2H, —NH_2), 6.02 (s, 1H, —CH— of pyrazole ring). ^{13}C-NMR (100 MHz, $CDCl_3$, δ ppm): 12.4, 13.6, 14.1, 22.6, 28.7, 28.8, 29.5, 31.3, 31.7, 108.1, 143.2, 147.5, 151.8, 152.2. ESI-MS *m/z* 309 $[M + H]^+$. Analytical calculated formulae $C_{14}H_{24}N_6S$: C, 54.52; H, 7.84; N, 27.25; S, 10.40. Found: C, 54.55; H, 7.80; N, 27.29; S, 10.46.

3-(3,5-Dimethyl-1H-pyrazol-1-yl)-5-(hexylthio)-4H-1,2,4-triazol-4-amine (4l). White color solid; yield 84%; mp 143–145°C; IR (KBr, υ_{max}, cm^{-1}): 3341 (—NH_2). ^{1}H-NMR (400 MHz, $CDCl_3$ + DMSO-d_6, δ ppm): 0.80 (t, 3H, *J* = 8 Hz, —CH_3), 1.24 (m, 4H, —$(CH_2)_2$—), 1.38 (m, 2H, —CH_2—), 1.71 (m, 2H, —CH_2—), 2.19 (s, 3H, —CH_3), 2.28 (s, 3H, —CH_3), 3.24 (t, 2H, *J* = 8 Hz, —SCH_2—), 4.26 (s, 2H, —NH_2), 5.96 (s, 1H, —CH— of pyrazole ring). ^{13}C-NMR (100 MHz, $CDCl_3$ + DMSO-d_6,

δ ppm): 11.1, 11.5, 13.7, 14.3, 29.5, 30.9, 31.2, 34.9, 107.8, 143.6, 144.8, 145.7, 151.5, 167.3. ESI-MS *m/z* 295 $[M + H]^+$. Analytical calculated formulae $C_{13}H_{22}N_6S$; C, 53.03; H, 7.53; N, 28.54; S, 10.89. Found: C, 52.97; H, 7.50; N, 28.57; S, 10.83.

3-(3,5-Dimethyl-1H-pyrazol-1-yl)-5-(pentylthio)-4H-1,2,4-triazol-4-amine (4m). White color solid; yield 78%; mp 126–128°C; IR (KBr, υ_{max}, cm^{-1}): 3341 (—NH_2). ^{1}H-NMR (400 MHz, $CDCl_3$ + DMSO-d_6, δ ppm): 0.82 (t, 3H, J = 8 Hz, —CH_3), 1.31 (m, 4H, —$(CH_2)_2$—), 1.71 (m, 2H, —CH_2—), 2.19 (s, 3H, —CH_3), 2.27 (s, 3H, —CH_3), 3.21 (t, 2H, J = 8 Hz, —SCH_2—), 4.02 (s, 2H, —NH_2), 5.96 (s, 1H, —CH— of pyrazole ring). ^{13}C-NMR (100 MHz, $CDCl_3$ + DMSO-d_6, δ ppm): 11.5, 13.8, 14.3, 22.1, 29.2, 30.7, 30.9, 107.8, 143.3, 148.9, 151.1, 151.4. ESI-MS *m/z* 281 $[M + H]^+$. Analytical calculated formulae $C_{12}H_{20}N_6S$: C, 51.40; H, 7.19; N, 29.97; S, 11.44. Found: C, 51.44; H, 7.15; N, 29.94; S, 11.40.

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