Multicomponent One-pot Synthesis of Oxadiazole Included Pyranopyrazoles as Promising Antioxidant Agents

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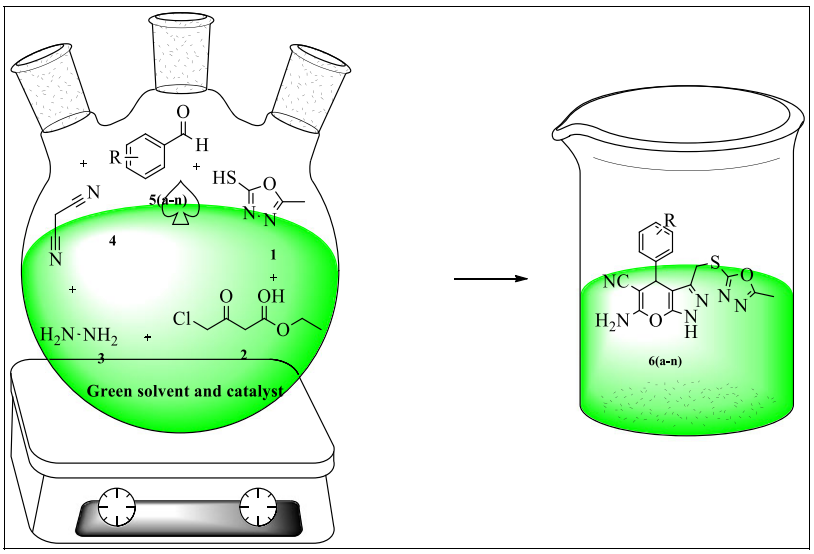
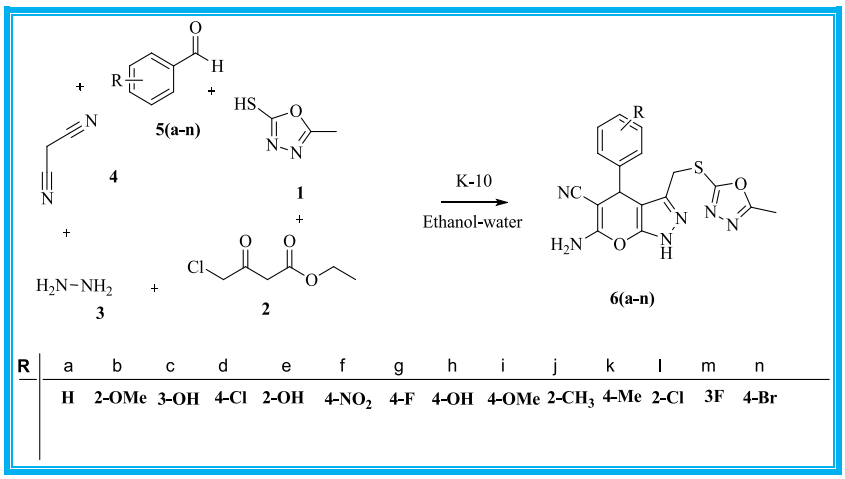


Oxadiazole-fused combinations are of great concern for the novelty of effective therapeutic agents. In this context, a series of oxadiazole included pyranopyrazoles were prepared under eco-friendly synthetic way by using montmorillonite k10 as a catalyst. All the final outcomes were formed with good yields. Further, compounds screened for their antioxidant assay. Most of the compounds revealed promising activity. Among all outcomes, electron rich-substituted compounds at *para* position demonstrated higher antioxidant activity than their corresponding *ortho*-substituted compounds. All belongings concluded that this eco-friendly path is preferable to prepare therapeutic compounds. Further, biotic results established that all these biologically active compounds fit for supplementary to develop exogenous antioxidant drugs.

INTRODUCTION

Ailments like atherosclerosis and cardiovascular, cancer, growing old, neurodegenerative syndromes inclusive of Parkinson's and Alzheimer's illnesses, autoimmune, and arthritis are due to cause of oxidative pressure only [1,2]. Because of cancer illness, universally, 80 lakh human beings have been died in the last 5 years, this is only because of oxidative pressure [3]. Human skeleton has its very individual antioxidant phenomena to switch injury from oxidative stress, but no longer completely remedy. In this case, the intake of exogenous antioxidants like natural nutrition or synthetic ones can increase security toward free radicals and enhance the excellence of life by avoiding from numerous syndromes. Moreover, to avoid the imbalance between reactive oxygen species and reactive nitrogen species, antioxidants are compulsory for accurate physiological task. Accordingly, the development of aggregates with antioxidant stuff has stepped forward in modern centuries, and many of structurally various motifs had been suggested. Further, risk-free reaction paths, budget controlled ways, quantitative outcome, and therapeutic compatibility are important strategies for development of antioxidant drug-related compounds. There are many heterocyclic compounds that possess several biological activities like antioxidant, antimicrobial, and anticancer. Among them, pyranopyrazoles are important motifs that showed anticancer, analgesic [4,5], antimicrobial [6], potential inhibitor of human Chk1 kinase [7], and anti-

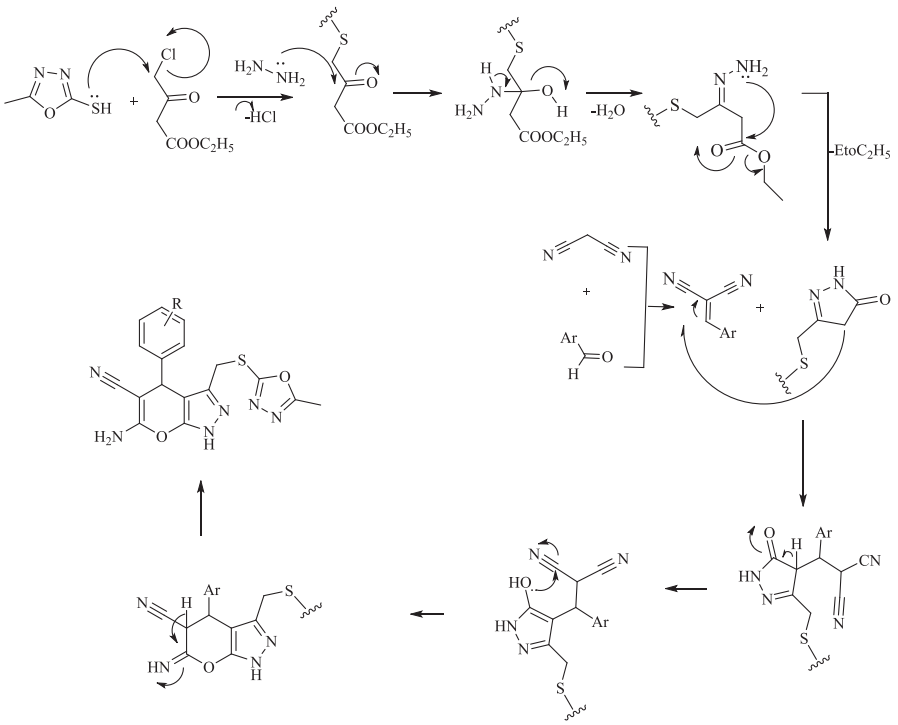
Scheme 1. Synthesis of pyranopyrazolyl oxadiazole derivatives. [Color figure can be viewed at wileyonlinelibrary.com]



inflammatory [8]. Moreover, the notice of pyranopyrazoles because of numerous series of flavanones and flavones has pyranopyrazole motif base that demonstrated admirable biotic properties [9–11]. Besides, 1,3,4-oxadiazoles presence worthy bioisosteres of amides and esters may work together with the receptors by making proton bonding and possibly raise the biotic profile significantly [12]. Several biologically active oxadizoles have been reported previously [13,14]. Biotic capacities of oxadiazoles were also reported in the literature as anticancer [15,16], antiproliferative [17], anti-HIV [18], anti-inflammatory [19], antitubercular [20], antimicrobial [21–23], anticonvulsant [24], antimalarial [25], antihepatitis B viral activities [26], and many more.

In extension of our investigation aims toward the enlargement of biologically energetic compounds with the help of eco-friendly synthetic manner [27,28], the present work green synthesis of oxadiazole attached

Scheme 2. Mechanism of product.



pyranopyrazoles has been taken up. All the compounds were screened for their free radical scavenging activity and the structure–activity relationships also discussed.

RESULTS AND DISCUSSION

Chemistry. The general production for the novel pyranopyrazoles having oxadaizole moiety as an attached one **6(a–n)** was depicted in Scheme 1. The vital step was the multicomponent one-pot condensation reaction of 2,5-substituted oxadiazole, ethyl 4-chloro-3-oxobutanoate, malononitrile, hydrazine hydrate, and different substituted aromatic aldehydes (**5a–n**). Montmorillonite k10 green acid catalyst was utilized for this synthetic path under ethanol–water eco-friendly solvent medium. All the compounds formed with quantitative yields. Among them, 4-(3-hydroxyphenyl)-3-(((5-methyl-1,3,4-oxadiazol-2-yl)thio)methyl)-6-amino-1,4-dihydropyrano[2,3-*c*]pyrazole-5-carbonitrile (**6c**) compound resulted with a yield of 92% followed by the compound **6g** and **6k** of yield 91%. Moreover, ortho methyl benzaldehyde (**5j**) used reaction gave the yield of 90% and this yield belongs to compound **6j**. Remaining compounds and their yields range from 80% to 89%. Final products characterized by proton NMR, carbon NMR, and high-resolution mass spectrometry (HRMS) spectral data. The proposed mechanism for the formation of product was drawn in Scheme 2. Further, green catalyst and eco-friendly solvent facilitated reaction path was distinguished manner to get the better yield of oxadiazole connected pyranopyrazoles. Thus, K 10 reagent is a main role to endorse this research path. Because of its acidic nature to recruit the reactions quickly, simple work-up process that means regained the catalyst easily without any complications, inexpensive and also its natural solvent compatibility. Totally ecofriendly outputs are expected with the use of K 10 catalyst.

Table 1

DPPH Method for the *in vitro* antioxidant action of test composites **6(a–n)**.

Composites	Concentration (μg/mL)	
	100	200
6a	51.18 ± 0.52	53.14 ± 0.08
6b	68.11 ± 0.61	74.18 ± 0.27
6c	45.73 ± 0.64	48.02 ± 0.39
6d	46.92 ± 0.22	50.10 ± 0.62
6e	56.70 ± 0.61	61.45 ± 0.11
6f	-	-
6g	-	-
6h	59.57 ± 0.51	65.18 ± 0.01
6i	70.10 ± 0.44	78.10 ± 0.05
6j	61.85 ± 0.55	66.47 ± 0.32
6k	65 ± 0.10	71.45 ± 0.86
6l	41.49 ± 0.06	44.58 ± 0.66
6m	-	-
6n	49.51 ± 0.32	5.72 ± 0.09
Ascorbic acid	71.15 ± 0.48	84.25 ± 0.32
Blank	-	

†Values are expressed in mean ± standard deviation of three replicates and "-" symbol indicated no scavenging activity.

Table 2

H_2O_2 Method for the *in vitro* antioxidant action of test compounds **6(a–n)**.

Composites	Concentration (μg/mL)	
	100	200
6a	49.18 ± 0.55	53.14 ± 0.41
6b	64.81 ± 0.64	72.10 ± 0.64
6c	42.14 ± 0.51	44.04 ± 0.28
6d	45.11 ± 0.42	47.09 ± 0.15
6e	51.43 ± 0.08	55.16 ± 0.15
6f	-	-
6g	-	-
6h	55.88 ± 0.46	59.41 ± 0.84
6i	66.28 ± 0.52	73.09 ± 0.71
6j	58.27 ± 0.01	64.33 ± 0.41
6k	60.10 ± 0.44	66.64 ± 0.19
6l	40.15 ± 0.88	43.17 ± 0.05
6m	-	-
6n	46.28 ± 0.01	50.58 ± 0.16
Ascorbic acid	69.18 ± 0.56	75.19 ± 0.49
Blank	-	

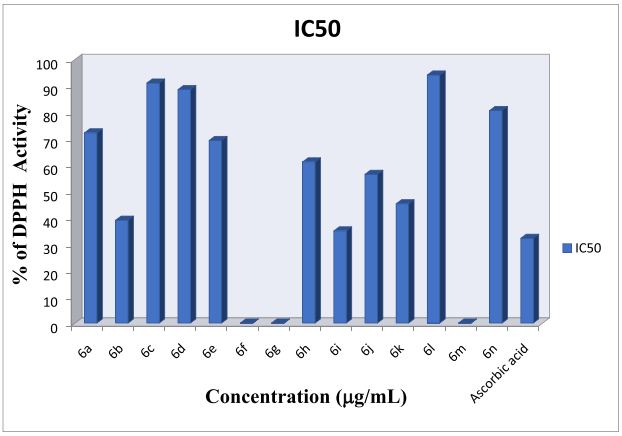
†Values are expressed in mean ± standard deviation of three replicates and "-" symbol indicated no scavenging activity.

Biological evaluation. ***Antioxidant results.*** The screened results of 2,2-diphenyl-1-picrylhydrazyl and hydrogen peroxide free radical scavenging activities of synthetic molecules were tabulated in Tables 1 and 2. These results were denoted as the concentration of the evaluated moiety that reduces 50% (IC_{50}) of 2,2-diphenyl-1-picrylhydrazyl and hydrogen peroxide free radicals (Table 3). From all the tested stuffs, superior free radical

Table 3

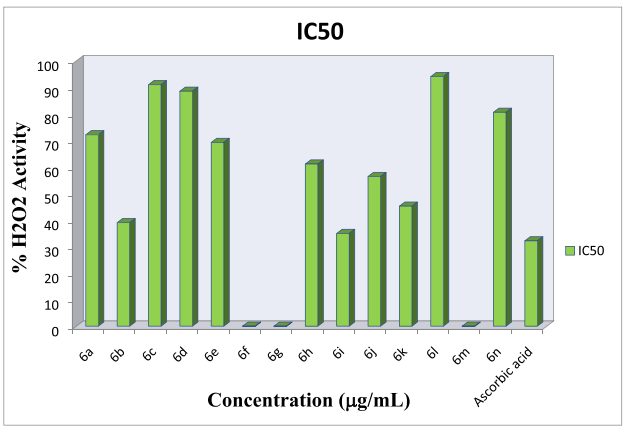
DPPH and H_2O_2 antioxidant assays of compounds **6(a–n)**.

Compound	IC_{50} (μg/mL)	
	DPPH	H_2O_2
6a	63.96	72.13
6b	25.17	39.01
6c	83.72	91.01
6d	80.56	88.54
6e	59.23	69.25
6f	0.0	0.0
6g	0.0	0.0
6h	50.01	61.11
6i	24.10	34.95
6j	46.96	56.41
6k	31.05	45.23
6l	88.12	94.06
6m	0.0	0.0
6n	77.91	80.61
Ascorbic acid	23.75	32.15



Graph 1. DPPH free radical scavenging activity of compounds **6**(**a**–**n**). [Color figure can be viewed at wileyonlinelibrary.com]

scavenging assay has seemed for those stuff that having electron rich substituent at *ortho* and *para* position on the core particularly para attached compounds. In this way, the combinations 4-(4-methoxyphenyl)-3-(((5-methyl-1,3,4-oxadiazol-2-yl)thio)methyl)-6-amino-1,4-dihydropyrano[2,3-*c*]pyrazole-5-carbonitrile (**6i**) and 4-(2-methoxyphenyl)-3-(((5-methyl-1,3,4-oxadiazol-2-yl)thio)methyl)-6-amino-1,4-dihydropyrano[2,3-*c*]pyrazole-5-carbonitrile (**6b**) displayed prominent antioxidant activity than other active compounds in two methods (Graphs 1 and 2). But there was a competition between these two compounds regarding the free radical scavenging activity. The motif contained *para* substitution core (**6i**) exhibited outstanding antioxidant assay than **6b** having *ortho* substitution core. In addition, composite **6k** showed heavier active than compound **6j** even though both motifs have the same substitution, while the same results observed in compounds **6h** and **6e** that compound **6h** showed good antioxidant activity than **6e** although two compounds have hydroxyl group as a substitution. There



Graph 2. H_2O_2 free radical scavenging activity of compounds **6**(**a**–**n**). [Color figure can be viewed at wileyonlinelibrary.com]

was thought-provoking point witnessed that all the combinations having attached group at *para* position possess excellent antioxidant activity than the compounds their corresponding group linked at *ortho* position. Further, compounds **6a**, **6c**, **6d**, **6l**, and **6n** displayed good to low through moderate biological activity. In fact, the other amalgams were inactive. From the earlier results recognized that all these biologically active amalgams fit for additional to develop exogenous antioxidant drugs.

CONCLUSION

Multicomponent reaction was carried out to prepare bis heterocyclic compounds by using green solvent and catalyst. Final products were formed with higher yields. This method may be used to prepare compounds under eco-friendly path. Later, total compounds were screened for their free radical scavenging activity by using two different methods and minimum inhibitory concentration also measured. From the biological results, para-substituted compounds displayed promising antioxidant activity than corresponding ortho-substituted compounds.

EXPERIMENTAL

General chemistry. Overall, initial components and reagent were pure and commercially accessible. For ^{1}H NMR, 400 MH_Z and for ^{13}C NMR, 100 MHz were used. Dimethyl sulfoxide and chloroform deuterated mixed solvent was used to record both NMR spectra's. Tetramethylsilane as a reference sample. Melting point statistics were distinguished with micro melting point operator and were uncorrected. HRMS info was calculated with the help of electrospray ionization.

Method for oxadiazole included pyranopyrazoles preparation 6(**a**–**n**). In a round bottom flask, the solution of ethyl 4-chloro-3-oxobutanoate (**2**) (1 mmol) and catalyst K 10 in 7.5 mL ethanol–water solvent mixture (2:0.5). To this, starting compounds such as 5-methyl-2-thiolyl-1,3,4-oxadiazole (**1**) (1.1 mmol), malononitrile (**4**) (1 mmol), hydrazine hydrate (**3**) (1 mmol), and benzaldehyde (**5a**) (1 mmol) were added. The whole blend was switched at 65–70°C for 5–7 h. After completion of the reaction checked by means of thin-layer chromatography, ethyl acetate solvent was added to crude (10 mL). The undissolved material was filtered over a cotton plug; the remaining result was intense under vacuum and decontaminated by separation method with hexane/ethyl acetate (1:2) as eluent, lead to compound **6a**. The cotton plug holding the substance and was dipped into the beaker having 8 mL of ethyl acetate, then the catalyst stables down to the lowest of the vessel. Detached the cotton monitored by decanted of solvent got the

uncontaminated catalyst and it was reused. Using the corresponding aldehydes compounds **6**(**b**–**n**) were prepared with this procedure.

3-(((5-Methyl-1,3,4-oxadiazol-2-yl)thio)methyl)-6-amino-4-phenyl-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (6a). Light yellow solid; yield 84%; mp 204–206°C; ^{1}H NMR: δ 2.35 (s, 3H, CH_3), 3.76 (s, 2H, CH_2), 4.61 (s, 1H, CH), 7.39–7.67 (m, 5H, Ar—H), 8.65 (br, 2H, NH_2) ppm; ^{13}C NMR: δ 166.3 (NH_2—C—O), 161.4 (N═C—S), 155.2 (O—C—NH), 144.5 (N═C—CH_3), 135.1, 133.9, 133.2, 131.4, 128.2, 125.3, 114.1 (CN), 56.6 (C—CN), 33.9 (CH), 29.5 (CH_2), 19.5 (CH_3) ppm; HRMS: *m/z* calcd for $C_{17}H_{15}N_6O_2S$ $(M + H)^+$ 367.0977; Found 367.0975.

4-(2-Methoxyphenyl)-3-(((5-methyl-1,3,4-oxadiazol-2-yl) thio)methyl)-6-amino-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (6b). Yellow solid; yield 87%; mp 211–213°C; ^{1}H NMR: δ 2.41 (s, 3H, CH_3), 3.69 (s, 2H, CH_2), 3.93 (s, 3H, OCH_3), 4.62 (s, 1H, CH), 7.34–7.82 (m, 4H, Ar—H), 8.61 (br, 2H, NH_2) ppm; ^{13}C NMR: δ 165.4 (NH_2—C—O), 160.1 (N═C—S), 157.8 (O—C—NH), 146.1 (N═C—CH_3), 137.4, 133.1, 129.5, 128.2, 126.5, 125.0, 123.9, 122.1, 112.3 (CN), 59.8 (OCH_3), 56.9 (C—CN), 33.1 (CH), 29.4 (CH_2), 19.5 (CH_3) ppm; HRMS: *m/z* calcd for $C_{18}H_{17}N_6O_3S$ $(M + H)^+$ 397.1083; Found 397.1080.

4-(3-Hydroxyphenyl)-3-(((5-methyl-1,3,4-oxadiazol-2-yl)thio) methyl)-6-amino-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (6c). Light yellow solid; yield 92%; mp 198–200°C; ^{1}H NMR: δ 2.40 (s, 3H, CH_3), 3.70 (s, 2H, CH_2), 4.62 (s, 1H, CH), 7.34–7.67 (m, 4H, Ar—H), 8.63 (br, 2H, NH_2) ppm; ^{13}C NMR: δ 166.2 (NH_2—C—O), 162.4 (N═C—S), 154.7 (O—C—NH), 146.2 (N═C—CH_3), 137.3, 136.1, 134.7, 132.2, 131.8, 130.5, 128.3, 126.8, 111.3 (CN), 57.2 (C—CN), 34.6 (CH), 29.2 (CH_2), 19.5 (CH_3) ppm; HRMS: *m/z* calcd for $C_{17}H_{15}N_6O_3S$ $(M + H)^+$ 383.0926; Found 383.0924.

4-(4-Chlorophenyl)-3-(((5-methyl-1,3,4-oxadiazol-2-yl)thio) methyl)-6-amino-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (6d). Light yellow solid; yield 83%; mp 184–186°C; ^{1}H NMR: δ 2.39 (s, 3H, CH_3), 3.78 (s, 2H, CH_2), 4.72 (s, 1H, CH), 7.31–7.80 (m, 4H, Ar—H), 8.65 (br, 2H, NH_2) ppm; ^{13}C NMR: δ 167.3 (NH_2—C—O), 162.8 (N═C—S), 153.6 (O—C—NH), 145.3 (N═C—CH_3), 137.2, 135.3, 132.1, 131.1, 129.6, 127.3, 116.1 (CN), 56.3 (C—CN), 34.2 (CH), 29.2 (CH_2), 19.1 (CH_3) ppm; HRMS: *m/z* calcd for $C_{17}H_{14}ClN_6O_2S$ $(M + H)^+$ 401.0587; Found 401.0582.

4-(2-Hydroxyphenyl)-3-(((5-methyl-1,3,4-oxadiazol-2-yl)thio) methyl)-6-amino-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (6e). Yellow solid; yield 86%; mp 224–226°C; ^{1}H NMR: δ 2.33 (s, 3H, CH_3), 3.65 (s, 2H, CH_2), 4.59 (s, 1H, CH), 7.41–7.82 (m, 4H, Ar—H), 8.61 (br, 2H, NH_2) ppm; ^{13}C NMR: δ 165.1 (NH_2—C—O), 160.6 (N═C—S), 154.3 (O—C—NH), 145.2 (N═C—CH_3), 134.6, 132.4, 131.7, 128.4, 126.3, 125.1, 123.0, 122.1, 113.5 (CN), 56.2 (C—CN), 36.0 (CH), 31.6 (CH_2), 19.6 (CH_3) ppm; HRMS: *m/z* calcd for $C_{17}H_{15}N_6O_3S$ $(M + H)^+$ 383.0926; Found 383.0923.

6-Amino-4-(4-nitrophenyl)-3-(((5-methyl-1,3,4-oxadiazol-2-yl)thio)methyl)-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (6f). Light yellow solid; yield 84%; mp 189–190°C; ^{1}H NMR: δ 2.41 (s, 3H, CH_3), 3.75 (s, 2H, CH_2), 4.64 (s, 1H, CH), 7.22–7.79 (m, 4H, Ar—H), 8.71 (br, 2H, NH_2), ppm; ^{13}C NMR: δ 169.4 (NH_2—C—O), 161.6 (N═C—S), 155.6 (O—C—NH), 146.2 (N═C—CH_3), 138.2, 136.4, 135.2, 132.6, 130.3, 128.8, 115.3 (CN), 57.2 (C—CN), 32.6 (CH), 30.1 (CH_2), 19.8 (CH_3) ppm; HRMS: *m/z* calcd for $C_{17}H_{14}N_7O_4S$ $(M + H)^+$ 412.0828; Found 412.0827.

3-(((5-Methyl-1,3,4-oxadiazol-2-yl)thio)methyl)-4-(4-fluorophenyl)-6-amino-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (6g). Light yellow solid; yield 91%; mp 170–172°C; ^{1}H NMR: δ 2.39 (s, 3H, CH_3), 3.84 (s, 2H, CH_2), 4.71 (s, 1H, CH), 7.29–7.84 (m, 4H, Ar—H), 8.82 (br, 2H, NH_2) ppm; ^{13}C NMR: δ 168.8 (NH_2—C—O), 162.6 (N═C—S), 155.2 (O—C—NH), 143.2 (N═C—CH_3), 137.0, 135.3, 133.4, 131.9, 129.4, 126.4, 112.7 (CN), 59.1 (C—CN), 31.8 (CH), 29.1 (CH_2), 19.7 (CH_3) ppm; HRMS: *m/z* calcd for $C_{17}H_{14}FN_6O_2S$ $(M + H)^+$ 385.0883; Found 385.0881.

4-(4-Hydroxyphenyl)-3-(((5-methyl-1,3,4-oxadiazol-2-yl)thio) methyl)-6-amino-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (6h). Light yellow solid; yield 84%; mp 218–220°C; ^{1}H NMR: δ 2.32 (s, 3H, CH_3), 3.74 (s, 2H, CH_2), 4.61 (s, 1H, CH), 7.17–7.74 (m, 4H, Ar—H), 8.70 (br, 2H, NH_2) ppm; ^{13}C NMR: δ 166.1 (NH_2—C—O), 160.6 (N═C—S), 154.0 (O—C—NH), 145.8 (N═C—CH_3), 135.4, 133.1, 131.5, 130.2, 127.3, 123.7, 111.7 (CN), 57.9 (C-CN), 32.0 (CH), 281 (CH_2), 19.4 (CH3) ppm; HRMS: *m/z* calcd for $C_{17}H_{15}N_6O_3S$ $(M + H)^+$ 383.0926; Found 383.0924.

4-(4-Methoxyphenyl)-3-(((5-methyl-1,3,4-oxadiazol-2-yl) thio)methyl)-6-amino-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (6i). Light yellow solid; yield 81%; mp 191–193°C; ^{1}H NMR: δ 2.31 (s, 3H, CH_3), 3.59 (s, 2H, CH_2), 3.89 (s, 3H, OCH_3), 4.62 (s, 1H, CH), 7.25–7.91 (m, 4H, Ar—H), 8.60 (br, 2H, NH_2) ppm; ^{13}C NMR: δ 168.2 (NH_2—C—O), 161.7 (N═C—S), 155.5 (O—C—NH), 146.5 (N═C—CH3), 135.2, 133.5, 132.2, 128.2, 125.9, 123.6, 112.16 (CN), 58.4 (OCH_3), 55.0 (C—CN), 32.2 (CH), 28.1 (CH_2), 19.2 (CH_3) ppm; HRMS: *m/z* calcd for $C_{18}H_{17}N_6O_3S$ $(M + H)^+$ 397.1083; Found 397.1079.

3-(((5-Methyl-1,3,4-oxadiazol-2-yl)thio)methyl)-4-(o-tolyl)-6-amino-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (6j). Pale yellow solid; yield 90%; mp 177–179°C; ^{1}H NMR: δ 2.29 (s, 3H, CH_3), 2.41 (s, 3H, CH_3), 3.60 (s, 2H, CH_2), 4.53 (s, 1H, CH), 7.24–7.69 (m, 4H, Ar—H), 8.62 (br, 2H, NH_2) ppm; ^{13}C NMR: δ 164.6 (NH_2—C—O), 160.3 (N═C—S), 155.1 (O—C—NH), 142.4 (N═C—CH_3), 135.2, 133.3, 130.4, 129.2, 127.1, 126.3, 124.2, 122.7, 111.3 (CN), 56.3 (C—CN), 33.9 (CH), 28.5 (CH_2), 19.6 (CH_3), 18.1 (CH_3) ppm; HRMS: *m/z* calcd for $C_{18}H_{17}N_6O_2S$ $(M + H)^+$ 381.1134; Found 381.1130.

3-(((5-Methyl-1,3,4-oxadiazol-2-yl)thio)methyl)-4-(p-tolyl)-6-amino-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (6k). Light yellow solid; yield 91%; mp 207–209°C; ^{1}H NMR: δ 2.32 (s, 3H, CH_3), 2.47 (s, 3H, CH_3), 3.58 (s, 2H, CH_2), 4.46 (s, 1H, CH), 7.19–7.73 (m, 4H, Ar—H), 8.66 (br, 2H, NH_2) ppm; ^{13}C NMR: δ 165.3 (NH_2—C—O), 159.1 (N=C—S), 152.4 (O—C—NH), 144.3 (N=C—CH_3), 132.6, 131.5, 130.1, 128.2, 126.5, 124.7, 118.2 (CN), 57.1 (C—CN), 32.5 (CH), 29.5 (CH_2), 19.4 (CH_3), 18.1 (CH_3) ppm; HRMS: *m/z* calcd for $C_{18}H_{17}N_6O_2S$ $(M + H)^+$ 381.1134; Found 381.1131.

4-(2-Chlorophenyl)-3-(((5-methyl-1,3,4-oxadiazol-2-yl)thio)methyl)-6-amino-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (6l). Yellow solid; yield 80%; mp 231–233°C; ^{1}H NMR: δ 2.32 (s, 3H, CH_3), 3.61 (s, 2H, CH_2), 4.58 (s, 1H, CH), 7.26–7.92 (m, 4H, Ar—H), 8.54 (br, 2H, NH_2) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): 168.2 (NH_2—C—O), 161.3 (N=C—S), 154.9 (O—C—NH), 146.1 (N=C—CH_3), 136.9, 135.1, 133.4, 132.2, 129.2, 125.2, 124.1, 122.3, 114.5 (CN), 55.3 (C—CN), 35.2 (CH), 29.3 (CH_2), 20.1 (CH_3) ppm; HRMS: *m/z* calcd for $C_{17}H_{14}ClN_6O_2S$ $(M + H)^+$ 401.0587; Found 401.0584.

4-(3-Fluorophenyl)-3-(((5-methyl-1,3,4-oxadiazol-2-yl)thio)methyl)-6-amino-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (6m). Yellow solid; yield 89%; mp 195–197°C; ^{1}H NMR: δ 2.33 (s, 3H, CH_3), 3.76 (s, 2H, CH_2), 4.72 (s, 1H, CH), 7.21–7.86 (m, 4H, Ar—H), 8.75 (br, 2H, NH_2) ppm; ^{13}C NMR: δ 169.3 (NH_2—C—O), 162.3 (N=C—S), 154.5 (O—C—NH), 144.1 (N=C—CH_3), 138.5, 136.2, 133.6, 131.3, 130.6, 128.5, 126.3, 124.1, 114.4 (CN), 56.9 (C—CN), 34.2 (CH), 29.6 (CH_2), 20.1 (CH_3) ppm; HRMS: *m/z* calcd for $C_{17}H_{14}FN_6O_2S$ $(M + H)^+$ 385.0883; Found 383.0881.

4-(4-Bromophenyl)-3-(((5-methyl-1,3,4-oxadiazol-2-yl)thio)methyl)-6-amino-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (6n). Pale yellow solid; yield 88%; mp 180–182°C; ^{1}H NMR: δ 2.30 (s, 3H, CH_3), 3.63 (s, 2H, CH_2), 4.65 (s, 1H, CH), 7.25–7.81 (m, 4H, Ar—H), 8.60 (br, 2H, NH_2) ppm; ^{13}C NMR: 166.6 (NH_2—C—O), 159.9 (N=C—S), 154.1 (O—C—NH), 144.6 (N=C—CH_3), 135.3, 133.2, 131.6, 128.3, 126.5, 124.1, 113.5 (CN), 56.2 (C—CN), 30.9 (CH), 29.5 (CH_2), 19.3 (CH_3), ppm; HRMS: *m/z* calcd for $C_{17}H_{14}BrN_6O_2S$ $(M + H)^+$ 445.0082; Found 445.0081.

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