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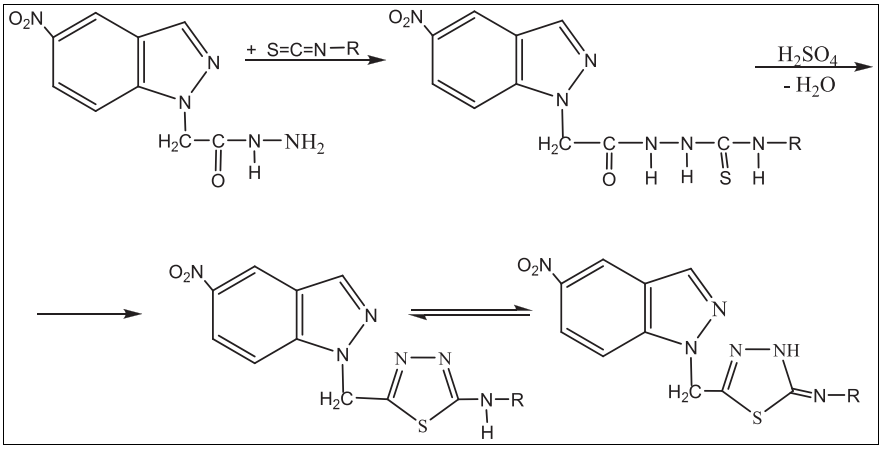

The synthesis of new derivatives of 1,3,4-thiadiazoles and 1,2,4-triazoles was achieved using the 1,4-disubstituted thiosemicarbazides as intermediaries.

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INTRODUCTION

The observation that compounds like thiadiazoles and triazoles have an essential role in the structure and function of certain molecules of importance from a biological point of view was only the beginning for the search of such compounds with significant pharmacological application.

Research in this direction showed the importance of the heterocycle structures in the composition of drugs with antibacterial [1–6], antifungal [3,5,7–10], tuberculostatic [11,12], analgesic [3,7,9,13], anti-inflammatory [3,7,9,14–17], cardioprotective [18], antidepressant [19] as well as antitumoural [6] activity.

The literature and various articles seem to indicate that indazole molecule has a wide range of biological properties, such as anti-inflammatory [20], hepatoprotective [21], analgesic [20], antibacterial [22], antiangiogenic [23], cytostatic [24] as well as tuberculostatic [25] activity. These are just some of the reasons why we directed our research towards the study of the thiadiazoles and triazoles.

The aim of our research is the synthesis of new heterocyclic compounds that would contain in their structure both the 5-nitroindazole and the 1,3,4-thiadiazole and/or the 1,2,4-triazole, all in an attempt to enhance the biological activity of the resulting compounds.

RESULTS AND DISCUSSIONS

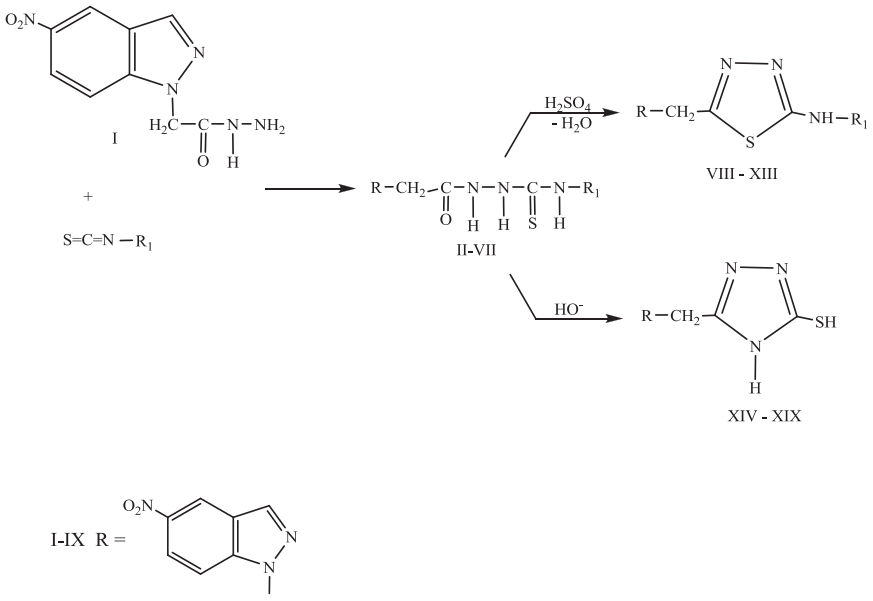
The synthesis of new derivatives of 1,3,4-thiadiazoles and 1,2,4-triazoles was achieved using the *N*-acylhydrazinecarbothioamides as intermediaries.

To this purpose, the 5-nitroindazole-1-yl-acethydrazide (**I**) [25] was treated with phenyl-, *p*-tolyl, *p*-methoxyphenyl-, *p*-bromophenyl-, *p*-chlorophenyl-, and *p*-iodophenyl-isothiocyanate in absolute methyl alcohol on reflux for 2 h, leading to new 2-[(5′-nitro-1*H*-indazol-1-yl)acetyl]-*N*-acyl-hydrazinecarbothioamide (**II–VII**) (Scheme 1).

The chemical structures of the synthesized compounds (**II–XIX**) were confirmed by means of elemental and spectral analysis (FTIR, ^{1}H-NMR, ^{13}C-NMR, SM).

FTIR spectra present an intense absorption band at 3120 cm^{-1}, specific for the NH group. The absorption band from 1621 cm^{-1} is specific for the CO group, and the C=S group is revealed by an absorption band at 1137 cm^{-1}. The NO_2 group is identified by υ_{NO2} symmetric at 1343 cm^{-1}

Scheme 1. Synthesis of aryl-hydrazincarbothioamides (**II–VII**), aryl-1,3,4-thiadiazole-2-amides (**VIII–XIII**), and aryl-1,2,4-triazole-5-thiones (**XIV–XIX**).



II, VIII, XIV R_1 = - C_6H_5; III, IX, XV R_1 = - C_6H_4–CH_3(p); IV, X, XVI R_1 = - C_6H_4–OCH_3(p)

V, XI, XVII R_1 = - C_6H–Br(p); VI, XII, XVIII R_1 = - C_6H_4–Cl(p); VII, XIII, XIX R_1 = - C_6H_4–I(p)

and by υ_{NO2} asymmetric at 1525 cm^{-1}, whereas for the compounds (**V–VII**), the absorption band appears at 630 cm^{-1}.

The ^{1}H-NMR spectra confirm the presence of the protons bound at nitrogen, showing signals at 9.66–11.02 ppm and at 7.17–8.95 ppm, respectively, aromatic protons. The protons from methyl group show signals at 2.30 ppm (s, 1H) and at 3.36 ppm (s, 2H).

In the ^{13}C-NMR spectra, C═S appears at 176.63–187.16 ppm and at 165.58–168.89 ppm for C═O.

The mass spectrum analysis confirms the expected chemical structures. In all *N*-acylhydrazinecarbothioamide, the signals of sodium containing adducts (M + Na), appear at values of *m/z* 393, 408, 423, 472, 833, 519. Protonated ionic species $[1 + H]^+$ were also identified in the same spectra.

New 2,5-disubstituted-5-aryl-amino-1,3,4-thiadiazoles (**VIII–XIII**) were obtained by intramolecular cyclization of 2-[(5′-nitro-1*H*-indazol-1-yl)acetyl]-*N*-acylhydrazinecarbothioamide (**II–VII**) in strong acid medium, as described in the literature [2,15,26,27].

The main change in IR spectra of thiadiazoles compared with those of 2-[(5′-nitro-1*H*-indazol-1-yl)acetyl]-*N*-acylhydrazinecarbothioamide (**II–VII**) from which they come consists in the disappearance of the intense absorption band at 1137 cm^{-1} (specific for C═S group of thiourea function) and the appearance of a new absorption band at 1070 cm^{-1} (specific for C-S-C in the thiadiazole heterocycle). There is also a wide absorption band at 3200cm^{-1} specific for N-H bond in position 5 from the side chain of thiadiazole. There are also medium intensity bands at 1240 cm^{-1} as well as at 1436 cm^{-1} because of the specific thiadiazole ring vibrations. For the compounds (**XI–XIII**), this reaches a peak around at 749–753 cm^{-1} corresponding to the C-halogen bonds.

In the ^{1}H-NMR spectra for all thiadiazoles, aromatics protons show signals at 6.89–9.01 ppm. The protons from CH_2 group in position 1′ of indazole ring show signals for singlets at 6.08–6.13 ppm, and the proton bound to nitrogen was detected as a singlet at 10.16–10.62 ppm. The methyl group protons from thiadiazoles (**IX**) and (**X**) show signals at 2.24 ppm (s, 1H) and 3.71 ppm (1, 2H), respectively.

In the ^{13}C-NMR spectra, signals for C-S appear at 165.84–173 ppm and for C-N group at 142.56–149.70 ppm.

The mass spectrum base peak recorded for thiadiazoles (**VIII–XII**) is situated at *m/z* 353, 367, 383, 432, 388, 479, which correspond to the (M + H) ion.

The series of indazole derivatives was thus enlarged, as a result of obtaining new compounds that contain the triazole heterocycle.

The conversion of 2-[(5′-nitro-1*H*-indazol-1-yl)acetyl]-*N*-acylhydrazinecarbothioamide (**II–VII**) into their corresponding triazoles (**XIV–XIX**) was achieved following a method indicated in the literature [2,15,28] under hydroxyl ions catalytic action (Scheme 1).

The chemical structures of the synthesized compounds were also confirmed by elemental and spectral analysis (FTIR, ^{1}H-NMR, ^{13}C-NMR, SM).

The absorption bands in the IR spectra for the cyclic C=S group appear at 1492–1494 cm^{-1}, which means that in solid state, the triazoles (**XIV–XIX**) have an ionic structure. In the region 3097 cm^{-1}, there are absorption bands characteristic for NH group, whereas the C=N group leads to characteristic absorption bands at 1622 cm^{-1}. The NO_2 group presents two absorption bands at 1336 cm^{-1} and 1522 cm^{-1}, whereas C-halogen groups from (**XVII–XIX**) compounds present absorption bands at around 750 cm^{-1}.

The (**XIV–XIX**) compounds ^{1}H-NMR spectra show a signal at 13.40–14.09 ppm as a singlet because of the proton of SH group, and at 7.11–8.21 ppm, there are signals specific for aromatic protons. The protons of methyl group of (**XV**) and (**XVI**) compounds appear at 2.12 ppm and 3.61 ppm.

In the ^{13}C-NMR spectra, the C-S group appears in the region 172.82–173.79 ppm, and the signals of C-N group were picked up at 142.09–149.88 ppm.

The mass spectrum of the triazole derivative (**XVII**) shows the base peak *m*/*z* at 431 that corresponds to the (M^+) ion. The mercapto-triazoles (**XIV**) and (**XVIII**) have the base peak at *m*/*z* 375 and 410, respectively, assigned to sodium containing adducts (M + Na), whereas the compounds (**XV**), (**XVI**), and (**XIX**) present their base peak at *m*/*z* 367, 383, and 479, again, assigned to (M + H) ions.

Evaluation of antibacterial activity of compounds VIII–XIX. Antibacterial activity of 1,3,4-thiadiazoles (**VIII–XIII**) and 1,2,4-triazoles derivatives (**XIV–XIX**) was studied by *in vitro* tests using the following reference bacterial strains: *Staphylococcus aureus* ATCC 25923, *Bacillus subtilis* ATCC6638, *Bacillus cereus* ATCC 10876, *Escherichia coli* ATCC25922, and *Salmonella enteritidis* P1131.

The germs were grown on Mueller–Hinton agar and were incubated at 37°C for 18 h. To assess the microbes' sensitivity to the action of compounds (**VIII–XIX**), we used powders of the substances analyzed, in concentrations of 1000 μg/disk. The results of antimicrobial effect for compounds were expressed as the inhibition zone diameter, determined by the diffusimetric method Kirby-Bauer [29] (Table 1), using as reference the active substance kanamycin.

The 1,3,4- thiadiazoles (**VIII–XIII**) are effective against the *S. aureus* and are moderately effective against *E. coli*. The *B. subtilis*, *B. cereus*, and *S. enteritidis* cultures are resistant to compounds (**VIII–XIII**). The 1,2,4-triazole derivatives (**XIV–XIX**) show high activity against *B. subtilis* and *B. cereus*, but they are inactive against *S. aureus, E. coli*, and *S. enteritidis*. From the compounds tested, the heterocyclic derivatives containing in their structure residuals of p-bromophenyl (**XI, XVII**) and residuals of p-iodophenyl, respectively (**XIII, XIX**), have proved to be the most active. The antimicrobial activity of tested compounds is, nevertheless, lower than that of the reference active substance, kanamycin.

To determine the minimal inhibitory concentration (MIC) by microdilution method, the compounds (**VIII–XIX**) were dissolved in DMSO to 100 mg/L. We further used solutions of different concentrations (dilutions of the initial solutions) for our tests. Following a preliminary sterilization at 120°C for 30 min, these solutions were placed in the culture medium. The readings were performed for 24 h (the control contained only the solvent) (Table 2).

The values of MIC confirm the results obtained by measuring the inhibition zone diameter of bacterial cultures tested. The values of MIC for 1,3,4-triazoles (**VIII–XIII**) are recorded against *S. aureus* followed by those for *E. coli*. The thiadiazole containing residual of p-iodophenol (**XIII**) is most active against *S. aureus*, whereas the one containing the residual of p-bromophenyl (**XI**) has the highest degree of inhibition for

Table 1

The antimicrobial activity of compounds **VIII–XIX** at concentration of 1000 μg/disk.

	The inhibition zone diameter (mm)				
Compound	*Staphylococcus aureus*	*Bacillus subtilis*	*Bacillus cereus*	*Escherichia coli*	*Salmonella enteritidis*
VIII	16–17	4–5	6–7	11–12	5–6
IX	18–19	5–6	8–10	12–13	8–9
X	19–20	6–7	6–7	14–15	7–8
XI	20–21	8–9	9–10	15–16	9–10
XII	19–20	6–7	6–7	13–14	7–8
XIII	23–24	6–7	7–8	16–17	8–9
XIV	7–8	18–19	19–20	6–7	5–6
XV	6–7	20–21	19–20	7–8	6–7
XVI	8–9	19–20	18–19	7–8	5–6
XVII	6–7	23–24	22–23	9–10	9–10
XVIII	5–6	21–22	20–21	10–11	7–8
XIX	9–10	25–26	23–24	6–7	8–9
Kanamicyn	31–32	27–28	30–31	29–30	28–29

Table 2

The minimal inhibitory concentration for compounds **VIII–XIX** (MIC mg/L).

Compound	MIC mg/L				
	Staphylococcus aureus	*Bacillus subtilis*	*Bacillus cereus*	*Escherichia coli*	*Salmonella enteritidis*
VIII	280	1143	1128	269	1132
IX	138	636	716	228	829
X	171	618	714	193	630
XI	114	622	780	170	785
XII	125	618	885	196	790
XIII	104	585	890	178	760
XIV	850	148	168	760	620
XV	532	130	148	770	1150
XVI	730	132	149	890	1210
XVII	640	120	126	870	1140
XVIII	750	152	198	630	560
XIX	460	116	124	852	530

MIC, minimal inhibitory concentration.

E. coli strain. The 1,2,4-triazole derivatives (**XIV–XIX**) show lower values of MIC for *B. subtilis* and *B. cereus*. Out of these, the compounds (**XVII**) and (**XIX**) containing in their molecule p-bromophenyl residual and p-iodophenyl residual, respectively, stand out in this respect—values of MIC.

CONCLUSIONS

We obtained 2-[(5′-nitro-1*H*-indazol-1-yl)acetyl]-*N*-acylhydrazinecarbothioamide (**II–VII**) intermediaries used in the synthesis of both 1,3,4-thiadiazoles (**VIII–XIII**) and 1,2,4-triazoles (**XIV–XIX**). We synthesized six *N*-acyl hydrazine carbo thio amides (**II–VII**) that were never mentioned in the literature before.

The intramolecular cyclization of 2-[(5′-nitro-1*H*-indazol-1-yl)acetyl]-*N*-acylhydrazinecarbothioamide (**II–VII**) in acidic and alkaline solution leads to new derivatives of 1,3,4-thiadiazoles and 1,2,4-triazoles, respectively, with 5-nitroindazole as support. The chemical structure of the newly synthesized compounds was confirmed by the results of elemental and spectral analysis (FTIR, ^{1}H-NMR, ^{13}C-NMR, MS).

Some of the newly synthesized compounds present promising antimicrobial activity especially against *S. aureus* and *E. coli*, whereas others are more efficient against *B. subtilis* and *B. cereus*, their activity being very close similar to that of kanamicyn.

The presence of a halogen atom in *p*-position of the aromatic ring enhances the antibacterial activity.

EXPERIMENTAL

Synthesis of 5-nitroindazole-1-yl-acethydrazide (I). This synthesis was performed by treating of ethyl ester of 5-nitroindazol-1-yl-acetic acid with hydrazine hydrate 98% [25].

Synthesis of 2-[(5′-nitro-1*H*-indazol-1-yl)acetyl]-*N*-acylhydrazinecarbothioamide (II–VII) (general procedure). In a reaction flask containing absolute methyl alcohol (50 mL), we added the hydrazide (I) (0.005 moles), mildly heating and stirring the solution until it becomes clear. Afterwards, we added isothiocyanate (0.005 moles in 5 mL absolute methyl alcohol). The mixture was refluxed on water bath for 3 h separating an abundant precipitate. This was filtered in vacuum, was dried, and finally purified by recrystallization from methyl alcohol.

2-[(5′-Nitro-1H-indazol-1-yl)acetyl]-N-phenylhydrazinecarbothioamide (II). Yellowish white solid, yield 82.06% (1, 51 g); mp = 186–188°C. IR (γ, cm^{-1}): 3096 (NH); 1623 (CO); 749 (CHAr); 1137 (C═S); 1492 (CH_2); 1338 (NO_2 sym.); 1535 (NO_2 asym.). ^{1}H-NMR (DMSO-d_6, 400 MHz), δ(ppm): 5.42 (s, 2H, CH_2); 7.18–7.21 (d, 1H, Ar); 7.35–7.44 (m, 4H, Ar); 7.75–7.83 (d, 1H, Ar); 8.01–8.04 (d, 1H, Ar); 8.26 (s, 1H, Ar); 8.44 (s, 1H, Ar); 9.76–9.82 (d, 2H, NH); 10.53–10.60 (d, 1H, NH). ^{13}C-NMR (DMSO-d_6, 400 MHz), δ(ppm): 56.18 (CH_2); 102.88; 110.12; 118.55; 122.24; 124.98; 129.56; 131.08 (Ar); 133.47; 135.81; 139.76; 142.14 (C-N); 166.62 (C═O); 183.08 (C═S). SM, *m/z*: 371 (M + H, PB); 393 (M + Na, 12%); 409 (M + K,7%). *Anal*. Calcd for $C_{16}H_{14}N_6O_3S$: 51.88% C; 3.81% H; 22.69% N; 8.66% S. Found: 52.04% C; 4.11% H; 22.87% N; 8.82% S.

2-[(5′-Nitro-1H-indazol-1-yl)acetyl]-N-(p-tolyl)-hydrazinecarbothioamide (III). Creamy-white solid, yield 86.97% (1.67 g); mp = 187–189°C. IR (γ, cm^{-1}): 3098 (NH); 1709 (CO); 750, 785 (CHAr); 1224 (C═S); 1498 (CH_2); 1342 (NO_2 sym.); 1525 (NO_2 asym.). ^{1}H-NMR (DMSO-d_6, 400 MHz), δ(ppm): 2.30 (s, 3H, CH_3); 5.35 (s, 2H, CH_2); 7.15–7.17 (d, 2H, Ar); 7.25–7.27 (d, 2H, Ar); 7.80–7.82 (d, 1H, Ar); 8.30–8.32 (d, 1H, Ar); 8.44 (s, 1H, Ar); 8.85 (s, 1H, Ar); 9.69–9.75 (d, 2H, NH); 10.50–10.57 (d, 1H, NH). ^{13}C-NMR (DMSO-d_6, 400 MHz), δ(ppm): 18.34 (CH_3); 52.79 (CH_2); 102.79; 111.31; 119.16; 121.55; 124.17; 131.67; 139.81 (Ar); 133.26; 136.83; 138.15; 143.44 (C-N); 168.64 (C═O); 184.19 (C═S). SM, *m/z*: 385 (M + H, PB); 408 (M + Na, 10%); 793 (2M + Na, 9%); 831 (2M + Na + K, 15%). *Anal*. Calcd for $C_{17}H_{16}N_6O_3S$: 53.11% C; 4.19% H; 21.86% N; 8.34% S. Found: 53.39% C; 4.38% H; 22.26% N; 8.43% S.

2-[(5′-Nitro-1H-indazol-1-yl)acetyl]-N-(p-methoxyphenyl)-hydrazinecarbothioamide (IV). White solid, yield 79.39% (1.58 g); mp = 202–204°C. IR (γ, cm^{-1}): 3100 (NH); 1621 (CO); 750 (CHAr); 1245 (C═S); 1495 (CH_2); 1342 (NO_2 sym.); 1535 (NO_2 asym.). ^{1}H-NMR (DMSO-d_6, 400 MHz), δ(ppm): 3.36 (s, 3H, OCH_3); 5.35 (s, 2H, CH_2); 6.92–6.96 (d, 2H, Ar); 7.25–7.28

(d, 2H, Ar); 7.79–7.82 (d, 1H, Ar); 8.26–8.29 (d, 1H, Ar); 8.43 (s, 1H, Ar); 8.95 (s, 1H, Ar); 9.66–9.71 (d, 2H, NH); 10.48 (s, 1H, NH). ^{13}C-NMR (DMSO-d_6, 400 MHz), δ(ppm): 50.91 (CH_3); 55.69 (CH_2); 108.70; 111.56; 118.45; 119.49; 121.25; 123.39; (Ar); 132.20; 137.06; 142.45; 149.40 (C-N); 137.43; 166.70 (C═O); 176.63 (C═S). SM, *m/z*: 401 (M + H, 99%); 423 (M + Na, PB); 439 (M + K, 15%); 823 (2M + Na, 90%). *Anal*. Calcd for $C_{17}H_{16}N_6O_4S$: 50.99% C; 4.02% H; 21.98% N; 8.00% S. Found: 51.37% C; 4.26% H; 21.31% N; 8.39% S.

2-[(5′-Nitro-1H-indazol-1-yl)acetyl]-N-(p-bromophenyl)-hydrazinecarbothioamide (V). Creamy-white solid, yield 80.71% (1.80 g); mp = 145–147°C. IR (γ, cm^{-1}): 3096 (NH); 1619 (CO); 749 (CHAr); 1249 (C═S); 1484 (CH_2); 1343 (NO_2 sym.); 1526 (NO_2 asym.); 629 (C-Br). ^{1}H-NMR (DMSO-d_6, 400 MHz), δ(ppm): 5.36 (s, 2H, CH_2); 7.42–7.44 (d, 2H, Ar); 7.54–7.56 (d, 2H, Ar); 7.80–7.82 (d, 1H, Ar); 8.26–8.29 (d, 1H, Ar); 8.42 (s, 1H, Ar); 8.84 (s, 1H, Ar); 9.85–9.93 (d, 2H, NH); 10.54 (s, 1H, NH). ^{13}C-NMR (DMSO-d_6, 400 MHz), δ(ppm): 51.50 (CH_2); 103.17 (Ar); 118.58 (C-Br) ; 121.15; 123.24; 124.29; 132.20; 133.17 (Ar); 133.77; 137.69; 139.15; 142.83 (C-N); 168.89 (C═O); 187.16 (C═S). SM, *m/z*: 450 (M + H, 8%); 472 (M + Na, PB); 488 (M + K, 20%). *Anal*. Calcd for $C_{16}H_{13}BrN_6O_3S$: 42.77% C; 2.91% H; 17.78% Br; 18.70% N; 7.13% S. Found: 42.87% C; 3.15% H; 18.13% Br; 19.03% N; 7.31% S.

2-[(5′-Nitro-1H-indazol-1-yl)acetyl]-N-(p-chlorophenyl)-hydrazinecarbothioamide (VI). Creamy-white solid, yield 78.80% (1.60 g); mp = 203–205°C. IR (γ, cm^{-1}): 3123 (NH); 1620 (CO); 750 (CHAr); 1250 (C═S); 1499 (CH_2); 1338 (NO_2 sym.); 1525 (NO_2 asym.); 664, 721 (C-Cl). ^{1}H-NMR (DMSO-d_6, 400 MHz), δ(ppm): 5.35 (s, 2H, CH_2); 7.43–7.46 (m, 4H, Ar); 7.75–7.82 (d, 1H, Ar); 8.44 (s, 2H, Ar); 8.60 (s, 1H, Ar); 9.80–9.86 (d, 2H, NH); 10.54 (s, 1H, NH). ^{13}C-NMR (DMSO-d_6, 400 MHz), δ(ppm): 52.12 (CH_2); 102.89; 111.62 118.38; 123.67; 130.15; 133.36 (Ar); 134.82 (C-Cl); 136.15; 138.81; 139.43; 142.17 (C-N); 168.13 (C═O); 187.05 (C═S). SM, *m/z*: 405 (M$^+$, 50%); 444 (M + K, PB); 833 (2M + Na, 16%). *Anal*. Calcd for $C_{16}H_{13}ClN_6O_3S$: 47.47% C; 3.23% H; 8.75% Cl; 20.75% N; 7.92% S. Found: 47.69% C; 3.47% H; 8.99% Cl; 21.11% N; 8.19% S.

2-[(5′-Nitro-1H-indazol-1-yl)acetyl]-N-(p-iodophenyl)-hydrazinecarbothioamide (VII). Yellowish white solid, yield 80.16% (1.98 g); mp = 179–181°C. IR (γ, cm^{-1}): 3120 (NH); 1620 (CO); 780 (CHAr); 1240 (C═S); 1490 (CH_2); 1340 (NO_2 sym.); 1526 (NO_2 asym.); 630 (C-I). ^{1}H-NMR (DMSO-d_6, 400 MHz), δ(ppm): 5.35 (s, 2H, CH_2); 7.40–7.44 (m, 4H, Ar); 7.68–7.73 (d, 1H, Ar); 8.02–8.04 (d, 1H, Ar); 8.44–8.48 (d, 2H, Ar); 9.80–9.85 (d, 2H, NH); 11.02 (s, 1H, NH). ^{13}C-NMR (DMSO-d_6, 400 MHz), δ(ppm): 51.95 (CH_2); 103.31; 111.27; 118.74; 122.58; 122.91; 138.44 (Ar); 131.89; 136.27; 139.13; 142.41 (C-N); 165.58 (C═O); 183.98 (C═S); 89.32 (C-I). SM, *m/z*: 496 (M$^+$, PB); 519 (M + Na, 14%); 1015 (2M + Na, 8%). *Anal*. Calcd for $C_{16}H_{13}IN_6O_3S$: 38.72% C; 2.63% H; 25.57% I; 16.93% N; 6.46% S. Found: 39.06% C; 2.89% H; 25.78% I; 17.2% N; 6.71% S.

Synthesis of 5-[(5′-nitro-1*H*-indazol-1-yl)methyl]-*N*-aryl-1,3,4-thiadiazoles-2-amine (VIII–XIII) (general procedure). In a reaction flask, we added 6 mL concentrated sulfuric acid 0.005 mol of 2-[(5′-nitro-1*H*-indazol-1-yl)acetyl]-*N*-acylhydrazinecarbothioamide (II–VII), stirring until the solution becomes clear. The mixture was kept at room temperature for 30–40 min for finalization of cyclization. Once that was achieved, the solution was poured over crushed ice when an abundant precipitate was separated, and then filtered under vacuum, was dried, and washed with distilled water until the pH of washing water became 7. The washed precipitate was dried under vacuum at 50–55°C and then purified by repeated recrystallization from boiling ethylic ethanol 96%.

5-[(5′-Nitro-1H-indazol-1-yl)methyl]-N-phenyl-1,3,4-thiadiazole-2-amine (VIII). Creamy-white solid, yield 74.43% (1.31 g); mp = 184–186°C. IR (γ, cm^{-1}): 3242 (NH); 1335 (NO_2 sym.); 1573 (NO_2 asym.); 1456 (N═C-S); 1072 (C-S-C); 1240, 1436, 1517 (thiadiazolic ring); 815 (CHAr). ^{1}H-NMR (DMSO-d_6, 400 MHz), δ(ppm): 6.13 (s, 2H, CH_2); 7.0–7.10 (t, 1H, Ar); 7.31–7.34 (m, 2H, Ar); 7.53–7.56 (m, 2H, Ar); 8.02 (s, 1H, Ar); 8.30 (s, 1H, Ar); 8.50–8.51 (d, 1H, Ar); 8.86–8.89 (d, 1H, Ar); 10.36 (s, 1H, NH). ^{13}C-NMR (DMSO-d_6, 400 MHz), δ(ppm): 53.89 (CH_2); 113.31; 117.90; 120.57; 121.31; 122.01 (Ar); 137.85; 140.79; 141.77; 142.56 (C-N); 154.65; 165.84 (C═S); SM, *m/z*: 353 (M + H, PB); 727 (2M + Na, 52%); 391 (M + K, 25%). *Anal*. Calcd for $C_{16}H_{12}N_6O_2S$: 54.53% C; 3.42% H; 23.84% N; 9.09% S. Found: 54.87% C; 3.68% H; 24.05% N; 9.35% S.

5-[(5′-Nitro-1H-indazol-1-yl)methyl]-N-p-tolyl-1,3,4-thiadiazole-2-amine (IX). Scarlet color solid, yield 75.95% (1.39 g); mp = 152–154°C. IR (γ, cm^{-1}): 2944 (NH); 1338 (NO_2 sym.); 1570 (NO_2 asym.); 1449 (N═C-S); 1070 (C-S-C); 1246, 1449, 1517 (thiadiazolic ring); 826 (aromatic ring p-disubstituted). ^{1}H-NMR (DMSO-d_6, 400 MHz), δ(ppm): 2.24 (s, 3H, CH_3); 6.11 (s, 2H, CH_2); 7.11–7.13 (d, 2H, Ar); 7.41–7.44 (d, 2H, Ar); 8.02 (s, 1H, Ar); 8.30 (s, 1H, Ar); 8.49–8.50 (d, 1H, Ar); 8.86–8.87 (d, 1H, Ar); 10.26 (s, 1H, NH). ^{13}C-NMR (DMSO-d_6, 400 MHz), δ(ppm): 23.56 (CH_3); 54.17 (CH_2); 111.89; 119.22; 121.14; 123.38; 130.67; 133.62 (Ar); 134.71; 139.23; 145.15; 149.70 (C-N); 157.72; 171.16 (C-S); SM, *m/z*: 367 (M + H, PB); 389 (M + Na, 18%); 755 (2M + Na, 11%). *Anal*. Calcd for $C_{17}H_{14}N_6O_2S$: 55.73% C; 3.84% H; 22.93% N; 8.75% S. Found: 55.93% C; 4.03% H; 23.16% N; 8.99% S.

5-[(5′-Nitro-1H-indazol-1-yl)methyl]-N-p-methoxyphenyl-1,3,4-thiadiazole-2-amine (X). Brown solid, yield 74.35% (1.42 g); mp = 113–115°C. IR (γ, cm^{-1}): 2900 (NH); 1337 (NO_2 sym.); 1509 (NO_2 asym.); 1438 (N═C-S); 1070 (C-S-C); 1247, 1519, 1615 (thiadiazolic ring); 784, 827 (aromatic ring p-disubstituted). ^{1}H-NMR (DMSO-d_6, 400 MHz), δ(ppm): 3.71 (s, 3H, CH_3); 6.01 (s, 2H, CH_2); 6.89–6.93 (d, 2H, Ar); 7.43–7.48 (d, 2H, Ar); 8.01–8.05 (d, 1H, Ar); 8.29–8.32 (d, 1H, Ar); 8.49 (s, 1H, Ar); 9.0 (s, 1H, Ar); 10.16 (s, 1H, NH). ^{13}C-NMR (DMSO-d_6, 400 MHz), δ(ppm): 53.58 (CH_2); 57.12 (CH_3); 111.73; 117.25; 119.84; 123.71; 124.52 (Ar); 135.17; 135.93; 146.29; 149.17 (C-N); 155.18; 172.61 (C-S); SM, *m/z*: 383 (M + H, PB); 787 (2M + Na, 25%). *Anal*. Calcd for $C_{17}H_{14}N_6O_3S$: 53.39% C; 3.68% H; 21.97% N; 8.38% S. Found: 53.56% C; 3.85% H; 22.19% N; 8.56% S.

5-[(5′-Nitro-1H-indazol-1-yl)methyl]-N-bromophenyl-1,3,4-thiadiazole-2-amine (XI). Brown solid, yield 77.20% (1.66 g); mp = 205–207°C. IR (γ, cm^{-1}): 2900 (NH); 1335 (NO_2 sym.); 1540 (NO_2 asym.); 1490 (N═C-S); 1070 (C-S-C); 1240, 1440, 1518 (thiadiazolic ring); 828 (aromatic ring p-disubstituted); 750 (C-Br). ^{1}H-NMR (DMSO-d_6, 400 MHz), δ(ppm): 6.01 (s, 2H, CH_2); 7.48–7.50 (d, 2H, Ar); 7.53–7.55 (d, 2H, Ar); 8.02–8.05 (d, 1H, Ar); 8.50–8.53 (d, 1H, Ar); 8.86 (s, 1H, Ar); 8.87 (s, 1H, Ar); 10.52 (s, 1H, NH). ^{13}C-NMR (DMSO-d_6, 400 MHz), δ(ppm): 54.78 (CH_2); 121.73; 122.12; 124.58; 132.44; 134.41 (Ar); 137.74; 141.15; 146.08; 149.28 (C-N); 157.25; 173.11 (C-S); 117.66 (C-Br). SM, *m/z*: 432 (M + H, PB); 885 (2M + Na, 14%). *Anal*. Calcd for $C_{16}H_{11}BrN_6O_2S$: 44.56% C; 2.56% H; 19.48% N; 7.43% S. Found: 44.72% C; 2.76% H; 19.71% N; 7.62% S.

5-[(5′-Nitro-1H-indazol-1-yl)methyl]-N-p-chlorophenyl-1,3,4-thiadiazole-2-amine (XII). Brown solid, yield 73.71% (1.43 g); mp = 204–206°C. IR (γ, cm^{-1}): 3326 (NH); 1342 (NO_2 sym.); 1542 (NO_2 asym.); 1493 (N═C-S); 1071 (C-S-C); 1260, 1470, 1520 (thiadiazolic ring); 828 (aromatic ring p-disubstituted); 753 (C-Cl). ^{1}H-NMR (DMSO-d_6, 400 MHz), δ(ppm): 6.13 (s, 2H, CH_2); 7.36–7.40 (d, 2H, Ar); 7.58–7.61 (d, 2H, Ar); 8.0–8.02 (d, 1H, Ar); 8.29–8.30 (d, 1H, Ar); 8.86 (s, 1H, Ar); 9.01 (s, 1H, Ar); 10.50 (s, 1H, NH). ^{13}C-NMR (DMSO-d_6, 400 MHz), δ(ppm): 54.18 (CH_2); 110.98; 119.88; 123.67; 124.13; 128.83 (Ar); 136.31; 139.77; 146.25; 149.39 (C-N); 159.70; 172.36 (C-S); 128.83 (C-Cl). SM, *m/z*: 388 (M + H, PB); 410 (M + Na, 8%); 775 (2M + H, 6%); 797 (2M + Na, 11%). *Anal*. Calcd for $C_{16}H_{11}ClN_6O_2S$: 49.68% C; 2.86% H; 9.16% Cl; 21.72% N; 8.28% S. Found: 49.88% C; 3.03% H; 9.4% Cl; 22.03% N; 8.57% S.

5-[(5′-Nitro-1H-indazol-1-yl)methyl]-N-p-iodophenyl-1,3,4-thiadiazole-2-amine (XIII). Brown solid, yield 73.22% (1.75 g); mp = 185–187°C. IR (γ, cm^{-1}): 2917 (NH); 1338 (NO_2 sym.); 1518 (NO_2 asym.); 1492 (N═C-S); 1070 (C-S-C); 1260, 1438, 1615 (thiadiazolic ring); 824 (aromatic ring p-disubstituted); 749 (C-I). ^{1}H-NMR (DMSO-d_6, 400 MHz), δ(ppm): 6.12 (s, 2H, CH_2); 7.40–7.42 (d, 2H, Ar); 7.63–7.65 (d, 2H, Ar); 8.03–8.04 (d, 1H, Ar); 8.30–8.33 (d, 1H, Ar); 8.50 (s, 1H, Ar); 8.80 (s, 1H, Ar); 10.60–10.62 (d, 1H, NH). ^{13}C-NMR (DMSO-d_6, 400 MHz), δ(ppm): 53.79 (CH_2); 111.34; 118.69; 119.83; 123.50; 136.44 (Ar); 139.45; 141.48; 147.18 (C-N); 155.72; 171.72 (C-S); 87.34 (C-I). SM, *m/z*: 479 (M + H, 35%); 501 (M + Na, PB); 517 (M + K, 21%). *Anal*. Calcd for $C_{16}H_{11}IN_6O_2S$: 40.18% C; 2.31% H; 26.53% I; 17.57% N; 6.70% S. Found: 40.44% C; 2.60% H; 26.74% I; 17.90% N; 6.92% S.

Synthesis of 5-[(5′-nitro-1*H*-indazol-1-yl)methyl]-*N*-acyl-1,2,4-triazole-5-thione (XIV–XIX) (general procedure). In a reaction flask containing 15 mL 2N sodium hydroxide, we added 0.0027 mol of 2-[(5′-nitro-1*H*-indazol-1-yl)acetyl]-*N*-acylhydrazinecarbothioamide (II–VII). The mixture was heated to boiling point for 1 h. Cooling and dilution with water was followed by the addition of a dilute hydrochloric acid solution, in small quantities until pH = 4,5; at which point, the 1,2,4-triazoles begun to separate as a precipitate. Purification was performed from ethyl alcohol on boiling.

3-[(5′-Nitro-1H-indazol-1-yl)methyl]-N-phenyl-1,2,4-triazole-5-thione (XIV). Brown-red solid, yield 55.78% (0.53 g); mp = 247–249°C. IR (γ, cm^{-1}): 1337 (NO_2 sym.); 1508 (NO_2 asym.); 2496 (SH); 1622 (C═N); 822 (CHAr). ^{1}H-NMR (DMSO-d_6, 400 MHz), δ(ppm): 5.74 (s, 2H, CH_2); 7.11–7.14 (d, 2H, Ar); 7.24–7.26 (d, 2H, Ar); 7.50–7.53 (t, 1H, Ar); 7.72–7.75 (d, 1H, Ar); 8.08 (s, 1H, Ar); 8.18 (s, 1H, Ar); 8.20–8.21 (d, 1H, Ar); 13.85 (s, 1H, SH). ^{13}C-NMR (DMSO-d_6, 400 MHz), δ(ppm): 54.70 (CH_2); 111.31; 119.23; 123.65; 131.77; 133.45 (Ar); 134.38; 146.17; 147.98; 148.15; 148.88 (C-N); 172.82 (C-S). SM, *m/z*: 352 (M^+, 90%); 375 (M + Na, PB); 727 (2M + Na, 5%). *Anal*. Calcd for $C_{16}H_{12}N_6O_2S$: 54.53% C; 3.42% H; 23.84% N; 9.09% S. Found: 54.71% C; 3.53% H; 24.08% N; 9.40% S.

3-[(5′-Nitro-1H-indazol-1-yl)methyl]-N-p-tolyl 1,2,4-triazole-5-thione (XV). Brown solid, yield 72.45% (0.71 g); mp = 249–251°C. IR (γ, cm^{-1}): 1338 (NO_2 sym.); 1514 (NO_2 asym.); 2560 (SH); 1622 (C═N); 896 (aromatic ring p-disubstituted). ^{1}H-NMR (DMSO-d_6, 400 MHz), δ(ppm): 2.12 (s, 3H, CH_3); 5.72 (s, 2H, CH_2); 6.91–6.93 (d, 2H, Ar); 6.98–7.0 (d, 2H, Ar); 7.47–7.49 (d, 1H, Ar); 7.73–7.75 (d, 1H, Ar); 8.30 (s, 1H, Ar); 8.71 (s, 1H, Ar); 13.75 (s, 1H, SH). ^{13}C-NMR (DMSO-d_6, 400 MHz), δ(ppm): 25.21 (CH_3); 55.14 (CH_2); 111.76; 119.23; 123.82; 131.02; 133.65; 135.72 (Ar); 139.32; 143.85; 145.16; 147.25; 147.89 (C-N); 173.79 (C-S). SM, *m/z*: 367 (M + H, PB); 755 (2M + Na, 8%). *Anal*. Calcd for $C_{17}H_{14}N_6O_2S$: 55.73% C; 3.84% H; 22.93% N; 8.75% S. Found: 56.01% C; 4.12% H; 23.17% N; 9.11% S.

3-[(5′-Nitro-1H-indazol-1-yl)methyl]-N-p-methoxyphenil-1,2,4-triazole-5-thione (XVI). Dark brown solid, yield 73.40% (0.69 g); mp = 232–234°C. IR (γ, cm^{-1}): 1339 (NO_2 sym.); 1514 (NO_2 asym.); 2590 (SH); 1613 (C═N); 821, 837 (aromatic ring p-disubstituted). ^{1}H-NMR (DMSO-d_6, 400 MHz), δ(ppm): 3.61 (s, 3H, OCH_3); 5.72 (s, 2H, CH_2); 6.71–6.73 (d, 2H, Ar); 6.94–6.96 (d, 2H, Ar); 7.50–7.55 (d, 1H, Ar); 8.08–8.11 (d, 1H, Ar); 8.35 (s, 1H, Ar); 8.73 (s, 1H, Ar); 13.90 (s, 1H, SH). ^{13}C-NMR (DMSO-d_6, 400 MHz), δ(ppm): 44.32 (CH_3); 55.65 (CH_2); 110.97; 114.75; 121.29; 123.0 (Ar); 128.97; 137.86; 142.09 (C-N); 159.94 (C-S); 13.90 (C-O). SM, *m/z*: 383 (M + H, PB); 405 (M + Na, 50%). *Anal*. Calcd for $C_{17}H_{14}N_6O_3S$: 53.39% C; 3.68% H; 21.97% N; 8.38% S. Found: 53.53% C; 3.84% H; 22.19% N; 8.55% S.

3-[(5′-Nitro-1H-indazol-1-yl)methyl]-N-p-bromophenyl-1,2,4-triazole-5-thione (XVII). Brown-red solid, yield 76.86% (0.88 g); mp = 210–212°C. IR (γ, cm^{-1}): 1341 (NO_2 sym.); 1520 (NO_2 asym.); 2486 (SH); 1616 (C═N); 804, 918 (aromatic ring p-disubstituted); 752 (C-Br). ^{1}H-NMR (DMSO-d_6, 400 MHz), δ(ppm): 6.12 (s, 2H, CH_2); 7.45–7.47 (d, 2H, Ar); 7.50–7.54 (d, 2H, Ar); 8.10–8.12 (d, 1H, Ar); 8.30–8.32(d, 1H, Ar) 8.50 (s, 1H, Ar); 8.90 (s, 1H, Ar); 13.40 (s, 1H, SH). ^{13}C-NMR (DMSO-d_6, 400 MHz), δ(ppm): 54.23 (CH_2); 119.72 (C-Br); 123.25; 125.88; 129.34; 133.30; 133.89 (Ar); 135.66; 145.09; 146.58; 147.35; 147.96 (C-N); 173.42 (C-S). SM, *m/z*: 431 (M^+, PB); 454 (M + Na, 17%); 470 (M + K, 43%). *Anal*. Calcd for $C_{16}H_{11}BrN_6O_2S$: 44.56% C; 2.56% H; 18.52% Br; 19.48% N; 7.43% S. Found: 44.82% C; 2.81% H; 18.70% Br; 19.74% N; 7.67% S.

3-[(5′-Nitro-1H-indazol-1-yl)methyl]-N-p-chlorophenyl-1,2,4-triazole-5-thione (XVIII). Brown solid, yield 77.88% (0.81 g); mp = 228–230°C. IR (γ, cm^{-1}): 1341 (NO_2 sym.); 1522 (NO_2 asym.); 2339 (SH); 1615 (C═N); 898 (aromatic ring p-disubstituted); 748 (C-Cl). ^{1}H-NMR (DMSO-d_6, 400 MHz), δ(ppm): 5.77 (s, 2H, CH_2); 7.09–7.11 (d, 2H, Ar); 7.25–7.27 (d, 2H, Ar); 7.53–7.55 d, 1H, Ar); 8.11–8.14 (d, 1H, Ar); 8.34 (s, 1H, Ar); 8.72 (s, 1H, Ar); 14.09 (s, 1H, SH). ^{13}C-NMR (DMSO-d_6, 400 MHz), δ(ppm): 53.85 (CH_2); 111.58; 119.24; 123.68; 129.55; 131.02 (Ar); 135.12 (C-Cl); 137.52; 145.22; 146.09; 149.18; 149.79 (C-N); 172.97 (C-S). SM, *m/z*: 388 (M + H, 30%); 410 (M + Na, PB); 426 (M + K, 9%). *Anal*. Calcd for $C_{16}H_{11}ClN_6O_2S$: 49.68% C; 2.86% H; 9.16% Cl; 21.72% N; 8.28% S. Found: 49.85% C; 3.02% H; 9.55% Cl; 21.90% N; 8.60% S.

3-[(5′-Nitro-1H-indazol-1-yl)methyl]-N-p-iodophenyl-1,2,4-triazole-5-thione (XIX). Brown-red solid, yield 72.09% (0.93 g); mp = 220–222°C. IR (γ, cm^{-1}): 1336 (NO_2 sym.); 1518 (NO_2 asym.); 2347 (SH); 1614 (C═N); 944 (aromatic ring p-disubstituted); 749 (C-I). ^{1}H-NMR (DMSO-d_6, 400 MHz), δ(ppm): 5.73 (s, 2H, CH_2); 7.44–7.47 (m, 4H, Ar); 7.73–7.75 (d, 1H, Ar); 8.20–8.21 (d, 1H, Ar); 8.31 (s, 1H, Ar); 8.70 (s, 1H, Ar); 13.80 (s, 1H, SH). ^{13}C-NMR (DMSO-d_6, 400 MHz), δ(ppm): 54.47 (CH_2); 97.34 (C-I); 111.36; 119.69; 123.52; 133.64; 133.37 (Ar); 139.71; 144.12; 145.22; 146.49; 149.13; 149.88 (C-N); 173.21 (C-S). SM, *m/z*: 479 (M + H, PB); 501 (M + Na, 75%); 517 (M + K, 12%). *Anal*. Calcd for $C_{16}H_{11}IN_6O_2S$: 40.18% C; 2.31% H; 26.53% I; 17.57% N; 6.70% S. Found: 40.52% C; 2.45% H; 26.84% I; 17.88% N; 6.91% S.

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