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Synthesis and Biological Evaluation of Some Bipyrazole Derivatives Containing Sulfonamide,Sulfonylurea and Thiourea pharmacophores as Anticancer and Antidiabetic Agents

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Abstract

The synthesis of a series of bipyrazoles substituted with benzenesulfonamide, N^1,N^3-disubstituted sulfonylurea, sulfonylthiourea pharmacophores, and some derived thiazolidinone and thiazoline ring were prepared as Anticancer and Antidiabetic agents. The key intermediate bipyrazoles were prepared by cyclocondensation of the appropriate chalcone with 4-hydrazinobenzenesulfonamide hydrochloride. The chemistry of the reactions employed in the synthesis of the target compounds together with their chemical behavior, are discussed. Preliminary biological screening of the prepared compounds revealed significant antidiabetic and antibacterial activities

Keywords: bi pyrazoles, Benzenesulfonylureas, Thioureas, Anticancer and Antidiabetic activity.

1. Introduction

The chemotherapy of neoplastic disease has become increasingly important in recent years. An indication of this importance is the establishment of a medical specialty in oncology, wherein the physicians practice various protocols of adjuvant therapy, chemotherapy and surgical operations. Consequently, the rapid spread of cancer has stimulated an unprecedented level of research activity directed towards the search for new structure leads that may be of use in designing novel antitumor drugs. In this context, compounds comprising the diarylsulfonylurea and –thiourea functionality have recently attracted great attention[1-6] especially after the discovery of Sulofenur (LY 186641)[7]. Sulofenur is a novel recently-discovered antineoplastic sulfonylurea and is now under clinical evaluation in lung, breast, colon, ovarian, pancreatic and gastric cancer[7]. It is generally assumed that the strong cytotoxicity and, as a consequence, the antitumor properties of the diarylsulfonylurea is due to the uncoupling of mitochondria[8,9] but other mechanisms, such as inhibition of the mitochondrial isozyme V of carbonic anhydrase (CA V) have also been hypothesized, since hydrolysis of the cytotoxic agent, leading to the formation of unsubstituted sulfonamides as the principal products, has been reported both in vivo and in vitro[10]. It is well known that aromatic / heterocyclic sulfonamides (formed after such a hydrolytic process) act as very potent inhibitors of CAs[11,12], and these enzymes are involved in a multitude of crucial physiologic processes[12].

On the other hand, numerous studies have been reported on the synthesis of a variety of pyrazole derivatives covering a wide range of bioactivities including . Among these, their antiparasitic[13], antitubercular[14], anticonvulscant[15] activities, in addition to their well known potential antipyretic, analgesic and anti-inflammatory[16-18] properties. Furthermore, the discovery of the naturally occurring C-glycoside antibiotic pyrazofurin; 4-hydroxy-3-β-D-ribofuranosyl-1H-pyrazole-5-carboxamide[19]; has provided a basis for more rationale design and synthesis of new pyrazoles as potential antimicrobial[20-22], antiviral [23-25] and anticancer agents [26-28]. It was also reported that several 3,5-dimethylpyrazoles possess hypoglycemic activities as much as 100

times that of tolbutamide in glucose-primed intact rats [26–29]. In continuation of our previous work in the preparation of di- and tri substituted pyrazoles, benzenesulfonylurea and thiourea derivatives as well as their cyclic sulfonylthioureas [30–40], many new bipyrazole derivatives of these classes were synthesized and were tested for hypoglycemic and anticancer activities.

2. Results and Discussion

2.1 Chemistry:

The synthetic strategies adopted for the preparation of the intermediate and target products are depicted in **Schemes 1 and 2**. The starting chalcones **2-8** were obtained by condensing equimolar amounts of the appropriate ketone with the appropriate 1-phenylpyrazole-4-carboxaldehyde **1a and 1b**, in an aqueous ethanolic solution of KOH. The IR spectra of the prepared chalcones, **2-8** showed a carbonyl absorption in the region 1644-1652 cm^{-1} which is the characteristic of the α,β-unsaturated carbonyl group as well as an olefinic C=C bond in the region 1604-1612 cm^{-1}. Their ^{1}H NMR spectra showed the olefinic protons, H-α and H-β, as two doublets (J = 16 Hz) at δ 6.56-6.60 and 6.94-7.08 respectively. The structures of the above compounds chalcones were further confirmed from their ^{13}C NMR data which showed the expected number of aliphatic and aromatic carbons signals as well as a carbonyl carbon at δ 180.71-203.30. Cyclocondensation of the above chalcones **2-8** with 4-hydrazinobenzenesulfonamide hydrochloride afforded the corresponding pyrazoline **9-15**. The IR spectra of the pyrazoline derivatives **9-15** revealed two strong bands at 3375-3392 cm^{-1} and 3240-3264 cm^{-1} due to NH_2 group and two bands at 1337-1372 cm^{-1} and 1137-1165 cm^{-1} for the unsymmetrical and symmetrical stretching vibrations of the SO_2N function. In agreement with the suggested structures, the ^{1}H NMR spectra of the above pyrazolines exhibited beside the aromatic protons, three multiplets at δ 4.97-5.39, 3.04-3.14 and 3.36-3.45. The low field multiplet is assigned to H-5 of the pyrazoline while the other two multiplets is attributed to H-4. The structures of the above compounds **9-15** were further confirmed from their ^{13}C NMR data which showed the expected number of aliphatic and aromatic carbons signals (see experimental section). Mild oxidation of the pyrazoline derivatives **9-15** with bromine water yielded the corresponding bipyrazoles **16-22**. In agreement with the suggested structures the ^{1}H NMR spectra of these bipyrazole derivatives displayed signals due to aromatic protons but lacked signals characteristic of H-4 and H-5 of the corresponding pyrazoline-pyrazoles. The structures of the above bipyrazoles **16-22** were further confirmed from their ^{13}C NMR data which showed the expected number of aliphatic and aromatic carbons signals.

Addition of pyrazolines **9-15** across the N=C bond of the appropriate isocyanate and isothiocyanate in dry acetone yielded the corresponding benzenesulfonylureas **23-29** and thioureas **30-37** respectively. The IR spectra of these compounds exhibited two absorptions at 1338-1390 cm^{-1} and 1150-1182 cm^{-1} for the SO_2N group and a urea carbonyl band at 1642-1658 cm^{-1} in case of the ureas compounds **23-29** and a thiourea carbonyl absorption at 1155-1168 cm^{-1} in case of compounds **30-37**. The ^{1}H NMR spectra of the urea and thiourea derivatives **23-37** exhibited beside the aromatic protons, three multiplets at δ 5.21-5.48, 3.28-3.85 and 3.23-3.34. The low field multiplet is assigned to H-5 of the pyrazoline while the other two multiplets is attributed to H-4. The structures of the above compounds were further confirmed from their ^{13}C NMR data which showed beside the expected number of aliphatic and aromatic carbons signals a carbonyl carbon at δ 175.8-180.2 for the urea derivatives **23-29** and a thiocarbonyl carbon at δ 198-202 for the thiourea analogs **30-37.** Cyclization of the thiourido group of compounds **31-34, 36** and, **37** by treatment with ethyl bromoacetate and -bromoacetophenone afforded the corresponding 4-oxothiazoline **38-43** and thiazoline derivatives **44-48** respectively. IR spectra of **44-48** showed cyclic carbonyl absorption at 1720-1733 cm^{-1} and the two bands of the SO_2N group 1333-1368 cm^{-1} and 1132-

1175 cm^{-1}. The structures of the above compounds **38-48** were supported by their ^{1}H & ^{13}C NMR data which showed the expected number of aliphatic and aromatic carbons signals. In addition, the ^{13}C NMR of the 4-oxothiazoline **44-48** showed a carbonyl carbon at δ 175.1-180.2 (experimental section).

2.2. Biological Activity

.2.1.In vitro MTT cytotoxicity assay2

Twenty five analogise **9, 10, 11, 12, 13, 14, 15, 19, 21, 22, 23, 25, 26, 27, 28, 33, 34, 35, 39, 40, 42, 44, 45, 47** and **48** were selected to be evaluated for their *in vitro* cytotoxic effect *via* the standard MTT [3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide] method [41,42] against a panel of three human tumor cell lines namely; Caucasian breast adenocarcinoma MCF7, hepatocellular carcinoma HepG2 and colon carcinoma HT29. The results are presented in (Table 1) as LC_{50} (µM) which is the lethal concentration of the compound which cause death of 50% of the cells in 24h. The obtained data revealed that, the three tested human tumor cell lines exhibited variable degree of sensitivity profiles towards fifteen of the tested compounds namely; **10, 12, 14, 15, 19, 21, 22, 23, 25, 26, 27, 28, 33, 34** and **35**. Among these, compounds **23, 26, 27** and **28** showed pronounced activity against the human colon carcinoma HT29 cell line with LC_{50} values 11.5 ,7.9, 10.1 and 12.6 µM, respectively. Moreover, a remarkable cytotoxic potential was displayed by compounds **25, 33, 34** and **35** against the same cell line with LC_{50} values range of 15.4 -21.3 µM. Compounds **14, 15, 19** and **22** revealed an obvious cytotoxicity profile against colon carcinoma HT29 with LC_{50} values 27.2, 25.4, 30.3 and 25.9 µM, respectively. However, the rest compounds were able to exhibit moderate activity against the same cell line with LC_{50} values range of 39.2-50.3 µM. Furthermore, the growth of the human hepatocellular carcinoma HePG2 cell line was found to be moderately inhibited by twelve of the active compounds **14, 15, 19, 22, 23, 25, 26, 27, 28, 33, 34** and **35** with LC_{50} values range of 20.2-45.3 µM. Among these, the highest cytotoxic activity was displayed by compounds **23, 26, 27** and **28** which were almost equipotent (LC_{50} values 22.7, 20.2,24.6 and 25.9 µM, respectively). On the other hand, human breast cancer MCF 7 was proved to be the least sensitive among the cell lines tested as it was affected by only eighty of the test compounds. However, an outstanding growth inhibition potential was shown by compounds **23, 26, 27** and **28** as evidenced from their LC_{50} values (3.8,2.0, 2.8 and 8.7 µM, respectively). The rest four active compounds namely **14, 22, 33** and **34** showed moderate to mild activity against the same cell line with LC_{50} values range of 28.4 - 44.5 µM, respectively **(Table 1)**. Further interpretation of the results revealed that, compounds **23, 26, 27** and **28** showed considerable broad spectrum of cytotoxic activity against the three tested human tumor cell lines. In particular, compound **26** proved to be the most active member in this study with a broad spectrum of activity against the tested cell lines, with special effectiveness against the human colon carcinoma HT29 and human breast cancer MCF 7 cell lines (LC_{50} values 7.9 and 2.0 µM, respectively) (**Table 1**). A close examination of the structure of the active compounds showed that the phenylsulfonylurea moiety counterpart at position-1 of the pyrazoline skeleton is the most favourable substituent when compared with other analogise. Moreover, the thiourea substituent at position-1 (as in compounds **34** and **35**) was responsible for the remarkable cytotoxic potential displayed by these analogise. On the other hand cyclization of the intermediate thiourea derivatives with ethyl bromoacetate and phenacyl bromide led to complete abolishment of the cytotoxic activity.

Table 1. Cytotoxic effects LC_{50}; µg/mL[a] of the active compounds on some human tumor cell lines using the MTT assay.

Compound	HT29[b]	Hep-G2 [c]	MCF 7 [d]
10	43.8	-	-
12	49.7	-[e]	-
14	27.2	45.3	44.5
15	25.4	32.9	-
19	30.3	38.2	-
21	39.2	-	-
22	25.9	36.5	38.4
23	11.5	22.7	3.8
25	15.4	32.8	-
26	7.9	20.2	2.0
27	10.1	24.6	2.8
28	12.6	25.9	8.7
33	16.4	33.7	31.8
34	18.2	38.3	28.4
35	21.3	41.3	-
Doxorubicin[f]	21.1	1.69	2.14

[a]LC_{50}: Lethal concentration of the compound which causes death of 50% of cells in 24h µg/mL(µg/mL).

[b]HT29 (Human colon carcinoma cell line).

[c]Hep-G2 (Human hepatocellular carcinoma cell line).

[d]MCF7 (Human breast cancer cell line).

[e]Totally inactive against this cell line.

[f]Positive control cytotoxic agent.

2.2.2 Antidiabetic activity

From the data presented in **Table 2**, it is obvious that the benzenesulfonylurea derivatives **23, 25, 27** and **29** possess marked hypoglycemic activity. The potency of these compounds is more than that of phenformine, and they are much more active than the parent compound 3,5-dimethylpyrazole. On the other hand although the hypoglycemic activity of the thioureas is low, their cyclic thio-analogs showed potent antidiabetic activity (**Table 2**).

Table 2: Antidiabetic activity of pyrazole derivatives

Compd.	**Reduction in plasma glucose level, %**	***P***
Phenformin	10	<0.01[a]
3,5-Dimethylpyrazole	4	<0.05
10	<1	0.05
12	<1	0.05
23	17	<0.01[a]
25	14	<0.01[a]
27	13	<0.01[a]
29	20	<0.01[a]
32	2	0.05
33	4	0.05
35	3	0.05
36	2.5	0.05
44	7	0.01[a]
45	10	0.01[a]
48	8	0.01[a]
41	7.5	0.01[a]
42	7	0.01[a]
43	9	0.01[a]

[a]Statistically significant

3. Experimental

3.1. Chemistry

Melting points were determined on a Gallenkamp melting point apparatus and are uncorrected. The infrared (IR) spectra were recorded on Shimadzu FT-IR 8400S infrared spectrophotometer using the KBr pellet technique. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker WM-600 FT NMR spectrometer using tetramethylsilane as the internal standard and DMSO-d_6 as a solvent (Chemical shifts in δ, ppm). Splitting patterns were designated as follows: *s*: singlet; *d*: doublet; *m*: multiplet; *q*: quartet. The impact ionization mass spectra were recorded on a Nermag R10-10C at 70ev. 1000 Ex spectrometer.Elemental analyses were performed on a 2400 Perkin Elmer Series 2 analyzer and the found values were within ±0.4% of the theoretical values. Follow up of the reactions and checking the homogeneity of the compounds were made by TLC on silica gel-protected aluminum.

3.1.1.General procedure for preparation of chalcones (2-8)

A solution of the appropriate 1-phenylpyrazole-4-carboxaldehyde **1a and 1b** (10 mmol) in ethanol (20 mL) was added to a stirred solution of the corresponding ketone (10 mmol) in (20%) ethanolic KOH (20 mL), and stirring was maintained at room temperature for 6 h. The reaction mixture was then poured onto water (200 mL) and set aside for an overnight. The precipitated solid product was collected by filtration, washed with water, dried and recrystallized from the appropriate solvent*.*

3-(1-Phenyl-1H-pyrazol-4-yl)-1-phenylprop-2-en-1-one 2:

Rrecrystallized from ethanol as needles. (2.3g, 88%) m.p.170-172°C. $\nu_{max.}$ (cm^{-1},KBr): 1646 (C=O), 1604(C=C). ^{1}H NMR (δ/ppm,DMSO-d_6): δ 6.60(*d*, J=16Hz, 1H, *H*-α), 7.08(*d*, J=16Hz, 1H, *H*-β), 7.33-7.82(*m*,10H, Ar- *H*), 7.73(s,1H pyrazole *H*-3), 7.95(s,1H pyrazole *H*-5). ^{13}C NMR (δ/ppm, DMSO-d_6): δ 129.30(*C*- α), 142.80(*C*-β), 107.30, 118.80, 126.01, 126.30, 128.50, 129.10, 135.60, 136.60, 139.80, 141.50, 145.70(Ar-*C*), 186.70(*C*=O). Anal.% Calcd for $C_{18}H_{14}N_2O$: C, 78.81; H, 5.14; N, 10.21. Found: C, 78.93; H, 5.26; N, 10.26.

3-(1-Phenyl-1H-pyrazol-4-yl)-1-(4-bromophenyl)prop-2-en-1-one 3:

Rrecrystallized from ethanol/benzene as needles. (3.1g, 99%) m.p.210-211°C. $\nu_{max.}$ (cm^{-1} ,KBr): 1648(C=O), 1608(C=C). ^{1}H NMR (δ/ppm,DMSO-d_6): δ 6.59(*d*, J=16Hz, 1H, *H*-α), 7.02 (*d*, J=16Hz, 1H, *H*-β), 7.34-7.90(*m*,9H, Ar-*H*), 7.76(s,1H pyrazole *H*-3), 7.92(s,1H pyrazole *H*-5). ^{13}C NMR (δ/ppm, DMSO-d_6): δ 129.10(*C*-α), 142.40(*C*-β), 107.20, 118.40, 126.10, 128.90, 129.01, 132.30, 135.70, 136.90, 139.70, 141.30, 145.40(Ar-*C*),187.20 (*C*=O). Anal.% Calcd for $C_{18}H_{13}BrN_2O$: C, 61.21; H, 3.71; N, 7.93. Found: C, 61.40; H, 3.78; N, 8.02.

3-(1-Phenyl-1H-pyrazol-4-yl)-1-(4-methoxyphenyl)prop-2-en-1-one 4:

Rrecrystallized from methanol as needles. (2.7g, 88%) m.p.166-168°C. $\nu_{max.}$ (cm^{-1} ,KBr): 1652(C=O), 1611(C=C). ^{1}H NMR (δ/ppm,DMSO-d_6): δ 3.73 (s,3H,OCH_3), 6.57(*d*, J=16Hz, 1H, *H*-α), 7.05(*d*, J=16Hz, 1H, *H*-β), 6.96-7.70(*m*,9H, Ar-*H*), 7.75(s,1H pyrazole *H*-3), 7.96(s,1H pyrazole *H*-5); ^{13}C NMR (δ/ppm, DMSO-d_6): δ 56.01(OCH_3), 129.30(*C*-α), 142.8 (*C*-β), 114.60, 107.71, 118.92, 126.01, 129.01, 129.10, 130.70, 133.70, 135.40, 139.70, 167.70(Ar-*C*), 188.30(*C*=O). Anal.% Calcd for $C_{19}H_{16}N_2O_2$: C, 74.98; H, 5.30; N, 9.20. Found: C, 74.77; H, 5.10; N, 9.50.

***3-(1-Phenyl-1H-pyrazol-4-yl)-1-(thiophen-2-yl)prop-2-en-1-one 5*:**

Rrecrystallized from ethanol as needles. (2.4g, 94%) m.p.218-220. ν max. (cm^{-1},KBr): 1649 (C=O), 1609(C=C) . ^{1}H NMR (DMSO-d_6/ $CDCl_3$) : δ 6.60(*d*, J=16Hz, 1H, *H*-α), 7.04(*d*, J=16Hz, 1H, *H*-β), 7.06-7.92(*m*,8H, Ar-*H*), 7.78(s,1H pyrazole *H*-3), 7.94(s,1H pyrazole *H*-5). ^{13}C NMR (δ/ppm, DMSO-d_6): δ 129.30(*C*-α), 142.80(*C*-β), 107.20, 118.80, 126.01, 126.30, 128.50, 129.10, 135.60, 136.60, 139.80, 141.50, 145.70(Ar-*C*), 180.70(*C*=O). Anal.% Calcd for $C_{16}H_{12}N_2OS$: C, 68.55; H, 4.31; N, 9.99. Found: C, 68.42; H, 4.42; N, 10.01.

3-((3,5-Dimethyl-1-phenyl-1H-pyrazol-4-yl)-1-phenylprop-2-en-1-one 6:

Rrecrystallized from methanol as needles. (2.5g, 82%) m.p.120-122°C. $\nu_{max.}$(cm^{-1},KBr): 1650 (C=O), 1608(C=C).^{1}HNMR (δ/ppm,DMSO-d_6): δ 2.69(s,3H,CH_3), 2.79(s,3H,CH_3), 6.59(*d*, J=16Hz, 1H, *H*-α), 7.01(*d*, J=16Hz, 1H, *H*-β), 7.30-7.81(*m*,10H, Ar-*H*). ^{13}C NMR (δ/ppm, DMSO-d_6): δ 8.90(CH_3), 7.80(CH_3), 129.20(*C*-α), 142.40(*C*-β), 109.20, 118.40, 126.10, 128.90, 129.01, 132.30, 135.70, 136.90, 139.70, 142.30, 154.50(Ar-*C*), 186.90(*C*=O). Anal.% Calcd for $C_{20}H_{18}N_2O$: C, 79.44; H, 6.00; N, 9.26. Found: C, 79.74; H, 6.19; N, 9.45.

3-(3,5-Dimethyl-1-phenyl-1H-pyrazol-4-yl)-1-(4-bromophenyl)prop-2-en-1-one 7:

Rrecrystallized from ethanol/DMF (5:1)l as needles. (3.1g, 86%) m.p.198-200°C. ν max. (cm^{-1} ,KBr): 1648(C=O), 1610(C=C). ^{1}H NMR (δ/ppm,DMSO-d_6): δ 2.68(s,3H,CH_3), 2.75(s,3H,CH_3), 6.52(*d*, J=16Hz, 1H, *H*-α), 7.03(*d*, J=16Hz, 1H, *H*-β), 7.32-7.76(*m*,9H, Ar-H). ^{13}C NMR (δ/ppm, DMSO-d_6): δ 9.10(CH_3), 8.20(CH_3), 129.50(*C*-α), 142.20(*C*-β), 109.40, 118.60, 126.01, 128.80, 129.10, 132.50, 135.60, 136.70, 139.70, 141.01, 155.10(Ar-*C*), 187.01(*C*=O). Anal.% Calcd for $C_{20}H_{17}BrN_2O$: C, 63.00; H, 4.49; N, 7.35. Found: C, 63.23; H, 4.75; N, 7.19.

3-(3,5-Dimethyl-1-phenyl-1H-pyrazol-4-yl)-1-(thiophen-2-yl)prop-2-en-1-one 8:

Rrecrystallized from methanol as needles. (3.1g, 84%) m.p.110-112°C. ν max. (cm^{-1},KBr): 1649(C=O), 1612(C=C).^{1}H NMR (DMSO-d_6/ $CDCl_3$): δ 2.68(s,3H,CH_3), 2.75(s,3H,CH_3), 6.58(*d*, J=16Hz, 1H, *H*-α), 7.06(*d*, J=16Hz, 1H, *H*-β), 7.04-7.88(*m*,8H, Ar-*H*). ^{13}C NMR (δ/ppm, DMSO-d_6): δ 8.50(CH_3), 7.30(CH_3), 129.10(*C*-α), 142.60(*C*-β), 109.50, 118.60, 126.10, 126.40, 128.70, 129.01, 135.60, 136.80, 139.90, 140.50, 154.70(Ar-*C*), 186.80(*C*=O). MS: *m/z* 308 (M^+,100), 280(20), 260(8), 198(37),144(38),112(13),84(15),83(12),77(16). Anal.% Calcd for $C_{18}H_{16}N_2OS$: C, 70.10; H, 5.23; N, 9.08. Found: C, 70.35; H, 5.40; N, 9.28.

3.1.2. Pyrazole- pyrazoline derivatives (9-15)

A solution of the appropriate chalcone **2-8** (10 mmol) in ethanol (25mL) was refluxed with p-hydrazinobenzenesulfonamide hydrochloride (2.45 g, 10 mmol) for 4 hr. On concentration, the separated product was filtered, washed with cold ethanol and recrystallized from the appropriate solvent.

4-[(3-phenyl-5-(1-phenylpyrazol-4-yl)-4,5-dihydropyrazol-1-yl]benzenesulfonamide 9:

Rrecrystallized from ethanol as needles (3.7g, 79%). m.p.208-210°C. ν_{max} (cm^{-1} ,KBr): 3387, 3289 cm^{-1}(NH_2), 1137, 1337 cm^{-1}(SO_2N). ^{1}H NMR (δ/ppm, DMSO-d_6): δ 3.14,3.37 (2m, 2H, pyrazoline *H-4*), 4.99(m, 1H, pyrazoline *H-5*), 7.12-7.87(*m*,18H, Ar-*H*+NH_2). ^{13}C NMR (δ/ppm, DMSO-d_6): δ 41.62(*C*-4), 55.72(*C-5*), 118.60, 119.05, 124.42, 125.34, 125.32, 126.62, 127.71, 129.38, 130.82, 135.44, 136.76, 137.23, 139.14, 140.10, 141.23, 160.54(Ar-*C*). Anal.% Calcd for $C_{24}H_{21}N_5O_2S$: C, 64.99; H, 4.77; N, 15.79. Found: C, 64.78; H, 4.54; N, 15.81.

4-[(3-(4-bromophenyl)-5-(1-phenylpyrazol-4-yl)-4,5-dihydropyrazol-1-yl]benzene-sulfonamide 10:

Rrecrystallized from ethanol as needles (4.2g, 81%). m.p.148-150°C). ν_{max} (cm^{-1} ,KBr): 3380, 3277 cm^{-1}(NH_2), 1158, 1345 cm^{-1}(SO_2N).^{1}H NMR (δ/ppm, DMSO-d_6): δ 3.09,3.33 (2m, 2H, pyrazoline *H-4*), 4.97(m,

1H, pyrazoline *H-5*), 7.19-7.83(*m*,17H, Ar-*H*+NH_2). ^{13}C NMR (δ/ppm, DMSO-d_6): δ 41.68(*C*-4), 55.71(*C- 5*), 118.67, 119.10, 124.50, 125.40, 125.30, 126.70, 127.75, 129.30, 130.80, 135.40, 136.80, 137.20, 139.10, 140.15, 141.25, 160.60(Ar-*C*). Anal.% Calcd for $C_{24}H_{20}BrN_5O_2S$: C, 55.18; H, 3.86; N, 13.41. Found: C, 55.23; H, 3.99; N, 13.54.

4-[(3-(4-anisyl)-5-(1-phenylpyrazol-4-yl)-4,5-dihydropyrazol-1-yl]benzensulfonamide 11:

Rrecrystallized from methanol as needles (3.7g, 79%). m.p.132-134°C). ν_{max} (cm^{-1} ,KBr): 3397, 3271 cm^{-1}(NH_2), 1156, 1378 cm^{-1}(SO_2N). ^{1}H NMR (δ/ppm, DMSO-d_6): δ 3.87(s, 3H, OCH_3), 3.06,3.44(2m, 2H, pyrazoline *H-4*), 4.97(m, 1H, pyrazoline *H-5*), 6.91-7.91(*m*,17H, Ar- *H*+NH_2). ^{13}C NMR (δ/ppm, DMSO-d_6): δ 55.49(CH_3O), 41.02(*C*-4), 55.36(*C-5*), 114.04, 119.07, 124.57, 125.38, 125.42, 126.59, 127.63, 129.46, 130.54, 135.24, 136.89, 137.01, 139.34, 139.98, 141.27, 160.41(Ar-*C*). Anal.% Calcd for $C_{25}H_{23}N_5O_2S$: C, 65.63; H, 5.07; N, 15.31. Found: C, 65.49; H, 5.17; N, 15.43.

4-[(3-(2-theinyl)-5-(1-phenylpyrazol-4-yl)-4,5-dihydropyrazol-1-yl]benzensulfonamide 12:

Rrecrystallized from ethanol/ benzene (1:1) as needles. (2.6g, 88%) m.p. 204-205°C.$\nu_{max.}$(cm^{-1} ,KBr): 3375, 3240 cm^{-1}(NH_2), 1137, 1337 cm^{-1}(SO_2N) .^{1}H NMR (δ/ppm,DMSO-d_6): δ 3.12, 3.82(2m, 2H, pyrazoline *H-4*), 5.37(m, 1H, pyrazoline *H-5*), 6.96-7.72(*m*,16H, Ar-*H*+ NH_2). ^{13}C NMR (δ/ppm, DMSO-d_6): δ 41.2(*C*-4), 55.37(*C-5*), 112.60, 118.20, 118.80, 125.60, 125.80, 126.10, 126.30, 126.60, 126.70, 127.70, 129.10, 139.70, 140.30, 146.70, 155.10, 160.45(Ar-*C*). Anal.% Calcd for $C_{22}H_{19}N_5O_2S_2$: C, 58.78; H, 4.26; N, 15.58. Found: C, 58.65; H, 4.32; N, 15.43.

4-[(3-phenyl-5-(3,5-dimethyl-1-phenylpyrazol-4-yl)-4,5-dihydropyrazol-1-yl]benzenesulfonam- ide 13:

Rrecrystallized from ethanol as needles. (3.4g, 74%). m.p.182-183°C. ν_{max} (cm^{-1} ,KBr): 3387, 3266 cm^{-1}(NH_2), 1146, 1358 cm^{-1}(SO_2N). ^{1}H NMR (δ/ppm,DMSO-d_6): δ 2.66 (s,3H,CH_3), 2.69(s,3H,CH_3), 3.17,3.44 (m, 2H, pyrazoline *H-4*), 5.35(m, 1H, pyrazoline *H-5*), 6.76-7.90(*m*,16H,Ar-*H*+NH_2). ^{13}C NMR(δ/ppm,DMSO-d_6): δ 11.40(CH_3), 12.60(CH_3), 43.40(*C*-4), 53.70(*C-5*), 112.20, 118.80, 119.50, 126.01, 126.30, 127.70, 128.90, 129.10, 129.20, 130.60, 131.40, 139.20, 139.90, 153.50, 155.60, 160.4 (Ar-*C*). Anal.% Calcd for $C_{26}H_{25}N_5O_2S$: C,66.22; H,5.34; N, 14.85. Found: C, 66.42; H, 5.23; N, 14.69.

4-[(3-(4-bromophenyl)-5-(3,5-dimethyl-1-phenylpyrazol-4-yl)-4,5-dihydropyrazol-1-yl]benzene-sulfonamide 14:

Rrecrystallized from DMF as needles. (2.4g, 75%). m.p.238-240°C. ν_{max} (cm^{-1} ,KBr): 3383, 3255 cm^{-1}(NH_2), 1141, 1359 cm^{-1}(SO_2N). ^{1}H NMR (δ/ppm,DMSO-d_6): δ 2.46 (s,3H,CH_3), 2.59(s,3H,CH_3), 3.12, 3.45(2m, 2H, pyrazoline *H-4*), 5.38(m, 1H, pyrazoline *H-5*), 7.10-7.90(*m*,15H, Ar-*H*+NH_2). ^{13}C NMR (δ/ppm, DMSO-d_6): δ 10.93(CH_3), 11.21(CH_3), 41.79(*C*-4), 55.52(*C-5*), 112.41, 118.83, 125.21, 127.45, 127.98, 128.16, 129.18, 129.32, 129.21, 129.87, 130.20, 131.90, 131.98, 146.87, 147.98, 160.12(Ar-*C*). MS: *m/z* 549 (M^+,100), 550(25), 547 (94), 467(18),392(22),378(15),298(12),144(32),77(34). Anal.% Calcd for $C_{26}H_{24}BrN_5O_2S$: C,56.73; H,4.39; N, 12.72. Found: C, 56.97; H, 4.50; N, 12.56.

4-[(3-(2-theinyl)-5-(3,5-dimethyl-1-phenylpyrazol-4-yl)-4,5-dihydropyrazol-1-yl]benzene-sulfonamide 15:
Rrecrystallized from ethanol/DMF (5:1) as needles. (3.75g, 78%). m.p.204-206°C. ν_{max} (cm^{-1} ,KBr): 3375, 3241 cm^{-1}(NH_2), 1138,1362 cm^{-1}(SO_2N). ^{1}H NMR (δ/ppm,DMSO-d_6): δ 2.48 (s,3H,CH_3), 2.51(s,3H,CH_3), 3.14, 3.37(2m, 2H, pyrazoline *H-4*), 5.33(m, 1H, pyrazoline *H-5*), 7.18-7.85(*m*,14H, Ar-*H*+ NH_2). ^{13}C NMR (δ/ppm, DMSO-d_6): δ 10.91(CH_3), 11.22(CH_3), 41.78(*C*-4), 55.53(*C-5*), 112.42, 125.20, 127.44, 127.97,

128.18, 129.13, 129.35, 129.27, 129.82, 130.30, 131.95, 131.91, 146.87, 147.98, 160.17(Ar-*C*). Anal.% Calcd for $C_{24}H_{23}N_5O_2S_2$: C, 60.36; H, 4.85; N, 14.66. Found: C, 60.21; H, 4.99; N, 14.57.

3.1.3. Bipyrazole derivatives (16-22)

To a stirred suspension of the appropriate pyrazoline derivative (10 mmol) in water (10 mL), bromine water (5%, 15 mL) was gradually added over a period of 30 min. at 25^{0}C. After stirring for 3 h at room temperature, the pyrazole derivatives thus formed, were collected by filtration, thoroughly washed with water and dried. They were recrystallized from the appropriate solvent to give pale yellow to yellowish brown needles

4-[(3-phenyl-5-(1-phenylpyrazol-4-yl)pyrazol-1-yl]benzenesulfonamide 16:

Rrecrystallized from ethanol as needles. (3.3g, 72%). m.p.162-164°C. ν_{max} (cm^{-1} ,KBr): 3371, 3251 cm^{-1}($NH_{2)}$, 1153, 1353 cm^{-1}(SO_2N).^{1}H NMR (δ/ppm, DMSO-d_6): δ 7.13-7.85(*m*,19H, Ar-*H*+NH_2). ^{13}C NMR (δ/ppm, DMSO-d_6): δ 114.28, 118.60, 119.05, 124.42, 125.34, 125.32, 126.62, 127.71, 129.38, 130.82, 135.44, 136.76, 137.23, 139.14, 140.10, 141.23, 155.67, 160.54(Ar-*C*). Anal.% Calcd for $C_{24}H_{19}N_5O_2S$: C, 65.29; H, 4.34; N, 15.86. Found: C, 65.50; H, 4.25; N, 15.71.

4-[(3-(4-bromophenyl)-5-(1-phenylpyrazol-4-yl)pyrazol-1-yl]benzenesulfonamide 17:

Rrecrystallized from methanol as needles. (3.8g, 73%) . m.p.130-132°C. ν_{max} (cm^{-1} ,KBr): 3254, 3362 cm^{-1}(NH_2), 1342, 1137 cm^{-1} (SO_2N). ^{1}H NMR (δ/ppm,DMSO-d_6): δ 6.76-7.90 (*m*,18H,Ar-*H*+NH_2). ^{13}CNMR(δ/ppm,DMSO-d_6): δ 106.70, 108.50, 115.60, 118.80, 119.70, 123.20, 126.01, 126.30, 127.50, 129.01, 129.20, 129.60, 132.40, 135.50, 139.90, 142.20, 144.40, 150.80(Ar-*C*). Anal.% Calcd for $C_{24}H_{18}BrN_5O_2S$: C, 55.39; H, 3.49; N, 13.46. Found: C, 55.45; H, 3.60; N, 13.35.

4-[(3-(4-anisyl)-5-(1-phenylpyrazol-4-yl)pyrazol-1-yl]benzenesulfonamide 18:

Rrecrystallized from methanol as needles. (3.3g, 70%) . m.p.138-140°C. ν_{max} (cm^{-1} ,KBr): 3373, 3252 cm^{-1}(NH_2), 1145, 1358 cm^{-1}(SO_2N). ^{1}H NMR (δ/ppm, DMSO-d_6): δ 3.81(s, 3H, OCH_3), 6.94-7.96(*m*,18H, Ar-*H*+NH_2). ^{13}C NMR (δ/ppm, DMSO-d_6): δ 55.43(CH_3O), 114.10, 118.40, 119.10, 124.60, 125.40, 125.38, 126.60, 127.68, 129.50, 130.47, 135.30, 136.90, 137.10, 139.38, 139.94, 141.30, 155.63, 160.40(Ar-*C*). Anal.% Calcd for $C_{25}H_{21}N_5O_3S$: C, 63.68; H, 4.49; N, 14.85. Found: C, 63.81; H, 4.29; N, 14.91.

4-[(3-(2-theinyl)-5-(1-phenylpyrazol-4-yl)pyrazol-1-yl]benzenesulfonamide 19:

Rrecrystallized from ethanol as needles. (3.8g, 73%) . m.p.168-170°C. ν_{max} (cm^{-1} ,KBr): 3259, 3384 cm^{-1}(NH_2), 1343, 1135 cm^{-1}(SO_2N). ^{1}HNMR(δ/ppm,DMSO-d_6): δ 6.82-7.84(*m*,17H,Ar-*H*+NH_2). ^{13}CNMR(δ/ppm,DMSO-d_6): δ 106.87, 108.79, 115.83, 118.72, 119.62, 123.45, 126.20, 126.31, 127.47, 129.01, 129.24, 129.76, 132.48, 135.47, 139.90, 142.25, 144.34, 150.93(Ar-*C*). Anal.% Calcd for $C_{22}H_{17}N_5O_2S_2$: C, 59.04; H, 3.83; N, 15.65. Found: C, 59.12; H, 3.69; N, 15.45.

4-[(3-phenyl-5-(3,5-dimethyl-1-phenylpyrazol-4-yl)pyrazol-1-yl]benzenesulfonamide 20:

Rrecrystallized from ethanol as needles. (2.8g, 76%). m.p.130-132°C. ν_{max} (cm^{-1} ,KBr): 3369, 3275 cm^{-1}(NH_2), 1137,1365 cm^{-1}(SO_2N). ^{1}H NMR (δ/ppm,DMSO-d_6): δ 2.54 (s,3H,CH_3), 2.69(s,3H,CH_3), 6.79-7.81(*m*,17H,Ar-*H*+NH_2). ^{13}C NMR(δ/ppm,DMSO-d_6): δ 11.42(CH_3), 12.62(CH_3), 112.24, 114.28, 118.77, 119.53, 126.10, 126.31, 127.72, 128.88, 129.04, 129.13, 130.70, 131.35, 139.24, 139.83, 141.65, 153.42, 155.67, 160.46(Ar-*C*). Anal.% Calcd for $C_{26}H_{23}N_5O_2S$: C,66.50; H,4.94; N, 14.91. Found: C, 66.42; H, 5.12; N, 14.69

4-[(3-(4-bromophenyl)-5-(3,5-dimethyl-1-phenylpyrazol-4-yl)pyrazol-1-yl]benzene-sulfonamide 21:

Rrecrystallized from ethanol/ DMF (8:1) as needles. (4.21g, 77%). m.p.212-214°C. ν_{max} (cm^{-1} ,KBr): 3361, 3250 cm^{-1}(NH_2), 1135, 1349 cm^{-1}(SO_2N). ^{1}H NMR (δ/ppm,DMSO-d_6): δ 2.58 (s,3H,CH_3), 2.63(s,3H,CH_3), 7.17-7.86(*m*,16H, Ar-*H*+NH_2). ^{13}C NMR (δ/ppm, DMSO-d_6): δ 10.97(CH_3), 11.28(CH_3), 112.43, 114.28, 118.88, 125.27, 127.53, 127.90, 128.13, 129.23, 129.40, 129.26, 129.94, 130.25, 131.95, 131.91, 146.80, 148.01, 155.61, 160.12(Ar-*C*). Anal.% Calcd for $C_{26}H_{22}BrN_5O_2S$: C,56.94; H,4.04; N, 12.77. Found: C, 56.79; H, 4.23; N, 12.65.

4-[(3-(2-theinyl)-5-(3,5-dimethyl-1-phenylpyrazol-4-yl)pyrazol-1-yl]benzenesulfonamide 22:

Rrecrystallized from ethanol as needles. (3.37g, 78%). m.p.148-150°C. ν_{max} (cm^{-1} ,KBr): 3342, 3270 cm^{-1}(NH_2), 1145, 1350 cm^{-1}(SO_2N). ^{1}H NMR (δ/ppm,DMSO-d_6): δ 2.57 (s,3H,CH_3), 2.63(s,3H,CH_3), 7.23-7.91(*m*,15H, Ar-*H*+ NH_2). ^{13}C NMR (δ/ppm, DMSO-d_6): δ 10.96(CH_3), 11.28(CH_3), 112.35, 114.25, 118.79, 125.26, 127.40, 127.91, 128.13, 129.18, 129.40, 129.21, 129.90, 130.34, 131.90, 131.85, 146.80, 147.90, 160.20(Ar-*C*). Anal.% Calcd for $C_{24}H_{21}N_5O_2S_2$: C, 60.61; H, 4.45; N, 14.73. Found: C, 60.78; H, 4.30; N, 14.87.

3.1.4. Benzenesulfonylureas (23-29)

A stirred mixture of the appropriate pyrazoline (10 mmol) and anhydrous K_2CO_3 (1.4 g, 10 mmol) in dry acetone (25 mL) was heated under reflux with the appropriate isocyanate (10 mmol) for 18 h. The solvent was removed under reduced pressure and the remaining solid residue was dissolved in water (30 mL). After neutralization of the resulting solution with 2N HCl, the precipitated crude product was filtered, washed with water, dried and recrystallized from proper solvent.

N^1-[4-[(3-(2-theinyl)-5-(1-phenylpyrazol-4-yl)-4,5-dihydropyrazol-1-yl]benzenesulfonyl]-N^3-cyclohexylurea 23:

Rrecrystallized from ethanol as needles. (4.5g, 79%) m.p.197-198°C. ν_{max} (cm^{-1} ,KBr): 3271, 3312 cm^{-1}(2NH), 1338, 1150 cm^{-1}(SO_2N), 1642(C=O). ^{1}H NMR (δ/ppm,DMSO-d_6): δ 1.62, 2.88(*m*, 11H,cyclohexyl-*H*), 3.24, 3.78(2m, 2H, pyrazoline *H-4*), 5.51(m, 1H, pyrazoline *H-5*), 6.98-7.68(*m*,15H,Ar-*H* +NH), 8.42(m,1H,NH). ^{13}CNMR(δ/ppm,DMSO-d_6): δ 21.60, 27.10, 32.70, 47.20(cyclohexyl-*C*), 38.40(*C*-4), 50.2(*C*-5), 113.40, 117.60, 119.40, 125.20, 125.70, 126.20, 126.50, 127.10, 127.80, 128.40, 129.30, 129.60, 136.40, 142.40, 145.20, 155.80(Ar-*C*), 172.20(CO). Anal.% Calcd for $C_{29}H_{30}N_6O_3S_2$: C, 60.61; H, 5.26; N, 14.62. Found: C, 60.72; H, 5.34; N, 14.52.

N^1-[4-[(3-(2-theinyl)-5-(1-phenylpyrazol-4-yl)-4,5-dihydropyrazol-1-yl]benzenesulfonyl]-N^3-phenylurea 24:

Rrecrystallized from ethanol as needles. (3.5g, 82%) m.p235-236°C. ν_{max} (cm^{-1} ,KBr): 3283, 3315 cm^{-1}(2NH), 1348, 1171 cm^{-1}(SO_2N), 1658(C=O). ^{1}H NMR (δ/ppm,DMSO-d_6): δ 3.28, 3.72(2m, 2H, pyrazoline *H-4*), 5.48(m, 1H, pyrazoline *H-5*), 6.75-7.74(*m*, 20H, Ar-*H*+NH), 8.01(s,1H,NH). ^{13}C NMR (δ/ppm,DMSO-d_6): δ 42.20(*C*-4), 55.31(*C-5*), 116.66, 119.74, 119.82, 119.98, 121.62, 124.22, 124.50, 125.67, 126.53, 126.69, 128.77, 128.98, 129.34, 131.21, 131.28, 135.72, 138.52, 139.16, 143.85, 145.72(Ar-*C*), 176.43(CO). Anal.% Calcd for $C_{29}H_{24}N_6O_3S_2$: C, 61.25; H, 4.25; N, 14.78. Found: C, 61.26; H, 4.35; N, 14.68.

N^1-[4-[(3-(2-theinyl)-5-(1-phenylpyrazol-4-yl)-4,5-dihydropyrazol-1-yl]benzenesulfonyl]-N^3-(4-chlorophenyl)urea 25:

Rrecrystallized from DMF as needles. (4.5g, 79%) m.p. 252-253°C. ν_{max} (cm^{-1} ,KBr): 3284, 3332 cm^{-1}(2NH), 1345, 1162 cm^{-1}(SO_2N), 1649(C=O). ^{1}H NMR (δ/ppm,DMSO-d_6): δ 3.31, 3.69(2m, 2H, pyrazoline *H-4*), 5.41(m, 1H, pyrazoline *H-5*), 6.98-7.68(*m*,15H,Ar-*H*+NH), 8.42(m,1H,NH). ^{13}CNMR(δ/ppm,DMSO-d_6): δ

38.40(*C*-4), 50.20(*C*-5), 113.38, 114.27, 117.64, 118.70, 119.45, 125.28, 125.67, 126.12, 126.53, 127.13, 127.83, 128.31, 129.40, 129.56, 136.41, 141.45, 142.3, 145.26, 155.7, 160.16(Ar-*C*), 172.2(CO). Anal.% Calcd for $C_{29}H_{23}ClN_6O_3S_2$: C, 57.75; H, 3.84;N, 13.93. Found: C, 57.89; H, 3.61;N, 13.73.

N^1-[4-[(3-(2-theinyl)-5-(3,5-dimethyl-1-phenylpyrazol-4-yl)-4,5-dihydropyrazol-1-yl]benzenesulfonyl]-N^3-phenylurea 26:

Rrecrystallized from DMF as needles. (4.6g, 82%) m.p224-226°C. ν_{max} (cm^{-1} ,KBr): 3277, 3305 cm^{-1}(2NH), 1342, 1162 cm^{-1}(SO_2N), 1648(C=O). ^{1}H NMR (δ/ppm,DMSO-d_6): δ 2.04 (s,3H,CH_3), 2.09(s,3H,CH_3), 3.25, 3.85(2m, 2H, pyrazoline *H-4*), 5.33(m, 1H, pyrazoline *H-5*), 6.78-7.72(*m*,18H, Ar-*H*+HN), 7.95(s,1H,NH). ^{13}C NMR (δ/ppm, DMSO-d_6): δ 14.53(CH_3), 15.01(CH_3), 42.15(*C*-4), 55.61(*C-5*), 116.98, 119,24, 119.68, 119.98, 121.84, 124.03, 124.53, 125.93, 126.58, 126.67, 128.81, 128.98, 129.44, 131.06, 131.24, 135.82, 138.40, 139.16, 143.90, 145.76(Ar-*C*),175.83 (CO). MS: *m/z* 596 (M^+,96), 398(100), 322(24), 202(8),152(12),144(32), 84(14), 77(16),70(9). Anal.% Calcd for $C_{31}H_{28}N_6O_3S_2$: C, 62.40; H, 4.73; N, 14.08. Found: C, 62.35; H, 4.65; N, 14.20.

N^1-[4-[(3-(2-theinyl)-5-(3,5-dimethyl-1-phenylpyrazol-4-yl)-4,5-dihydropyrazol-1-yl]benzenesulfonyl]-N^3-(4-chlorophenyl)urea 27:

Rrecrystallized from DMF as needles. (5.04g, 80%) m.p182-184°C. ν_{max} (cm^{-1} ,KBr): 3271, 3312 cm^{-1}(2NH), 1391, 1148 cm^{-1}(SO_2N), 1636(C=O). ^{1}H NMR (δ/ppm,DMSO-d_6): δ 2.12 (s,3H,CH_3), 2.15(s,3H,CH_3), 3.28, 3.82(2m, 2H, pyrazoline *H-4*), 5.37(m, 1H, pyrazoline *H-5*), 6.72-7.74(*m*,17H, Ar-*H*+HN), 7.93(s,1H,NH). ^{13}C NMR (δ/ppm, DMSO-d_6): δ 14.57(CH_3), 15.10(CH_3), 42.19(*C*-4), 55.63(*C-5*), 116.90, 119,20, 119.60, 119.90, 121.80, 124.12, 124.57, 125.98, 126.53, 126.64, 128.86, 128.90, 129.47, 131.11, 131.27, 135.85, 138.43, 139.12, 143.96, 145.74(Ar-*C*), 175.87(CO). Anal.% Calcd for $C_{31}H_{27}ClN_6O_3S_2$: C, 58.99; H, 4.31; N, 13.32. Found: C, 59.12; H, 4.47; N, 13.54.

N^1-[4-[(3-(4-bromophenyl)-5-(3,5-dimethyl-1-phenylpyrazol-4-yl)-4,5-dihydropyrazol-1-yl]-benzenesulfonyl]-N^3-phenylurea 28:

Rrecrystallized from DMF as needles. (5.28g, 80%) m.p 224-226°C. ν_{max} (cm^{-1} ,KBr): 3265, 3307 cm^{-1}(2NH), 1391, 1178 cm^{-1}(SO_2N), 1658(C=O). ^{1}H NMR (δ/ppm,DMSO-d_6): δ 2.17(s,3H,CH_3), 2.19(s,3H,CH_3), 3.34, 3.79(2m, 2H, pyrazoline *H-4*), 5.41(m, 1H, pyrazoline *H-5*), 6.76-7.81(*m*,19H, Ar-*H*+HN), 7.97(s,1H,NH). ^{13}C NMR (δ/ppm, DMSO-d_6): δ 14.53(CH_3), 15.16(CH_3), 42.13(*C*-4), 55.67(*C-5*), 116.92, 119.23, 119.67, 119.94, 121.82, 124.19, 124.51, 125.90, 126.51, 126.69, 128.81, 128.94, 129.43, 131.15, 131.26, 135.86, 138.49, 139.18, 143.92, 145.78(Ar-*C*), 175.83(CO). Anal.% Calcd for $C_{33}H_{29}BrN_6O_3S$: C, 59.19; H, 4.37; N, 12.55. Found: C, 59.35; H, 4.49; N, 12.37.

N^1-[4-[(3-(4-bromophenyl)-5-(3,5-dimethyl-1-phenylpyrazol-4-yl)-4,5-dihydropyrazol-1-yl]benzenesulfonyl]-N^3-(4-chlorophenyl)urea 29:

Rrecrystallized from DMF as needles. (5.27g, 75%) m.p 160-162°C. ν_{max} (cm^{-1} ,KBr): 3299, 3319 cm^{-1}(2NH), 1394, 1150 cm^{-1}(SO_2N), 1662 (C=O). ^{1}H NMR (δ/ppm,DMSO-d_6): δ 2.23(s,3H,CH_3), 2.27(s,3H,CH_3), 3.41, 3.82(2m, 2H, pyrazoline *H-4*), 5.47(m, 1H, pyrazoline *H-5*), 6.72-7.87(*m*,18H, Ar-*H*+HN), 7.89(s,1H,NH). ^{13}C NMR (δ/ppm, DMSO-d_6): δ 14.57(CH_3), 15.24(CH_3), 42.21(*C*-4), 55.72(*C-5*), 116.93, 119.27, 119.61, 119.98, 121.84, 124.10, 124.54, 125.91, 126.53, 126.63, 128.87, 128.93, 129.47, 131.23, 131.29, 135.84, 138.53, 139.21, 143.96, 145.74(Ar-*C*), 175.85 (CO). Anal.% Calcd for $C_{33}H_{28}BrClN_6O_3S$: C, 56.30; H, 4.01; N, 11.94. Found: C, 56.53; H, 4.26; N, 12.04.

3.1.5. Benzenesulfonylthioureas (30-37)

A solution of the appropriate isothiocyanate (10 mmol) in dry acetone (5 mL), was added to a stirred mixture of the pyrazoline (10 mmol) and anhydrous K_2CO_3 (1.4 g, 10 mmol) in dry acetone (25 mL) and the reaction mixture was heated under reflux for 10 h. Working up of the reaction mixture was done as mentioned above for compounds **55-64**. The crude products were recrystallized from the proper solvent.

N^1-[4-[(3-(2-theinyl)-5-(1-phenylpyrazol-4-yl)-4,5-dihydropyrazol-1-yl]benzenesulfonyl]-N^3-methylthiourea 30:

Rrecrystallized from ethanol as needles. (4.2g, 82%) m.p. 200-201°C. ν_{max} (cm^{-1},KBr): 3271, 3319 cm^{-1}(2NH), 1338, 1150 cm^{-1}(SO_2N), 1155(C=S). ^{1}H NMR (δ/ppm,DMSO-d_6): δ 3.48 (d, *J*=6.5*Hz*,3H,CH_3), 3.33,3.71(2m, 2H, pyrazoline *H-4*), 5.28(m, 1H, pyrazoline *H-5*), 6.66-7.68(*m*,15H,Ar-*H*+ NH), 8.82(m,1H,NH).^{13}CNMR(δ/ppm,DMSO-d_6): δ 26.80(CH_3), 40.10(*C*-4), 50.30(*C*-5), 112.90, 116.90, 118.20, 120.10, 125.20, 125.80, 126.80, 127.10, 127.60, 129.80, 134.40, 136.20, 139.70, 142.20, 149.10, 155.60(Ar-*C*), 202.40(CS). Anal.% Calcd for $C_{24}H_{22}N_6O_2S_3$: C, 55.15; H, 4.24; N, 16.08. Found: C, 55.26; H, 4.35; N, 16.11.

N^1-[4-[(3-(2-theinyl)-5-(1-phenylpyrazol-4-yl)-4,5-dihydropyrazol-1-yl]benzenesulfonyl]-N^3-phenylthiourea 31:

Rrecrystallized from ethanol as needles. (4.67g, 80%) m.p. 232-234°C. ν_{max} (cm^{-1},KBr): 3268, 3324 cm^{-1}(2NH), 1348, 1174 cm^{-1}(SO_2N), 1159(C=S). ^{1}H NMR (δ/ppm,DMSO-d_6): δ 3.43(d *J*=6.5*Hz*,3H,CH_3), 3.37, 3.79(2m, 2H, pyrazoline *H-4*), 5.25(m, 1H, pyrazoline *H-5*), 6.63-7.62(*m*,20H,Ar-*H*+ NH), 8.87(m,1H,NH).^{13}CNMR(δ/ppm,DMSO-d_6): δ 26.87(CH_3), 40.16(*C*-4), 50.40(*C*-5), 112.89, 113.53,116.91, 118.12, 119.11, 119.18, 119.34, 120.20, 125.30, 125.83, 126.82, 127.14, 127.52, 129.83, 134.49, 136.30, 139.80, 142.10, 149.17, 155.62(Ar-*C*), 202.50(CS). Anal.% Calcd for $C_{29}H_{24}N_6O_2S_3$: C, 59.57; H, 4.14; N, 14.37. Found: C, 59.83; H, 4.27; N, 14.45.

N^1-[4-[(3-(2-theinyl)-5-(1-phenylpyrazol-4-yl)-4,5-dihydropyrazol-1-yl]benzenesulfonyl]-N^3-(4-chlorophenyl)thiourea 32:

Rrecrystallized from ethanol as needles. (4.7g, 80%) m.p156-158°C. ν_{max} (cm^{-1} ,KBr): 3282, 3312 cm^{-1}(2NH), 1351, 1168 cm^{-1}(SO_2N), 1157(C=S). ^{1}H NMR (δ/ppm,DMSO-d_6): δ 3.26, 3.84(2m, 2H, pyrazoline *H-4*), 5.36(m, 1H, pyrazoline *H-5*), 7.08-7.86(*m*,19H, Ar-*H*+HN), 9.75(s,1H,NH). ^{13}C NMR (δ/ppm, DMSO-d_6): δ 43.37(*C*-4), 55.53(*C-5*), 113.52, 119.01, 119.28, 119.32, 124.66, 124.85, 126.40, 126.55, 127.32, 127.45, 128.86, 128.99, 129.37, 129.43, 129.62, 130.76, 136.73, 138.42, 151.67, 159.05(Ar-*C*), 196.21(CS). Anal.% Calcd for $C_{29}H_{23}ClN_6O_2S_3$: C, 56.25; H, 3.74; N, 13.57. Found: C, 56.26; H, 3.65; N, 13.41.

N^1-[4-[(3-(2-theinyl)-5-(1-phenylpyrazol-4-yl)-4,5-dihydropyrazol-1-yl]benzenesulfonyl]-N^3-(4-flourophenyl)urea 33:

Rrecrystallized from ethanol as needles. (4.3g, 76%) m.p.142-144°C. ν_{max} (cm^{-1} ,KBr): 3281, 3345 cm^{-1}(2NH), 1365, 1173 cm^{-1}(SO_2N), 1151(C=S). ^{1}H NMR (δ/ppm,DMSO-d_6): δ 3.23, 3.86(2m, 2H, pyrazoline *H-4*), 5.40(m, 1H, pyrazoline *H-5*), 7.12-7.79(*m*,19H, Ar-*H*+HN), 9.69(s,1H,NH). ^{13}C NMR (δ/ppm, DMSO-d_6): δ 43.41(*C*-4), 55.59(*C-5*), 113.5, 119.11, 119.27, 119.31, 124.69, 124.82, 126.46, 126.53, 127.31, 127.48, 128.85, 128.92, 129.33, 129.47, 129.6, 130.72, 136.78, 138.4, 151.69, 159.15(Ar-*C*), 196.23(CS). Anal.% Calcd for $C_{29}H_{23}FN_6O_2S_3$: C, 57.79; H, 3.85; N, 13.94. Found: C, 57.58; H, 3.91; N, 13.74.

N^1-[4-[(3-(2-theinyl)-5-(3,5-dimethyl-1-phenylpyrazol-4-yl)-4,5-dihydropyrazol-1-yl]benzene- sulfonyl]-N^3-phenylthiourea 34:

Rrecrystallized from DMF as needles. (4.83g, 79%) m.p230-232°C. ν_{max} (cm^{-1} ,KBr): 3268, 3315 cm^{-1}(2NH), 1382, 1183 cm^{-1}(SO_2N), 1157(C=S). ^{1}H NMR (δ/ppm,DMSO-d_6): δ 2.14 (s,3H,CH_3), 2.19(s,3H,CH_3), 3.29, 3.81(2m, 2H, pyrazoline *H-4*), 5.34(m, 1H, pyrazoline *H-5*), 6.76-7.78(*m*, 18H, Ar-*H*+HN), 7.96(s,1H,NH). ^{13}C NMR (δ/ppm, DMSO-d_6): δ 14.57(CH_3), 15.11(CH_3), 42.12(*C*-4), 55.63(*C-5*), 116.94, 119,26, 119.64, 119.97, 121.82, 124.13, 124.52, 125.94, 126.55, 126.68, 128.86, 128.95, 129.43, 131.16, 131.23, 135.84, 138.45, 139.14, 143.93, 145.77(Ar-*C*), 198.83(CS). Anal.% Calcd for $C_{31}H_{28}N_6O_2S_3$: C, 60.76; H, 4.61; N, 13.71. Found: C, 60.49; H, 4.65; N, 13.89.

N^1-[4-[(3-(2-theinyl)-5-(3,5-dimethyl-1-phenylpyrazol-4-yl)-4,5-dihydropyrazol-1-yl]benzene- sulfonyl]-N^3-(4-chlorophenyl)thiourea 35:

Rrecrystallized from DMF as needles. (4.84g, 75%) m.p170-172°C. ν_{max} (cm^{-1} ,KBr): 3269, 3324 cm^{-1}(2NH), 1389, 1168 cm^{-1}(SO_2N), 1157(C=S). ^{1}H NMR (δ/ppm,DMSO-d_6): δ 2.17 (s,3H,CH_3), 2.13(s,3H,CH_3), 3.29, 3.81(2m, 2H, pyrazoline *H-4*), 5.35(m, 1H, pyrazoline *H-5*), 6.77-7.79(*m*,17H, Ar-*H*+HN), 7.91(s,1H,NH). ^{13}C NMR (δ/ppm, DMSO-d_6): δ 14.54(CH_3), 15.16(CH_3), 42.24(*C*-4), 55.61(*C-5*), 116.91, 119,22, 119.63, 119.94, 121.85, 124.14, 124.50, 125.90, 126.50, 126.67, 128.86, 128.98, 129.46, 131.19, 131.23, 135.80, 138.40, 139.17, 143.90, 145.70(Ar-*C*), 201.87(CS). Anal.% Calcd for $C_{31}H_{27}ClN_6O_2S_3$: C, 57.53; H, 4.20; N, 12.98. Found: C, 57.61; H, 4.47; N, 12.74.

N^1-[4-[(3-(4-bromophenyl)-5-(3,5-dimethyl-1-phenylpyrazol-4-yl)-4,5-dihydropyrazol-1-yl]benzenesulfonyl]-N^3-phenylthiourea 36:

Rrecrystallized from DMF as needles. (5.68g, 83%) m.p 160-162°C. ν_{max} (cm^{-1} ,KBr): 3283, 3347 cm^{-1}(2NH), 1390, 1168 cm^{-1}(SO_2N), 1158 (C=S). ^{1}H NMR (δ/ppm,DMSO-d_6): δ 2.18(s,3H,CH_3), 2.14(s,3H,CH_3), 3.37, 3.74(2m, 2H, pyrazoline *H-4*), 5.43(m, 1H, pyrazoline *H-5*), 6.75-7.83(*m*,19H, Ar-*H*+HN), 7.96(s,1H,NH). ^{13}C NMR (δ/ppm, DMSO-d_6): δ 14.52(CH_3), 15.15(CH_3), 42.19(*C*-4), 55.63(*C-5*), 116.95 ,119.22 ,119.64 ,119.91, 121.85, 124.17, 124.52, 125.90, 126.50, 126.63, 128.89, 128.93, 129.47, 131.16, 131.28, 135.87, 138.45, 139.14, 143.96, 145.74(Ar-*C*), 198.83(CS). Anal.% Calcd for $C_{33}H_{29}BrN_6O_2S_2$: C, 57.81; H, 4.26; N, 12.26. Found: C, 57.75; H, 4.49; N, 12.37.

N^1-[4-[(3-(4-bromophenyl)-5-(3,5-dimethyl-1-phenylpyrazol-4-yl)-4,5-dihydropyrazol-1-yl]-benzenesulfonyl]-N^3-(4-chlorophenyl)thiourea 37:

Rrecrystallized from DMF as needles. (5.54g, 77%) m.p 218-220°C. ν_{max} (cm^{-1} ,KBr): 3268, 3334 cm^{-1}(2NH), 1376, 1154 cm^{-1} (SO_2N), 1153 (C=S). ^{1}H NMR (δ/ppm,DMSO-d_6): δ 2.24(s,3H,CH_3), 2.28(s,3H,CH_3), 3.46, 3.89(2m, 2H, pyrazoline *H-4*), 5.49(m, 1H, pyrazoline *H-5*), 6.73-7.86(*m*,18H, Ar-*H*+HN), 7.82(s,1H,NH). ^{13}C NMR (δ/ppm, DMSO-d_6): δ 14.59(CH_3), 15.26(CH_3), 42.26(*C*-4), 55.74(*C-5*), 116.91, 119.22, 119.63, 119.94, 121.85, 124.14, 124.50, 125.94, 126.52, 126.69, 128.80, 128.94, 129.48, 131.26, 131.21, 135.87, 138.56, 139.26, 143.99, 145.7(Ar-*C*), 204.1(CS). Anal.% Calcd for $C_{33}H_{28}BrClN_6O_2S_2$: C, 55.04; H, 3.92; N, 11.67. Found: C, 55.15; H, 3.78; N, 11.50.

3.1.6. Thiazoline pyrazole derivatives (38-43)

A solution of the appropriate thiourea derivative (10 mmol) in absolute ethanol (20 mL) was refluxed with 2-bromo-1-phenylethanone (2.2 g, 11 mmol) and anhydrous sodium acetate (1.64 g, 20 mmol) for 3 h during which the solid product was partially crystallized out. The mixture was left to attain room temperature then filtered, washed with cold ethanol, dried and recrystallized.

***2-[4-[(3-(2-theinyl)-5-(1-phenylpyrazol-4-yl)-4,5-dihydropyrazol-1-yl)benzenesulfonyl-imino]-3-phenylthiazoline 38*:**

Recystallized from DMF as needles (4.7g, 72%) m.p. 224-226°C. ν_{max} (cm^{-1},KBr): 1362, 1162 cm^{-1}(SO_2N). ^1H NMR (δ/ppm,DMSO-d_6): δ 3.25, 3.86(2m, 2H, pyrazoline *H-4*), 5.37 (m, 1H, pyrazoline *H-5*), 6.83-8.17(*m*,25H, Ar-*H*). ^{13}C NMR (δ/ppm, DMSO-d_6): δ 43.15 (*C*-4), 56.35(*C-5*), 113.79, 119.12, 119.34, 119.56, 120.74, 120.98, 124.65, 125.8, 126.60, 127.28, 127.55, 128.45, 128.66, 128.80, 129.03, 129.41, 129.57, 129.64, 132.65, 132.75, 134.82, 138.23, 139.84, 139.94, 140.31, 144.91, 147.50(Ar-*C*). Anal.% Calcd for $C_{37}H_{28}N_6O_2S_3$: C, 64.89; H, 4.12; N, 12.27. Found: C, 64.97; H, 4.22; N, 12.41.

***2-[4-[(3-(2-theinyl)-5-(1-phenylpyrazol-4-yl)-4,5-dihydropyrazol-1-yl)benzenesulfony-limino]-3-(4-chlorophenyl)thiazoline 39*:**

Recystallized from DMF as needles (5.1g, 74%) m.p. 216-218°C. ν_{max} (cm^{-1},KBr): 1353, 1151 cm^{-1}(SO_2N). ^1H NMR (δ/ppm,DMSO-d_6): δ 3.22, 3.84(2m, 2H, pyrazoline *H-4*), 5.31 (m, 1H, pyrazoline *H-5*), 6.84-8.19(*m*,24H, Ar-*H*). ^{13}C NMR (δ/ppm, DMSO-d_6): δ 43.21(*C*-4), 56.37(*C-5*), 113.72, 119.18, 119.32, 119.57, 120.72, 120.99, 124.62, 125.83, 126.64, 127.22, 127.53, 128.43, 128.61, 128.87, 129.13, 129.42, 129.58, 129.62, 132.68, 132.77, 134.83, 138.27, 139.85, 139.90, 140.34, 144.95, 147.52(Ar-*C*). Anal.% Calcd for $C_{37}H_{27}ClN_6O_2S_3$: C, 61.78; H, 3.78; N, 11.68. Found: C, 61.91; H, 3.55; N, 11.83.

***2-[4-[(3-(2-theinyl)-5-(1-phenylpyrazol-4-yl)-4,5-dihydropyrazol-1-yl)benzenesulfonyl-imino]-3-(4-fluorophenyl)thiazoline 40*:**

Recystallized from DMF as needles (4.7g, 70%) m.p. 213-215°C. ν_{max} (cm^{-1},KBr): 1345, 1161 cm^{-1}(SO_2N). ^1H NMR (δ/ppm,DMSO-d_6): δ 3.27, 3.83(2m, 2H, pyrazoline *H-4*), 5.36 (m, 1H, pyrazoline *H-5*), 6.91-8.24(*m*,24H, Ar-*H*). ^{13}C NMR(δ/ppm, DMSO-d_6): δ 43.19 (*C*-4), 56.30(*C-5*), 113.80, 119.22, 119.29, 119.54, 120.69, 120.9, 124.57, 125.76, 126.69, 127.30, 127.61, 128.52, 128.57, 128.91, 129.21, 129.47, 129.64, 129.58, 132.72, 132.73, 134.84, 138.31, 139.81, 139.92, 140.37, 144.96, 147.59(Ar-*C*). Anal.% Calcd for $C_{37}H_{27}FN_6O_2S_3$: C, 63.23; H, 3.87; N, 11.96. Found: C, 63.43; H, 3.96; N, 11.82.

***2-[4-[(3-(2-theinyl)-5-(3,5-dimethyl-1-phenylpyrazol-4-yl)-4,5-dihydropyrazol-1-yl)-benzenesulfonylimino]-3-phenylthiazoline 41*:**

Recystallized from DMF as needles (5.41g, 76%) m.p. 202-204°C. ν_{max} (cm^{-1},KBr): 1342, 1153 cm^{-1}(SO_2N). ^1H NMR (δ/ppm,DMSO-d_6): δ 2.42(s,3H,CH_3), 2.78(s,3H,CH_3), 3.21, 3.84(2m, 2H, pyrazoline *H-4*), 5.32(m, 1H, pyrazoline *H-5*), 6.80-8.14(*m*,23H, Ar-*H*). ^{13}C NMR (δ/ppm, DMSO-d_6): δ 14.51(CH_3), 15.11(CH_3), 43.21(*C*-4), 56.33(*C-5*), 113.80, 119.22, 119.42, 119.57, 120.71, 121.08, 124.75, 125.83, 126.66, 127.25, 127.53, 128.48, 128.61, 128.83, 129.13, 129.49, 129.54, 129.60, 132.64, 132.72, 134.83, 138.29, 139.82, 139.92, 140.32, 144.95, 147.53(Ar-*C*).Anal.% Calcd for $C_{39}H_{32}N_6O_2S_3$: C, 65.71; H, 4.52; N, 11.79. Found: C, 65.96; H, 4.37; N, 11.83.

***2-[4-[(3-(4-bromophenyl)-5-(3,5-dimethyl-1-phenylpyrazol-4-yl)-4,5-dihydropyrazol-1-yl)benzenesulfonylimino]-3-phenylthiazoline 42*: :**

Recystallized from DMF as needles (6.19g, 79%) m.p. 235-237°C. ν_{max} (cm^{-1},KBr): 1343, 1157 cm^{-1}(SO_2N). ^1H NMR (δ/ppm,DMSO-d_6): δ 2.42(s,3H,CH_3), 2.73(s,3H,CH_3), 3.24, 3.85(2m, 2H, pyrazoline *H-4*), 5.36(m, 1H, pyrazoline *H-5*), 6.87-8.18(*m*,24H, Ar-*H*). ^{13}C NMR (δ/ppm, DMSO-d_6): δ 14.51(CH_3), 15.03(CH_3), 43.12(*C*-4), 56.34(*C-5*), 113.71, 119.12, 119.33, 119.54, 120.75, 120.96, 124.67, 125.88, 126.69, 127.30, 127.51, 128.42, 128.63, 128.84, 129.05, 129.46, 129.57, 129.66, 132.68, 132.79, 134.90, 138.21, 139.82, 139.93, 140.34, 144.95,147.56(Ar-*C*). MS: *m/z* 784 (M^+,100), 630(72), 394(25), 316(44),239(17),240(28),155(18),144(27), 84(13), 77(18). Anal.% Calcd for $C_{41}H_{33}BrN_6O_2S_2$: C, 62.67; H, 4.23; N, 10.70. Found: C, 62.81; H, 4.17; N, 10.56.

***2-[4-[(3-(4-bromophenyl)-5-(3,5-dimethyl-1-phenylpyrazol-4-yl)-4,5-dihydropyrazol-1-yl)benzenesulfonylimino]-3-(4-chlorophenyl)thiazoline 43*:**

Recystallized from DMF as needles (6.15g, 75%) m.p. 236-238°C. ν_{max} (cm^{-1},KBr): 1339, 1150 (SO_2N). ^1H NMR (δ/ppm,DMSO-d_6): δ 2.40 (s,3H,CH_3), 2.79 (s,3H,CH_3), 3.28, 3.87(2m, 2H, pyrazoline *H-4*), 5.36 (m, 1H, pyrazoline *H-5*), 6.85-8.14 (*m*,25H, Ar-*H*). ^{13}C NMR (δ/ppm, DMSO-d_6): δ 14.52(CH_3), 15.07(CH_3), 43.16 (*C*-4), 56.32 (*C-5*), 113.70, 119.19, 119.38, 119.57, 120.76, 120.95, 124.64, 125.83, 126.62, 127.21, 127.6, 128.49, 128.68, 128.87, 129.06, 129.45,129.56, 129.65, 132.64, 132.73, 134.82, 138.21, 139.80, 139.9, 140.39, 144.98,147.57 (Ar-*C*). Anal.% Calcd for $C_{41}H_{32}BrClN_6O_2S_2$: C, 60.04; H, 3.93; N, 10.25. Found: C, 60.18; H, 3.87; N, 10.45.

3.1.7. 4-Oxothiazoline pyrazole derivatives (44-48)

To a solution of the appropriate thiourea derivative (10 mmol) in absolute ethanol (20 mL) was added ethyl bromoacetate (1.84 g, 11 mmol) and anhydrous sodium acetate (1.64 g, 20 mmol), and the reaction mixture was heated under reflux for 2 h. The mixture was left to attain room temperature then poured into ice-cold water (30 mL), and the solid product thus formed was filtered, washed with water, dried and recrystallized from the proper solvent.

2-[4-[(3-(2-theinyl)-5-(1-phenylpyrazol-4-yl)-4,5-dihydropyrazol-1-yl)benzenesulfonyl-imino]-3-(4-chlorophenyl)thiazolidin-4-one 44:

Recystallized from ethanol/benzene mixture (1:1) as needles (4.8g, 77%) m.p. 242-244°C. ν_{max} (cm^{-1},KBr): 1348, 1171 (SO_2N), 1726 (CO). ^1H NMR (δ/ppm,DMSO-d_6): δ 3.21, 3.83(2m, 2H, pyrazoline *H-4*), 5.41(m, 1H, pyrazoline *H-5*), 4.54(s,2H, *H*-5, Thiazolidin-4-one), 7.11-7.78(*m*,18H,Ar-*H*).^{13}CNMR(δ/ppm,DMSO-d_6): δ 34.32(*C*-5, Thiazolidin-4-one), 37.69(*C*-4), 46.24(*C*-5), 112.52, 118.44, 118.29, 120.14, 121.98,124.62, 125.78, 126.04, 126.22, 126.98, 127.34, 129.01, 129.47, 129.65, 130.34, 133,35 138.78, 140.88, 146.44, 155.34, 163.45(Ar-*C*), 175.10(CO). Anal.% Calcd for $C_{31}H_{23}ClN_6O_4S_2$: C, 57.89; H, 3.61; N, 13.07. Found: C, 57.59; H, 3.64; N, 12.95.

2-[4-[(3-(2-theinyl)-5-(1-phenylpyrazol-4-yl)-4,5-dihydropyrazol-1-yl)benzenesulfonyl-imino]-3-(4-fluorophenyl)thiazolidin-4-one 45:

Recystallized from DMF as needles (4.5g, 74%) m.p. 197-199°C. ν_{max} (cm^{-1},KBr): 1362, 1178 cm^{-1}(SO_2N), 1720(CO). ^1H NMR (δ/ppm,DMSO-d_6): δ 3.34, 3.77(2m, 2H, pyrazoline *H-4*), 5.39(m, 1H, pyrazoline *H-5*), 4.50(s,2H, *H*-5, Thiazolidin-4-one), 7.14-7.76 (*m*,18H,Ar-*H*). ^{13}CNMR(δ/ppm,DMSO-d_6): δ 34.09(*C*-5, Thiazolidin-4-one), 37.6(*C*-4), 46.32(*C*-5), 112.50, 118.74, 118.53, 120.24, 121.75, 124.26, 125.58, 126.01, 126.23, 127.00, 127.32, 129.04, 129.65, 129.69, 130.54, 133.25, 138.73, 140.78, 146.34, 155.21, 163.39 (Ar-*C*), 180.20(CO). Anal.% Calcd for $C_{31}H_{23}FN_6O_3S_3$: C, 57.93; H, 3.61; N, 13.08. Found: C, 57.84; H, 3.64; N, 12.91.

2-[4-[(3-(2-theinyl)-5-(1-phenylpyrazol-4-yl)-4,5-dihydropyrazol-1-yl)benzenesulfonyl-imino]-3-methylthiazolidin-4-one 46:

Recystallized from DMF as needles (4.5g, 74%) m.p. 227-229°C. ν_{max} (cm^{-1},KBr): 1339, 1174 cm^{-1}(SO_2N), 1725(CO). ^1H NMR (δ/ppm,DMSO-d_6): δ 3.52(s,3H,CH_3), 3.34, 3.76(2m, 2H, pyrazoline *H-4*), 5.39(m, 1H, pyrazoline *H-5*), 4.60(s,2H, *H*-5, Thiazolidin-4-one), 6.58-7.72(*m*,14H,Ar-*H*). ^{13}C NMR(δ/ppm,DMSO-d_6): δ 26.32(CH_3), 34.24(*C*-5, Thiazolidin-4-one), 37.55(*C*-4), 46.31(*C*-5), 112.59, 118.78, 120.34, 121.65, 124.16, 125.74, 126.01, 126.23, 127.32, 129.04, 129.65, 130.32, 133.65, 138.43, 146.37, 155.41, 163.09(Ar-*C*), 176.67(CO). MS: *m/z* 562(M^+,100), 480(82), 370(35), 288(19), 193(52), 144(10), 130(12), 116(16),

101(18), 84(15), 77(13). Anal.% Calcd for $C_{26}H_{22}N_6O_3S_3$: C, 55.50; H, 3.94; N, 14.94. Found: C, 55.43; H, 3.71; N, 14.85.

2-[4-[(3-(2-theinyl)-5-(3,5-dimethyl-1-phenylpyrazol-4-yl)-4,5-dihydropyrazol-1-yl)-benzene-sulfonylimino]-3-phenylthiazolin-4-one 47:

Rrecrystallized from ethanol as needles. (4.8g, 78%) m.p.220-222°C. ν_{max} (cm^{-1} ,KBr): 1365, 1144 cm^{-1}(SO_2N), 1733(CO). ^{1}H NMR (δ/ppm,DMSO-d_6): δ 2.49(s,3H,CH_3), 2.71 (s,3H,CH_3), 3.23, 3.81(2m, 2H, pyrazoline *H-4*), 4.61(s,2H, *H*-5, Thiazolidin-4-one), 5.44 (m, 1H, pyrazoline*H-5*), 7.08-7.92(*m*,17H,Ar-*H*). ^{13}C NMR(δ/ppm,DMSO-d_6): δ 10.01(CH_3), 10.42(CH_3), 32.32(*C*-5, Thiazolidin-4-one), 42.60(*C*-4), 54.65(*C*-5), 112.13, 113.67, 118.41, 119.65, 119.93, 122.13, 123.90, 125.59, 126.18, 127.09, 128.91, 128.95, 130.41, 131.24, 131.47, 138.35, 139.17, 140.17, 146.10, 149.12,162.03(Ar-*C*), 175.15(CO). Anal.% Calcd for $C_{31}H_{28}N_6O_3S_3$: C, 60.72; H, 4.32; N, 12.87. Found: C, 60.66; H, 4.45; N, 12.98.

2-[4-[(3-(2-theinyl)-5-(3,5-dimethyl-1-phenylpyrazol-4-yl)-4,5-dihydropyrazol-1-yl)-benzenesulfonylimino]-3-(4-chlorophenyl)thiazolidin-4-one 48:

Rrecrystallized from ethanol as needles. (4.7g, 75%) m.p.226-228°C. ν_{max} (cm^{-1} ,KBr): 1345, 1157 cm^{-1}(SO_2N), 1726(CO). ^{1}H NMR (δ/ppm,DMSO-d_6): δ 2.48(s,3H,CH_3), 2.72 (s,3H,CH_3), 3.24, 3.87(2m, 2H, pyrazoline *H-4*), 4.69(s,2H, *H*-5, Thiazolidin-4-one), 5.47 (m, 1H,pyrazoline*H-5*), 7.18-7.98(*m*,16H,Ar-*H*). ^{13}C NMR(δ/ppm,DMSO-d_6): δ 10.11(CH_3), 10.32(CH_3), 32.42(*C*-5, Thiazolidin-4-one), 42.65(*C*-4), 54.63(*C*-5), 112.11, 113.62, 118.43, 119.64, 119.95, 122.16, 123.97, 125.58, 126.19, 127.1, 128.99, 128.98, 130.47, 131.26, 131.45, 138.34,139.13,140.12, 146.11, 149.1,162.02 (Ar-*C*), 175.14 (CO). Anal.% Calcd for $C_{33}H_{27}ClN_6O_3S_3$: C, 57.67; H, 3.96; N, 12.23. Found: C, 57.67; H, 3.96; N, 12.23.

3.2. Methodology of the In vitro MTT cytotoxicity assay

The synthesized compounds were investigated for their *in vitro* cytotoxic effect *via* the standard [3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide] method (MTT)[41,42] against a panel of three human tumor cell lines namely; Caucasian breast adenocarcinoma MCF7, hepatocellular carcinoma HepG2 and colon carcinoma HT29. The procedures were done in a sterile area using a Laminar flow cabinet biosafety class II level (Baker, SG403INT, Stanford, ME, USA). Cells were batch cultured for 10 days, then seeded at concentration of $10x10^3$ cells/well in fresh complete growth medium in 96-well microtiter plastic plates at 37°C for 24h under 5% CO_2 using a water jacketed carbon dioxide incubator (Sheldon, TC2323, Cornelius, OR, USA). Media was aspirated, fresh medium (without serum) was added and cells were incubated either alone (negative control) or with different concentrations of the test compounds to give a final concentration of (100 – 50 – 25 – 12.5 – 6.25 – 3.125 – 1.56 – 0.78 µg/mL). DMSO was employed as a vehicle for dissolution of the tested compounds and its final concentration on the cells was less than 0.2%. Cells were suspended in RPMI 1640 medium (for HepG2 and HT29 cell lines) and DMEM (for MCF 7 cell line), 1% antibiotic-antimycotic mixture (10,000 IU/mL penicillin potassium, 10,000 µg/mL streptomycin sulphate and 25 µg/mL amphotericin B), and 1% L-glutamine in 96-well flat bottom microplate at 37°C under 5% CO_2. After 24h of incubation, the medium was aspirated, 40 µL of MTT salt (2.5 µg/mL) were added to each well and incubated for further 4h at 37°C under 5% CO_2. To stop the reaction and dissolve the formed crystals, 200 µL of 10% sodium dodecyl sulphate (SDS) in deionized water was added to each well and incubated overnight at 37°C. The absorbance was then measured using a microplate multi-well reader (Bio-Rad Laboratories Inc., model 3350, Hercules, California, USA) at 595nm and a reference wavelength of 620nm. A statistical significance was tested between samples and negative control (cells with vehicle) using independent *t*-test by SPSS 11 program. The results are presented in Table 1 as LC_{50} (µg/mL) which is the lethal concentration of the compound which causes death of 50% of the cells in 24 h.

3.3. Procedure for antidiabetic activity

Antidiabetic activity of sixteen compounds namely **10, 12, 23, 25, 27, 29, 32, 33, 35, 36, 41, 42, 43, 44, 45,** and **48** were tested for hypoglycemic activity using alloxan-treated female albino mice weighing 20 g. Alloxan 100 mg/kg was injected into the tail vein in a 10 mg/mL saline solution. Three days later the mice were given the test compounds orally in suspension in 1% carboxymethylcellulose solution at the rate of 0.2 mmol/kg of the body weight. Each day a group of four mice was used as a control group and one group of five mice was given the standard 100 mg of phenformin/kg. Up to six groups of four mice received the test compounds. Blood samples were collected into 0.04% NaF solution at 0, 1 and 3 h. Glucose was determined by the micro-colorimetric copper reduction technique of Haslewood and Strookman[43] . Results are expressed as a percentage reduction of the plasma glucose levels compared with the control value. Statistical significance was assessed by a Student's t-test. Statistical significance was accepted where the calculated t-value exceeded the tabulated t-value at the p = 0.05 level.

4. Conclusions

In this paper, some new bipyrazoles benzenesulfonyl urea and thiourea derivatives were synthesized from the reaction of the proper bipyrazole with the appropriate isocyanate and

isothiocyanate. Cyclization of the thiourea derivatives with the appropriate reagent afforded the corresponding cyclic compounds. The structures of the prepared compound were confirmed

by elemental analysis, IR, ^{1}H and ^{13}C NMR spectral analysis. Preliminary biological testing of some of these compounds revealed that some bipyrazole derivatives exhibited significant

anticancer as well as antidiabetic activities.

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