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Synthesis and evaluation of some new pyrazoline substituted benzenesulfonylureas as potential antiproliferative agents

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ABSTRACT

Twenty six new pyrazoline substituted benzenesulfonylureas (**2a**–**z**) were synthesized and tested for in vitro anticancer activity. Fourteen derivatives (**2i**, **2k**–**2p**, **2r**, **2s**–**2x**) were screened for their antiproliferative activity towards 60 human cancer cell lines by the National Cancer Institute (USA). Among them four compounds (**2i**, **2n**, **2v** and **2x**) exhibited significant growth inhibition and further screened at 10-fold dilutions of five different concentrations (0.01, 0.1, 1, 10 and 100 μM). The compounds **2i**, **2n**, **2v** and **2x** showed effective growth inhibition (GI_{50} MID) values of 2.62, 3.93, 3.33, 3.74 μM respectively beside cytostatic activity TGI (MG-MID) values of 8.42, 65.80, 24.00 and 36.06 μM respectively. The compound **2i** displayed remarkable antiproliferative activity in 8 different cell lines with GI_{50} less than 2 μM. Compounds **2n**, **2v** and **2x** also displayed good antiproliferative activity against 11, 18 and 14 different cell lines respectively with GI_{50} less than 3 μM.

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Cancer is a group of illness that results from cells in the body growing abnormally. These cells divide and produce new cells in an uncontrolled way that can spread throughout the body and cause damage to essential organs. Cancer treatment includes many strategies and chemotherapy plays a central role.[1] Chemotherapy involves the use of low-molecular-weight drugs to selectively destroy tumour cells or at least limit their proliferation. Despite immense advances in the field of basic and clinical research, which have resulted in higher cure rates for a number of malignancies, cancer remains the second leading cause of death after heart disorders in developing as well as advanced countries.[2] Although major advances have been made in the chemotherapeutic management of some patients, the continued commitment to the difficult task of discovering new anticancer agents remains critically important.

Among the wide range of compounds tested as potential anticancer agents, derivatives comprising the sulfonamide, N^1,N^3-diarylsulfonylurea and -thiourea functionalities have attracted great attention.[3,4] Recently three sulphonamides derivatives E7010, ER-34410 and E7070 (Fig. 1I–III) have been reported as potent antitumor agents and are in advanced clinical trials.[5] Sulofenur (Fig. 1IV) is a sulfonylurea that has been clinically evaluated in lung, breast, colon, ovarian, pancreatic and gastric cancer.[6] The antitumor properties of the diarylsulfonylurea is due to the uncoupling of mitochondria[7,8] 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.[9] However, clinical trials of sulofenur have yielded unsatisfactory results because of its high protein binding and dosing being limited by the appearance of anemia due to methemoglobinemia, a side effect likely associated with its aniline-related metabolites.[10]

Pyrazol(in)e derivatives have attracting continuing attention over the years because of their broad spectrum biological activities and strong efficacy. Some representative of this heterocyclic exihibit antiproliferative,[11–13] anti-inflammatory,[14–16] anti-infective,[17] antidepressant[18] and analgesic[19] activity.

Recently, Lv et al.,[11] discovered (V) (Fig. 1) displayed the most potent EGFR TK inhibitory activity with IC_{50} of 0.06 μM, which was comparable to positive control Erlotirib. This compound (I) also showed significant antiproliferative activity against MCF-7 with IC_{50} of 0.07 μM. The present work is an extension of our ongoing efforts towards developing promising biologically active agents using a hybrid pharmacophore approach. We made the design (Fig. 1) and synthesized hybrid compounds by linking pyrazoline ring system with benzene sulfonylurea. In these derivatives we

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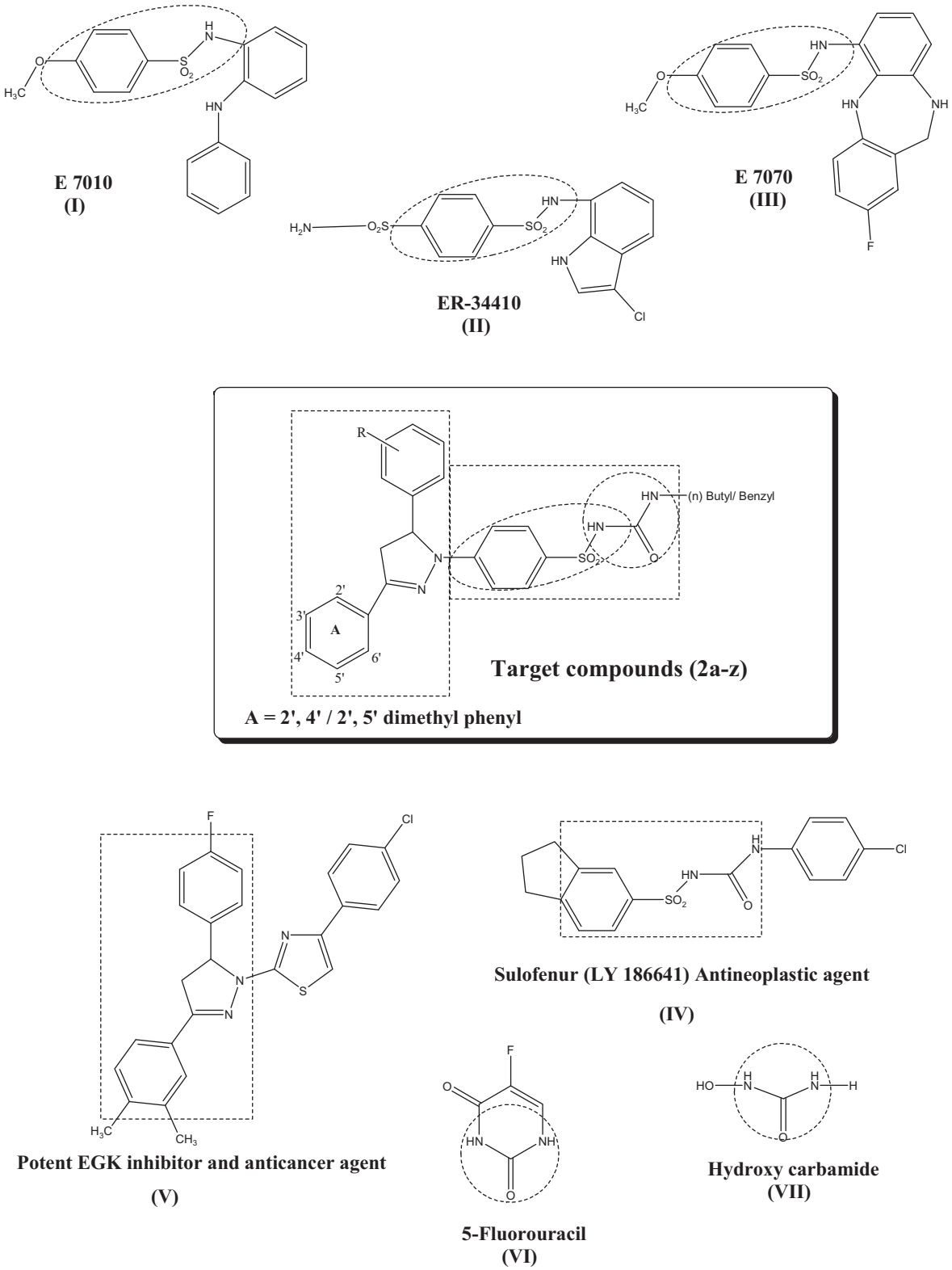


Figure 1. Structure of some biologically active anticancer drugs and rationally designed template for target compounds (**2a**–**z**).

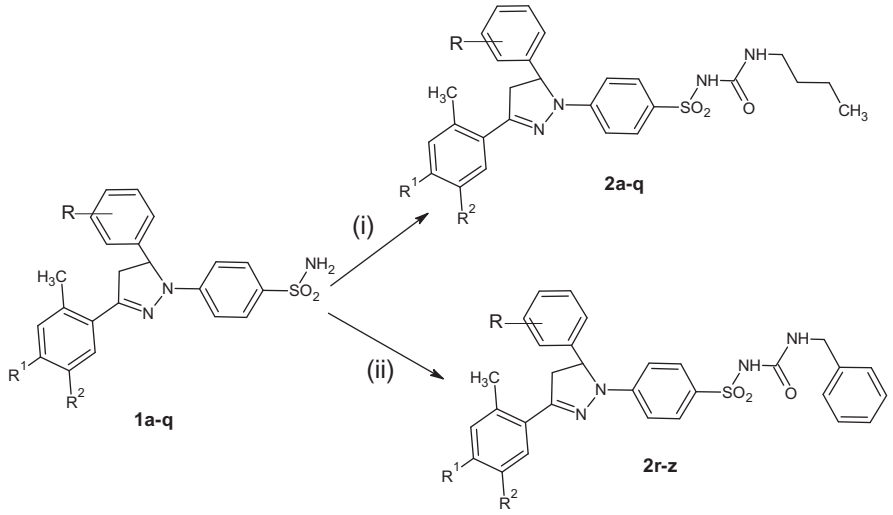
introduced butyl or benzyl group at N^3 position in order to avoid possible side effects associated with aniline-related metabolites generating from the aryl substituted derivatives.[10] As per the protocol of NCI, only fourteen representative compounds **2i**, **2k**–**2p**, **2r**, **2s**–**2x** were selected and granted NSC codes Viz; NSC 765376, NSC 772443, NSC 765379, NSC 772444, NSC 765378, NSC 765377, NSC 762442, NSC 765372, NSC 762441,NSC 772440, NSC 765373, NSC 765371, NSC 765375 and NSC 765374 respectively and screened at NCI for antiproliferative activity at a single high dose (10^{-5} M) in full 60 cell panel. Four compounds namely **2i**, **2n**, **2v** and **2x**

exhibited good activity at a single dose and were selected for further evaluation at five dose concentration level against full NCI 60 cell panel.

The synthetic pathway used to synthesize compounds (**2a**–**z**) is outlined in Scheme 1. The substituted benzenesulfonylureas were obtained by refluxing different pyrazolines (**1a**–**q**) with appropriate isocyanates in presence of potassium carbonate as a mild catalyst in dry acetone.[21] The pyrazolines were synthesised by reacting appropriate chalcones with 4-hydrazinobenzenesulphonamide.[20] The purity of compounds was checked by TLC. The structures of **2a**–**z** were determined on the basis of elementary analysis (C, H, N & S) and various spectroscopic methods (IR, ^{1}H NMR, ^{13}C NMR and MS). Elemental analysis (C, H, N & S) data were within ±0.4% of the theoretical values. Spectral data IR, ^{1}H NMR, ^{13}C NMR and MS of compounds were found in full agreement with the proposed structure. In general IR spectrum exhibited two bands at 1395–1321 cm^{-1} and 1165–1125 cm^{-1} due to SO_2N group. Carbonyl group showed absorption at 1705–1628 cm^{-1} while C=N showed peak at 1628–1532 cm^{-1}. The spectrum displayed band for the ureido group (HN-CO-NH) at 3392–3159 cm^{-1}. In ^{1}H NMR spectra, the pyrazoline ring protons showed characteristics of ABX spin system due to germinal-vicinal multiple coupling between two protons at C-4 and a proton at C-5 of pyrazoline ring. The H-4 (*trans*) protons of pyrazoline ring showed double doublets at δ 2.42-3.28. H-4 (*cis*) of pyrazoline moiety appeared as double-doublets at δ 3.90–4.13. H-5 proton of pyrazoline ring also appeared as double doublet at δ 5.15–5.78 due to vicinal coupling with two magnetically non-equivalent protons at C-4 of pyrazoline. SO_2N*H*CO— showed a one proton broad singlet at δ 7.45–10.38. The signal for proton attached with nitrogen in CON*H*CH_2 system appeared as triplet or distorted triplet at between δ 6.20 and 7.57. The scans of all the spectra (^{1}H and ^{13}C NMR) are given in the Supplementary data.

In vitro one-dose (10^{-5} M) anticancer assay was performed using full panel of about 60 human tumor cell lines representing nine different cancer types: Leukemia, melanoma, lung, colon, CNS, ovarian, renal, prostate and breast cancers, in accordance with the protocol of the Drug Evaluation Branch, National Cancer Institute (NCI), Bethesda and described elsewhere.[22–24]

Out of the synthesized compounds (**2a**–**z**), fourteen compounds, namely **2i**, **2k**–**2p**, **2r** and **2s**–**2x** were selected by the National Cancer Institute (NCI). The compounds **2k**–**m**, **2o**, **2p**, **2r**–**u** and **2w** displayed mild sensitivity against few cell lines (Table S1). In the present study four compounds like **2i**, **2n**, **2v** and **2x** possessed considerable anti-proliferative activity (Table S2) and they were selected for an advanced assay against a full panel (approximately 60 cell lines) at five concentrations at 10-fold dilution (100, 10, 1, 0.1 and 0.001 μM). A 48 h continuous drug exposure protocol was used and sulforhodamine B (SRB)[24] protein assay was used to estimate cell growth. The result of tested compound is given by three response parameters (GI_{50}, TGI and LC_{50}) for each cell line from log concentration versus% growth inhibition curves on nine cancer disease. The GI_{50} value (growth inhibitory activity) corresponds to the concentration of the compound causing 50% decrease in net cell growth, the TGI value (cytostatic activity) is the concentration of the compound resulting in total growth inhibition and LC_{50} value (cytotoxic activity) is the concentration of the compound causing net 50% loss of initial cells at the end of the incubation period of 48 h. Furthermore, a mean graph midpoint (MG-MID) is calculated giving an averaged activity parameter over all cell lines. The compounds **2i**, **2n**, **2v** and **2x** exhibited considerable broad spectrum antitumor activities and showed effective growth inhibition (GI_{50} MID) values of 2.62, 3.93, 3.33 and 3.74 μM respectively (Table 1), beside cytostatic activity TGI (MG-MID) values of 8.42, 65.80, 24.00 and 36.06 μM respectively, (Table S3). In addition, the active compounds **2i**, **2n**, **2v** and **2x** exhibited a variable



1a, 2a, R^1=H, R^2=CH_3, R=H, 1b, 2b, R^1=H, R^2=CH_3, R=2-chloro, 1c, 2c, R^1=H, R^2=CH_3, R=3-nitro,
1d, 2d, R^1=H, R^2=CH_3, R=4-chloro, 1e, 2e, R^1=H, R^2=CH_3, R=4-methyl, 1f, 2f, R^1=H, R^2=CH_3, R=4-dimethylamino,
1g, 2g, R^1=H, R^2=CH_3, R=4-methoxy, 1h, 2h, R^1=H, R^2=CH_3, R=3,4-dimethoxy, 1i, 2i,R^1=H, R^2=CH_3, R=3,4,5-trimethoxy,
1j, 2j, R^1=H, R^2=CH_3, R=H, 1k, 2k, R^1=CH_3, R^2=H, R=2-chloro, 1l, 2l, R^1=CH_3, R^2=H, R=4-chloro,
1m, 2m, R^1=CH_3, R^2=H, R=4-methyl, 1n, 2n, R^1=CH_3, R^2=H, R=4-dimethylamino, 1o, 2o, R^1=CH_3, R^2=H, R=4-methoxy,
1p, 2p, R^1=CH_3, R^2=H, R=3,4-dimethoxy, 1q, 2q, R^1=CH_3, R^2=H, R=3,4,5-trimethoxy, 2r, R^1=H, R^2=CH_3, R=2-chloro,
2s, R^1=H, R^2=CH_3, R=4-chloro, 2t, R^1=H, R^2=CH_3, R=,4-methoxy, 2u, R^1=H, R^2=CH_3, R=3,4-dimethoxy,
2v, R^1=H, R^2=CH_3, R=3,4,5-trimethoxy, 2w, R^1=CH_3, R^2=H, R= 2-chloro, 2x, R^1=CH_3, R^2=H, R= 4-dimehtylamino,
2y, R^1=CH_3, R^2=H, R=4-methoxy, 2z, R^1=CH_3, R^2=H, R= 3,4-dimethoxy.

Scheme 1. Synthesis of pyrazoline substitued benzenesulfonylureas (**2a**–**z**). Regents and conditions; (i) =C_4H_9NCO, acetone/K_2CO_3, (ii) =$C_6H_5CH_2NCO$, acetone/K_2CO_3.

Table 1
Growth inhibitory concentration (GI_{50}, μM) of compounds **2i**, **2n**, **2v** and **2x**[a]

Panel	Cell line	5FU	**2i**	**2n**	**2v**	**2x**
Leukemia	CCRF-CEM	9.97	2.2	3.32	3.15	3.19
	HL-60	2.3	2.28	2.48	3.62	3.01
	K-562	3.58	3.14	3.58	4	3.51
	MOLT	0.35	2.74	3.61	3.24	3.65
	RPMI-8226	0.04	1.95	2.99	2.8	2.88
Non-small cell lung						
Cancer	A549/ATCC	0.18	2.53	3.2	3.31	3.46
	HOP-62	0.39	3.15	6.86	4.3	5.69
	HOP-92	77.9	1.27	2.39	1.96	2.64
	NCI-H226	54.7	3.29	4.54	3.63	3.91
	NCI-H23	0.33	2.35	4.92	3.37	3.6
	NCI-H322M		3.35	5.19	5.41	4.86
	NCI-H460	0.05	2.46	3.33	2.53	3.33
	NCI-H522	7.27	2.39	3.25	3.55	4.48
Colon cancer	COLO 205	0.15	2.6	3.19	2.48	3.71
	HCC-2998	0.05	2.32	2.25	2.63	2.45
	HCC-116	0.22	1.84	3.86	3.21	4
	HCC-15	0.11	2.81	3.09	3.18	3.27
	HT29	0.17	2.42	4.2	3.87	4.53
	KM12	0.21	2.25	3.72	3.44	3.49
	SW-620	0.92	3.26	4.14	3.62	3.94
CNS cancer	SF-268	1.62	3.15	5.73	4.9	4.37
	SF-539	0.06	1.9	3.22	2.02	2.43
	SNB-19	3.81	2.75	4.59	3.75	4.6
	SNB-75	78.7	2.12	3.81	2.33	2.44
	U251	0.92	2.11	3.59	3.31	3.53
Melonoma	LOX IMVI	0.24	2.24	4.4	3.79	4.08
	MALME-3M	0.05	2.4	3.08	3.48	2.9
	M14	0.98	2.14	4.06	3.04	3.57
	MDA-MB-435	0.07	1.75	2.55	2.27	2.51
	SK-MEL-2	56.7	2.2	3.13	2.81	3.32
	SK-MEL-28	1.03	1.97	2.56	2.26	2.36
	SK-MEL-5	0.46	2.54	2.22	2.04	2.32
	UACC-257	3.55	3.4	4.04	3.53	4.64
	UACC-62	0.52	1.83	2.18	1.98	2.5
Ovarian cancer	IGROV1	1.22	3.19	4.87	3.95	4.31
	OVCAR-3	0.01	2.07	2.5	2.42	2.24
	OVCAR-4	4.43	2.52	5.41	3.28	3.54
	OVCAR-5	10.9	3.39	5.24	4.19	5.4
	OVCAR-8	1.74	3.03	3.68	3.77	3.81
	NCI/ADR-RES	0.31	2.95	4.12	4.18	3.93
	SK-OV-3	21.8	3.53	8.16	4.98	8.43
Renal cancer	786-0	0.72	3.51	5.45	3.79	4.37
	A498	0.35	2.31	3.9	3.09	3.08
	ACHN	0.27	3.69	3.93	3.47	3.97
	CAKI-1	0.07	3.07	3.38	3.17	3.45
	RXF 393	2.61	2.61	4.06	2.9	3
	SN 12C	0.49	3.36	3.07	3.15	3.35
	TK-10	1.12	3.44	5.64	4.74	6.46
	UO-31	1.42	3.07	4.57	3.56	4.27
Prostrate cancer	PC-3	2.36	1.94	3.34	2.54	3.33
	DU-145	0.36	3.46	5.75	6.05	4.6
Breast cancer	MCF7	0.07	2.06	2.63	2.58	2.99
	MDA-MB-231/ATCC	6.6	2.36	5.36	2.96	4.17
	HS 578T	9.77	2.2	3.95	2.68	2.48
	BT-549	10.6	2.73	4.11	3.08	3.98
	T-47D	8.12	3.91	5.16	4.19	6.74
	MDA-MB-468		2.17	2.22	2.32	2.36
MID	60	7.14	2.62	3.93	3.33	3.74

[a] Data obtained from NCI's in vitro disease-oriented human tumor cell screen.

degree of cytotoxic efficacy with LC_{50} (MG-MID) values of 66.3, 93.5, 94.8 and 84.3 μM, respectively (Table S4).

The compound **2i** displayed remarkable antiproliferative activity in 8 different cell lines with GI_{50} less than 2 μM. Compounds **2n**, **2v** and **2x** displayed activity against 11, 18 and 14 different cell lines respectively with GI_{50} less than 3 μM (Table 1).

With regard to sensitivity against some individual cell lines, compound **2i** showed high activity against non small cell lung cancer, HOP-92 (GI_{50} 1.27 μM), melanoma, MDA-MB-435 (GI_{50} 1.75 μM), UACC-62 (GI_{50} 1.85 μM), SK-MEL-28 (GI_{50} 1.97 μM), CNS, SF-539 (GI_{50} 1.90 μM), colon, HCC-116 (GI_{50} 1.84 μM), prostate, PC-3 (GI_{50} 1.94 μM), leukemia, RPMI-8226 (GI_{50} 1.95 μM). Compound **2v** showed activity against non small cell lung cancer, HOP-92 (GI_{50} 1.96 μM), melanoma, MDA-MB-435 (GI_{50} 1.98 μM). Obtained data revealed an obvious sensitivity profile of compound **2n** towards melanoma SK-MEL-5 (GI_{50} 2.22 μM), breast cancer MDA-MB-468 (GI_{50} 2.22 μM) and compound **2x** showed sensitivity towards cell line like ovarian cancer, OVCAR-3 (GI_{50} 2.24 μM), melanoma SK-MEL-5 (GI_{50} 2.32 μM) (Table 1).

The ratio obtained by dividing the full panel MG-MID (μM) of the compounds by their individual subpanel MG-MID (μM) is considered as a measure of compound selectivity. Ratio of 3–6 refer to moderate selectivity, ratios greater than six indicate high selectivity towards the corresponding cell line, while compounds not meeting either of these criteria are rated as nonselective.[25] In this context, the active compounds in the present study were found to be nonselective with broad spectrum antitumor activity against the nine tumor subpanels tested with selectivity ratios ranges of 0.72–1.19 at the GI_{50} respectively. From the present data it is difficult to extract any SAR of these compounds.

In conclusion, the present study describes the synthesis of twenty six pyrazoline substituted benzenesulfonylureas (**2a**–**z**). Fourteen compounds **2i**, **2k**–**2p**, **2r**, **2s**–**2x** were screened at NCI for antiproliferative activity. The results of this assay indicated an activity in the micro-molar range, particularly four compounds (**2i**, **2n**, **2v** and **2x**). Therefore, this study has provided meaningful information for further improving the potency of this class of compound as antiproliferative agents.

Crystallographic data for compound **2m** has been deposited with Cambridge Crystallographic Data Centre as supplementary publication number CCDC 986819. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via http://www.ccdc.cam.ac.uk/data_request/cif.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bmcl.2014.02.059.

References and notes

1. Shewach, D. S.; Kuchta, R. D. *Chem. Rev.* **2009**, *109*, 2859.
2. Thurston, D. E.; Taylor, C. R. C. P.; Francis, G.; Raton, B. *Chem. Pharm. Anticancer Drugs* **2007**, 281.
3. Casini, A.; Scozzafava, A.; Mastrolorenzo, A.; Supuran, C. T. *Curr. Cancer Drug Targets* **2002**, *2*, 55.
4. Rostom, S. A. F. *Bioorg. Med. Chem.* **2006**, *14*, 6475.
5. Owa, T.; Nagasu, T. *Expert Opin. Ther.* **2000**, *10*, 1725.
6. Howbert, J. J.; Grossman, C. S.; Crowell, T. A.; Rieder, B. J.; Harper, R. W.; Grindey, G. B. *J. Med. Chem.* **1990**, *33*, 2393.
7. Chern, J. W.; Leu, Y. L.; Wang, S. S.; Jou, R.; Lee, C. F.; Tsou, P. C.; Hsu, S. C.; Liaw, Y. C.; Lin, H. M. *J. Med. Chem.* **1997**, *40*, 2276.
8. Toth, J. E.; Grindey, G. B.; Ehlhardt, W. J.; Ray, J. E.; Boder, G. B.; Bewley, J. R.; Klingerman, K. K.; Gates, S. B.; Rinzel, S. M.; Schultz, R. M.; Weir, L. C.; Worzalla, J. F. *J. Med. Chem.* **1997**, *1018*, 40.
9. Supuran, C. T.; Briganti, F.; Tilli, S.; Chegwidden, W. R.; Scozzafava, A. *Bioorg. Med. Chem.* **2001**, *9*, 703.
10. Guan, X.; Hoffman, B. N.; Mcfarland, D. C.; Gilkerson, K. K.; Dwivedi, C.; Erickson, A. K.; Bebensee, S.; Pellegrini, J. *Drug Metab. Dispos.* **2002**, *30*, 331.

11. Lv, P. C.; Li, D. D.; Li, Q. S.; Lu, X.; Xiao, Z. P.; Zhu, H. L. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 5374.
12. Bashir, R.; Ovais, S.; Yaseen, S.; Hamid, H.; Alam, M. S.; Samim, M. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 4301.
13. Bano, S.; Javed, K.; Ahmad, S.; Rathish, I. G.; Singh, S.; Alam, M. S. *Eur. J. Med. Chem.* **2011**, *46*, 5763.
14. Amir, M.; Kumar, H.; Khan, S. A. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 918.
15. Amir, M.; Kumar, S. *Indian J. Chem.* **2005**, *44B*, 2532.
16. Kumar, A.; Sharma, S.; Bajaj, K.; Bansal, D.; Sharma, S.; Saxena, K. K.; Lata, S.; Gupta, B.; Srivastava, V. K. *Indian J. Chem.* **1979**, *2003*, 42B.
17. Sivakumar, P. M.; Seenivasan, P. S.; Kumar, V.; Doble, M. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 3169.
18. Palaska, E.; Aytemir, M.; Uzbay, I. T.; Erol, D. *Eur. J. Med. Chem.* **2001**, *36*, 539.
19. Sahu, S. K.; Banerjee, M.; Samantray, A.; Behera, A.; Azam, M. A. *Trop. J. Pharm. Res.* **2008**, *7*, 961.
20. Rathore, P. Ph.D. Thesis, Jamia Hamdard at New Delhi. To be submitted by March 2014.
21. *General procedure for the synthesis of pyrazoline substituted benzenesulfonylureas (**2a–z**)*: A solution of appropriate pyrazoline (1 mmol) (**1a–q**) in dry acetone was refluxed over anhydrous K_2CO_3 (2 mmol) for 1–1.5 h. At this temperature, a solution of the appropriate isocyanate (1.2 mmol) in dry acetone 5 ml was added in a drop wise manner. It was stirrer and refluxed for 24–72 h. Acetone was removed under reduced pressure. The solid residue thus obtained was suspended in water and acidified with acetic acid. It was filtered and residue was washed with plenty of distilled water. It was dried and crystallized with methanol. The purity of compound was checked on TLC plate.

*N-(Butylamino-hydroxy-methyl)-4-[3-(2,5-dimethyl-phenyl)-5-phenyl-4,5-dihydro-pyrazol-1-yl]-benzenesulfonamide (**2a**).* Off white crystals (mp 145-146 °C). Yield 65%. R_f = 0.65, (toluene/ethylacetate/formic acid, 5:4:1). IR ν_{max} (KBr, in cm^{-1}): 3221 and 3208 (NHCONH), 1702 (C=O), 1598 (C=N), 1334 and 1165 (SO_2N). ^1H NMR (300 MHz, DMSO, δ): 0.79 (3H, t, $CH_3CH_2CH_2CH_2$—), 1.12–1.18 (2H, m, $CH_3CH_2CH_2CH_2$—), 1.24–1.29 (2H, m, $CH_3CH_2CH_2CH_2$—), 2.27 (3H, s, CH_3, C-5′), 2.75 (3H, s, CH_3, C-2′), 2.89–2.91 (2H, m, $CH_3CH_2CH_2CH_2$—), 3.21 [1H, dd, J = 4.2 Hz, J = 17.1 Hz, H-4 *trans* (pyrazoline)], 4.0 [1H, dd, J = 8.3 Hz, J = 17.3 Hz, H-4 *cis* (pyrazoline)], 5.51 [1H, dd, J = 7.5 Hz, J = 19.1 Hz, H-5 (pyrazoline)], 6.29 (1H, t, CO<u>N</u>*H*CH_2—), 6.98–7.08 (3H, m, H-2″ H-6″, H-3′), 7.08 (1H, s, H-6′), 7.16–7.35 (6H, m, H-2, H-3, H-4, H-5, H-6, H-4′), 7.57-7.63 (2H, m, H-3″, H-5″). ESI-MS (m/z); 504 [M^+], 505 [M+1], 503 [M−1]. ^{13}C NMR; (100 MHz, DMSO, δ): 13.70, 19.86, 21.20, 23.90, 31.60, 39.91, 45.78, 62.38, 112.36, 125.62, 126.48, 126.89, 127.61, 127.95, 128.43, 128.59, 129.36, 132.78, 137.78, 138.84, 141.30, 147.75, 150.60, 152.89. Elemental Analysis for: $C_{28}H_{32}N_4O_3S$, Found (Calculated) C: 66.61 (66.64%), H: 6.41 (6.39%), N: 11.11 (11.10%), S: 6.39 (6.35%).

*N-(Butylamino-hydroxy-methyl)-4-[5-(2-chloro-phenyl-3-(2,5-dimethyl-phenyl)-4,5-dihydro-pyrazol-1-yl]-benzenesulfonamide (**2b**).* Light yellow crystals (mp 180–182 °C). Yield 60%. R_f = 0.82, (toluene/ethylacetate/formic acid, 5:4:1). IR ν_{max} (KBr, in cm^{-1}): 3204 and 3153 (NHCONH), 1693 (C=O), 1599 (C=N), 1381 and 1156 (SO_2N). ^1H NMR (300 MHz, DMSO, δ): 0.77–0.85 (3H, m, $CH_3CH_2CH_2CH_2$—), 0.90–0. 91 (2H, m, $CH_3CH_2CH_2CH_2$—), 1.22–1.29 (2H, m, $CH_3CH_2CH_2CH_2$—), 2.27 (3H, s, CH_3, C-5′), 2.66 (3H, s, CH_3, C-2′), 2.86–2.92 (2H, m, $CH_3CH_2CH_2CH_2$—), 3.15 [1H, dd, J = 8.6 Hz, J = 17.2 Hz, H-4 *trans* (pyrazoline)], 4.13 [1H, dd, J = 12.9 Hz, J = 17.1 Hz, H-4 *cis* (pyrazoline)], 5.72 [1H, dd, J = 4.2 Hz, J = 11.1 Hz, H-5 (pyrazoline)], 6.20 (1H, t, CO<u>N</u>*H*CH_2—), 6.89 (2H, d, J = 9.38 Hz, H-2″, H-6″), 7.05–7.40 [6H, m, aromatic protons (H-3, H-4, H-5, H-4′, H-6′) and SO_2<u>N</u>*H*CO–], 7.56 (1H, d, J = 7.8 Hz, H-3′), 7.61 (2H, d, J = 8.4 Hz, H-3″, H-5″). ESI-MS (m/z): 539 [M^+], 540 [M+1], 541 [M+2], 538 [M−1], 537 [M−2]. ^{13}C NMR; (100 MHz, DMSO, δ): 14.02, 19.77, 21.33, 23.87, 31.79, 39.21, 45.72, 61.74, 112.08, 112.56, 121.42, 123.16, 126.19, 127.06, 127.93, 128.11, 128.82, 129.38, 129.48, 129.61, 132.18, 138.81, 142.15, 147.39, 151.39, 152.11. Elemental Analysis for: $C_{28}H_{31}ClN_4O_3S$, Found (Calculated) C: 62.40 (62.38%), H: 5.76 (5.80%), N: 10.38 (10.39%), S: 5.58 (5.59%).

*N-(Butylamino-hydroxy-methyl)-4-[3-(2,5-dimethyl-phenyl-5-(3-nitro-phenyl)-4,5-dihydro-pyrazol-1-yl]-benzenesulfonamide (**2c**).* Light yellow crystals (mp 182–185 °C). Yield 60%. R_f = 0.55, (toluene/ethylacetate/formic acid, 7.5:2:0.5). IR ν_{max} (KBr, in cm^{-1}): 3259 and 3181 (NHCONH), 1704 (C=O), 1596 (C=N), 1374 and 1161 (SO_2N). ^1H NMR (300 MHz, DMSO, δ): 0.78 (3H, t, J = 7.5 Hz, J = 13.2 Hz, $CH_3CH_2CHCH_2$—), 1.10–1.17 (2H, m, $CH_3CH_2CH_2CH_2$—), 1.23–1.28 (2H, m, $CH_3CH_2CH_2CH_2$—), 2.31 (3H, s, CH_3, C-5′), 2.68 (3H, s, CH_3, C-2′), 2.90–2.92 (2H, m, $CH_3CH_2CH_2CH_2$—), 2.78 [1H, dd, J = 6.3 Hz, J = 17.6 Hz, H-4 *trans* (pyrazoline)], 4.07 [1H, dd, J = 5.7 Hz, J = 17.4 Hz, H-4 *cis* (pyrazoline)], 5.78 [1H, dd, J = 4.2 Hz, J = 6.9 Hz, H-5 (pyrazoline)], 6.40 (1H, t, CO<u>N</u>*H*CH_2—), 7.05–7.10 (3H, m, H-3′, H-2″, H-6″), 7.18 (1H, s, H-6′), 7.36 (1H, o, m coupled doublet H-4′), 7.65–7.68 (4H, m, H-3″, H-5″, H-5, H-6), 8.15 (1H, d, J = 6.0 Hz, H-4), 8.19 (1H, s, H-2), 10.28 (1H, br s, SO_2NH–). ESI-MS (m/z): 549 [M^+], 550 [M+1], 548 [M−1]. ^{13}C NMR; (100 MHz, DMSO, δ): 13.97, 19.74, 21.23, 23.82, 31.76, 40.63, 45.41, 60.97, 112.23, 121.42, 123.18, 126.18, 127.06, 127.73, 129.19, 129.15, 129.56, 131.31, 132.88, 137.36, 139.03, 144.26, 147.19, 148.67, 151.84, 151.94. Elemental Analysis for: $C_{28}H_{31}N_5O_5S$, Found (Calculated) C: 61.19 (61.19%), H: 5.66 (5.68%), N: 12.75 (12.74%), S: 5.86 (5.83%).

*N-(Butylamino-hydroxy-methyl)-4-[5-(4-chloro-phenyl)-3-(2,5-dimethyl-phenyl)-4,5-dihydro-pyrazol-1-yl]-benzenesulfonamide (**2d**).* Off white crystals (mp 188–190 °C). Yield 60%. R_f = 0.73, (toluene/ethylacetate/formic acid, 5:4:1). IR ν_{max} (KBr, in cm^{-1}): 3392 and 3170 (NHCONH), 1695 (C=O), 1596 (C=N), 1381 and 1156 (SO_2N). ^1H NMR (300 MHz, $CDCl_3$, δ): 0.87 (3H, t, J = 7.2 Hz, J = 14.2 Hz, $CH_3CH_2CH_2CH_2$—), 1.20–1.30 (2H, m, $CH_3CH_2CH_2CH_2$—), 1.40–1.47 (2H, m, $CH_3CH_2CH_2CH_2$—), 2.32 (3H, s, CH_3, C-5′), 2.67 (3H, s, CH_3, C-2′), 2.86–2.92 (2H, m, $CH_3CH_2CH_2CH_2$—), 3.15 [1H, dd, J = 7.2 Hz, J = 12.9 Hz, H-4 *trans* (pyrazoline)], 4.13 [1H, dd, J = 12.3 Hz, J = 17.1 Hz, H-4 *cis* (pyrazoline)], 5.72 [1H, dd, J = 4.8 Hz, J = 10.5 Hz, H-5 (pyrazoline)], 6.53 (1H, t, CO<u>N</u>*H*CH_2—), 6.89 (2H, d, J = 9.3 Hz, H-2″, H-6″), 6.97–7.19 (5H, m, H-4′, H-3′, H-6′, H-3, H-5), 7.32 (2H, d, J = 8.4 Hz, H-2, H-6), 7.64 (2H, d, J = 8.4 Hz, H-3″, H-5″). ESI-MS (m/z): 539 [M^+], 540 [M+1], 542 [M+2], 538 [M−1], 537 [M−2]. ^{13}C NMR; (100 MHz, $CDCl_3$, δ): 13.68, 19.86, 21.22, 23.88, 31.57, 39.95, 45.72, 61.74, 112.43, 121.32, 126.58, 127.38, 128.49, 128.71, 129.62, 131.42, 132.43, 137.83, 139.42, 144.46, 147.64, 148.42, 150.92, 151.23. Elemental Analysis for: $C_{28}H_{31}ClN_4O_3S$. Found (Calculated) C: 62.40 (62.38%), H: 5.76 (5.80%), N: 10.37 (10.39%), S: 5.92 (5.95%).

*N-(Butylamino-hydroxy-methyl)-4-[3-(2,5-dimethyl-phenyl)-5-tolyl-4,5-dihydro-pyrazol-1-yl]-benzenesulfonamide (**2e**).* Light yellow crystals (mp 188–190 °C). Yield 55%. R_f = 0.76 (toluene/ethylacetate/formic acid, 5:4:1). IR ν_{max} (KBr, in cm^{-1}): 3197 (NHCONH), 1691 (C=O), 1532 (C=N), 1378 and 1161 (SO_2N). ^1H NMR (300 MHz, DMSO, δ): 0.79 (3H, t, J = 6.9 Hz, J = 13.2 Hz, $CH_3CH_2CH_2CH_2$—), 1.10–1.17 (2H, m, $CH_3CH_2CH_2CH_2$—), 1.23–1.28 (2H, m, $CH_3CH_2CH_2CH_2$—), 2.24 (3H, s, CH_3, C-4), 2.30 (3H, s, CH_3, C-5′), 2.30 (3H, s, CH_3, C-2′), 2.90–2.92 (2H, m, $CH_3CH_2CH_2CH_2$—), 3.18 [1H, dd, J = 7.2 Hz, J = 12.9 Hz, H-4 *trans* (pyrazoline)], 4.02 [1H, dd, J = 12.3 Hz, J = 17.1 Hz, H-4 *cis* (pyrazoline)], 5.50 [1H, dd, J = 4.2 Hz, J = 11.4 Hz, H-5 (pyrazoline)], 6.45 (1H, t, CO<u>N</u>*H*CH_2—), 7.00–7.14 (9H, m, H-3′, H-4′, H-5′, H-2″, H-6″, H-2, H-3, H-5, H-6), 7.69 (2H, d, J = 9.3 Hz, H-3″, H-5″), 10.27 (1H, br s, SO_2NHCO–). ESI-MS (m/z): 518 [M^+], 519 [M+1], 517 [M−1]. ^{13}C NMR; (100 MHz, DMSO, δ): 14.00, 19.76, 21.11, 21.23, 23.89, 31.79, 39.20, 45.71, 112.09, 126.12, 126.91, 127.06, 127.96, 128.58, 128.94, 129.31, 130.15, 132.18, 137.32, 138.78, 139.14, 147.40, 151.63, 152.00. Elemental Analysis for: $C_{29}H_{34}N_4O_3S$. Found (Calculated) C: 67.44 (67.42%), H: 6.24 (6.24%), N: 10.87 (10.84%), S: 6.25 (6.21%).

*N-(Butylamino-hydroxy-methyl)-4-[5-(4-dimethylamino-phenyl)-3-(2,5-dimethyl-phenyl)-4,5-dihydro-pyrazol-1-yl]-benzenesulfonamide (**2f**).* Light yellow crystals (mp 190–192 °C). Yield 65%. R_f = 0.46 (petrolleum ether/acetone, 7:3). IR ν_{max} (KBr, in cm^{-1}): 3241 and 3202 (NHCONH), 1697 (C=O), 1594 (C=N), 1321 and 1161 (SO_2N). ^1H NMR (300 MHz, DMSO, δ): 0.79 (3H, t, J = 6.9 Hz, J = 13.2 Hz, $CH_3CH_2CH_2CH_2$—), 1.14–1.17 (2H, m, $CH_3CH_2CH_2CH_2$—), 1.25–1.27 (2H, m, $CH_3CH_2CH_2CH_2$—), 2.30 (3H, s, CH_3, C-5′), 2.66 (3H, s, CH_3 C-2′), 2.84 (6H, s, $(CH_3)_2N$–), 2.90–2.92 (2H, m, $CH_3CH_2CH_2CH_2$—), 3.17 [1H, dd, J = 6.0 Hz, J = 24 Hz, H-4 *trans* (pyrazoline)], 3.96 [1H, dd, J = 11.7 Hz, J = 16.8 Hz, H-4 *cis* (pyrazoline)], 5.40 [1H, dd, J = 4.2 Hz, J = 11.4 Hz, H-5 (pyrazoline)], 6.45 (1H, t, CO<u>N</u>*H*CH_2), 6.66 (2H, d, J = 7.5 Hz, H-3, H-5), 7.01-7.08 (5H, m, H-2″, H-6″, H-2, H-6, H-3′), 7.16 (1H, s, H-5′), 7.35 (1H, d, J = 6.9 Hz, H-4′), 7.62 (2H, d, J = 8.1 Hz, H-3″, H-5″), 10.23 (1H, br s, SO_2<u>N</u>*H*CO–). ESI-MS (m/z): 547 [M^+], 548 [M+1], 546 [M−1]. ^{13}C NMR; (100 MHz, DMSO, δ): 14.00, 19.77, 21.33, 23.89, 31.87, 40.16, 42.67, 43.04, 61.46, 112.11, 113.2, 126.45, 126.93, 127.08, 127.53, 128.15, 128.32, 129.21, 129.46, 132.79, 137.41, 138.90, 140.26, 150.27, 151.73. Elemental Analysis for: $C_{30}H_{37}N_5O_3S$. Found (Calculated) C: 65.76 (65.79%), H: 6.80 (6.81%), N: 12.77 (12.79%), S: 5.84 (5.85%).

*N-(Butylamino-hydroxy-methyl)-4-[3-(2,5-dimethyl-phenyl)-5-(4-methoxy-phenyl)-4,5-dihydro-pyrazol-1-yl]-benzenesulfonamide (**2g**).* Light yellow crystals (mp 188–190 °C). Yield 55%. R_f = 0.76 (toluene/ethylacetate/formic acid, 5:4:1). IR ν_{max} (KBr, in cm^{-1}): 3319 (NHCONH), 1693 (C=O), 1597 (C=N), 1369 and 1162 (SO_2N). ^1H NMR (300 MHz, $CDCl_3$, δ): 0.84–0.94 (3H, m, $CH_3CH_2CH_2CH_2$—), 1.20–1.30 (2H, m, $CH_3CH_2CH_2CH_2$—), 1.52–1.65 (2H, m, $CH_3CH_2CH_2CH_2$—), 2.35 (3H, s, CH_3, C-5′), 2.72 (3H, s, CH_3 C-2′), 3.18–3.22 (2H, m, $CH_3CH_2CH_2CH_2$—), 3.26 [1H, dd, J = 5.7 Hz, J = 14.4 Hz, H-4 *trans* (pyrazoline)], 3.78 (3H, s, OCH_3), 3.92 [1H, dd, J = 12.0 Hz, J = 17.1 Hz, H-4 *cis* (pyrazoline)], 5.23 [1H, dd, J = 5.7 Hz, J = 12.0 Hz, H-5 (pyrazoline)], 6.53 (1H, t, CO<u>N</u>*H*CH_2—), 6.86 (2H, d, J = 8.4 Hz, H-3, H-5), 7.00–7.04 (3H, m, H-2″, H-6″, H-4′), 7.14–7.26 (4H, m, H-3′, H-6′, H-2, H-6), 7.62 (2H, d, J = 7.8 Hz, H-3″, H-5″). ESI-MS (m/z): 534 [M^+], 535 [M+1], 533 [M−1]. ^{13}C NMR; (100 MHz, $CDCl_3$, δ): 13.67, 19.88, 21.23, 23.95, 31.58, 39.89, 45.84, 55.31, 61.87, 112.38, 112.74, 126.53, 126.91, 127.41, 128.23, 128.73, 128.89, 132.81, 133.29, 137.28, 138.88, 147.91, 150.81, 152.64, 159.23. Elemental Analysis for: $C_{29}H_{34}N_4O_4S$. Found (Calculated) C: 65.17 (65.14%), H: 6.44 (6.41%), N: 10.47 (10.48%), S: 6.01 (6.00%).

*N-(Butylamino-hydroxy-methyl)-4-[5-(3,4-dimethoxy-phenyl)-3-(2,5-dimethyl-phenyl)-4,5-dihydro-pyrazol-1-yl]-benzenesulfonamide (**2h**).* Off white crystals (mp 158–160 °C). Yield 65%. R_f = 0.49 (toluene/ethylacetate/formic acid, 7.5: 2: 0.5). IR ν_{max} (KBr, in cm^{-1}): 3262 and 3219 (NHCONH), 1693 (C=O), 1596 (C=N), 1376 and 1161 (SO_2N). ^1H NMR (300 MHz, $CDCl_3$, δ): 0.87 (3H, t, J = 7.2 Hz, J = 14.4 Hz, $CH_3CH_2CH_2CH_2$—), 0.92–1.24 (2H, m, $CH_3CH_2CH_2CH_2$—) 1.26–1.33 (2H, m, $CH_3CH_2CH_2CH_2$—), 2.36 (3H, s, CH_3, C-5′), 2.72 (3H, s, CH_3, C-2′), 3.23(3H, s, OCH_3), 3.12–3.23 (2H, m, $CH_3CH_2CH_2CH_2$—) 3.28 [1H, dd, J = 6 Hz, J = 17.4 Hz, H-4 *trans* (pyrazoline)], 3.58 (3H, s, OCH_3), 3.93 [1H, dd, J = 12.3 Hz, J = 17.4 Hz, H-4 *cis* (pyrazoline)], 5.20 [1H, dd, J = 6.0 Hz, J = 11.7 Hz, H-5 (pyrazoline)], 6.54 (1H, s, H-2), 6.55 (1H, t, CO<u>N</u>*H*CH_2—), 6.56–6.68 (2H, m, H-5, H-6), 6.87 [3H, d, J = 20.1 Hz, superimposed 2 doublet (H-4′), (H-2″, H-6″)], 7.05 (1H, s, H-6′), 7.17 (1H, d, J = 16.2 Hz, H-3′), 7.67 (2H, d, J = 9.0 Hz, H-3″, H-5″). ESI-MS (m/z): 564 [M^+], 565 [M+1], 563 [M−1]. ^{13}C NMR; (100 MHz, $CDCl_3$, δ): 14.60, 19.77, 21.23, 23.81, 31.80, 40.62, 45.46, 55.80, 56.05, 61.73, 110.12, 112.17, 114.41, 117.90, 127.07, 129.35, 132.77, 134.38, 135.15, 137.12, 138.77, 144.42, 148.63, 149.57, 151.73, 152.46. Elemental Analysis for: $C_{30}H_{36}N_4O_5S$, Found (Calculated) C: 63.84 (63.81%), H: 6.42 (6.43%), N: 9.95 (9.92%), S: 5.67 (5.68%).

*N-(Butylamino-hydroxy-methyl)-4-[3-(2,5-dimethyl-phenyl)-5-(3,4,5-trimethoxy-phenyl)-4,5-dihydro-pyrazol-1-yl]-benzenesulfonamide (**2i**).* White crystals (mp

200–204 °C). Yield 65%. R_f = 0.81(toluene/ethylacetate/formic acid, 5:4:1). IR ν_{max} (KBr, in cm^{-1}): 3325 and 3265 (NHCONH), 1690 (C=O), 1595 (C=N), 1348 and 1131 (SO_2N). ^1H NMR (300 MHz, DMSO, δ): 0.78 (3H, t, $CH_3CH_2CH_2CH_2$—), 1.11–1.12 (2H, m, $CH_3CH_2CH_2CH_2$—), 1.25–1.29 (2H, m, $CH_3CH_2CH_2CH_2$—), 2.31 (3H, s, CH_3, C-5′), 2.66 (3H, s, CH_3, C-2′), 2.89–2.95 (2H, m, $CH_3CH_2CH_2CH_2$—), 3.24 [1H, dd, J = 5.6 Hz, J = 17.4 Hz, H-4 *trans* (pyrazoline)], 3.58 (3H, s, OCH_3,C-4), 3.69 (6H, s, 2 × OCH_3, C-3, C-5), 4.0 [1H, dd, J = 5.1 Hz, J = 17.4 Hz, H-4 *cis* (pyrazoline)], 5.43 [1H, dd, J = 5.4 Hz, J = 11.1 Hz, H-5 (pyrazoline)], 6.32 (1H, t, CO<u>N</u>*H*CH_2—), 6.57 (2H, s, H-2, H-6), 7.05-7.10 (3H, m, H-4′, H-2″, H-6″), 7.17 (1H, s, H-6′), 7.36 (1H, d, J = 8.1 Hz, H-3′), 7.67 (2H, d, J = 9.0 Hz, H-3″, H-5″). ESI-MS (m/z): 594 [M^+], 595 [M+1], 593 [M−1]. ^{13}C NMR; (100 MHz, DMSO, δ): 14.00, 19.75, 21.33, 23.78, 32.41, 40.61, 45.41, 55.59, 56.24, 61.45, 103.22, 112.41, 126.41, 127.54, 128.26, 129.14, 131.41, 132.05, 134.41, 136.47, 137.19, 147.40, 147.91, 150.25, 151.80, 153.80. Elemental Analysis for: $C_{31}H_{38}N_4O_6S$, Found (Calculated) C: 62.64 (62.61%), H: 6.45 (6.44%), N: 9.41 (9.42%), S: 5.37 (5.39%).

N-(Butylamino-hydroxy-methyl)-4-[3-(2,4-dimethyl-phenyl)-5-phenyl-4,5-dihydro-pyrazol-1-yl]-benzenesulfonamide (***2j***). Off white crystals (mp 155–158 °C). Yield 60%. R_f = 0.55 (toluene/ethylacetate/formic acid, 5:4:1). IR ν_{max} (KBr, in cm^{-1}): 3221 and 3160 (NHCONH), 1696 (C=O), 1596 (C=N), 1390 and 1159 (SO_2N). ^1H NMR (300 MHz, $CDCl_3$, δ): 0.84 (3H, t, $CH_3CH_2CH_2CH_2$—), 1.24–1.36 (2H, m, $CH_3CH_2CH_2CH_2$—), 1.39–1.43 (2H, m, $CH_3CH_2CH_2CH_2$—), 2.35 (3H, s, CH_3, C-4′), 2.79 (3H, s, CH_3 C-2′), 3.12 (2H, d, J = 6.6 Hz, $CH_3CH_2CH_2CH_2$—), 3.26 [1H, dd, J = 6.0 Hz, J = 12.8 Hz, H-4 *trans* (pyrazoline)], 3.90 [1H, dd, J = 11.1 Hz, J = 18.2 Hz, H-4 *cis* (pyrazoline)], 5.23 [1H, dd, J = 6.6 Hz, J = 11.1 Hz, H-5 (pyrazoline)], 6.44 (1H, t, CO<u>N</u>*H*CH_2), 6.98–7.04 (3H, m, H-5′, H-2″, H-6″), 7.13–7.16 (2H, m, H-4, H-3′), 7.19–7.34 (5H, m, H-4', H-2, H-3, H-5, H-6), 7.65 (2H, d, J = 9.0 Hz, H-3″, H-5″). ESI-MS (m/z): 504 [M^+], 505 [M+1], 503 [M−1]. ^{13}C NMR; (100 MHz, $CDCl_3$, δ): 13.70, 19.86, 21.20, 23.90, 31.60, 39.91, 45.78, 62.38, 112.36, 125.62, 126.48, 126.89, 127.61, 127.95, 128.43, 128.59, 129.36, 132.78, 137.78, 138.84, 141.30, 147.75, 150.60, 152.89. Elemental Analysis for: $C_{28}H_{32}N_4O_3S$, Found (Calculated) C: 66.62 (66.64%), H: 6.37 (6.39%), N: 11.13 (11.10%), S: 6.37 (6.35%).

N-(Butylamino-hydroxy-methyl)-4-[5-(2-chloro-phenyl)-3-(2,4-dimethyl-phenyl)-4,5-dihydro-pyrazol-1-yl]-benzenesulfonamide (***2k***). Off white crystals (mp 178–180 °C). Yield 60%. R_f = 0.50 (toluene/ethylacetate/formic acid, 5: 4: 1). IR ν_{max} (KBr, in cm^{-1}): 3197 (NHCONH), 1692 (C=O), 1598 (C=N), 1334 and 1158 (SO_2N). ^1H NMR (300 MHz, DMSO, δ): 0.79 (3H, t, J = 7.2 Hz, J = 14.1 Hz, $CH_3CH_2CH_2CH_2$—), 1.11–1.18 (2H, m, $CH_3CH_2CH_2CH_2$—), 1.25–1.29 (2H, m, $CH_3CH_2CH_2CH_2$—), 2.30 (3H, s, CH_3, C-4′), 2.66 (3H, s, CH_3 C-2′), 2.90–2.93 (2H, m, $CH_3CH_2CH_2CH_2$—), 3.20 [1H, dd, J = 6.0 Hz, J = 18.3 Hz, H-4 *trans* (pyrazoline)], 4.13 [1H, dd, J = 12.0 Hz, J = 17.4 Hz, H-4 *cis* (pyrazoline)], 5.73 [1H, dd, J = 4.5 Hz, J = 12.0 Hz, H-5 (pyrazoline)], 6.33 (1H, t, CO<u>N</u>*H*CH_2—), 6.93 (2H, d, J = 14.7, H-2″, H-6″), 7.05–7.16 (2H, m, H-5′, H-6), 7.16 (1H, s, H-3′), 7.24–7.38 (3H, m, H-2, H-3, H-5), 7.56 (1H, d, J = 9.0 Hz, H-6′), 7.68 (2H, d, J = 9.0, H-3″, H-5″), 10.23 (1H, br s, SO_2NHCO–). ESI-MS (m/z): 539 [M^+], 540 [M+1], 542 [M+2], 537 [M−2]. ^{13}C NMR; (75 MHz, DMSO, δ): 13.68, 19.86, 21.22, 23.86, 31.59, 40.01, 44.56, 59.25, 112.34, 112.47, 126.54, 126.76, 127.04, 127.89, 128.57, 128.73, 129.28, 130.16, 137.81, 132.83, 137.69, 137.85, 139.20, 147.69, 151.44, 152.24. Elemental Analysis for: $C_{28}H_{31}ClN_4O_3S$. Found (Calculated) C: 62.48 (62.47%), H: 5.83 (5.80%), N: 10.37 (10.39%), S: 5.97 (5.95%).

N-(Butylamino-hydroxy-methyl)-4-[5-(4-chloro-phenyl)-3-(2,4-dimethyl-phenyl)-4,5-dihydro-pyrazol-1-yl]-benzenesulfonamide (***2l***). Light yellow crystals (mp 164–166 °C). Yield 60%. R_f = 0.84 (toluene/ethylacetate/formic acid, 5: 4: 1). IR ν_{max} (KBr, in cm^{-1}): 3235 (NHCONH), 1700 (C=O), 1596 (C=N), 1364 and 1156 (SO_2N). ^1H NMR (300 MHz, DMSO, δ): 0.79 (3H, t, J = 7.2 Hz, J = 14.1 Hz, $CH_3CH_2CH_2CH_2$—), 1.10–1.18 (2H, m, $CH_3CH_2CH_2CH_2$—), 1.24–1.29 (2H, m, $CH_3CH_2CH_2CH_2$—), 2.31 (3H, s, CH_3, C-4′), 2.67 (3H, s, CH_3, C-2′), 2.88–2.98 (2H, m, $CH_3CH_2CH_2CH_2$—), 3.23 [1H, dd, J = 6.0 Hz, J = 18.0 Hz, H-4 *trans* (pyrazoline)], 4.03 [1H, dd, J = 12.0 Hz, J = 17.4 Hz, H-4 *cis* (pyrazoline)], 5.58 [1H, dd, J = 4.5 Hz, J = 11.5 Hz, H-5 (pyrazoline)], 6.33 (1H, t, CO<u>N</u>*H*CH_2), 7.01 (2H, d, J = 9.0 Hz, H-2″, H-6″), 7.08 (1H, d, J = 7.8 Hz, H-5′), 7.17 (1H, s, H-3′), 7.25 (2H, d, J = 14.7 Hz, H-2″, H-6″), 7.35 (1H, d, J = 9.0 Hz, H-6′), 7.41 (2H, d, J = 7.5 Hz, H-3, H-5), 7.65 (2H, d, J = 9.0 Hz, H-3″, H-5″),10.23 (1H, br s, SO_2<u>N</u>*H*CO–). ESI-MS (m/z): 539 [M^+], 540 [M+1], 542 [M+2], 537 [M−2]. ^{13}C NMR; (100 MHz, DMSO, δ): 13.70, 21.25, 23.94, 31.56, 39.95, 45.72, 61.71, 112.43, 116.40, 126.58, 126.79, 127.34, 127.54, 128.72, 128.76, 129.54, 129.62, 131.25, 132.87, 133.84, 137.86, 139.68, 147.76, 150.64. Elemental Analysis for: $C_{28}H_{31}ClN_4O_3S$. Found (Calculated) C: 62.36 (62.38%), H: 5.83 (5.80%), N: 10.38 (10.39%), S: 5.97 (5.95%).

N-(Butylamino-hydroxy-methyl)-4-[3-(2,4-dimethyl-phenyl)-5-p-tolyl-4,5-dihydro-pyrazol-1-yl]-benzenesulfonamide (***2m***). Light yellow crystals (mp 158–159 °C). Yield 60%. R_f = 0.79 (toluene/ethylacetate/formic acid, 5:4:1). IR ν_{max} (KBr, in cm^{-1}): 3159 (NHCONH), 1699 (C=O), 1595 (C=N), 1336 and 1158 (SO_2N). ^1H NMR (300 MHz, $CDCl_3$, δ): 0.92–0.94 (3H, m, $CH_3CH_2CH_2CH_2$—), 1.21–1.33 (2H, m, $CH_3CH_2CH_2CH_2$—), 1.36–1.48 (2H, m, $CH_3CH_2CH_2CH_2$—), 2.31 (3H, s, CH_3, C-4), 2.35 (3H, s, CH_3, C-4′), 2.72 (3H, s, CH_3, C-2′), 3.14–3.20 (2H, m, $CH_3CH_2CH_2CH_2$—), 3.25 [1H, dd, J = 5.7 Hz, J = 17.1 Hz, H-4 *trans* (pyrazoline)], 3.92 [1H, dd, J = 12.0 Hz, J = 17.1 Hz, H-4 *cis* (pyrazoline)], 5.23 [1H, dd, J = 5.7 Hz, J = 12.0 Hz, H-5 (pyrazoline)], 6.50 (1H, t, CO<u>N</u>*H*CH_2), 6.99–7.04 (3H, m, H-2, H-2″, H-6″), 7.08 (1H, d, J = 7.8 Hz, H-5′), 7.13–7.17 (5H, m, H-3, H-5, H-6, H-6′), 7.19 (1H, d, J = 12.6 Hz, H-3′), 7.62 (2H, d, J = 9.0 Hz, H-3″, H-5″). ESI-MS (m/z): 518 [M^+], 519 [M+1], 517 [M−1]. ^{13}C NMR; (100 MHz, $CDCl_3$, δ): 13.67, 19.85, 21.10, 21.21, 23.88, 31.59, 39.95, 45.86, 62.16, 112.56, 125.54, 126.51, 127.12, 127.59, 128.46, 128.59, 129.32, 129.64, 130.06, 132.79, 137.79, 138.18, 138.94, 147.90, 150.93. Elemental Analysis for: $C_{29}H_{34}N_4O_3S$. Found (Calculated) C: 67.17 (67.15%), H: 6.62 (6.61%), N: 10.83 (10.80%), S: 6.15 (6.18%).

N-(Butylamino-hydroxy-methyl)-4-[5-(4-dimethyamino-phenyl)-3-(2,4-dimethyl-phenyl)-4,5-dihydro-pyrazol-1-yl]-benzenesulfonamide (***2n***). Light brown crystals (mp 194–195 °C). Yield 60%. R_f = 0.64 (petroleum ether/acetone, 6: 4). IR ν_{max} (KBr, in cm^{-1}): 3245 and 3182 (NHCONH), 1688 (C=O), 1596 (C=N), 1337 and 1162 (SO_2N). ^1H NMR (300 MHz, $CDCl_3$, δ):, δ): 0.85–0.92 (3H, m, $CH_3CH_2CH_2CH_2$—), 1.23–1.33 (2H, m, $CH_3CH_2CH_2CH_2$—), 1.39–1.49 (2H, m, $CH_3CH_2CH_2CH_2$—), 2.35 (3H, s, CH_3, C-4′), 2.72 (3H, s, CH_3, C-2′), 2.92 [6H, s, $N(CH_3)_2$], 3.16–3.24 (2H, m, $CH_3CH_2CH_2CH_2$—), 3.28 [1H, dd, J = 5.4 Hz, J = 17.1 Hz, H-4 *cis* (pyrazoline)], 5.19 [1H, dd, J = 5.7 Hz, J = 12.0 Hz, H-5 (pyrazoline)], 6.53 (1H, t, CO<u>N</u>*H*CH_2—), 6.66 (2H, J = 8.7 Hz, H-2″, H-6″), 7.02–7.13 (6H, m, H-5′, H-2, H-6, H-3′, H-3, H-5), 7.20 (1H, d, J = 8.1 Hz, H-6′), 7.62 (2H, d, J = 9.0 Hz, H-3″, H-5″). ESI-MS (m/z): 547 [M^+], 548 [M+1], 546 [M−1]. ^{13}C NMR; (100 MHz, $CDCl_3$, δ): 14.00, 19.77, 21.33, 23.89, 31.87, 40.16, 42.67, 43.04, 61.46, 112.11, 113.2, 126.45, 126.93, 127.08, 127.53, 128.15, 128.32, 129.21, 129.46, 132.79, 137.41, 138.90, 140.26, 150.27, 151.73. Elemental Analysis for: $C_{30}H_{37}N_5O_3S$. Found (Calculated) C: 65.77 (65.79%), H: 6.82 (6.81%), N: 12.78 (12.79%), S: 5.84 (5.85%).

N-(Butylamino-hydroxy-methyl)-4-[3-(2,4-dimethyl-phenyl)-5-(4-methoxy-phenyl)-4,5-dihydro-pyrazol-1-yl]-benzenesulfonamide (***2o***). Light yellow crystals (mp 170–172 °C). Yield 62%. R_f = 0.88 (petroleum ether/acetone, 6:4). IR ν_{max} (KBr, in cm^{-1}): 3245 and 3182 (NHCONH), 1688 (C=O), 1596 (C=N), 1337 and 1162 (SO_2N). ^1H NMR (300 MHz, $CDCl_3$, δ): 0.89–0.94 (3H, m, $CH_3CH_2CH_2CH_2$—), 1.23–1.33 (2H, m, $CH_3CH_2CH_2CH_2$—), 1.36–1.49 (2H, m, $CH_3CH_2CH_2CH_2$—), 2.17 (3H, s, CH_3, C-4′), 2.72 (3H, s, CH_3, C-2′), 3.16–3.20 (2H, m, $CH_3CH_2CH_2CH_2$—), 3.26 [1H, dd, J = 5.7 Hz, J = 17.1 Hz, H-4 *trans* (pyrazoline)], 3.78 (3H, s, OCH_3), 3.92 [1H, dd, J = 12.0 Hz, J = 16.8 Hz, H-4 *cis* (pyrazoline)], 5.24 [1H, dd, J = 5.7 Hz, 12.3 Hz, H-5 (pyrazoline)], 6.53 (1H, t, CO<u>N</u>*H*CH_2—), 6.86 (2H, d, J = 8.4 Hz, H-3, H-5), 7.00–7.03 (3H, m, H-2″, H-6″, H-5′), 7.14–7.22 (4H, m, H-2, H-6, H-3′, H-6′), 7.62 (2H, d, J = 8.7 Hz, H-3″, H-5″). ESI-MS (m/z): 534 [M^+], 535 [M+1], 533 [M−1]. ^{13}C NMR; (100 MHz, $CDCl_3$, δ): 13.70, 19.86, 21.23, 23.93, 31.57, 39.94, 45.85, 55.29, 61.84, 112.40, 114.72, 126.52, 126.83, 127.58, 127.64, 128.84, 128.60, 129.41, 132.81, 133.16, 138.95, 147.94, 150.92, 152.16, 159.22. Elemental Analysis for: $C_{29}H_{34}N_4O_4S$. Found (Calculated) C: 65.43 (65.40%), H: 6.42 (6.41%), N: 10.50 (10.48%), S: 6.02 (6.00%).

N-(Butylamino-hydroxy-methyl)-4-[5-(3,4-dimethoxy-phenyl)-3-(2,4-dimethyl-phenyl)-4,5-dihydro-pyrazol-1-yl]-benzenesulfonamide (***2p***). White crystals (mp 168–169 °C). Yield 70%. R_f = 0.73 (toluene/ethylacetate/formic acid, 5:4:1). IR ν_{max} (KBr, in cm^{-1}): 3261 and 3183 (NHCONH), 1699 (C=O), 1596 (C=N), 1333 and 1161 (SO_2N). ^1H NMR (300 MHz, $CDCl_3$, δ): 0.87 (3H, t, J = 7.2 Hz, J = 14.4 Hz, $CH_3CH_2CH_2CH_2$—), 0.92–1.24 (2H, m, $CH_3CH_2CH_2CH_2$—) 1.26–1.33 (2H, m, $CH_3CH_2CH_2CH_2$—), 2.36 (3H, s, CH_3, C-4′), 2.72 (3H, s, CH_3 C-2′), 3.23 (3H, s, OCH_3), 3.12–3.23 (2H, m, $CH_3CH_2CH_2CH_2$—), 3.28 [1H, dd, J = 6.0 Hz, J = 17.4 Hz, H-4 *trans* (pyrazoline)], 3.58 (3H, s, OCH_3), 3.93 [1H, dd, J = 12.3 Hz, J = 17.4 Hz, H-4 *cis* (pyrazoline)], 5.20 [1H, dd, J = 6.0 Hz, J = 11.7 Hz, H-5 (pyrazoline)], 6.54 (1H, s, H-2), 6.55 (1H, t, CO<u>N</u>*H*CH_2—), 6.56–6.68 (2H, m, H-5, H-6), 6.87 [3H, d, J = 20.1 Hz, superimposed 2 doublet (H-4′), (H-2″, H-6″)], 7.05 (1H, s, H-6′), 7.17 (1H, d, J = 16.2 Hz, H-3′), 7.67 (2H, d, J = 9.0 Hz, H-3″, H-5″). ESI-MS (m/z): 564 [M^+], 565 [M+1]. ^{13}C NMR; (100 MHz, $CDCl_3$, δ): 14.03, 19.77, 21.24, 23.90, 31.80, 39.94, 45.71, 55.29, 55.76, 61.72, 101.65, 111.69, 126.19, 127.09, 127.93, 128.49, 129.61, 132.81, 133.14, 137.25, 138.82, 142.15, 147.38, 148.46, 151.63, 153.35. Elemental Analysis for: $C_{30}H_{36}N_4O_5S$. Found (Calculated) C: 63.82 (63.81%), H: 6.42 (6.43%), N: 9.90 (9.92%), S: 5.55 (5.58%).

N-(Butylamino-hydroxy-methyl)-4-[3-(2,4-dimethyl-phenyl)-5-(3,4,5-trimethoxy-phenyl)-4,5-dihydro-pyrazol-1-yl]-benzenesulfonamide (***2q***). White crystals (mp 200–202 °C). Yield 72%. R_f = 0.74 (toluene/ethylacetate/formic acid, 5:4:1). IR ν_{max} (KBr, in cm^{-1}): 3251 and 3162 (NHCONH), 1690 (C=O), 1595 (C=N), 1347 and 1131 (SO_2N). ^1H NMR (300 MHz, $CDCl_3$, δ): 0.87 (3H, t, J = 7.2 Hz, J = 14.4 Hz, $CH_3CH_2CH_2CH_2$—), 1.25–1.32 (2H, m, $CH_3CH_2CH_2CH_2$—) 1.41–1.56 (2H, m, $CH_3CH_2CH_2CH_2$—), 2.36 (3H, s, CH_3, C-4′), 2.72 (3H, s, CH_3, C-2′), 3.80 (6H, s, 2 × OCH_3), 3.83 (3H, s, OCH_3), 3.17–3.24 (2H, m, $CH_3CH_2CH_2CH_2$—) 3.30 [1H, dd, J = 6.0 Hz, J = 17.1 Hz, H-4 *trans* (pyrazoline)], 3.93 [1H, dd, J = 11.7 Hz, J = 15.8 Hz, H-4 *cis* (pyrazoline)], 5.16 [1H, dd, J = 6.3 Hz, J = 11.7 Hz, H-5 (pyrazoline)], 6.44 (2H, s, H-2, H-6), 7.05 (3H, doublet of H-5′ merged with 2 proton doublet, J = 8.7 Hz, H-2″, H-6″), 6.55 (1H, t, CO<u>N</u>*H*CH_2—), 7.18 (2H, d, J = 1.8 Hz, H-3′, H-6′), 7.66 (2H, d, J = 9.0 Hz, H-3″, H-5″). ESI-MS (m/z): 594 [M^+], 595 [M+1], 593 [M−1]. ^{13}C NMR; (100 MHz, $CDCl_3$, δ): 14.03, 19.77, 21.24, 23.90, 31.80, 39.94, 45.71, 55.29, 55.76, 61.72, 101.65, 111.69, 126.19, 127.09, 127.93, 128.49, 129.61, 132.81, 133.14, 137.25, 138.82, 142.15, 147.38, 148.46, 151.63, 153.35. Elemental Analysis for: $C_{31}H_{38}N_4O_6S$. Found (Calculated) C: 62.65 (62.61%), H: 6.45 (6.44%), N: 9.43 (9.42%), S: 5.40 (5.39%).

N-(Benzylamino-hydroxy-methyl)-4-[5-(2-chloro-phenyl)3-(2,5-dimethyl-phenyl)-4,5-dihydro-pyrazol-1-yl]-benzenesulfonamide (***2r***). White crystals (mp 190–192 °C). Yield 70%. R_f = 0.53 (toluene/ethylacetate/formic acid, 7.5:2:0.5). IR ν_{max} (KBr, in cm^{-1}): 3197 (NHCONH), 1691 (C=O), 1597 (C=N), 1335 and 1156 (SO_2N). ^1H NMR (300 MHz, $CDCl_3$, δ): 2.34 (3H, s, CH_3, C-5′), 2.76 (3H, s, CH_3, C-2′), 2.42 [1H, dd, J = 14.0 Hz, J = 17.1 Hz, H-4 *trans* (pyrazoline)], 4.09 [1H, dd, J = 11.7 Hz, J = 17.4 Hz, H-4 *cis* (pyrazoline)], 5.68 [1H, dd, J = 5.7 Hz, J = 12.6 Hz, H-5 (pyrazoline)], 6.9–7.7 (16H, m, H-3′, H-4′, H-6′, H-3, H-4, H-5, H-6, H-2″, H-3″, H-5‴, H-6″, H-2‴, H-3‴, H-4‴, H-5‴, H-6‴). ESI-MS (m/z): 573 [M^+], 574 [M+1], 575 [M+2], 571 [M−2]. ^{13}C NMR; (100 MHz, $CDCl_3$, δ): 21.27, 23.94, 43.30, 59.32, 111.88, 126.77, 127.19, 127.33, 127.51, 128.06, 128.51, 128.76, 128.91, 129.32, 129.52, 130.33, 131.79, 132.74, 135.24, 137.46, 138.16, 138.82, 139.67, 142.41, 147.21, 151.28, 152.12. Elemental Analysis for: $C_{31}H_{29}ClN_4O_3S$.

Found (Calculated) C: 64.97 (64.97%), H: 5.13 (5.10%), N: 9.77 (9.78%), S: 5.60 (5.59%).

*N-(Benzylamino-hydroxy-methyl)-4-[5-(4-chloro-phenyl)-3-(2,5-dimethyl-phenyl)-4,5-dihydro-pyrazol-1-yl]-benzenesulfonamide (**2s**).* Off white crystals (mp 148–152 °C). Yield 70%. R_f = 0.64 (toluene/ethylacetate/formic acid, 7.5:2:0.5). IR ν_{max} (KBr, in cm^{-1}): 3225 and 3168 (NHCONH), 1705 (C=O), 1596 (C=N), 1363 and 1125 (SO_2N). ^1H NMR (300 MHz, DMSO, δ): 2.30 (3H, s, CH_3, C-5′), 2.66 (3H, s, CH_3, C-2′), 3.19 [1H, dd, J = 12.6 Hz, J = 17.7 Hz, H-4 *trans* (pyrazoline)], 3.97 [1H, dd, J = 18.0 Hz, J = 20.1 Hz, H-4 *cis* (pyrazoline)], 4.07 (2H, s, $CH_2C_6H_5$), 5.48 [1H, dd, J = 5.7 Hz, J = 12.6 Hz, H-5 (pyrazoline)], 6.87 (2H, d, J = 6.0 Hz, H-2″, H-6″), 6.88–7.04 (1H, t, CO<u>N</u>*H*CH_2—) 7.04–7.41 (12H, m, H-2, H-3, H-5, H-6, H-3′, H-4′, H-6′, H-2‴, H-3‴, H-4‴, H-5‴, H-6‴), 7.18 (1H, d, J = 1.8 Hz, H-6′), 7.53 (2H, d, J = 9.0 Hz, H-3″, H-5″). ESI-MS (m/z): 573[M^+], 574[M+1], 575[M+2], 571[M−2].^{13}C NMR; (100 MHz, DMSO, δ): 21.46, 23.75, 39.62, 43.59, 54.26, 112.21, 126.24, 126.76, 127.18, 127.38, 128.18, 128.56, 129.34, 130.32, 131.81, 132.73, 135.11, 137.24, 138.12, 138.81, 139.24, 142.02, 147.19, 151.14, 153.24. Elemental Analysis for: $C_{31}H_{29}ClN_4O_3S$. Found (Calculated) C: 64.97 (64.97%), H: 5.12 (5.10%), N: 9.77 (9.78%), S: 5.57 (5.59%).

*N-(Benzylamino-hydroxy-methyl)-4-[3-(2,5-dimethyl-phenyl)-5-(4-methoxy-phenyl)-4,5-dihydro-pyrazol-1-yl]-benzenesulfonamide (**2t**).* Off white crystals (mp 136–137 °C). Yield 65%. R_f = 0.41 (toluene/ethylacetate/formic acid, 5:4:1). IR ν_{max} (KBr, in cm^{-1}): 3225 and 3268 (NHCONH), 1697 (C=O), 1594 (C=N), 1395 and 1159 (SO_2N). ^1H NMR (300 MHz, DMSO, δ): 2.28 (3H, s, CH_3, C-5′), 2.72 (3H, s, CH_3, C-2′), 3.21 [1H, dd, J = 7.5 Hz, J = 16.9 Hz, H-4 *trans* (pyrazoline)], 3.70 (3H, s, OCH_3, C-4), 3.98 [1H, dd, J = 11.7 Hz, J = 17.8 Hz, H-4 *cis* (pyrazoline)], 4.12 (2H, d, J = 5.7 Hz, $CH_2C_6H_5$), 5.48 [1H, dd, J = 5.7 Hz, J = 12.6 Hz, H-5 (pyrazoline)], 6.44–6.46 (1H, t, CO<u>N</u>*H*CH_2), 6.80–7.05 (5H, m, H-2″, H-6″, H-3, H-5 + SO_2<u>N</u>*H*CO–), 7.06–7.36 (10H, m, H-2, H-6, H-3′, H-4′, H-6′, H-2‴, H-3‴, H-4‴, H-5‴, H-6‴), 7.60 (2H, d, J = 1.8 Hz, H-3″, H-5″). ESI-MS (m/z): 568 [M^+], 569 [M+1], 570 [M+2], 567 [M−1]. ^{13}C NMR; (100 MHz, DMSO, δ): 21.23, 23.76, 39.76, 43.71, 55.24, 58.32, 112.29, 112.73, 126.89, 126.91, 127.32, 128.44, 128.61, 128.74, 129.46, 129.62, 132.41, 135.25, 138.24, 138.37, 139.41, 141.41, 146.55, 147.24, 151.25, 153.29. Elemental Analysis for: $C_{32}H_{32}N_4O_4S$. Found (Calculated) C: 64.97 (64.97%), H: 5.09 (5.10%), N: 9.77 (9.78%), S: 5.61 (5.59%).

*N-(Benzylamino-hydroxy-methyl)-4-[5-(3,4-dimethoxy-phenyl)-3-(2,5-dimethyl-phenyl)-4,5- dihydro-pyrazol-1-yl]-benzenesulfonamide (**2u**).* Light yellow crystals (mp 181–183 °C). Yield 65%. R_f = 0.82 (toluene/ethylacetate/formic acid, 5:4:1). IR ν_{max} (KBr, in cm^{-1}): 3366 and 3271 (NHCONH), 1694 (C=O), 1594 (C=N), 1398 and 1156 (SO_2N). ^1H NMR (400 MHz, DMSO, δ): 2.30 (3H, s, CH_3, C-5′), 2.66 (3H, s, CH_3, C-2′), 3.20 [1H, dd, J = 4.8 Hz, J = 17.6 Hz, H-4 *trans* (pyrazoline)], 3.68 (3H, s, OCH_3, C-3), 3.70 (3H, s, OCH_3, C-4), 3.99 [1H, dd, J = 12.0 Hz, J = 17.6 Hz, H-4 *cis* (pyrazoline)], 4.33 (2H, d, J = 6.0 Hz, $CH_2C_6H_5$), 5.19 [1H, dd, J = 5.3 Hz, J = 11.6 Hz, H-5 (pyrazoline)], 6.72 (2H, d, J = 8.4 Hz, o, m coupling H-6), 6.81 (1H, t, CO<u>N</u>*H*CH_2—), 6.84–7.22 (10H, m, H-2, H-5, H-4′, H-6′, H-2″, H-6″, H-2‴, H-3‴, H-5‴, H-6‴), 7.35 (1H, d, J = 7.6 Hz, H-3′), 7.64 (2H, d, J = 8.8 Hz, H-3″, H-5″), 10.38 (1H, br s, SO_2<u>N</u>*H*CO–). ESI-MS (m/z): 598 [M^+], 599 [M+1], 600 [M+2], 597 [M−1]. ^{13}C NMR; (100 MHz, DMSO, δ): 21.24, 23.82, 43.13, 45.84, 55.90, 56.24, 61.75, 110.12, 112.31, 112.76, 117.93, 127.10, 127.25, 127.43, 128.06, 128.45, 128.67, 129.40, 132.80, 134.43, 137.22, 138.81, 139.70, 147.73, 148.05, 149.60, 151.84, 152.17. Elemental Analysis for: $C_{33}H_{34}N_4O_5S$. Found (Calculated) C: 64.17 (66.20%), H: 5.75 (5.72%), N: 9.37 (9.36%), S: 5.33 (5.36%).

*N-(Benzylamino-hydroxy-methyl)-4-[3-(2,5-dimethyl-phenyl-5-(3,4,5,trimethoxy-phenyl)-4,5-dihydro-pyrazol-1-yl]-benzenesulfonamide (**2v**).* Off white crystals (mp 140–142 °C). Yield 65%. R_f = 0.81 (toluene/ethylacetate/formic acid, 5:4:1). IR ν_{max} (KBr, in cm^{-1}): 3238 and 3192 (NHCONH), 1690 (C=O), 1594 (C=N), 1330 and 1157 (SO_2N). ^1H NMR (400 MHz, $CDCl_3$, δ) 2.37 (3H, s, CH_3, C-5'), 2.73 (3H, s, CH_3, C-2′), 3.81 (6H, s, 2 × OCH_3, C-3, C-5), 3.82 (3H, s, OCH_3, C-4), 3.31 [1H, dd, J = 6.4 Hz, J = 17.2 Hz, H-4 *trans* (pyrazoline)], 3.94 [1H, dd, J = 12.4 Hz, J = 17.6 Hz, H-4 *cis* (pyrazoline)], 4.33 (2H, s, $CH_2C_6H_5$), 5.15 [1H, dd, J = 6.4 Hz, J = 12.0 Hz, H-5 (pyrazoline)], 6.31 (2H, s, H-2, H-6), 6.81 (1H, t, CO<u>N</u>*H*CH_2—), 7.01–7.33 (10H, m, H-3, H-4, H-6, H-2″, H-6″, H-2‴, H-3‴, H-4‴, H-5‴, H-6‴), 7.45 (1H, br s, SO_2<u>N</u>*H*), 7.60 (2H, d, J = 8.8 Hz, H-3″, H-5″). ESI-MS (m/z): 528 [M^+], 529 [M+1], 527 [M−1]. ^{13}C NMR; (100 MHz, $CDCl_3$, δ): 21.23, 23.81, 39.41, 44.76, 56.22, 60.87, 102.12, 102.18, 112.58, 126.62, 127.28, 127.36, 127.51, 128.57, 128.63, 128.68, 128.74, 128.81, 132.86, 137.04, 137.70, 137.78, 138.21, 148.45, 151.27, 151.76, 154.12. Elemental Analysis for: $C_{34}H_{36}N_4O_6S$. Found (Calculated) C: 64.94 (64.95%), H: 5.75 (5.77%), N: 8.88 (8.91%), S: 5.13 (5.10%).

*N-(Benzylamino-hydroxy-methyl)-4-[5-(2-chloro-phenyl)3-(2,4-dimethyl-phenyl)-4,5-dihydro-pyrazol-1-yl]-benzenesulfonamide (**2w**).* Off white crystals (mp 170–173 °C). Yield 50%. R_f = 0.62 (toluene/ethylacetate/formic acid, 7.5:2:0.5). IR ν_{max} (KBr, in cm^{-1}): 3189 and 3197 (NHCONH), 1692 (C=O), 1598 (C=N), 1335 and 1156 (SO_2N). ^1H NMR (400 MHz, DMSO, δ) 2.17 (3H, s, CH_3, C-4′), 2.40 (3H, s, CH_3, C-2′), 3.02 [1H, dd, J = 5.2 Hz, J = 17.2 Hz, H-4 *trans* (pyrazoline)], 3.91[1H, dd, J = 12.4 Hz, J = 17.6 Hz, H-4 *cis* (pyrazoline)], 4.77 (2H, d, J = 7.0 Hz, $CH_2C_6H_5$), 5.50 [1H, dd, J = 6.5 Hz, J = 12.5 Hz, H-5 (pyrazoline)], 6.43 (1H, t, CO<u>N</u>*H*CH_2—), 6.76 (2H, d, H-2″, H-6″), 6.85–7.56 (14H, m, H-3″, H-5″, H-2, H-3, H-4, H-5, H-3′, H-5′, H-6′, H-2‴, H-3‴, H-4‴, H-5‴, H-6‴), 10.24 (1H, br s, SO_2<u>N</u>*H*CO–). ESI-MS (m/z): 573 [M^+], 574 [M+1], 575 [M+2], 572 [M−1]. ^{13}C NMR; (100 MHz, DMSO, δ): 21.25, 23.93, 43.13, 44.32, 54.19, 111.96, 127.11, 127.27, 127.67, 128.24, 128.51, 128.35, 128.61, 129.26, 129.50, 129.64, 130.01, 131.22, 135.21, 132.81, 137.33, 138.40, 139.73, 142.61, 147.23, 151.23, 154.21. Elemental Analysis for: $C_{31}H_{29}ClN_4O_3S$. Found (Calculated) C: 64.98 (64.97%), H: 5.13 (5.10%), N: 9.75 (9.78%), S: 5.60 (5.59%).

*N-(Benzylamino-hydroxy-methyl)-4-[5-(4-dimethylamino-phenyl)-3-(2,4-dimethyl-phenyl)-4,5-dihydro-pyrazol-1-yl]-benzenesulfonamide (**2x**).* White crystals (mp 180–182 °C). Yield 55%. R_f = 0.41 (toluene/ethylacetate/formic acid, 5:4:1). IR ν_{max} (KBr, in cm^{-1}): 3218 (NHCONH), 1699 (C=O), 1594 (C=N), 1376 and 1158 (SO_2N). ^1H NMR (400 MHz, DMSO, δ): 2.36 (3H, s, CH_3C-4′), 2.74 (3H, s, CH_3, C-2′), 2.95 [6H, s, $N(CH_3)_2$, C-4], 3.27 [1H, dd, J = 5.2 Hz, J = 17.2 Hz, H-4 *trans* (pyrazoline)], 3.91 [1H, dd, J = 12.0 Hz, J = 17.2 Hz, H-4 *cis* (pyrazoline)], 434–4.46 (2H, m, $CH_2C_6H_5$), 5.22 [1H, dd, J = 5.2 Hz, J = 11.6 Hz, H-5 (pyrazoline)], 6.84–7.57 [18H, m, all aromatic protons (H-3′, H-5′, H-6′, H-2, H-3, H-5, H-6, H-2″, H-3″, H-5‴, H-6″, H-2‴, H-3‴, H-4‴, H-5‴, H-6‴) + (SO_2<u>N</u>*H*CO–) + (CO<u>N</u>*H*CH_2—)]. ESI-MS (m/z): 581 [M^+], 582 [M+1], 583 [M+2], 580 [M−1]. ^{13}C NMR; (100 MHz, DMSO, δ): 21.23, 23.79, 43.28, 44.12, 45.78, 55.43, 61.23, 112.17, 114.78, 127.10, 127.25, 127.44, 127.47, 128.01, 128.44, 128.68, 129.40, 132.82, 134.03, 137.45, 138.70, 139.50, 147.50, 151.72, 152.20, 159.13. Elemental Analysis for: $C_{33}H_{35}N_5O_3S$. Found (Calculated) C: 68.12 (68.13%), H: 6.03 (6.06%), N: 12.01 (12.04%), S: 5.52 (5.51%).

*N-(Benzylamino-hydroxy-methyl)-4-[3-(2,4-dimethyl-phenyl)-5-(4-methoxy-phenyl)-4,5-dihydro-pyrazol-1-yl]-benzenesulfonamide (**2y**).* Light yellow crystals (mp 179–183 °C). Yield 65%. R_f = 0.66 (toluene/ethylacetate/formic acid, 5:4:1). IR ν_{max} (KBr, in cm^{-1}): 3209 and 3171 (NHCONH), 1699 (C=O), 1593 (C=N), 1386 and 1158 (SO_2N). ^1H NMR (300 MHz, $CDCl_3$, δ): 2.48 (3H, s, CH_3, C-4′), 2.66 (3H, s, CH_3, C-2′), 3.17 [1H, dd, J = 4.8 Hz, J = 17.2 Hz, H-4 *trans* (pyrazoline)], 3.69 (3H, s, OCH_3, C-4), 3.99 [1H, dd, J = 12.0 Hz, J = 17.2 Hz, H-4 *cis* (pyrazoline)], 4.12 (2H, s, $CH_2C_6H_5$), 5.47 [1H, dd, J = 4.4 Hz, J = 11.8 Hz, H-5 (pyrazoline)], 6.84–6.90 (3H, m, H-3, H-5, CO<u>N</u>*H*CH_2—), 7.01 (2H, d, J = 8.8 Hz, H-2″, H-6″), 7.06–7.09 (3H, m, H-3′, H-5, H-2‴), 7.16–7.22 (6H, m, H-2, H-6, H-3‴, H-4‴ H-5‴, H-6‴), 7.34 (1H, d, J = 8.0 Hz, H-6′), 7.63 (2H, d, J = 9.2 Hz, H-3″, H-5″), 10.38 (1H, br s, SO_2<u>N</u>*H*CO–). ESI-MS (m/z): 568 [M^+], 569 [M+1], 567 [M−1]. ^{13}C NMR; (100 MHz, $CDCl_3$, δ): 21.23, 23.79, 43.28, 44.12, 45.78, 55.43, 61.23, 112.17, 114.78, 127.10, 127.25, 127.44, 127.47, 128.01, 128.44, 128.68, 129.40, 132.82, 134.03, 137.45, 138.70, 139.50, 147.50, 151.72, 152.20, 159.13. Elemental Analysis for: $C_{32}H_{32}N_4O_4S$. Found (Calculated) C: 64.97 (64.97%), H: 5.14 (5.10%), N: 9.77 (9.78%), S: 5.60 (5.59%).

*N-(Benzylamino-hydroxy-methyl)-4-[5-(3,4-dimethoxy-phenyl)-3-(2,4-dimethyl-phenyl)-4,5-dihydro-pyrazol-1-yl]-benzenesulfonamide (**2z**).* Light yellow crystals (mp 170–172 °C). Yield 55%. R_f = 0.66 (toluene/ethylacetate/formic acid, 5:4:1). IR ν_{max} (KBr, in cm^{-1}): 3224 and 3170 (NHCONH), 1694 (C=O), 1628 (C=N), 1386 and 1158 (SO_2N). ^1H NMR (300 MHz, $CDCl_3$, δ): 0.36 (3H, s, CH_3, C-4′), 2.74 (3H, s, CH_3, C-2′), 3.27 [1H, dd, J = 5.7 Hz, J = 17.1 Hz, H-4 *trans* (pyrazoline)], 3.82 (3H, s, OCH_3, C-3), 3.85 (3H, s, OCH_3, C-4), 3.94 [1H, dd, J = 12.0 Hz, J = 16.8 Hz, H-4 *cis* (pyrazoline)], 4.41 (2H, s, $CH_2C_6H_5$), 5.20 [1H, dd, J = 5.7 Hz, J = 12.0 Hz, H-5 (pyrazoline)], 6.74 (1H, s, H-2), 6.58 (2H, d, J = 9.0 Hz, H-3″, H-5″), 6.82–7.31 [10H, m, H-3, H-5, H-6, H-3′, H-5′, H-6′, H-2″, H-6″ + (SO_2<u>N</u>*H*CO–) + (CO<u>N</u>*H*CH_2—)]. ESI-MS (m/z): 598 [M^+], 599 [M+1], 600 [M+2], 597 [M−1]. ^{13}C NMR; (100 MHz, $CDCl_3$, δ): 21.29, 23.87, 44.09, 44.64, 55.96, 56.00, 62.46, 108.36, 111.79, 112.54, 117.87, 126.59, 127.04, 127.50, 128.54, 128.63, 128.68, 128.74, 132.35, 133.70, 137.71, 137.79, 139.10, 148.32, 148.81, 149.88, 151.16, 152.91. Elemental Analysis for: $C_{33}H_{34}N_4O_5S$. Found (Calculated) C: 66.22 (66.20%), H: 5.75 (5.72%), N: 9.40 (9.36%), S: 5.33 (5.36%).

22. Grever, M. R.; Schepartz, S. A.; Chabner, B. A. *Semin. Oncol.* **1992**, *19*, 622.
23. Boyd, M. R.; Paull, K. D. *Drug Rev. Res.* **1995**, *34*, 91.
24. Monks, A.; Scudiero, D.; Skehan, P.; Shoemaker, R.; Paull, K.; Vistica, D.; Hose, C.; Jangley, J.; Cronisie, P.; Viagro-Wolff, A.; Gray-Goodrich, M.; Campell, H.; Boyd, M. *J. Natl Cancer Inst.* **1991**, *83*, 757.
25. Acton, E. M.; Narayanan, V. L.; Risbood, P. A.; Shoemaker, R. H.; Vistica, D. T.; Boyd, M. R. *J. Med. Chem.* **1994**, *37*, 2185.