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Design, ultrasound assisted synthesis and anticancer screening of 4-[5-(aryl)-4,5-dihydro-1-phenyl-pyrazol-3-yl]-3-(substitutedphenyl)sydnones

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Present research works focused on "Green synthesis of novel mesoionic compounds containing sydnone moiety and their anticancer screening". Compounds synthesized by ultrasound assisted. Synthesis of 4-[5-(aryl)-4,5-dihydro-1-phenyl-pyrazol-3-yl]-3-(substitutedphenyl)sydnones (**2a-x**) by cyclization of sydnonyl-substituted α,β-unsaturated ketones (**1a-x**) with phenyl hydrazine. All compounds were characterized by spectral study. Molecules **2g**, **2i**, **2j**, **2k**, **2l**, **2m** were evaluated against 60 human cancer cell lines for *in vitro* anticancer activity. Most prominent compounds are **2i** [SR (Leukemia), %GI = 61.87] and **2k** [CCRF-CEM (Leukemia), %GI = 41.57] are found to have greater anticancer activity than standard vincristine sulphate against some specific cell lines. Further structural modification of the active mesoionic sydnones might lead to development of potent anticancer, antimicrobial and antioxidant molecules.

Keywords: 1,2,3-Oxadiazol-5-olate, anticancer sydnones, 1-phenyl-pyrazole sydnones.

Introduction

Cancer is a leading cause of death in the world and tightening its grip with the increase in mortality rate day by day. The mortality rates due to cancer are likely to increase to a great extent by 2020. The word cancer refers to "abnormal and uncontrolled growth of cells" and antineoplastic means "against new growth". Most of the anti-neoplastic agents act by interfering with cellular synthesis or functioning of DNA/RNA or proteins[1].

Sydnones as anticancer agents:

Mesoionic sydnone derivatives have been described for a variety of antitumor activities as shown in Table 1[2–12]. It has been observed that the ionic resonance structure of sydnone ring enhances interactions with cancer cells. Based on literature survey and reported antitumor molecules we have designed and synthesized molecule **2a-x.**

Materials and methods:

All chemicals used from Sigma-Aldrich, Mumbai, India. Melting points were recorded on Systolic apparatus. TLC was carried out to monitor the completion of reaction by using E. Merck precoated 60 F254 plates. IR spectra were recorded by using KBr pellets on Jasco FTIR 1460. NMR spectra were recorded on a BRUKER AVANCE II 400 (are expressed in δ, ppm). MS were performed on WATERS, Q-TOF instrument. The ultra-sonication study was performed at frequency, 40 KHz.

*Synthesis and characterization of 4-[5-(aryl)-4,5-dihydro-1-phenyl-pyrazol-3-yl]-3-(substitutedphenyl)sydnones **2a-x**:*

*4-[5-(4-Methoxyphenyl)-4,5-dihydro-1-phenyl-pyrazol-3-yl]-3-(4-fluorophenyl)sydnone **(2b)**:* To an ice cooled solution of phenyl hydrazine hydrate (2.00 mM) in glacial acetic acid (3 ml), 4-[1-oxo-3-(4-methoxyphenyl)-2-propenyl]-3-(4-fluorophenyl)sydnone (**1b**, 0.50 mM) (synthesized as per reported procedure by Bhosale *et al.*[13]) was added under ultra-sonication and allowed to react at RT for 2 h. The reaction mixture was poured in to crushed ice. The precipitate solid was collected by filtration and washed with cold water and cold ethanol, to get yellow orange colour crystals of **2b**

Table 1. Reported sydnones and their derivatives having antitumor activity

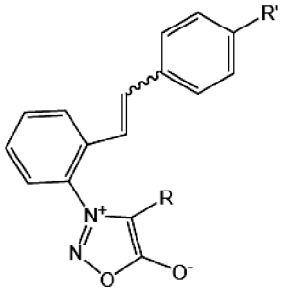
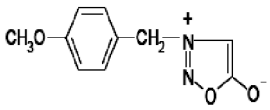
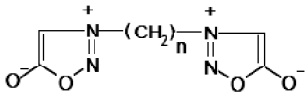
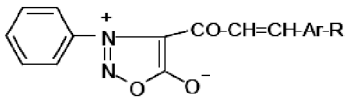
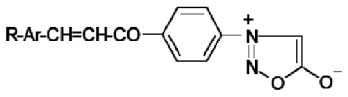
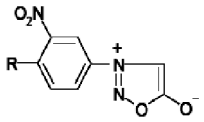
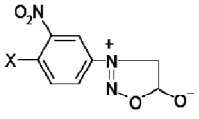
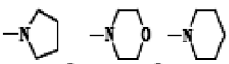
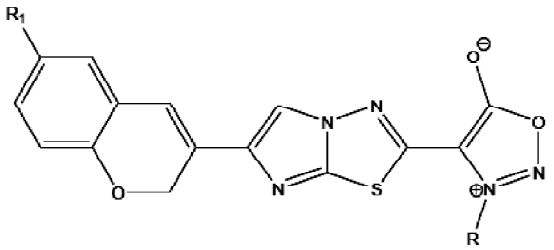
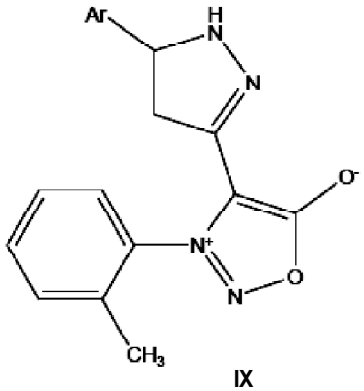
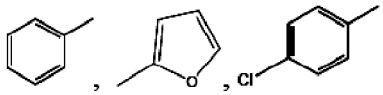
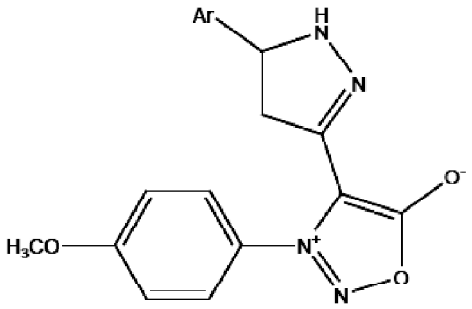
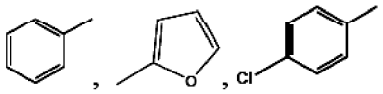
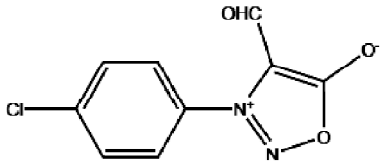
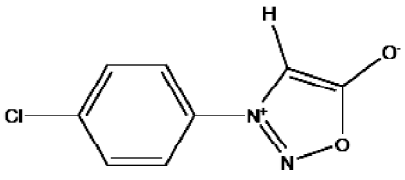
Biologically active sydnones	Substituents	Biological activity	Ref.
 **Ia, Ib**	**Ia**; R=CH_3, R′=CH_3 **Ib**; R=Ph, R′=Cl *cis*-4-Methyl-3-[2-[2-(4-methylphenyl)-ethenyl]phenyl]sydnone (**Ia)** *cis*-4-Phenyl-3-[2-[2-(4-chlorophenyl)-ethenyl]-phenyl]sydnone (**Ib)**	Anticancer	2
 **II**	3-(*p*-Methoxybenzyl)sydnone	Anticancer against carcinoma-755	3
 **III**	Polymethylene-bis-sydnones	Potent antitumor	4
 **IV**	**IVa**; Ar=Ph, R=4-CH_3 **IVb**; Ar=Ph, R=3-OCH_3, 4-OH **IVc**; Ar=Ph, R=4-CF_3	Highly selective against SNB-75 tumour cell line of CNS	5
 **V**	**Va**; Ar=Ph, R=H **Vb**; Ar=Ph, R=4CH_3 **Vc**; Ar=Ph, R=4-OCH_3 **Vd**; Ar=Ph, R=2,4-$(OCH_3)_2$ **Ve**; Ar=Ph, R=4-$NHCOCH_3$ **Vf**; Ar=Ph, R=4-Cl **Vg**; Ar=Ph, R=3-Cl **Vh**; Ar=Ph, R=2-Cl **Vi**; R=F	Anticancer	5, 6
 **VI**	4-Substituted-3-nitrophenyl sydnone	Anticancer against MCF7 (Breast), NCI-H460 (Lung) and SF-268 (CNS) cell lines	7, 8
 **VII**	**VIIa, VIIb, VIIc, VIId**; X= Cl,  3-[4-X-3-Nitrophenyl]-1,2,3-oxadiazolium-5-olates	Anticancer against Sarcoma 180, *Ehrlich carcinoma*, B10MCII (*Fibrous histiocytoma*) and L1210 leukemia ascitic tumours	7, 8

Table-1 (contd.)

 4-[6′-(Caumarin-3″-yl)-imidazo-[2,1-*b*][1,3,4]thiadiazol-2′-yl]-3-arylsydnone **VIII**	R_1=H, Br, Cl, H, Br, Cl, H, Br, Cl, H, Br, Cl R=C_6H_5, C_6H_5, C_6H_5, *p*-CH_3-C_6H_4, *p*-CH_3-C_6H_4, *p*-CH_3-C_6H_4, *p*-OCH_3-C_6H_4, *p*-OCH_3-C_6H_4, *p*-OCH_3-C_6H_4, *p*-Cl-C_6H_4, *p*-Cl-C_6H_4, *p*-Cl-C_6H_4	Anticancer	9
 **IX**	Ar= 	Antitumor against human breast cancer cell line MDA-MB-231 and human prostate cancer cell line PC3	10
 **X**	Ar= 	Antitumor against non-small cell lung cancer cell line (HOP-92), melanoma (M-14) and human prostate cancer cell line (PC3)	11
 3-(4-Chlorophenyl)-4-sydnone carboxaldehyde, **XI**	 4-Chlorophenyl sydnone **XII**	Antitumor against non-small cell lung cancer cell line (NCI-H23), CNS cancer cell line (SNB-75)	12

(100 mg R_f = 0.498, ethyl acetate:benzene, 2:8). In similar way remaining compounds (**2a-x**) were synthesized from respective (**1a-x**). Characterizations for compounds **2a-x** were illustrated in Table 2.

Table 2. Characterization for compounds **2a-x**

Compounds with IUPAC name	IR (cm^{-1})	^1H NMR (δ)	^{13}C NMR (δ)	Physicochemical data
4-[5-(4-Methoxyphenyl)-4,5-dihydro-1-phenyl-pyrazol-3-yl]-3-(4-chlorophenyl)sydnone **2a**	1751.43 (C=O), 3217.32 (Ar, CH)	3.19 (d, 1H), 3.69 (s, 3H), 4.64 (d, 1H), 6.84 (d, 2H), 7.65 (d, 2H), 7.27–7.34 (m, 5H), 7.70 (d, 2H), 7.97 (d, 1H), 8.12 (d, 2H)	137.84, 160.42, 127.2, 127.2, 126.78, 126.76, 141.39, 121.83, 121.84, 143.25, 153.83, 43.84, 124.72, 113.83, 113.83, 140.39, 129.15, 129.15, 59.35, 171.3, 136.19, 55.46, 124.57, 124.57	$C_{24}H_{19}ClN_4O_3$, Mol. wt. 446.886, *m/z* 446.115. C, 64.50; H, 4.29; N, 12.54. Yield 53%, R_f = 0.635, m.p. 129–131°C
4-[5-(4-Methoxyphenyl)-4,5-dihydro-1-phenyl-pyrazol-3-yl]-3-(4-fluorophenyl)sydnone **2b**	1762.78 (C=O), 3223.32 (Ar, CH)	3.73 (3H, OCH_3), 7.0 (C_6H_4F, 2H), 7.2 (C_6H_4F, 2H), 6.43–7.04 (C_6H_5), 6.72 (C_6H_4, 2H), 7.01 (C_6H_4, 2H), 3.9 (pyrazole, 5CH, 1H), 1.9 (pyrazole, $4CH_2$, 2H)	116–162 (C_6H_4F), 113.9–160 (C_6H_4), 112.3–143.5 (C_6H_5), 55.14 (OCH_3), 38 (pyrazole, 4C), 53.1 (pyrazole, 5C), 155.6 (pyrazole, 3C), 105.7 (sydnone, 5C), 121.67 (sydnone, 4C)	$C_{24}H_{19}FN_4O_3$, Mol. wt. 430.144, *m/z* 430.144. C, 66.97; H, 3.77; N, 13.02. Yield 52%, R_f = 0.49 m.p. 136–138°C
4-[5-(4-Methoxyphenyl)-4,5-dihydro-1-phenyl-pyrazol-3-yl]-3-(2,4-dichlorophenyl) sydnone **2c**	1762.11 (C=O), 3241.02 (Ar, CH)	7.1–7.3 ($C_6H_3Cl_2$, 3H), 7.04 (C_6H_5, 2H), 7.01 ($C_6H_4OCH_3$, 2H), 6.72 ($C_6H_4OCH_3$, 2H), 6.58 (C_6H_5, 1H), 6.43 (C_6H_5, 2H), 3.9 (pyrazole, 5CH, 1H), 3.73 (OCH_3, 3H), 1.9 (pyrazole, $4CH_2$, 2H)	40 (pyrazole, 4C), 53.4 (pyrazole, 5C), 56.12 (OCH_3), 105.7 (sydnone, 5C), 112.3–143.5 (C_6H_5), 121.67 (sydnone, 4C), 127–135 ($C_6H_3Cl_2$), 155.6 (pyrazole, 3C), 113.9–160 ($C_6H_4OCH_3$)	$C_{24}H_{18}Cl_2N_4O_3$, Mol. wt. 481.331, *m/z* 480.076. C, 59.89; H, 3.77; N, 11.64. Yield 62%, R_f = 0.783, m.p. 141–143°C
4-[5-(4-Methoxyphenyl)-4,5-dihydro-1-phenyl-pyrazol-3-yl]-3-(4-bromophenyl)sydnone **2d**	1765.87 (C=O), 3229.65(Ar, CH)	7.0 (C_6H_4Br, 2H), 7.2 (C_6H_4Br, 2H), 7.06–7.09 (C_6H_5), 7.06 (C_6H_4, 2H), 7.09 (C_6H_4, 2H), 3.36 (3H, -OCH_3), 2.5 (pyrazole, $4CH_2$, 2H)	116–162 (C_6H_4Br), 113.9–160 (C_6H_4), 55.14 (OCH_3), 40.08 (pyrazole, 4C), 49.1 (pyrazole, 5C), 159.6 (pyrazole, 3C), 95.13 (sydnone, 5C), 123 (sydnone, 4C)	$C_{24}H_{19}BrN_4O_3$, Mol. wt. 491.337, *m/z* 490.064. C, 58.67; H, 3.90; N, 11.40. Yield 60%, R_f = 0.63, m.p. 169–171°C
4-[5-(Furyl)-4,5-dihydro-1-phenyl-pyrazol-3-yl]-3-(4-chlorophenyl)sydnone **2e**	1750.43 (C=O), 3221.25 (Ar, CH)	3.22 (d, 1H), 3.50 (s, 3H), 7.04 (d, 2H), 7.31–7.39 (m, 5H), 7.73 (d, 2H), 7.52 (d, 2H), 7.97 (d, 1H), 8.11 (d, 2H)	43.83, 56.8, 109.6, 110.52, 121.83, 121.83, 124.72, 124.57, 124.57, 126.77, 126.77, 129.15, 129.15, 136.19, 140.39, 141.39, 142.42, 143.25, 149.39, 153.83, 171.3	$C_{21}H_{15}ClN_4O_3$, Mol. wt. 406.822, *m/z* 406.083. C, 62.00; H, 3.72; N, 13.77. Yield 71%, R_f = 0.57, m.p. 148–151°C
4-[5-(Furyl)-4,5-dihydro-1-phenyl-pyrazol-3-yl]-3-(4-fluorophenyl)sydnone **2f**	1765.21 (C=O), 3225.42 (Ar, CH)	7.0 (C_6H_4F, 2H), 7.2 (C_6H_4F, 2H), 6.43 (C_6H_5, 2H), 7.04 (C_6H_5, 2H), 7.58 (C_6H_5 1H), 6.06 (furyl, 3CH, 1H), 6.24 (furyl, 4CH, 1H), 7.28 (furyl, 5CH, 1H), 4.1 (pyrazole, 5CH, 1H), 1.9 (pyrazole, $4CH_2$, 2H)	116–162 (C_6H_4F), 112.3–143.5 (C_6H_5), 104.9–157.6 (furyl, C_4H_3O) 105.7 (sydnone, 5C), 121.67 (sydnone, 4C), 38 (pyrazole, 4C), 53.1 (pyrazole, 5C), 155.6 (pyrazole, 3C)	$C_{21}H_{15}FN_4O_3$, Mol. wt. 390.36, *m/z* 390.113. C, 64.61; H, 3.87; N, 14.35. Yield 59%, R_f = 0.65, m.p. 135–137°C
4-[5-(Furyl)-4,5-dihydro-1-phenyl-pyrazol-3-yl]-3-(2,4-dichlorophenyl)sydnone **2g**	1759.44 (C=O), 3229.17 (Ar, CH)	7.1–7.3 ($C_6H_3Cl_2$, 3H), 7.28 (furyl, 5CH, 1H), 7.04 (C_6H_5, 2H), 6.58 (C_6H_5, 1H), 6.43 (C_6H_5, 2H), 6.24 (furyl, 4CH, 1H), 6.06 (furyl, 3CH, 1H) 4.1 (pyrazole, 5CH, 1H), 1.9 (pyrazole, $4CH_2$, 2H)	38 (pyrazole, $4CH_2$), 53.1 (pyrazole, 5C), 105.7 (sydnone, 5C), 112.3–143.5 (C_6H_5), 121.67 (sydnone, 4C), 127–135 ($C_6H_3Cl_2$), 155.6 (pyrazole, 3C), 104.9 (furyl, 3C), 110 (furyl, 4C), 140.6 (furyl, 5C), 157.6 (furyl, 2C)	$C_{21}H_{14}Cl_2N_4O_3$, Mol. wt. 441.267, *m/z* 440.044. C, 57.16; H, 3.20; N, 12.70. Yield 62%, R_f = 0.48, m.p. 159–161°C
4-[5-(Furyl)-4,5-dihydro-1-phenyl-pyrazol-3-yl]-3-(4-bromophenyl)sydnone **2h**	1762.12 (C=O), 3224.78 (Ar, CH)	7.0 (C_6H_4Br, 2H), 7.2 (C_6H_4Br, 2H), 6.43 (C_6H_5, 2H), 7.04 (C_6H_5, 2H), 7.58 (C_6H_5, 1H), 6.06 (furyl, 3CH, 1H), 6.24 (furyl, 4CH, 1H), 7.28 (furyl, 5CH, 1H), 4.1 (pyrazole, 5CH, 1H), 1.9 (pyrazole, $4CH_2$, 2H)	116–162 (C_6H_4Br), 112.3–143.5 (C_6H_5), 104.9–157.6 (furyl, C_4H_3O), 105.7 (sydnone, 5C), 121.67 (sydnone 4C), 38 (pyrazole, 4C), 53.1 (pyrazole, 5C), 155.6 (pyrazole, 3C)	$C_{21}H_{15}BrN_4O_3$, Mol. wt. 451.273, *m/z* 450. C, 55.89; H, 3.35; N, 12.42. Yield 66%, R_f = 0.55, m.p. 113–116°C

Table-2 (contd.)

4-[5-(4-Nitrophenyl)-4,5-dihydro-1-phenyl-pyrazol-3-yl]-3-(4-chlorophenyl) sydnone **2i**	1750.47 (C=O), 3121.59 (Ar, CH)	3.34 (d, 1H), 3.42 (d, 1H), 4.70 (t, 1H), 7.10–6.39 (m, 5H), 7.22–7.43 (m, 2H), 8.10 (d, 2H), 8.11 (d, 1H)	39.87, 40.08, 95, 111, 111, 114, 114, 118, 123, 126, 128, 129, 130, 136, 145, 159, 168.40	$C_{23}H_{16}ClN_5O_4$, Mol. wt. 461.86, *m/z* 462. C, 59.81; H, 3.49; N, 15.16. Yield 68%, R_f = 0.78, m.p. 143–144°C
4-[5-(4-Nitrophenyl)-4,5-dihydro-1-phenyl-pyrazol-3-yl]-3-(4-fluorophenyl) sydnone **2j**	1752.65 (C=O), 3113.54 (Ar, CH)	8.14 ($C_6H_4NO_2$, 2H), 7.38 ($C_6H_4NO_2$, 2H), 7.2 (C_6H_4F, 2H), 7.3 (C_6H_4F, 2H), 8.14 ($C_6H_4NO_2$, 2H), 7.38 ($C_6H_4NO_2$, 2H), 6.43 (C_6H_5, 2H), 7.04 (C_6H_5, 2H), 7.58 (C_6H_5, 1H), 3.9 (pyrazole, 5CH, 1H), 1.9 (pyrazole, $4CH_2$, 2H)	116–162 (C_6H_4F), 112.3–143.5 (C_6H_5), 123.4–148.5 (C_6H_4), 43 (pyrazole, 4C), 49.1 (pyrazole, 5C), 155.6 (pyrazole, 3C), 105.7 (sydnone, 5C), 121.67 (sydnone, 4C)	$C_{23}H_{16}FN_5O_4$, Mol. wt. 445.40, *m/z* 445.119. C, 62.02; H, 3.62; N, 15.72. Yield 68%, R_f = 0.69, m.p. 156–158°C
4-[5-(4-Nitrophenyl)-4,5-dihydro-1-phenyl-pyrazol-3-yl]-3-(2,4-dichlorophenyl) sydnone **2k**	1756.43 (C=O), 3243.21 (Ar, CH)	8.14 ($C_6H_4NO_2$, 2H), 7.38 ($C_6H_4NO_2$, 2H), 7.1–7.3 ($C_6H_3Cl_2$, 3H), 7.04 (C_6H_5, 2H), 7.01 ($C_6H_4OCH_3$, 2H), 6.72 ($C_6H_4NO_2$, 2H), 6.58 (C_6H_5, 1H), 6.43 (C_6H_5, 2H), 3.9 (pyrazole, 5CH, 1H), 1.9 (pyrazole, $4CH_2$, 2H)	40 (pyrazole, $4CH_2$), 53.4 (pyrazole, 5C), 105.7 (sydnone, 5C), 112.3–143.5 (C_6H_5), 121.67 (sydnone, 4C), 127–135 ($C_6H_3Cl_2$), 155.6 (pyrazole, 3C), 123.4–148.5 ($C_6H_4NO_2$)	$C_{23}H_{15}Cl_2N_5O_4$, Mol. wt. 496.302, *m/z* 495.050. C, 55.66; H, 3.05; N, 14.11. Yield 74%, R_f = 0.81, m.p. 123–125°C
4-[5-(4-Nitrophenyl)-4,5-dihydro-1-phenyl-pyrazol-3-yl]-3-(4-bromophenyl) sydnone **2l**	1750.08, 3124.47	8.14 ($C_6H_4NO_2$, 2H), 7.38 ($C_6H_4NO_2$, 2H), 7.2 (C_6H_4Br, 2H), 7.3 (C_6H_4Br, 2H), 8.14 ($C_6H_4NO_2$, 2H), 7.38 ($C_6H_4NO_2$, 2H), 6.43 (C_6H_5, 2H), 7.04 (C_6H_5, 2H), 7.58 (C_6H_5, 1H), 3.9 (pyrazole, 5CH, 1H), 1.9 (pyrazole, $4CH_2$, 2H)	116–162 (C_6H_4Br), 123.4–148.5 (C_6H_4), 40.08 (pyrazole, 4C), 49.1 (pyrazole, 5C), 155.6 (pyrazole, 3C), 99 (sydnone, 5C), 123, (sydnone, 4C)	$C_{23}H_{16}BrN_5O_4$, Mol. wt. 506.308, *m/z* 505.039. C, 54.56; H, 3.19; N, 3.83. Yield 54%, R_f = 0.70, m.p. 143–145°C
4-[5-(Phenyl)-4,5-dihydro-1-phenyl-pyrazol-3-yl]-3-(4-methylphenyl)sydnone **2m**	1753.44 (C=O), 3147.22 (Ar, CH)	1.98–1.90 (m, 1H), 2.26–2.29 (m, 1H), 4.12 (1H). δ 2.36 (t, 3H), 2.43 (d, 1H), 3.21 (d, 1H), 4.58 (t, 1H), 7.07–6.40 (5H), 7.23–7.10 (5H), 7.41 (d, 2H), 7.63 (d, 2H), 7.81 (d, 1H)	20.74, 40.06, 94.52, 121.13, 121.13, 121.13, 121.13, 126.36, 128, 129, 130, 131, 132, 142.65, 142.65, 168.50	$C_{24}H_{20}N_4O_2$, Mol. wt. 396.44, *m/z* 397. C, 72.71; H, 5.08; N, 14.12. Yield 48%, R_f = 0.43, m.p. 143–145°C
4-[5-(Phenyl)-4,5-dihydro-1-phenyl-pyrazol-3-yl]-3-(4-methoxylphenyl)sydnone **2n**	1757.18 (C=O), 3174.57 (Ar, CH)	3.36 (3H, OCH_3), 2.50 (d, 1H), 3.21 (d, 1H), 4.63 7.06–6.40 (5H), 7.09–7.28 (5H), 7.41 (d, 2H), 7.64 (d, 2H), 7.87 (d, 1H)	40.08, 55.14, 111.74, 114.13, 118.28, 123.44, 126.99, 128.41, 129.03, 130.19, 136.52, 145.52, 159.25, 168.40	$C_{24}H_{20}N_4O_3$, Mol. wt. 412.44, *m/z* 412.9. C, 69.89; H, 4.89; N, 13.58. Yield 78%, R_f = 0.62, m.p. 149–151°C
4-[5-(Phenyl)-4,5-dihydro-1-phenyl-pyrazol-3-yl]-3-(2-methylphenyl)sydnone **2o**	1753.25 (C=O), 3109.22 (Ar, CH)	1.98–1.90 (m, 1H), 2.26–2.29 (m, 1H), 4.12 (1H). δ 2.36 (t, 3H), 2.43 (d, 1H), 3.21 (d, 1H), 4.61 (t, 1H), 7.07–6.45 (5H), 7.23–7.10 (5H), 7.41 (d, 2H), 7.63 (d, 2H), 7.81 (d, 1H)	20.05, 40.06, 94.55, 121.16, 130.46, 132.18, 142.66, 168.50	$C_{24}H_{20}N_4O_2$, Mol. wt. 396.441, *m/z* 398.2. C, 72.58; H, 5.02; N, 14.42. Yield 56%, R_f = 0.38, m.p. 135–137°C
4-[5-(Phenyl)-4,5-dihydro-1-phenyl-pyrazol-3-yl]-3-(phenyl)sydnone *2***p**	1749.25 (C=O), 3207.22 (Ar, CH)	7.19 (C_6H_5, 5H), 7.3 (N-C_6H_5, 5H), 6.43 (C_6H_5, 2H), 7.04 (C_6H_5, 2H), 7.58 (C_6H_5, 1H), 3.9 (pyrazole, 5CH, 1H) 1.9 (pyrazole, $4CH_2$, 2H)	129 (N-C_6H_5), 127.3–140.9 (C_6H_5), 112.3–143.5 (C_6H_5), 105.7 (sydnone, 5C), 121.67 (sydnone, 4C), 43 (pyrazole, 4C), 49.1 (pyrazole, 5C), 155.6 (pyrazole, 3C)	$C_{23}H_{18}N_4O_2$, Mol. wt. 382.415, *m/z* 382.143. C, 72.24; H, 4.74; N, 14.65. Yield 62%, R_f = 0.548, m.p. 127–129°C
4-[5-(Furyl)-4,5-dihydro-1-phenyl-pyrazol-3-yl]-3-(4-methylphenyl)sydnone **2q**	1755.85 (C=O), 3156.22 (Ar, CH)	2.17 (s, 3H), 2.29 (d, 1H), 3.18 (d, 1H), 4.94 (d, 1H), 6.91–6.97 (m, 2H), 7.19–7.32 (m, 5H), 7.37–7.44 (m, 3H), 7.59 (d, 2H), 7.97 (d, 1H)	20.82, 38.81, 40.06, 94.52, 121.13, 121.13, 121.13, 121.13, 126, 128, 129, 130, 131, 132, 142.65, 142.65, 168.50	$C_{22}H_{18}N_4O_3$, Mol. wt. 386.403, *m/z* 386.138. C, 68.38; H, 4.70; N, 14.50. Yield 68%, R_f = 0.66, m.p. 129–131°C

Table-2 (contd.)

4-[5-(Furyl)-4,5-dihydro-1-phenyl-pyrazol-3-yl]-3-(4-methoxylphenyl)sydnone **2r**	1753.87 (C=O), 3145.27 (Ar, CH)	2.02 (s, 3H), 2.42 (d, 1H), 3.17 (d, 1H), 4.76 (d, 1H), 6.91–6.97 (m, 2H), 7.19–7.32 (m, 5H), 7.37–7.44 (m, 3H), 7.59 (d, 2H), 7.97 (d, 1H)	40.08, 55.14, 95.13, 111, 114, 118, 123, 126, 128, 129, 130, 136, 145, 159, 168	$C_{22}H_{18}N_4O_4$, Mol. wt. 402.403, *m/z* 402.131. C, 65.66; H, 4.50; N, 13.90. Yield 60%, R_f = 0.475, m.p. 141–143°C
4-[5-(Furyl)-4,5-dihydro-1-phenyl-pyrazol-3-yl]-3-(2-methylphenyl)sydnone **2s**	1756.12 (C=O), 3155.02 (Ar, CH)	2.10 (s, 3H), 2.29 (d, 1H), 3.14 (d, 1H), 3.98 (d, 1H), 6.75–6.95 (m, 2H), 7.00–7.11 (m, 5H), 7.13–7.37 (m, 3H), 7.49 (d, 2H), 7.58 (d, 1H)	20.76, 40.07, 94.57, 121.18, 128.97, 129.3, 130.46, 132.19, 142.66, 168.50	$C_{22}H_{18}N_4O_3$, Mol. wt. 386.403, *m/z* 386.138. C, 68.38; H, 4.70; N, 14.50. Yield 74%, R_f = 0.78, m.p. 142–146°C
4-[5-(Furyl)-4,5-dihydro-1-phenyl-pyrazol-3-yl]-3-(phenyl)sydnone *2***t**	1753.25 (C=O), 3233.31 (Ar, CH)	7.3 (C_6H_5, 5H), 6.19 (furyl, 3CH, 1H), 6.25 (furyl, 4CH, 1H), 7.30 (furyl, 5CH, 1H), 6.43 (C_6H_5, 2H), 7.04 (C_6H_5, 2H), 7.58 (C_6H_5, 1H), 4.1 (pyrazole, 5CH, 1H), 1.9 (pyrazole, 4CH_2, 2H)	129 (C_6H_5), 104.9–157.6 (furyl, C_4H_3O), 112.3–143.5 (C_6H_5), 105.7 (sydnone, 5C), 121.67 (sydnone, 4C), 38 (pyrazole, 4C), 53.1 (pyrazole, 5C), 155.6 (pyrazole, 3C)	$C_{21}H_{16}N_4O_3$, Mol. wt. 372.37, *m/z* 372.12. C, 67.73; H, 4.33; N, 15.05. Yield 57%, R_f = 0.528, m.p. 137–139°C
4-[5-(4-Chlorophenyl)-4,5-dihydro-1-phenyl-pyrazol-3-yl]-3-(4-methylphenyl) sydnone **2u**	1752.15 (C=O), 3198.22 (Ar, CH)	2.17 (s, 3H), 2.58 (d, 1H), 3.24 (d, 1H), 4.70 (t, 1H), 7.10–6.39 (m, 5H), 7.22–7.43 (m, 2H), 7.83 (d, 2H), 7.99 (d, 1H)	20.75, 40.06, 94.53, 121.14, 121.14, 121.14, 121.14, 121.14, 130.45, 130.45, 130.45, 130.45, 132.17, 132.17, 132.17, 132.17, 142.65, 142.65, 146, 168.50	$C_{24}H_{19}ClN_4O_2$, Mol. wt. 430.886, *m/z* 430.120. C, 66.90; H, 4.44; N, 13. Yield 68%, R_f = 0.415, m.p. 131–134°C
4-[5-(4-Chlorophenyl)-4,5-dihydro-1-phenyl-pyrazol-3-yl]-3-(4-methoxylphenyl) sydnone **2v**	1750.80 (C=O), 3114.47 (CH, Ar-H)	3.36 (s, 3H, OCH_3), 7.06–7.08 (m, 5H), 7.09–7.242 (4H), 7.246–7.41 (m, 2H), 7.66 (d, 2H), 7.87 (d, 1H)	40.08, 55.14, 95.13, 111.74, 114.13, 118.28, 123.44, 126.99, 128.45, 129.03, 130.19, 136.52, 145.52, 159.25, 168.40	$C_{24}H_{19}ClN_4O_3$, Mol. wt. 446.886, *m/z* 446. C, 64.92; H, 4.34; N, 12.33. Yield 72%, R_f = 0.568, m.p. 125–127°C
4-[5-(4-Chlorophenyl)-4,5-dihydro-1-phenyl-pyrazol-3-yl]-3-(2-methylphenyl) sydnone **2w**	1753.43 (C=O), 3178.22 (Ar, CH)	2.51 (s, 3 H), 2.50 (d, 1H), 4.76 (d, 1H), 7.21–7.47 (m, 5H), 7.48–7.80 (m, 2H), 7.98 (d, 2H), 8.01 (d, 1H)	20.76, 40.07, 94.57, 121.18, 128.97, 129.3, 130.46, 132.19, 142.66, 168.50	$C_{24}H_{19}ClN_4O_2$, Mol. wt. 430.886, *m/z* 430.120. C, 66.90; H, 4.44; N, 13. Yield 53%, R_f = 0.82, m.p. 141–143°C
4-[5-(4-Nitrophenyl)-4,5-dihydro-1-phenyl-pyrazol-3-yl]-3-(phenyl)sydnone **2x**	3105.83 (Ar, CH), 1749.41 (C=O)	7.3 (N-C_6H_5, 5H), 7.13 (C_6H_4, 2H), 7.20 (C_6H_4, 2H), 6.43 (C_6H_5, 2H), 7.04 (C_6H_5, 2H), 6.58 (C_6H_5, H), 7.0 (pyrazole, N-H, 1H), 3.9 (pyrazole, 5CH, 1H), 1.9 (pyrazole, 4CH_2, 2H)	129 (N-C_6H_5), 128.7–139 (C_6H_4), 112.3–143.5 (C_6H_4), 43 (pyrazole, 4C), 49.1 (pyrazole, 5C), 155.6 (pyrazole, 3C), 105.7 (sydnone, 5C), 121.67 (sydnone, 4C)	$C_{23}H_{17}N_5O_4$, Mol. wt. 427.41, *m/z* 426.89. C, 64.62; H, 4.01; N, 16.39. Yield 62%, R_f = 0.405, m.p. 137–139°C

Anti-cancer screening:

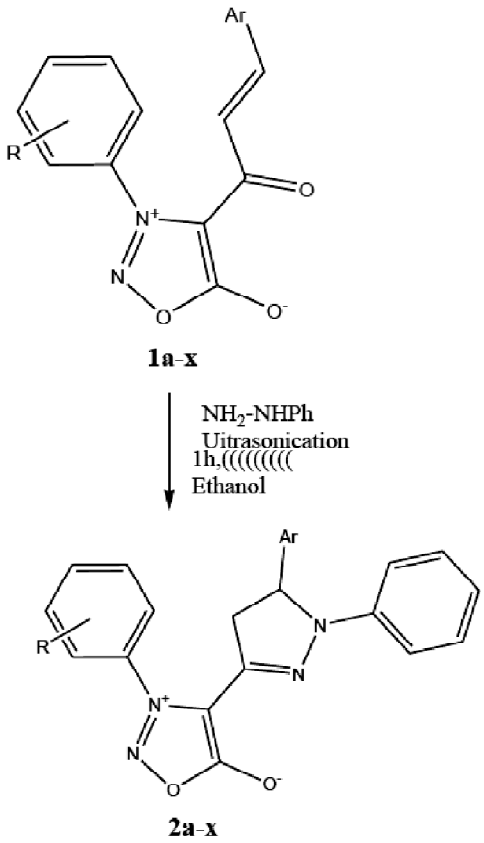
'Brine shrimp lethality bioassay' (Preliminary cytotoxicity study).

Screened against a panel of 60 different human tumor cell lines (*in vitro* study).

Preliminary anticancer activity by Brine shrimp lethality bioassay: (Meyer *et al.*[14] and Zhao *et al.*[15]) performed using Meyer's method. The lethal concentrations resulting in 50% mortality of the brine shrimp (LC_{50}) was determined from the 24 h counts. The dose-response data were transformed into a straight line through trade line fit linear regression analysis. It reported in Table 3.

In vitro anticancer evaluation against 60 human tumor cell lines[16–20]:

Evaluation of compounds **2g**, **2i**, **2j**, **2k**, **2l** and **2m** for anticancer activity was done at NCI, Bethesda, USA as per standard procedure. The screening was performed against various nine neoplastic cancers cell lines (leukemia, non-small cell lung, colon, CNS, melanoma, ovarian, renal, prostate and breast cancers). The results recorded as a mean graph for % growth inhibition of treated cells and represented as one dose DTP curve.



Comp.	R	Ar	Comp.	R	Ar
1a, 2a,	4-Cl	H_3CO	**1m, 2m**	4-CH_3	
1b, 2b	4-F	H_3CO	**1n, 2n**	4-OCH_3	
1c, 2c	2,4-Cl_2	H_3CO	**1o, 2o**	2-CH_3	
1d, 2d	4-Br	H_3CO	**1p, 2p**	H	
1e, 2e	4-Cl		**1q, 2q**	4-CH_3	
1f, 2f	4-F		**1r, 2r**	4-OCH_3	
1g, 2g	2,4-Cl_2		**1s, 2s**	2-CH_3	
1h, 2h	4-Br		**1t, 2t**	H	
1i, 2i	4-Cl	O_2N	**1u, 2u**	4-CH_3	Cl
1j, 2j	4-F	O_2N	**1v, 2v**	4-OCH_3	Cl
1k, 2k	2,4-Cl_2	O_2N	**1w, 2w**	2-CH_3	Cl
1l, 2l	4-Br	O_2N	**1x, 2x**	H	Cl

Scheme 1. Synthesis of 4-[5-(aryl)-4,5-dihydro-1-phenyl-pyrazol-3-yl]-3-(substituted phenyl)sydnones **2a-x** from 4-[1-oxo-3-(aryl)-2-propenyl]-3-(substitutedphenyl)sydnone **1a-x**.

Table 3. Brine shrimp lethality assay of compounds **2a-x**

Compd.	LC_{50} (μg/ml)	Comp.	LC_{50} (μg/ml)
2a	15.33	**2m**	10.64
2b	12.44	**2n**	11.21
2c	14.22	**2o**	17.67
2d	13.65	**2p**	10.64
2e	14.22	**2q**	13.56
2f	10.87	**2r**	12.98
2g	11.92	**2s**	14.41
2h	12.51	**2t**	14.21
2i	12.43	**2u**	15.08
2j	10.94	**2v**	13.68
2k	9.66	**2w**	7.42
2l	11.89	**2x**	5.97

Conclusion

Based on *in vitro* evaluation, compounds showed higher and broader spectrum of anticancer activity. Compound **2i** is highly efficient against leukemia (CCRF-CEM, K-562, RPMI-8226, SR), colon cancer (HCT-15), CNS cancer (SNB-75), melanoma (MALME-3M), ovarian cancer (IGROV1), renal cancer (UO-31) and breast cancer (MCF7). Compound **2k** is highly efficient against leukemia (SR), non-small cell lung cancer (A549/ATCC, NCI-H226), renal cancer (UO-31, SN-12C), CNS (SNB-75) and ovarian cancer (OVCAR-04, SK-OV-3). Compound **7l** is highly efficient against leukemia (CCRF-CEM) and melanoma (MALME-3M).

Compound **2i** showed prominent anticancer activity due to active sydnone ring and substitution of 3rd and 4th posi-

Table 4. Anticancer screening data for compound **2g**, **2i** and **2j**

Human tumour cell line	% GI for **2g**	% GI for **2i**	% GI for **2j**	% GI for std.
		Leukemia		
CCRF-CEM	6.73	15.33	6.54	4.49
HL-80	–	22.99	–	35.39
K-562	–	39.17	–	10.89
RPMI-8226	6.25	15.09	13.89	16.2
SR	8.76	61.87	–	0.5
		Non-small cell lung cancer		
NCI-H322M	–	–	14.75	–33.4
NCI-H522	20.08	3.62	–	23.4
		Colon cancer		
HCT-116	7.12	12.39	3.74	47.00
HCT-15	4.68	11.79	0.3	–0.6
SW-620	–	8.69	3.64	–5.2
HT29	–	7.01	–	13.3
KM-12	–	13.90	–	4.5
		CNS cancer		
SNB-75	–	18.20	8.26	–5.4
SF-295	7.79	–	–	–3.3
		Melanoma		
SK-MEL-28	–7.13	–	–	–47.7
MALME-3M	2.11	12.89	0.70	–35.1
UACC-62	–1.98	–	–1.51	–13.6
LOXIMVI	–	5.59	–	–18.5
MDA-MB-435	–	26.76	–	54.00
		Ovarian cancer		
OVCAR-4	–4.26	–	–	–38.9
SK-OV-3	4.77	–	4.83	18.2
IGROV1	3.20	13.06	14.96	6.3
		Renal cancer		
A498	–	–	9.62	ND
CAKI-1	14.22	–	5.66	–16.2
UO-31	23.68	15.89	19.12	–18.3
		Prostate cancer		
PC-3	–2.09	–0.81	3.95	–8.00
DU-145	–24.01	–14.56	–10.06	–52.00
		Breast cancer		
HS-578T	6.83	–	–	ND
MCF7	8.64	31.78	34.08	7.9
BT-549	12.10	–	–	34.5
T-47D	–	–	7.84	–48.5
Mean	100.47	90.55	101.67	10.298
Delta	23.67	61.87	34.798	83.798
Range	47.69	98.09	74.63	363.9

Range = highest growth percent – lowest growth percent, Delta = mean growth percent – lowest growth percent, % GI: % growth inhibition = mean growth percent – % growth, Standard – Vincristine sulphate, ND – not determined, – Poor anticancer activity.

Table 5. Anticancer screening data for compound **2k**, **2l** and **2m**

Human tumour cell line	% GI for **2k**	% GI for **2l**	% GI for **2m**	% GI for std.
		Leukemia		
CCRF-CEM	41.57	–	11.06	4.49
MOLT-4	16.08	–	–	5.30
SR	–	–	4.78	0.5
RPMI-8226	18.38	11.99	–	16.2
		Non-small cell lung cancer		
NCI-H226	–	–	7.57	–17.9
NCI-H322M	–	15.43	–	–33.4
HOP-92	–	–	22.73	–62.0
		Colon cancer		
SW-620	–	–	2.30	–5.2
		CNS cancer		
SNB-75	27.68	–	17.46	–5.4
		Melanoma		
MALME-3M	–	–	6.86	–35.1
UACC-62	–	–	7.17	–13.6
		Ovarian cancer		
SK-OV-3	–	–	8.98	18.2
		Renal cancer		
A498	–	–	10.89	ND
UO-31	14.00	11.77	18.29	–18.3
		Prostate cancer		
PC-3	–	–	15.60	–8.00
		Breast cancer		
MDA-MB-231/ATCC	–	–	8.55	37.4
MCF7	10.19	–	4.62	7.9
BT-549	–	–	28.15	34.5
HS-578T	–	–	6.51	ND
Mean	99.82	100.93	99.44	10.298
Delta	41.57	15.43	28.15	83.798
Range	66.01	42.25	63.64	363.9

Range = highest growth percent – lowest growth percent, Delta = mean growth percent – lowest growth percent, % GI: % growth inhibition = mean growth percent – % growth, Standard – Vincristine sulphate, ND – not determined, – Poor anticancer activity.

tion of sydnone with aryl ring having electron withdrawing functional groups like chloro (-Cl) and nitro (-NO_2) which make benzene ring more stable and may also increases lipophilicity to penetrate easily into cancer cells. Compound may exhibited anticancer activities over multiple mechanisms with inhibiting protein kinase (CDK, MK-2, PLK1, kinase-like protein Eg5 and IKK), topoisomerase I and II, microtubule inhibition and many others[21]. Further research and development with designing necessary structural modifications of molecules **2i** and **2k** may lead to safer and effective potential anticancer drug candidates. The finding of the study inferred that the molecules **2i** and **2k** are renders as a lead for further development of novel potent anticancer molecules against specific tumor cell line.

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