European Journal of Medicinal Chemistry 67 (2013) 352–358

Contents lists available at SciVerse ScienceDirect

European Journal of Medicinal Chemistry

journal homepage: http://www.elsevier.com/locate/ejmech

Original article

Synthesis, antiproliferative and anti-inflammatory activities of some novel 6-aryl-2-(*p*-(methanesulfonyl)phenyl)-4,5-dihydropyridazi-3(2*H*)-ones

Syed Ovais, Kalim Javed*, Shafiya Yaseen, Rafia Bashir, Pooja Rathore, Raed Yaseen, Alhamzah D. Hameed, Mohammad Samim

Department of Chemistry, Faculty of Science, Jamia Hamdard (Hamdard University), New Delhi 110 062, India

ARTICLE INFO

Article history:
Received 19 October 2012
Received in revised form
13 June 2013
Accepted 19 June 2013
Available online 5 July 2013

Keywords:
Pyridazinone
(*p*-(Methanesulfonyl)phenyl)hydrazine
Antiproliferative activity
Anti-inflammatory activity
Ulcerogenic effect

ABSTRACT

Sixteen new 6-aryl-2-(*p*-(methanesulfonyl)phenyl)-4,5-dihydropyridazi-3(2*H*)-ones (**2a**–**p**) were synthesized and tested for *in vitro* anticancer and *in vivo* anti-inflammatory activities. Eleven (**2b**, **2d**, **2e**–**j** and **2m**–**p**) of the obtained compounds were screened for their antiproliferative activity towards 60 human cancer cell lines by the National Cancer Institute (USA). Compound **2f** showed remarkable activity with GI_{50} less than 1 μM on 36 human tumor cell lines and has been referred to Biological Evaluation Committee (NCI) for advance study. Compound **2g** also displayed promising antiproliferative activity against 20 different cell lines with GI_{50} less than 1 μM. Compounds **2k** and **2n** were found to have a comparable anti-inflammatory activity to that of standard drug etoricoxib in carrageenan-induced rat hind paw edema model at 5 h.

1. Introduction

Cancer is not a single pathological state but a broad group of diseases characterized by a high proliferative index and the spread of aberrant cells from their site of origin [1]. It is the major cause of death in the 21st century [2,3]. Despite major breakthroughs in many areas of cancer therapies over the past few years, the successful treatment of cancer remains a significant challenge in the 21st century. The therapeutic treatment of cancer is a combination of surgery and/or radiotherapy with chemotherapy [4,5]. Current chemotherapy consists of cytotoxic (cell-killing) agents and anti-hormonal drugs, which reduce the proliferation of the tumors [4,5]. However, therapeutic use of anticancer drugs is complicated by systemic toxicity, usually observed in the bone narrow, the gastrointestinal (GI) tract and hair, and by development of resistance. Therefore, the design of new antitumor agents is one of the most urgent research areas in medicinal chemistry.

Pyridazinone derivatives have been reported to exhibit wide range of pharmacological activities such as antidepressant [6], antihypertensive [7,8], antithrombotic [9], anticonvulsant [10], cardiotonic [11], antibacterial, diuretic [12], anti-HIV [13], aldose reductase inhibitors [14], hepatoprotective agents [15], anti-inflammatory [16–18] and COX-2 inhibitors [19]. Pyridazinone derivatives have also been reported to have remarkable anticancer activity [20,21]. Recently, our research group has reported the interesting anticancer activity of 6-arylpyridazinones bearing benzenesulfonamide moiety (16, 22). Some compounds of the series were found to have GI_{50} values in the low micromolar or submicromolar concentration range against human cancer cell lines and reaching, in the case of most active derivative bearing NSC code 747558 (Fig. 1). This compound showed remarkable activity against SR (leukemia) and NCI-H522 (non-small cell lung) with a GI_{50} value of less than 0.1 μM. It also displayed good activity against leukemia (CCRF-CEM, HL-60 (TB), K-562, MOLT-4, RPMI-8226), non-small cell lung cancer (NCI-H460), colon (HCT-116, HCT-15, HT29, KMI2, SW-620), CNS (SF-295), melanoma (MALME-3M, M14, MDA-MB-435 SK-MEL-5), ovarian (OVCAR-3, NCI/ADR-RES) and breast (MCF7) cancer cell lines with a GI_{50} less than 1.0 μM. The acute toxicity study of the compound (NSC 747558) indicated that it is well tolerated intra-peritoneally (400 mg/kg) by athymic nude mice [22].

In continuation of an ongoing program aiming at finding new structure leads (based on pyridazinone skeleton) with potential

* Corresponding author. Tel.: +91 9873463272.
E-mail addresses: kjaved@jamiahamdard.ac.in, Kjavedchem@yahoo.co.in (K. Javed).

0223-5234/$ – see front matter © 2013 Elsevier Masson SAS. All rights reserved.
http://dx.doi.org/10.1016/j.ejmech.2013.06.050

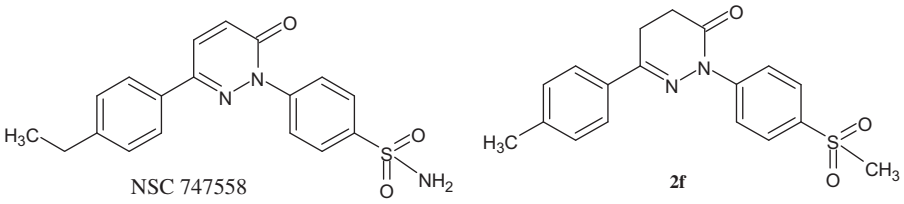


Fig. 1. Structure of the most potent antiproliferative agents.

chemotherapeutic activities, here, we report the synthesis and evaluation for *in vitro* anticancer efficacy against human cancer cell lines of a series of new 6-aryl-2-(*p*-(methanesulfonyl)phenyl)-4,5-dihydropyridazi-3(2*H*)-ones molecules (**2a**–**p**). The data of these synthesized compounds (structure, stereoisomerism, molecular formula, molecular weight and melting point) were submitted to National Cancer Institute (NCI), USA for antiproliferative activity. As per the protocol of NCI, only eleven representative compounds **2b**, **2d**, **2e**–**j** and **2m**–**p** were selected and granted NSC codes Viz; NSC 762909, NSC 763763, NSC 762910, NSC 762908, NSC 762911, NSC 763765, NSC 762913, NSC 762915, NSC 763764, NSC 762912 and NSC 762914 respectively and screened at NCI for antiproliferative activity at a single high dose (10^{-5} M) in full 60 cell panel. Three compounds namely **2f**, **2g** and **2p** exhibited good activity at a single dose and were selected for further evaluation at five dose level screening. Among these three compounds **2f** (NSC 762908) (Fig. 1) showed remarkable antiproliferative activity at five dose level screening. This compound has been referred to Biological Evaluation Committee of NCI for advanced study.

Inflammation is closely linked to cancer, and many anticancer agents are also used to treat inflammatory diseases, such as rheumatoid arthritis. Moreover, chronic inflammation increases the risk for various cancers, indicating that eliminating inflammation may represent a valid strategy for cancer prevention and therapy [23]. Several studies have shown that the pyridazinone ring can serve as excellent core template for designing anti-inflammatory agent [16,17and18]. It prompted us to investigate the anti-inflammatory potential of these synthesized compounds (**2a**–**p**).

This paper describes the synthesis, *in vitro* anticancer and *in vivo* anti-inflammatory activity of some new 6-aryl-2-(*p*-(methanesulfonyl)phenyl)-4,5-dihydropyridazi-3(2*H*)-ones molecules (**2a**–**p**).

2. Result and discussion

2.1. Chemistry

The synthetic route used to synthesize titled compounds (**2a**–**p**) is outlined in Scheme 1. The β-aroylpropionic acids (**1a**–**p**) required for the synthesis of pyridazinones were obtained from Friedel–Crafts acylation through reported methods [24,25]. The cyclization to the pyridazinone derivatives bearing *p*-(methanesulfonyl)phenyl moiety was afforded by the condensation of appropriate aroylpropionic acid and (*p*-(methanesulfonyl)phenyl)hydrazine. The purity of compounds was checked by TLC. The structures of compounds (**2a**–**p**) was determined on the basis of elemental analysis and by various spectroscopic methods such as IR, ^{1}H NMR, ^{13}C NMR and MS. IR spectra showed a band at 1648–1697 cm^{-1} for cyclic carbonyl, 1579–1594 cm^{-1} for C=N and two bands for SO_2C at 1311–1379 cm^{-1} and 1137–1155 cm^{-1}. In the ^{1}H NMR spectra aromatic protons were observed at expected ppms. The signal for SO_2CH_3 was observed as three-proton singlet in the range of δ 3.20–3.24. In the ^{13}C NMR spectra of these compounds, the chemical shift values of carbon atoms of pyridazinone ring were observed in the expected range C-5 (δ 21.98–22.93), C-4 (δ 28.47–28.96), C-6 (δ 153.01–δ 155.21) and C-3 (δ 165.10–166.87). All other peaks (^{13}C NMR spectra) were observed at expected ppms and are provided as Supplementary data.

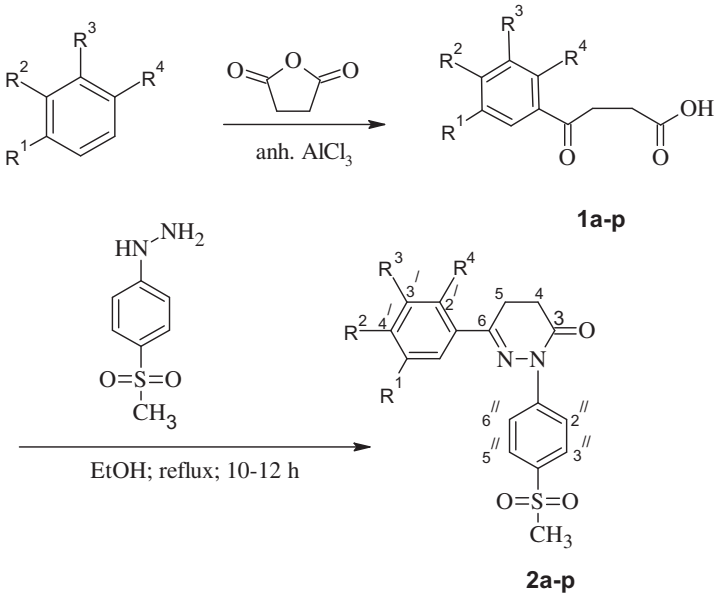
2.2. Pharmacology

2.2.1. In vitro antiproliferative activity

Primary *in vitro* one-dose (10^{-5} M) anticancer assay was performed using full panel of about 59 or 60 human tumor cell lines in accordance with the protocol of the Drug Evaluation Branch, National Cancer Institute (NCI), Bethesda, and described elsewhere [26–32]. The human tumor cell lines were derived from nine different cancer types: Leukemia, melanoma, lung, colon, CNS, ovarian, renal, prostate, and breast cancers. Out of the synthesized compounds (**2a**–**p**), eleven compounds, namely **2b**, **2d**–**j**, **2m**, **2n** and **2p** were selected by the National Cancer Institute (NCI). The compounds **2b**, **2d**, **2e**, **2h**–**j**, **2m** and **2n** displayed mild sensitivity against few cell lines (Table S1 Supplementary data). Compounds **2f**, **2g** and **2p** displayed considerable antitumor activity (Table S2 Supplementary data) and were therefore 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 0.01 μM). A 48 h continuous drug exposure protocol was used and sulforhodamine B (SRB) protein assay was used to estimate cell growth. Details of this system and the information which is encoded by the activity pattern over all cell lines have been published [26–28]. The anticancer activity of tested compounds is given by three parameters for each cell line: log GI_{50} value (GI_{50} = molar concentration of the compound that inhibits 50% net cell growth), log TGI value (TGI = molar concentration of the compound leading to total inhibition) and log LC_{50} value (LC_{50} = molar concentration of the compound leading to 50% net cell death). Furthermore, a mean graph midpoint (MG_MID) is calculated for each of the mentioned parameters, giving an averaged activity parameter over all cell lines. For the calculation of the MG_MID, insensitive cell lines are included with the highest concentration tested. Selectivity of the compound with respect to one or more cell lines of the screen is characterized by a high deviation (Δ) of the particular cell line parameter compared to the MG_MID value.

Compounds **2f**, **2g** and **2p** exhibited considerable broad spectrum antitumor activities and showed effective growth inhibition GI_{50} (MG_MID) values of 0.93, 1.94 and 9.54 μM, respectively (Table 1), beside a cytostatic activity TGI (MG_MID) 45.7, 43.6, and 75.8 μM, respectively (Supplementary Table S3). The compound **2f** displayed remarkable antiproliferative activity in 36 different cell lines with GI_{50} less than 1 μM and showed better activity than that of 5-fluorouracil (5-FU) a clinically used anticancer drug in 29 different cell lines. This compound **2f** has been referred to Biological Evaluation Committee (NCI) for *in vivo* anticancer activity.

Compound **2g** displayed significant antiproliferative activity in 20 different cell lines with GI_{50} less than 1 μM (Table 1). Compound **2p** displayed moderate activity against 4 cells of the tested 59 tumor cell lines (GI_{50} less than 3 μM) (Table 1). The cytotoxic effects



1a, 2a: $R^1=R^2=R^3=R^4=H$

1b, **2b**: $R^2=$ Cl, $R^1=R^3=R^4=H$

1c, **2c**: $R^2=$ Br, $R^1=R^3=R^4=H$

1d, **2d**: $R^2=$ F, $R^1=R^3=R^4=H$

1e, **2e**: $R^2=OCH_3$, $R^1=R^3=R^4=H$

1f, **2f**: $R^2=CH_3$, $R^1=R^3=R^4=H$

1g, **2g**: $R^2=C_2H_5$, $R^1=R^3=R^4=H$

1h, **2h**: $R^2=$ -C(Me)$_3$, $R^1=R^3=R^4=H$

1i, **2i**: $R^2=C_6H_5$, $R^1=R^3=R^4=H$

1j, **2j**: $R^2=OC_6H_5$, $R^1=R^3=R^4=H$

1k, **2k**: $R^2=R^3=OCH_3$, $R^1=R^4=H$

1l, **2l**: $R^2=R^3=$ Cl, $R^1=R^4=H$

1m, **2m**: $R^2=$ OH, $R^3=$Cl, $R^1=R^4=H$

1n, **2n**: $R^4=$ OH, $R^1=CH_3$, $R^2=R^3=H$

1o, **2o**: $R^2=$OH, $R^3=CH_3$, $R^1=R^4=H$

1p, **2p**: $R^2=$OH, $R^4=CH_3$, $R^1=R^3=H$

Scheme 1. Synthesis of 6-aryl-2-(*p*-(methanesulfonyl)phenyl)-4,5-dihydropyridazi-3(2*H*)-ones (**2a**–**p**).

associated with these compounds **2f**, **2g** and **2p** were measured by LC_{50} displayed in supplementary data (Table S4). The LC_{50} values for compounds **2f** and **2p** are greater than 100 for all cell lines, while as LC_{50} values for compounds **2g** are greater than 100 except for two cell lines (COLO 205 and SK-MEL-5). These LC_{50} values indicate low toxicity of these compounds for normal human cell lines, as required for development of potential antitumor agent.

2.2.2. *In vivo anti-inflammatory activity*

The anti-inflammatory activity of target compounds (**2a**–**p**) was evaluated by applying carrageenan-induced hind paw edema bioassay in rats [33]. Results were compared with etoricoxib as it has some chemical structural resemblance with target compounds. The results are summarized in Table 2. These compounds (**2a**–**p**) showed moderate to strong anti-inflammatory activity (6.6–66.6% at 3 h and 21.0–86.4% at 5 h). The anti-inflammatory activity of **2k** and **2n** at 5 h was almost comparable to that exhibited by standard drug etoricoxib (83.3% at 3 h and 86.8% at 5 h).

With regard to structural activity relationship (SAR) it was observed that introduction of alkyl group at C-4′ position caused elevation in the activity and it was further increased when the bulk of alkyl was increased (**2a** vs **2f**–**h**) at both 3 h and 5 h. Introduction of oxy group (hydroxyl, methoxyl and phenoxyl) in phenyl ring also seems to be favorable for increasing the activity as compounds **2e**, **2j**, **2k**, **2m**, **2n**, **2o** and **2p** showed better activity than that of **2a**. Introduction of second methoxyl group at C-3′ increased the activity at both 3 h and 5 h (**2k** vs **2e**). Introduction of chlorine or bromine atom at C-4′ diminished the activity at both study time 3 h and 5 h (**2a** vs **2b**, **2a** vs **2l**, **2a** vs **2c**) while the introduction of fluorine at same position increased the activity (**2a** vs **2d**). In compounds **2n**, **2o** and **2p** hydroxyl group was found more effective at ortho position (**2n** vs **2o** and **2p**) while as methyl group was found more effective at *meta* position (**2n** and **2o** vs **2p**). Compound **2i** with phenyl moiety at C-4′ exhibited least activity in this study.

2.2.3. *Ulcerogenic effect*

The ulcerogenic effect of the most potent anti-inflammatory compounds **2k** and **2n** was studied at dose of 0.15 mmol/kg and compared with that of reference drug etoricoxib (0.15 mmol/kg). Like the etoricoxib, compounds **2k** and **2n** were found safe from the point of view of ulcer induction.

3. Conclusion

Cyclocondensation of appropriate aroylpropionic acid and (*p*-(methanesulfonyl)phenyl)hydrazine yielded pyridazinone derivatives (**2a**–**p**). The structures proposed for the synthesized compounds are well supported by spectroscopic data and elemental analysis. The data of these synthesized compounds were submitted to National Cancer Institute (NCI), USA for anti-proliferative activity. As per the protocol of NCI, only eleven representative compounds **2b**, **2d**, **2e**–**j** and **2m**–**p** were selected.

Table 1
Growth inhibitory concentration (GI_{50}, μM) in tumor cell lines assay.[a]

Cancer type	Cell	GI_{50}[b]			
		5-FU	**2f**	**2g**	**2p**
Leukemia	CCRF-CEM	9.79	1.16	2.31	9.09
	HL-60(TB)	2.30	0.40	1.20	3.52
	K-562	3.58	0.37	0.42	3.74
	MOLT-4	0.35	0.86	3.52	14.3
	SR	0.02	0.29	5.65	3.39
	RPMI-8226	0.04	2.78	0.42	25.6
Non-small cell lung	A549/ATCC	0.18	0.52	0.91	6.20
	EKVX	61.8	3.02	4.19	57.9
	HOP-62	0.39	1.30	4.30	9.07
	HOP-92	77.9	0.42	1.58	6.49
	NCI-H226	54.7	0.43	0.20	>100
	NCI-H23	0.33	2.50	3.19	38.5
	NCI-H460	0.05	0.38	0.82	3.87
	NCI-H522	7.27	0.22	0.33	2.53
Colon	COLO 205	0.15	0.52	1.02	6.62
	HCC-2998	0.05	2.75	5.27	46.7
	HCT-116	0.22	0.41	0.73	3.78
	HCT-15	0.11	0.61	1.90	7.91
	HT29	0.17	0.33	0.41	3.70
	KM12	0.21	0.44	0.93	4.22
	SW-620	0.92	0.34	43.1	3.32
CNS	SF-268	1.62	2.94	6.99	40.0
	SF-295	0.22	0.40	0.93	2.87
	SF-539	0.06	1.02	2.35	13.2
	SNB-19	3.81	1.25	0.13	50.4
	SNB-75	78.7	0.54	1.32	5.53
	U251	0.90	0.45	1.91	4.30
Melanoma	LOX IMVI	0.24	0.74	3.50	7.25
	MALME-3M	0.05	–	6.80	5.37
	M14	0.98	0.38	0.63	3.85
	MDA-MB-435	0.07	0.12	0.22	1.28
	SK-MEL-2	56.7	0.43	0.90	3.48
	SK-MEL-28	1.03	0.66	1.84	9.56
	SK-MEL-5	0.46	0.41	1.48	5.49
	UACC-257	3.55	0.61	3.30	5.65
	UACC-62	0.52	0.46	0.78	4.00
Ovarian	IGROV1	1.22	0.83	1.48	7.13
	OVCAR-3	0.01	0.36	0.93	3.41
	OVCAR-4	4.43	>100	0.01	76.9
	OVCAR-5	10.9	3.69	8.51	53.8
	OVCAR-8	1.74	0.74	3.25	12.3
	NCI/ADR-RES	0.31	0.27	0.40	3.26
	SK-OV-3	21.8	1.15	2.44	9.77
Renal	786-0	0.72	5.78	5.13	92.5
	A498	0.35	0.14	0.14	2.78
	ACHN	0.29	4.02	8.59	37.8
	CAKI-1	0.07	0.29	1.00	27.9
	RXF 393	2.61	0.63	2.04	12.8
	SN12C	0.49	–	4.81	7.18
	TK-10	1.12	7.69	8.31	80.5
	UO-31	1.42	4.72	5.23	14.8
Prostate	PC-3	2.36	1.43	2.76	14.8
	DU-145	0.36	2.91	5.66	24.7
Breast	MCF7	0.07	1.38	3.13	20.7
	MDA-MB-231/ATCC	6.60	0.83	3.46	17.1
	HS 578T	9.77	0.46	0.83	4.15
	BT-549	10.6	0.60	0.96	4.97
	T-47D	8.12	2.08	4.40	20.2
	MDA-MB-468	–	1.23	3.75	11.0
MG_MID			0.93	1.94	9.54

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

[b] GI_{50} was the drug concentration resulting in a 50% reduction in the net protein increase (as measured by SRB staining) in the control cells during the drug incubation, determined at five concentration levels (100, 10, 1.0, 0.1 and 0.01 μM).

The *in vitro* antiproliferative activity showed that, among the eleven compounds selected and evaluated by NCI, compounds **2f**, **2g** and **2p** exhibited higher activity. Compounds **2f**, **2g** and **2p** exhibited considerable broad-spectrum antitumor activities with effective growth inhibition GI_{50} (MG_MID) values of 0.93, 1.94 and 9.54 μM, respectively, beside a cytostatic activity TGI (MG_MID) 45.7, 43.6, and 75.8 μM, respectively. Particularly compound **2f** displayed most remarkable activity against 36 different cell lines with GI_{50} less than 1 μM. This compound (**2f**) can be used as lead compound for developing new anticancer agents. Two compounds (**2k** and **2n**) were found to have a comparable anti-inflammatory activity to that of standard drug etoricoxib in carrageenan-induced hind rat paw edema model at 5 h and were also found safe from the point of view of ulcer induction.

Table 2
Effect of pyridazinones derivatives on carrageenan induced hind paw edema in rats.

Group no.	Treatment (0.05 mmol/kg)	Increase in paw volume ml ± SEM after carrageenan administration	
		3 h	5 h
I	Vehicle	0.30 ± 0.02	0.38 ± 0.04
II	Etoricoxib	0.05 ± 0.02*** (83.3%)	0.05 ± 0.02** (86.8%)
III	**2a**	0.22 ± 0.02* (26.6%)	0.20 ± 0.01** (47.3%)
IV	**2b**	0.22 ± 0.03** (26.6%)	0.24 ± 0.02* (36.8%)
V	**2c**	0.27 ± 0.01* (10.0%)	0.26 ± 0.01* (31.5%)
VI	**2d**	0.12 ± 0.02* (60.0%)	0.10 ± 0.01* (73.6%)
VII	**2e**	0.16 ± 0.04** (46.7%)	0.12 ± 0.01** (68.4%)
VIII	**2f**	0.16 ± 0.02** (46.7%)	0.15 ± 0.02*** (60.5%)
IX	**2g**	0.16 ± 0.02* (46.7%)	0.13 ± 0.02** (65.7%)
X	**2h**	0.15 ± 0.02** (50.0%)	0.12 ± 0.02* (68.4%)
XI	**2i**	0.28 ± 0.01** (6.6%)	0.30 ± 0.01* (21.0%)
XII	**2j**	0.15 ± 0.02** (50.0%)	0.13 ± 0.01** (65.7%)
XIII	**2k**	0.1 ± 0.01*** (66.6%)	0.06 ± 0.03** (82.4%)
XIV	**2l**	0.22 ± 0.03* (26.6%)	0.25 ± 0.02* (34.2%)
XV	**2m**	0.17 ± 0.01** (43.3%)	0.17 ± 0.02** (55.2%)
XVI	**2n**	0.1 ± 0.01*** (66.6%)	0.05 ± 0.02** (86.8%)
XVII	**2o**	0.22 ± 0.01* (26.6%)	0.15 ± 0.02** (60.5%)
XVIII	**2p**	0.2 ± 0.03* (33.3%)	0.18 ± 0.02** (52.6%)

*$P < 0.05$, **$p < 0.01$, ***$p < 0.001$, compared to control (one-way ANOVA followed by Dunnett's test). Values are presented as mean ± S.E.M. ($n = 6$). Values in parentheses represent percent inhibitions.

4. Experimental

4.1. Chemistry

Melting points were determined using open capillary tubes and are uncorrected. All Fourier Transform Infrared (FTIR) spectra were recorded on a bio-rad FTS-135 spectrophotometer using KBr pellets; ν_{max} values are given in cm^{-1}. ^1H NMR spectra were recorded on a Bruker spectrospin DPX 300-MHz spectrometer using deuterated dimethylsulfoxide (DMSO) as solvent and tetramethylsilane (TMS) as internal standard. Chemical shifts are given in (ppm) scale and coupling constants (*J* values) are expressed in Hz. Mass spectra (MS) were recorded on ESI Q-TOF Water. ^{13}C NMR spectra were recorded on a Bruker spectrospin DPX at 75 MHz using deuterated DMSO as a solvent and tetramethylsilane (TMS) as internal standard. Purity of the compounds was checked on thin layer chromatography (TLC) plates (silica gel G) which were visualized by exposing to iodine vapors. Elemental analysis was carried out on a CHNS elementar (Vario El III) system.

4.1.1. General procedure for the synthesis of aroylpropionic acids (*1a–p*)

To liquid aromatic hydrocarbon (30 ml), anhydrous aluminum chloride (16.6 g, 0.125 mol) was added. Nitrobenzene (30 ml) was used as solvent in case of solid aromatic hydrocarbons. The mixture was stirred using a magnetic stirrer at room temperature for 30 min. To this, succinic anhydride (5 g, 0.05 mol) was added in five portions with continuous stirring. Vigorous reaction started with the evolution of HCl gas. Stirring was continued for another 6 h at room temperature. The mixture was left at room temperature for

48 h and then decomposed by adding ice-cold hydrochloric acid (50%, 100 ml). The excess solvent was removed by steam distillation. The solid precipitated out was treated with aqueous saturated sodium bicarbonate solution and filtered. Filtrate was acidified with dilute HCl (4% v/v) to give a precipitate. It was filtered and residue was washed with cold water, dried and crystallized from the appropriate solvent to give **1a**–**p** [24,25].

*4.1.2. General procedure for the synthesis of pyridazinones (**2a**–**p**)*

A mixture of the appropriate aroylpropionic acid (**1a**–**p**) (0.001 mol) and (*p*-(methanesulfonyl)phenylhydrazine) (0.001 mol) in absolute ethanol (20–30 ml) was refluxed for 10–12 h. The reaction mixture was concentrated to one-third of its volume and left at room temperature, when a solid separated out. The crude product was filtered off, washed with a small volume of alcohol, and stirred with 5% sodium bicarbonate solution (25 ml). It was filtered, and washed with 2% acetic acid and then with water. The product was dried and recrystallized from the appropriate solvent to give pure compounds **2a**–**p**. The solvent system used for TLC was toluene:ethyl acetate:formic acid (5: 4:1).

*4.1.2.1. 2-(p-(Methanesulfonyl)phenyl)-6-phenyl-4,5-dihydropyridazi-3(2H)-one (**2a**).* Light yellow crystals (m.p. 167–168 °C) from acetone–methanol. Yield = 31%. R_f = 0.44. IR ν_{max} (KBr): 1690 cm^{-1} (C=O), 1591 cm^{-1} (C=N) 1137 cm^{-1} & 1314 cm^{-1} (SO_2C). ^1H NMR (300 MHz, DMSO, δ): 2.79 (2H, t, J = 8.1 Hz, H-5), 3.14 (2H, t, J = 8.1 Hz, H-4), 3.20 (3H, s, SO_2CH_3), 7.47–7.49 (3H, m, H-3′, H-4′, H-5′), 7.86–7.91 (4H, m, H-2′, H-6′, H-3″, H-5″), 7.98 (2H, d, J = 9.0 Hz, H-2″, H-6″). ESI-MS (m/z): 328 [M^+], 327 [$M^+ - 1$]. ^{13}C NMR (75 MHz, DMSO, δ): 22.81 (C-5), 28.47 (C-4), 44.61 (SO_2C), 153.29 (C-6), 166.87 (C-3). Elemental analysis for: $C_{17}H_{16}N_2O_3S$ found (calculated) C: 62.21 (62.18), H: 4.89 (4.91), N: 8.55 (8.53), S: 9.78 (9.76).

*4.1.2.2. 6-(4-Chloro-phenyl)-2-(p-(methanesulfonyl)phenyl)-4,5-dihydropyridazi-3(2H)-one (**2b**).* White crystals (m.p. 157–159 °C) from methanol. Yield = 56%. R_f = 0.37. IR ν_{max} (KBr): 1693 cm^{-1} (C=O), 1590 cm^{-1} (C=N) 1150 cm^{-1} & 1311 cm^{-1} (SO_2C). ^1H NMR (300 MHz, DMSO, δ): 2.79 (2H, t, J = 8.4 Hz, H-5), 3.17 (2H, t, J = 8.4 Hz, H-4), 3.24 (3H, s, SO_2CH_3), 7.55 (2H, d, J = 8.7 Hz, H-3″, H-5″), 7.87 (2H, d, J = 6.3 Hz, H-3′, H-5′), 7.90 (2H, d, J = 6.3 Hz, H-2′, H-6′), 7.98 (2H, d, J = 8.7 Hz, H-2″, H-6″). ESI-MS (m/z): 362, 364 [M^+], 363 [$M^+ + 1$], 359 [$M^+ - 3$]. ^{13}C NMR (75 MHz, DMSO, δ): 21.98 (C-5), 28.01 (C-4), 44.22 (SO_2C), 153.42 (C-6), 166.17 (C-3). Elemental analysis for: $C_{17}H_{15}ClN_2O_3S$ found (calculated) C: 56.25 (56.27), H: 4.15 (4.17), N: 7.74 (7.72), S: 8.86 (8.84).

*4.1.2.3. 6-(4-Bromo-phenyl)-2-(p-(methanesulfonyl)phenyl)-4,5-dihydropyridazi-3(2H)-one (**2c**).* White crystals (m.p. 161–162 °C) from methanol. Yield = 42%. R_f = 0.34. IR ν_{max} (KBr): 1692 cm^{-1} (C=O), 1588 cm^{-1} (C=N), 1140 cm^{-1} & 1379 cm^{-1} (SO_2C). ^1H NMR (300 MHz, DMSO, δ): 2.79 (2H, t, J = 7.5 Hz, H-5), 3.15 (2H, t, J = 7.8 Hz, H-4), 3.24 (3H, s, SO_2CH_3), 7.48–7.50 (2H, m, H-3′, H-5′), 7.89–7.92 (4H, m, H-2′, H-6′, H-3″, H-5″), 7.98 (2H, d, J = 8.7 Hz, H-2″, H-6″). ESI-MS (m/z): 406, 408 [M^+]. ^{13}C NMR (75 MHz, DMSO, δ): 22.52 (C-5), 28.41 (C-4), 44.44 (SO_2C), 153.45 (C-6), 166.82 (C-3). Elemental analysis for: $C_{17}H_{15}BrN_2O_3S$ found (calculated) C: 50.16 (50.13), H: 3.73 (3.71), N: 6.91 (6.88) S: 7.89 (7.87).

*4.1.2.4. 6-(4-Fluoro-phenyl)-2-(p-(methanesulfonyl)phenyl)-4,5-dihydropyridazi-3(2H)-one (**2d**).* White crystals (m.p. 68–69 °C) from methanol. Yield = 59%. R_f = 0.47. IR ν_{max} (KBr): 1691 cm^{-1} (C=O), 1591 cm^{-1} (C=N), 1143 cm^{-1} & 1356 cm^{-1} (SO_2C). ^1H NMR (300 MHz, DMSO, δ): 2.78 (2H, t, J = 8.1 Hz, H-5), 3.15 (2H, t, J = 9.0 Hz, H-4), 3.23 (3H, s, SO_2CH_3), 7.28–7.34 (2H, m, H-3′, H-5′), 7.86–7.98 (6H, m, H-2′, H-6′, H-3″, H-5″, H-2″, H-6″). ESI-MS (m/z): 346 [M^+], 347 [$M^+ + 1$], 348 [$M^+ + 2$]. ^{13}C NMR (75 MHz, DMSO, δ): 22.01 (C-5), 28.38 (C-4), 43.89 (SO_2C), 153.21 (C-6), 165.76 (C-3). Elemental analysis for: $C_{17}H_{15}FN_2O_3S$ found (calculated) C: 58.98 (58.95), H 4.33 (4.36), N: 8.08 (8.09), S: 9.27 (9.26).

*4.1.2.5. 2-(p-(Methanesulfonyl)phenyl)-6-(4-methoxy-phenyl)-4,5-dihydropyridazi-3(2H)-one (**2e**).* Light yellow crystals (m.p. 170–171 °C) from methanol. Yield = 57%. R_f = 0.39. IR ν_{max} (KBr): 1693 cm^{-1} (C=O), 1592 cm^{-1} (C=N) 1144 cm^{-1} & 1366 cm^{-1} (SO_2C). ^1H NMR (300 MHz, DMSO, δ): 2.76 (2H, t, J = 8.1 Hz, H-5), 3.13 (2H, t, J = 7.8 Hz, H-4), 3.23 (3H, s, SO_2CH_3), 3.81 (3H, s, OCH_3), 7.03 (2H, d, J = 9.0 Hz, H-3′, H-5′), 7.84 (2H, d, J = 9.0 Hz, H-2′, H-6′), 7.89 (2H, d, J = 8.7 Hz, H-3″, H-5″), 7.97 (2H, d, J = 8.7 Hz, H-2″, H-6″). ESI-MS (m/z): 358 [M^+], 359 [$M^+ + 1$]. ^{13}C NMR (75 MHz, DMSO, δ): 22.81 (C-5), 28.92 (C-4), 44.14 (SO_2C), 46.81 (OCH_3), 153.26 (C-6), 166.46 (C-3). Elemental analysis for: $C_{18}H_{18}N_2O_4S$ found (calculated) C: 60.34 (60.32), H: 5.04 (5.06) N: 7.85 (7.82) S: 8.93 (8.95).

*4.1.2.6. 2-(p-(Methanesulfonyl)phenyl)-6-p-tolyl-4,5-dihydropyridazi-3(2H)-one (**2f**).* Brown crystals (m.p. 169–170 °C) from acetone. Yield = 54%, R_f = 0.40 (toluene:ethyl acetate:formic acid, 5:4:1), IR ν_{max} (KBr): 1692 cm^{-1} (C=O), 1586 cm^{-1} (C=N), 1145 cm^{-1} & 1326 cm^{-1} (SO_2C). ^1H NMR (300 MHz, DMSO, δ): 2.36 (3H, s, CH_3 at C-4′), 2.77 (2H, t, J = 8.1 Hz, H-5), 3.14 (2H, t, J = 8.1 Hz, H-4), 3.23 (3H, s, SO_2CH_3), 7.29 (2H, d, J = 7.8 Hz, H-3′, H-5′), 7.78 (2H, d, J = 7.8 Hz, H-2′, H-6′), 7.89 (2H, d, J = 8.7 Hz, H-3″, H-5″), 7.99 (2H, d, J = 8.7 Hz, H-2″, H-6″). ESI-MS (m/z): 342 [M^+], 343 [$M^+ + 1$]. ^{13}C NMR (75 MHz, DMSO, δ): 21.39 (CH_3), 22.62 (C-5), 28.03 (C-4), 44.15 (SO_2C), 153.75 (C-6), 166.36 (C-3). Elemental analysis for: $C_{18}H_{18}N_2O_3S$ found (calculated) C: 63.17 (63.14), H: 5.31 (5.30), N: 8.20 (8.18) S: 9.39 (9.36).

*4.1.2.7. 6-(4-Ethyl-phenyl)-2-(p-(methanesulfonyl)phenyl)-4,5-dihydropyridazi-3(2H)-one (**2g**).* Yellow crystals (m.p. 165–166 °C) from methanol. Yield = 59%, R_f = 0.58. IR ν_{max} (KBr): 1691 cm^{-1} (C=O), 1586 cm^{-1} (C=N), 1155 cm^{-1} & 1316 cm^{-1} (SO_2C). ^1H NMR (300 MHz, DMSO, δ): 1.19 (3H, t, J = 7.5 Hz, $-CH_2-CH_3$), 2.66 (2H, q, J = 7.5 Hz, $-CH_2-CH_3$), 2.77 (2H, t, J = 8.1 Hz, H-5), 3.15 (2H, t, J = 7.8 Hz, H-4), 3.24 (3H, s, SO_2CH_3), 7.32 (2H, d, J = 6.9 Hz, H-3′, H-5′), 7.80 (2H, d, J = 6.6 Hz, H-2′, H-6′), 7.89 (2H, d, J = 8.7 Hz, H-3″, H-5″), 7.97 (2H, d, J = 8.7 Hz, H-2″, H-6″). ESI-MS (m/z): 357 [$M^+ + 1$], 358 [$M^+ + 2$]. ^{13}C NMR (75 MHz, DMSO, δ): 15.91 (CH_3-CH_2-), 22.68 (CH_3-CH_2-), 24.03 (C-5), 28.47 (C-4), 44.14 (SO_2C), 153.80 (C-6), 166.36 (C-3). Elemental analysis for: $C_{19}H_{20}N_2O_3S$ found (calculated) C: 64.00 (64.02), H: 5.63 (5.66), N: 7.88 (7.86), S: 8.88 (9.00).

*4.1.2.8. 6-(4-tert-Butyl-phenyl)-2-(p-(methanesulfonyl)phenyl)-4,5-dihydropyridazi-3(2H)-one (**2h**).* Yellow crystals (m.p. 179–180 °C) from methanol. Yield = 53%, R_f = 0.53. IR ν_{max} (KBr): 1693 cm^{-1} (C=O), 1579 cm^{-1} (C=N), 1145 cm^{-1} & 1352 cm^{-1} (SO_2C). ^1H NMR (300 MHz, DMSO, δ): 1.29 [9H, s, $-C(CH_3)_3$], 2.77 (2H, t, J = 8.1 Hz, H-5), 3.14 (2H, t, J = 8.7 Hz, H-4), 3.23 (3H, s, SO_2CH_3), 7.49 (2H, d, J = 8.4 Hz, H-3′, H-5′), 7.80 (2H, d, J = 8.4 Hz H-2′, H-6′), 7.89 (2H, d, J = 8.7 Hz, H-3″, H-5″), 7.98 (2H, d, J = 8.7 Hz, H-2″, H-6″). ESI-MS (m/z): 384 [M^+], 385 [$M^+ + 1$]. ^{13}C NMR (75 MHz, DMSO, δ): 21.80 (C-5), 28.61 (C-4), 31.5 [$C(CH_3)_3$], 34.2 [$C(CH_3)_3$], 44.80 (SO_2C), 153.21 (C-6), 165.89 (C-3). Elemental analysis for: $C_{21}H_{24}N_2O_3S$ found (calculated) C: 65.62 (65.60) H 6.27 (6.29) N: 7.28 (7.29) S: 8.37 (8.34).

*4.1.2.9. 6-Biphenyl-4-yl-2-(p-(methanesulfonyl)phenyl)-4,5-dihydropyridazi-3(2H)-one (**2i**).* Brown crystals (m.p. 147–148 °C) from chloroform. Yield = 59%, R_f = 0.62. IR ν_{max} (KBr): 1693 cm^{-1}

(C═O), 1586 cm^{-1} (C═N), 1141 cm^{-1} & 1317 cm^{-1} (SO_2C). ^1H NMR (300 MHz, DMSO, δ): 2.81 (2H, t, J = 8.1 Hz, H-5), 3.21 (2H, t, J = 8.4 Hz, H-4), 3.25 (3H, s, SO_2CH_3), all aromatic protons appeared between δ 7.82–8.01. ESI-MS (m/z): 404 [M^+], 405 [$M^+ + 1$]. ^{13}C NMR (75 MHz, DMSO, δ): 22.14 (C-5), 28.71 (C-4), 44.09 (SO_2C), 153.20 (C-6), 165.74 (C-3). Elemental analysis for: $C_{23}H_{20}N_2O_3S$ found (calculated) C: 68.28 (68.30), H: 4.96 (4.98), N: 6.95 (6.93) S: 7.95 (7.93).

*4.1.2.10. 2-(p-(Methanesulfonyl)phenyl)-6-(4-phenoxy-phenyl)-4,5-dihydropyridazi-3(2H)-one (**2j**).* Yellow crystals (m.p. 168–169 °C) from acetone-methanol. Yield = 51%, R_f = 0.58. IR ν_{max} (KBr): 1693 cm^{-1} (C═O), 1586 cm^{-1} (C═N), 1147 cm^{-1} & 1319 cm^{-1} (SO_2C). ^1H NMR (300 MHz, DMSO, δ): 2.78 (2H, t, J = 8.1 Hz, H-5), 3.16 (2H, t, J = 8.4 Hz, H-4), 3.24 (3H, s, SO_2CH_3), all aromatic protons appeared between δ 7.07–7.98. ESI-MS (m/z): 420 [M^+], 421 [$M^+ + 1$]. ^{13}C NMR (75 MHz, DMSO, δ): 22.48 (C-5), 28.61 (C-4), 43.14 (SO_2C), 153.44 (C-6), 165.10 (C-3). Elemental analysis for: $C_{23}H_{20}N_2O_4S$ found (calculated) C: 62.97 (63.00) H: 5.03 (5.06) N: 6.41 (6.39) S: 7.33 (7.31).

*4.1.2.11. 6-(4-Dimethoxy-phenyl)-2-(p-(methanesulfonyl)phenyl)-4,5-dihydropyridazi-3(2H)-one (**2k**).* Off-white crystals (m.p. 173–174 °C) acetone–methanol. Yield = 57%. R_f = 0.48. IR ν_{max} (KBr): 1694 cm^{-1} (C═O), 1588 cm^{-1} (C═N), 1148 cm^{-1} & 1348 cm^{-1} (SO_2C). ^1H NMR (300 MHz, DMSO, δ): 2.76 (2H, t, J = 8.1 Hz, H-5), 3.15 (2H, t, J = 7.8 Hz, H-4), 3.23 (3H, s, SO_2CH_3), 3.81 (6H, s, OCH_3 ×2), 7.04 (1H, d, J = 8.4 Hz, H-6′), 7.41–7.46 (2H, m, H-2′, H-5′), 7.90 (2H, d, J = 9.0 Hz, H-3″, H-5″), 7.98 (2H, d, J = 9.0 Hz, H-2″, H-6″). ESI-MS (m/z): 388 [M^+], 389 [$M^+ + 1$]. ^{13}C NMR (75 MHz, DMSO, δ): 22.79 (C-5), 28.65 (C-4), 44.04 (SO_2C), 56.55 [$(OCH_3)_2$], 153.58 (C-6), 166.25 (C-3). Elemental analysis for: $C_{19}H_{20}N_2O_5S$ found (calculated) C: 58.78 (58.75), H: 5.23 (5.19), N: 7.25 (7.21), S: 8.27 (8.25).

*4.1.2.12. 6-(3,4-Dichloro-phenyl)-2-(p-(methanesulfonyl)phenyl)-4,5-dihydropyridazi-3(2H)-one (**2l**).* Light yellow crystals (m.p. 206–208 °C) from methanol. Yield = 42%. R_f = 0.41. IR ν_{max} (KBr): 1694 cm^{-1} (C═O), 1589 cm^{-1} (C═O), 1150 cm^{-1} & 1313 cm^{-1} (SO_2C). ^1H NMR (300 MHz, DMSO, δ): 2.81 (2H, t, J = 8.1 Hz, H-5), 3.17 (2H, t, J = 7.8 Hz, H-4), 3.24 (3H, s, SO_2CH_3), 7.75 (1H, d, J = 8.7 Hz, H-6′), 7.84–7.88 (3H, m, H-2″, H-6″, H-5″), 7.98 (2H, d, J = 8.7 Hz, H-3″, H-5″), 8.08 (1H, d, J = 2.1 Hz, *meta* coupled H-2′). ESI-MS (m/z): 396, 398, 400 [M^+]. ^{13}C NMR (75 MHz, DMSO, δ): 22.46 (C-5), 28.24 (C-4), 44.54 (SO_2C), 153.80 (C-6), 166.47 (C-3). Elemental analysis for: $C_{17}H_{14}Cl_2N_2O_3S$ found (calculated) C: 51.43 (51.40), H: 3.54 (3.55), N: 7.08 (7.05), S: 8.09 (8.07).

*4.1.2.13. 6-(3-Chloro-4-hydroxy-phenyl)-2-(p-(methanesulfonyl) phenyl)-4,5-dihydropyridazi-3(2H)-one (**2m**).* Yellow crystals (m.p. 230–231 °C) from methanol. Yield = 48%. R_f = 0.61. IR ν_{max} (KBr): 1697 cm^{-1} (C═O), 1588 cm^{-1} (C═N), 1155 cm^{-1} & 1352 cm^{-1} (SO_2C). ^1H NMR (300 MHz, DMSO, δ): 2.75 (2H, t, J = 8.1 Hz, H-5), 3.11 (2H, t, J = 7.8 Hz, H-4), 3.24 (3H, s, SO_2CH_3), 7.04 (1H, d, J = 8.7 Hz, H-6′), 7.69 (1H, d, J = 8.7 Hz, H-5′), 7.84–7.89 (3H, m, H-2′ H-3″, H-5″), 7.98 (2H, d, J = 8.7 Hz, H-2″, H-6″), 10.77 (1H, s, OH). ESI-MS (m/z): 378, 380 [M^+]. ^{13}C NMR (75 MHz, DMSO, δ): 22.67 (C-5), 28.44 (C-4), 44.34 (SO_2C), 153.01 (C-6), 166.81 (C-3). Elemental analysis for: $C_{17}H_{15}ClN_2O_4S$ found (calculated) C: 53.91 (53.90), H: 3.97 (3.99), N: 7.38 (7.39), S: 8.49 (8.46).

*4.1.2.14. 6-(2-Hydroxy-5-methyl-phenyl)-2-(p-(methanesulfonyl) phenyl)-4,5-dihydropyridazi-3(2H)-one (**2n**).* Yellow crystals (m.p. 248–249 °C) from methanol. Yield = 37%. R_f = 0.47. IR ν_{max} (KBr): 1649 cm^{-1} (C═O), 1592 cm^{-1} (C═N), 1148 cm^{-1} & 1342 cm^{-1} (SO_2C). 1H NMR (300 MHz, DMSO, δ) 2.17 (3H, s, CH_3 at C-5′), 2.73 (2H, t, J = 8.4 Hz, H-5), 3.09 (2H, t, J = 8.0 Hz, H-4), 3.24 (3H, s, SO_2CH_3), 6.85 (1H, d, J = 8.4 Hz, H-3′), 7.56 (1H, *ortho–meta* coupled double doublet, J = 2.0 Hz, J = 8.0 Hz, H-4′), 7.63 (1H, d, J = 1.2 Hz, *meta* coupled H-6′), 7.89 (2H, d, J = 8.8 Hz, H-3″, H-5″), 7.97 (2H, d, J = 8.8 Hz, H-2″, H-6″), 9.88 (1H, s, OH). ESI-MS (m/z): 358 [M^+], 359 [$M^+ + 1$], 360 [$M^+ + 2$]. ^{13}C NMR (75 MHz, DMSO, δ): 21.9 (CH_3), 22.66 (C-5), 28.42 (C-4), 44.61 (SO_2C), 153.10 (C-6), 166.18 (C-3). Elemental analysis for: $C_{18}H_{18}N_2O_4S$ found (calculated) C: 60.33 (60.32), H: 5.08 (5.06) N: 7.81 (7.82) S: 8.93 (8.95).

*4.1.2.15. 6-(4-Hydroxy-3-methyl-phenyl)-2-(p-(methanesulfonyl) phenyl)-4,5-dihydropyridazi-3(2H)-one (**2o**).* Cream white crystals (m.p. 243–244 °C) from methanol. Yield = 41%. R_f = 0.33. IR ν_{max} (KBr): 1648 cm^{-1} (C═O), 1592 cm^{-1} (C═N), 1148 cm^{-1} & 1340 cm^{-1} (SO_2C). ^1H NMR (300 MHz, DMSO, δ): 2.50 (3H, s, CH_3), 2.73 (2H, t, J = 8.4 Hz, H-5), 3.09 (2H, t, J = 7.5 Hz, H-4), 3.23 (3H, s, SO_2CH_3), 6.85 (1H, d, J = 8.4 Hz, H-5′), 7.55 (1H, *ortho–meta* coupled double doublet, J = 2.5 Hz, J = 8.7 Hz, H-6′), 7.63 (1H, d, J = 2.1 Hz, *meta* coupled H-2′), 7.89 (2H, d, J = 9.0 Hz, H-3″, H-5″), 7.96 (2H, d, J = 9.0 Hz, H-2″, H-6″), 9.86 (1H, s, OH). ESI-MS (m/z): 358 [M^+], 359 [$M^+ + 1$]. ^{13}C NMR (75 MHz, DMSO, δ): 12.70 (CH_3 at C-3′), 22.61 (C-5), 28.44 (C-4), 44.10 (SO_2C), 154.67 (C-6), 166.75 (C-3). Elemental analysis for: $C_{18}H_{18}N_2O_4S$ found (calculated) C: 60.30 (60.32), H: 5.07 (5.06) N: 7.84 (7.82) S: 8.92 (8.95).

*4.1.2.16. 6-(4-Hydroxy-2-methyl-phenyl)-2-(p-(methanesulfonyl) phenyl)-4,5-dihydropyridazi-3(2H)-one (**2p**).* Light yellow crystals (m.p. 248–250 °C) from methanol. Yield = 39%. R_f = 0.47. IR ν_{max} (KBr): 1648 cm^{-1} (C═O), 1594 cm^{-1} (C═N), 1141 cm^{-1} & 1340 cm^{-1} (SO_2C). ^1H NMR (300 MHz, DMSO, δ): 2.28 (3H, s, CH_3), 2.77 (2H, t, J = 7.8 Hz, H-5), 3.14 (2H, t, J = 8.4 Hz, H-4), 3.25 (3H, s, SO_2CH_3), 6.75 (1H, s, H-3′), 6.77 (1H, d, J = 7.2 Hz, H-5′), 7.51 (1H, d, J = 8.4 Hz, H-6′), 7.80 (2H, d, J = 8.7 Hz, H-3″, H-5″), 8.00 (2H, d, J = 8.7 Hz, H-2″, H-6″), 11.04 (1H, s, OH). ESI-MS (m/z): 358 [M^+], 359 [$M^+ + 1$]. ^{13}C NMR (75 MHz, DMSO, δ): 16.50 (CH_3 at C-2′), 22.50 (C-5), 28.44 (C-4), 44.14 (SO_2C), 154.20 (C-6), 166.46 (C-3). Elemental analysis for: $C_{18}H_{18}N_2O_4S$ found (calculated) C: 60.33 (60.32), H: 5.08 (5.06), N: 7.81 (7.82) S: 8.93 (8.95).

4.2. Pharmacology

4.2.1. In vitro anticancer activity

A total of 60 human tumor cell lines, derived from nine cancer types (leukemia, lung, colon, brain, melanoma, ovarian, renal, prostate and breast) formed the basis of this test. The tumor cells were cultured in PMI1640 medium supplemented with 5% fetal calf serum and 2 mM L-glutamine. The tumor cells are inoculated over a series of standard 96-well microtiter plates in 100 ml of medium [30,31]. Density of inoculum depends on the type of tumor cell and from its growth characteristics [28]. These cells are then pre-incubated on the microtiter plate for 24 h before adding the compounds. These were tested in DMSO solution at five different concentrations (10^{-4}, 10^{-5}, 10^{-6}, 10^{-7} and 10^{-8} M). After an incubation of the chemical agent for 48 h with the tumor cell lines a sulforhodamine B (SRB) protein assay was used to estimate cell viability or growth. The cytotoxic effects are evaluated and the assay results and dose–response parameters were calculated as previously described [32].

4.2.2. Anti-inflammatory activity

Carrageenan induced hind paw edema method was used for evaluating anti-inflammatory activity [33]. Wistar rats (either sex) weighing 150–175 g were procured from Central Animal House facility of Jamia Hamdard, New Delhi (Registration no. 173/CPCSEA). The experiments were performed in accordance with the guidelines for the care and use of laboratory animals, laid down by the

Committee for the Purpose of Control and Supervision of Experiments in Animals (CPCSEA), Ministry of Social Justice and Empowerment, Govt. of India, Jan. 2000. Overnight fasted rats (16 h) were divided into 18 groups of 6 animals each. One group of rats, which served as control was given vehicle (1% CMC in water in a volume of 10 ml/kg) only. Test compounds (0.05 mmol/kg b.w), etricoxib (0.05 mmol/kg b.w) suspended in vehicle (10 ml/kg) were administered orally to respective groups. After 30 min, all animals were injected with 0.1 ml of 1% carrageenan solution (prepared in normal saline) in the subplantar aponeurosis of left hind paw to induce inflammation and the volume of injected paw was measured by using plethysmometer immediately (at 0 h). The paw volume was again measured after 3 h and 5 h. The average paw volume in a group of treated rats was compared with vehicle (control group) and the percentage inhibition of edema was calculated by using the formula:

$$\text{Percent inhibition} = (1 - Vt/Vc) \times 100$$

Where *Vt* is the mean paw volume of the test drug treated rats and *Vc* is the mean paw volume of the control.

4.2.3. Ulcerogenic effect

Acute gastric ulcerogenic effect of the compound **2k** and **2n** were evaluated in Wistar rats [34]. Albino rats of Wistar strain (160–220 g) fasted over 24 h were randomly allotted into four groups of six animals each. The animals of first group were given vehicle 10 ml/kg (CMC 1% w/v in distilled water) orally. Group second served as standard and was administered orally etoricoxib (0.15 mmol/kg) suspended in vehicle. Group third and forth were administered orally compounds **2k** and **2n** (0.15 mmol/kg) suspended in vehicle respectively. They were scarified under deep ether anesthesia after 6 h of the treatment. Their stomach were removed and opened through greater curvature for examining lesions or bleedings.

Acknowledgments

The authors are very grateful to the staff members of Department of Health and Human Services, National Cancer Institute (NCI), Bethesda, Maryland, USA, for carrying out *in vitro* anticancer screening of the newly synthesized compounds.

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.ejmech.2013.06.050.

References

[1] I.J. Fidler, Nat. Rev. Cancer 3 (2003) 453–458.
[2] H.M. Coley, Cancer Treat. Rev. 34 (2008) 378–390.
[3] D.G. Lloyd, G. Golfis, A.J. Knox, D. Fayne, M.J. Meegan, T.I. Oprea, Drug Discov. Today 11 (2006) 149–159.
[4] B.A. Chabner, P.C. Amrein, B.J. Druker, M.D. Michaelson, C.S. Mitsiades, P.E. Goss, D.P. Ryan, S. Ramachandra, P.G. Richardson, J.G. Supko, W.H. Wilson, in: L.L. Brunton, J.S. Lazo, K.L. Parker (Eds.), Goodman & Gilman's the Pharmacological Basis of Therapeutics, eleventh ed., Mc Graw-Hill Professional, New York, NY, USA, 2006, pp. 1315–1403.
[5] B.A. Gilchrest, M.S. Eller, Drugs Future 34 (2009) 205–216.
[6] A. Coelho, E. Sotelo, E. Ravina, Tetrahedron 59 (2003) 2477–2484.
[7] S. Demirayak, A.C. Karaburun, R. Beis, Eur. J. Med. Chem. 39 (2004) 1089–1095.
[8] A.A. Siddiqui, R. Mishra, M. Shaharyar, Eur. J. Med. Chem. 45 (2010) 2283–2290.
[9] A. Monge, P. Parrado, M. Font, E.F. Alvarez, J. Med. Chem. 30 (1987) 1029–1035.
[10] C. Rubat, P. Coudert, B. Refouvelet, P. Tronche, P. Bastide, Chem. Pharm. Bull. 38 (1990) 3009–3013.
[11] I. Sircar, R.E. Weishaar, D. Kobylarz, W.H. Moos, J.A. Bristol, J. Med. Chem. 30 (1987) 1955–1962.
[12] A. Akahane, H. Katayamam, T.J. Mitsunaga, Med. Chem. 42 (1999) 779–783.
[13] D.G.H. Livermone, R.C. Bethell, N.J. Cammack, Med. Chem. 36 (1993) 3784–3794.
[14] L.G. Costantino, G. Rastelli, D.B. Cignarella, IL Farmaco 55 (2000) 544–552.
[15] S.K. Kwon, A. Moon, Arch. Pharm. Res. 28 (2005) 391–394.
[16] S. Ahmad, I.G. Rathish, S. Bano, M.S. Alam, K. Javed, J. Enzyme Inhib. Med. Chem. 25 (2010) 266–271.
[17] R. Bashir, S. Yaseen, S. Ovais, S. Ahmad, H. Hamid, M.S. Alam, M. Samim, K. Javed, J. Enzyme Inhib. Med. Chem. 27 (2012) 92–96.
[18] C.S. Li, C. Brideau, C.C. Chan, C. Savoie, D. Claveau, S. Charleson, R. Gordon, G. Greig, J.Y. Gauthier, C.K. Lau, D. Riendeau, M. Therien, E. Wong, P. Prasit, Bioorg. Med. Chem. Lett. 13 (2003) 597–600.
[19] R.R. Harris, L. Black, S. Surapaneni, T. Kolasa, S. Majest, M.T.n Namovic, G. Grayson, V. Komater, D. Wilcox, L. King, K. Marsh, M.F. Jarvis, M. Nuss, H. Nellans, L. Pruesser, G.A. Reinhart, B. Cox, P. Jacobson, A. Stewart, M. Coghlan, G. Carter, R.L.J. Bell, Pharmacol. Exp. Ther. 311 (2004) 904–912.
[20] W. Malinka, A. Redzicka, O. Lozach, IL Farmaco 59 (2004) 457–462.
[21] F.A.E.-G. Nahed, K.M. Mona, S.K. Mona, M.R. Azza, G.H.S. Radwan, H.S. Galal, N.A.A. Sara, J. Chem. Pharm. Res. 3 (2011) 248–259.
[22] I.G. Rathish, K. Javed, S. Ahmad, S. Bano, M.S. Alam, M. Akhter, K.K. Pillai, S. Ovais, M. Samim, Eur. J. Med. Chem. 49 (2012) 304–309.
[23] E.R. Rayburn, S.J. Ezell, R. Zhang, Mol. Cell. Pharmacol. 1 (2009) 29–43.
[24] M.S.Y. Khan, A.A. Siddiqui, Indian J. Chem. 39B (2000) 614–619.
[25] M.S.Y. Khan, A. Hussain, S. Sharma, Indian J. Chem. 41B (2002) 2160–2171.
[26] M.R. Boyd, Am. Assoc. Cancer Res. 30 (1989) 652–663.
[27] A. Monks, D. Scudiero, P. Skehan, R. Shoemaker, K. Paull, D. Vistica, C. Hose, J. Langley, P. Cronise, A.V. Wolff, M.G. Goodrich, H. Campbell, J. Mayo, M.J. Boyd, Natl. Cancer Inst. 83 (1991) 757–766.
[28] J.N. Weinstein, T.G. Myers, P.M.O. Connor, S.H. Friend, A.J. Fornance Jr., K.W. Kohn, T. Fojo, S.E. Bates, L.V. Rubinstein, N.L. Anderson, J.K. Buolamwini, W.W.V. Osdol, A.P. Monks, D.A. Scudiero, E.A. Sausville, D.W. Zaharevitz, B. Bunow, V.N. Viswanadhan, G.S. Johnson, R.E. Wittes, K.D. Paull, Science 275 (1997) 343–349.
[29] M.G. Hollingshead, M.C. Alley, R.F. Camalier, B.J. Abbott, J.G. Mayo, L. Malspeis, M.R. Grever, Life Sci. 57 (1995) 131–141.
[30] M.R. Grever, S.A. Schepartz, B.A. Chabner, Semin. Oncol. 19 (1992) 622–638.
[31] M.R. Boyd, K.D. Paull, Drug Dev. Res. 34 (1995) 91–109.
[32] M.R. Boyd, Princ. Pract. Oncol. 3 (1989) 1–12.
[33] C.A. Winter, E.A. Risley, G.W. Nuss, Proc. Soc. Exp. Biol. Med. 111 (1962) 544–547.
[34] G. Daidone, B. Maggio, D. Raffa, S. Plescia, M.L. Bajardi, A. Caruso, V.M.C. Cutuli, M. Amico-Roxas, Eur. J. Med. Chem. 29 (1994) 707–711.