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ORIGINAL ARTICLE

Discovery of (±)-3-(1*H*-pyrazol-1-yl)-6,7-dihydro-5*H*-[1,2,4] triazolo[3,4-*b*][1,3,4] thiadiazine derivatives with promising in vitro anticoronavirus and antitumoral activity

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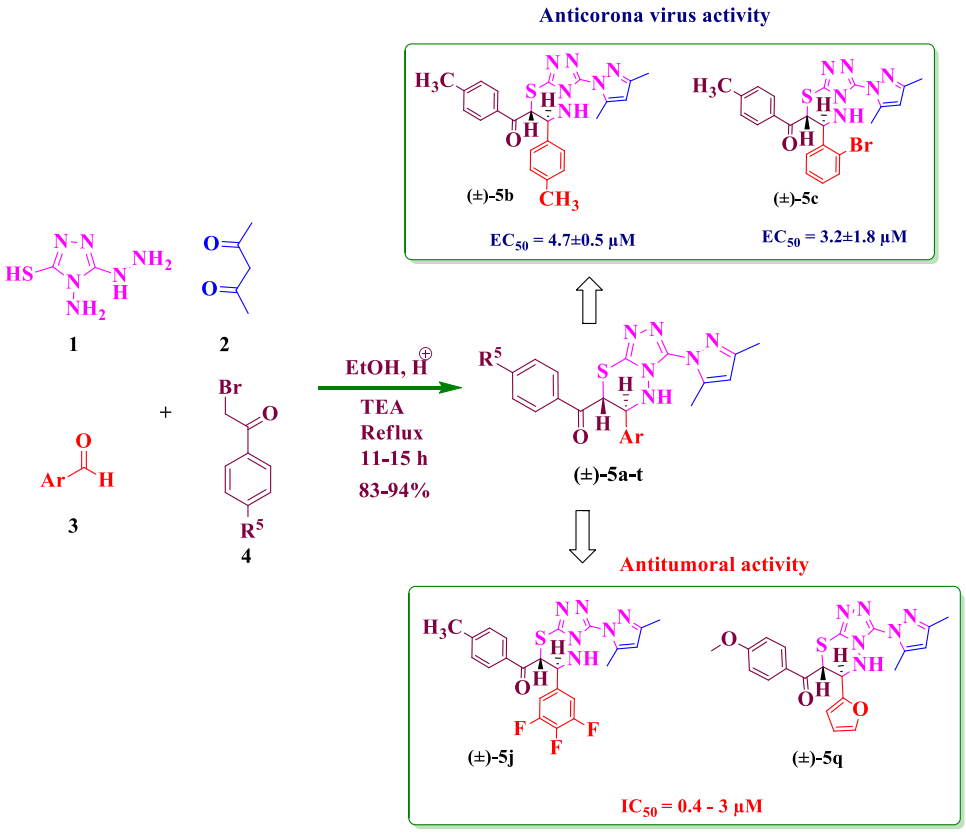
Abstract

A new series of (±)-(3-(3,5-dimethyl-1*H*-pyrazol-1-yl)-6-phenyl-6,7-dihydro-5*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazin-7-yl)(phenyl)methanones were efficiently synthesized starting from 4-amino-5-hydrazinyl-4*H*-1,2,4-triazole-3-thiol 1, acetyl acetone 2, various aromatic and heterocyclic aldehydes 3 and phenacyl bromides 4. All the newly synthesized compounds were tested for their antiviral and antitumoral activity. It was shown that subtle structural variations on the phenyl moiety allowed to tune biological properties toward antiviral or antitumoral activity. Mode-of-action studies revealed that the antitumoral activity was due to inhibition of tubulin polymerization.

Graphic abstract



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Keywords Triazole · Pyrazole · Antiviral · Antitumoral · Dihydrothiadiazine · Multi-component reaction

Introduction

Heterocyclic structures are well-known components of various biologically active compounds. Nitrogen-containing hetero aromatics [1–7], such as triazole and pyrazole are well known to impart biological activity. Examples of marketed drugs based on a 1,2,4-triazole scaffold include voriconazole (an antifungal drug), forasartan (used for the treatment of hypertension), sitagliptin (an antidiabetic drug) and letrozole (a non-steroidal aromatase inhibitor for the treatment of breast cancer) (Fig. 1) [8]. In addition, a wide range of 1,2,4-triazole derivatives have been synthesized and tested in a wide variety of biological assays, leading to the discovery of anti-bacterial [9, 10], antiviral [11, 12], antifungal [13, 14], anti-inflammatory [15, 16], anti-proliferative [17, 18], anti-convulsant [19], anti-oxidant [20] and anti-Parkinson [21] triazole analogues. Pyrazole ring is another example of a hetero aromatic scaffold, exhibiting a wide range of biological properties. Examples of drugs based on a pyrazole scaffold that received marketing include celecoxib and deracoxib (both cyclo-oxygenase-2 inhibitors), surinabant (a cannabinoid receptor type 1 antagonist) and crizotinib (an ALK inhibitor). However, a plethora of other activities, such as anti-HIV [22, 23], anti-malarial [24], anti-oxidant [25], anti-inflammatory [26], anti-bacterial [27, 28], anti-tumor [29], anti-pyretic [30], anti-analgesic [31], anti-cancer [32] and anti-leishmanial [33] activities have been associated with the pyrazole scaffold.

Although sulfur-containing heterocyclic compounds were found to have extensive biological applications, 1,3,4-thiadiazines are explored to a much lesser extent in medicinal chemistry, when compared to 1,2,4-triazole and pyrazole motifs. Thiadiazines are themselves showing good biological activities [34–39].

Multi-component reactions (MCRs), also known as multi-component assembly processes (MCAPs), are attractive synthetic methodologies in medicinal chemistry. The synthetic procedures in MCRs use mild reaction conditions and all, or most, of the atoms from the various reactants contribute to formation of the target compounds. The main advantages of MCRs are their atom economy, eco-friendliness and the fact that it allows to quickly generate structural diversity [40–44].

We recently reported the synthesis of [1, 2, 4]triazolo[3,4-*b*][1,3,4]thiadiazines through the multi-component reaction (MCR) process [45]. The presence of a hydrazino group in these molecules offers the possibility to convert them into pyrazole moieties. In view of the numerous biological applications of triazoles, pyrazoles and thiadiazines we became interested in the synthesis of the title compounds. Final compounds were subjected to a variety of assays in order to find antiviral and/or antitumoral activity.

Results and discussions

The synthesis of the (±)-3-(1*H*-pyrazol-1-yl)-6,7-dihydro-5*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine derivatives was performed using a two-step, one pot procedure. In order to optimize the chemistry, a model reaction was carried out using 4-amino-3-hydrazino-5-mercapto-1,2,4-triazole 1, acetylacetone 2, 2,3-dimethoxybenzaldehyde 3 and 4-methoxyphenacylbromide 4 as starting materials (Scheme 1).

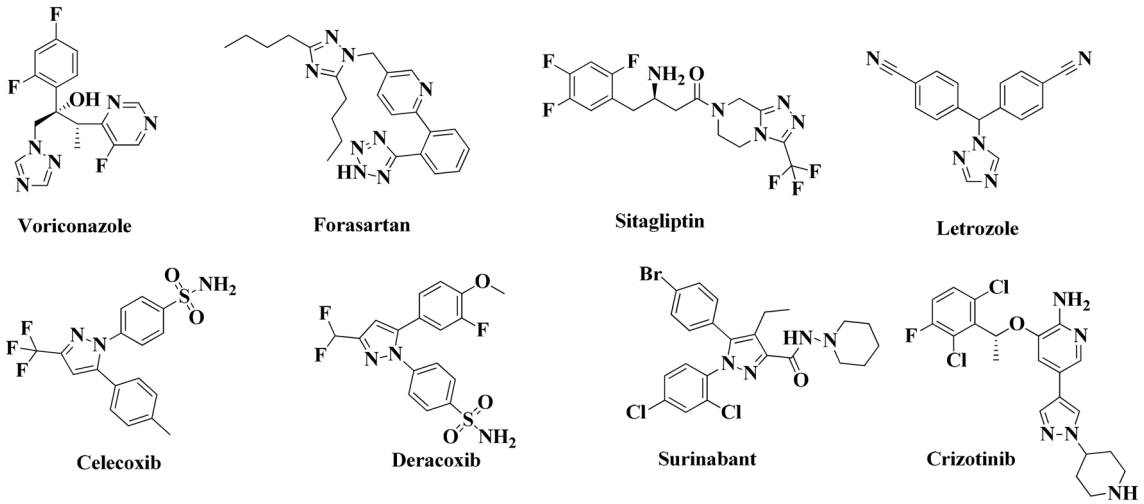
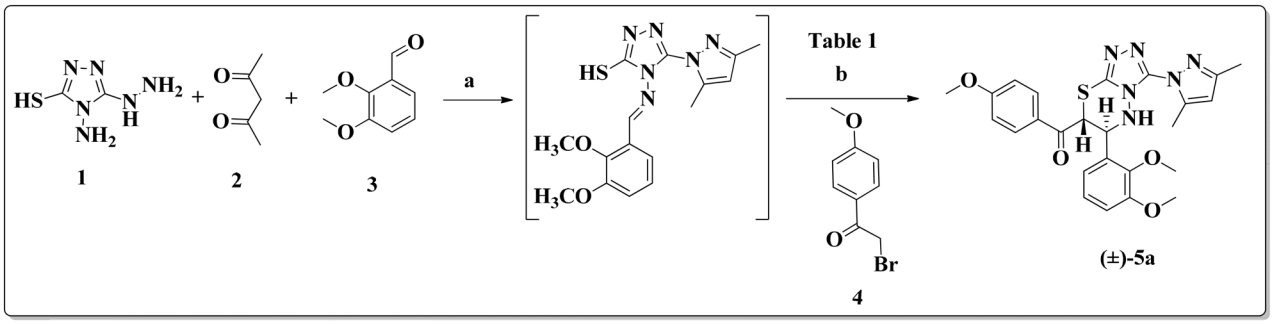


Fig. 1 Marketed drugs based on a 1,2,4-triazole and pyrazole scaffold



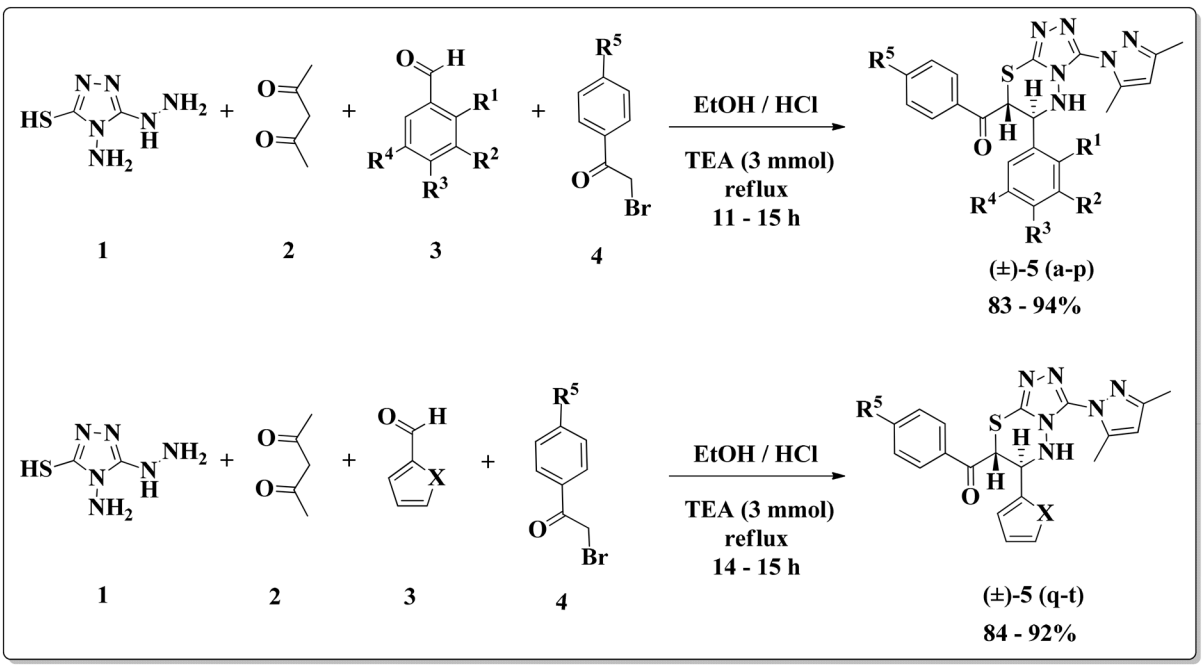
Scheme 1 Model reaction. *Reaction conditions*: **a** 1 (1 mmol), 2 (1 mmol), 3 (1 mmol), EtOH, HCl (one drop), **b** 4 (1 mmol), TEA (3 mmol), EtOH, reflux

Table 1 Screening of the base catalyst

Entry	Solvent	Base	Temp. (°C)	Time (h)	Yield (%) of (±)-5a
1	EtOH	–	70	10	0
2	EtOH	Pyridine	70	16	55
3	EtOH	Piperidine	70	12	48
4	EtOH	Triethylamine	70	11.30	92

The first step of the reaction was carried out in ethanol as solvent at reflux temperature, in the presence of a catalytic amount of HCl yielding the intermediate 5-(3,5-dimethyl-1*H*-pyrazol-1-yl)-4-((4-methoxybenzylidene) amino)-4*H*-1,2,4-triazole-3-thiol [46]. The intermediate was not isolated instead of it 4-methoxyphenacylbromide 4 was added to the reaction mixture. In order to drive the ring closure to form the thiadiazine moiety, various reaction conditions were explored (Table 1). Running this reaction, either at room temperature or at reflux temperature failed to yield the desired product. Upon the addition of an organic base (such as Pyridine, Piperidine or Triethylamine), the desired product was formed. Using triethylamine as base and running the reaction at reflux temperature (entry 4) resulted in the formation of desired compound (±)-5a in excellent yield (Table 1).

Using this methodology (Scheme 2), a series of compounds was prepared using various benzaldehydes,



Scheme 2 One-pot, four-component synthesis of (±)-3-(1*H*-pyrazol-1-yl)-6,7-dihydro-5*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine derivatives (5a-t)

heterocyclic aldehydes and phenacyl bromides (Table 2). This approach is simple and affords the desired products in yields ranging from 83 to 94%. (Table 3).

In the present investigation, pyrazole and dihydrothiadiazine skeletons were developed using one-pot, four-component reaction. Initially, hydrazino functional group of compound 1 underwent cyclocondensation with acetylacetone 2 to form pyrazole ring [47]. Then an appropriate amount of different aldehydes 3 and substituted phenacyl bromides 4 were reacted with amine ($–NH_2$) and thiol (–SH) groups of compound 1 respectively by using triethylamine to establish the dihydrothiadiazines (Scheme 3) [48].

The structures of the final products were confirmed by their spectral data. The FT-IR spectrum of product (±)-5b showed a characteristic stretching band at 1681 cm^{-1} corresponding to the –C=O functional group, whereas the –NH– group appeared at 3135 cm^{-1}. The ^{1}H-NMR spectrum of compound (±)-5b showed characteristic peaks, such as two singlets at 2.21 and 2.95 ppm, arising from the two methyl groups on the pyrazole ring. Another two singlets appeared at 2.37 and 2.43 ppm that were assigned to the methyl groups on both phenyl moieties. The two –CH– protons of the dihydrothiadiazine skeleton were visible as two doublets at 5.05 and 5.25 ppm, respectively. The proton of the pyrazole ring showed up as a singlet at 6.00 ppm, whereas the –NH– proton appeared at 7.42 ppm. The remaining aromatic protons appeared in the region of 7.11–7.80 ppm. The ^{13}C-NMR spectrum of compound (±)-5b showed peaks at 11.9 and 13.6 ppm for the carbon atoms of two methyl groups on the pyrazole ring at 21.1 and 21.8 ppm for the carbons of two methyl groups on the phenyl moiety. The characteristic carbons of the dihydrothiadiazine skeleton appeared at 44.2 and 59.3 ppm respectively. The pyrazole carbon displayed a peak at 107.8 ppm, whereas the carbonyl peak appeared as the most downfield signal at 193.7 ppm. The remaining aromatic carbons appeared in the range of 127.3 to 151.8 ppm. Mass spectral analysis of compound (±)-5b showed a molecular ion peak at *m/z* 445.

Table 3 Hydrogen bonding interactions

S. no	D–H…A	H…A (Å)	D…A (Å)	D–H…A (°)
1	N(6)-H(6) … N(2)^{i}	2.50	3.1298	130
2	C(4)-H(4) … N(4)^{i}	2.38	3.2637	150
3	C(19)-H(19) … O(1)^{ii}	2.46	3.3727	160

Symmetry transformations used: (i) ½-x, ½+y, ½+z; (ii) -½-x, ½+y,½-z;

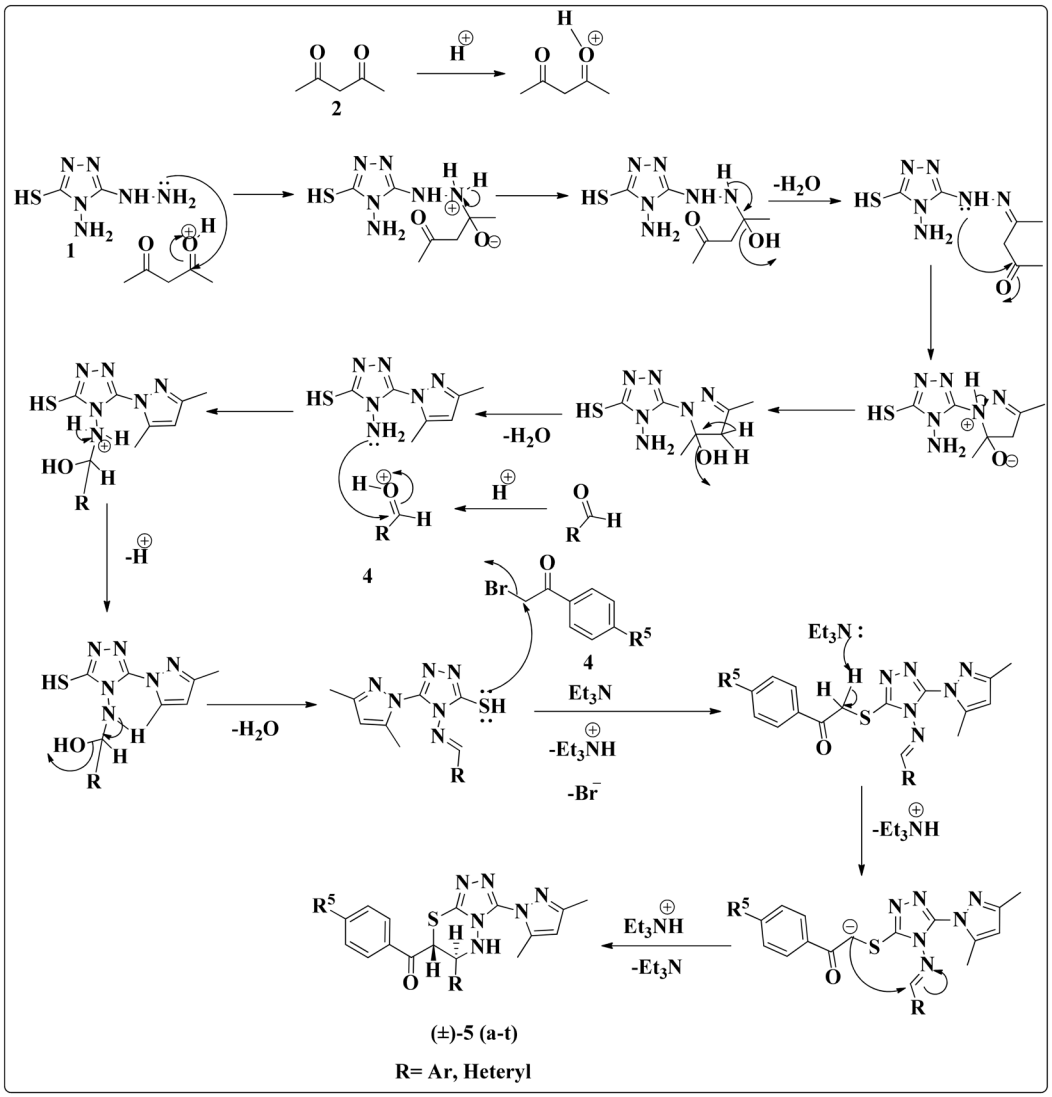
X-ray crystallography

To confirm the structure, crystalline material of compound (±)-5 h was isolated, and single crystal X-ray diffraction data were obtained. The compound crystallizes in a monoclinic $P2_1/n$ space group. The molecular structure of (±)–5 h in ORTEP representation is shown in Fig. 2.

Compound (±)–5 h has a 4-methylbenzoyl group and 4-chlorophenyl group on two adjacent chiral centers of the

Table 2 Derivatives of (±)-3-(1*H*-pyrazol-1-yl)-6,7-dihydro-5*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine (5a-t)

Product	R^1	R^2	R^3	R^4	R^5	X	Time (h)	Yield (%)
5a	OCH_3	OCH_3	H	H	OCH_3	–	11.30	92
5b	H	H	CH_3	H	CH_3	–	11.00	91
5c	H	H	NO_2	H	NO_2	–	14.30	83
5d	H	OCH_3	H	H	Cl	–	12.00	86
5e	Br	H	H	H	F	–	12.30	90
5f	Br	H	H	H	CH_3	–	11.50	92
5 g	H	H	Cl	H	Br	–	13.00	90
5 h	H	H	Cl	H	CH_3	–	12.00	93
5i	H	OCH_3	OH	OCH_3	H	–	11.40	89
5j	H	F	F	F	CH_3	–	14.00	92
5 k	H	F	F	F	H	–	13.30	90
5 l	H	OCH_3	OCH_3	OCH_3	F	–	13.15	88
5 m	H	OCH_3	OCH_3	OCH_3	H	–	11.40	94
5n	Cl	H	H	H	OCH_3	–	14.15	86
5o	OCH_3	H	OCH_3	H	OCH_3	–	12.00	94
5p	OCH_3	H	OCH_3	H	NO_2	–	14.00	92
5q	–	–	–	–	OCH_3	O	14.30	87
5r	–	–	–	–	CH_3	O	14.15	85
5 s	–	–	–	–	NO_2	S	15.00	89
5t	–	–	–	–	NO_2	O	14.50	92



Scheme 3 Plausible mechanism for the synthesis of compounds (±)–5a-t

six-membered dihydrothiadiazine ring. The dihydrothiadiazine moiety is fused with a triazole ring, further connected to a pyrazole ring through a carbon–nitrogen single bond. The phenyl rings of 4-methylbenzoyl and 4-chlorophenyl groups are almost perpendicular (79.92° and 82.28° respectively) to the mean plane of the fused six- and five-membered rings. The pyrazole ring attached to triazole makes an angle of 55.59° with the mean plane of the fused six- and five-membered rings. The bond distances and angles are consistent with the structure derived from NMR data. The centrosymmetric space group ($P2_1/n$) indicates (Table 4) that the material is a racemic mixture. The unit cell contains two pairs of enantiomers and is connected through non-covalent interactions.

Non-covalent intermolecular interactions, such as hydrogen bonding, play an essential role in binding of drugs to their targets, such as DNA or proteins. In this context, the possibility of the presence of non-covalent interactions in the solid state structure of compound (±)–5 h was explored. As a result, we were able to identify one N–H … N hydrogen bonding, one C–H … O interaction and one C–H … N interaction (Fig. 3). The interactions and corresponding symmetry transformations are listed in Table 3.

Biological evaluation

In vitro antiviral screening

Compounds ((±)–5a-t) were subjected to a broad antiviral screening. At a concentration of 100 µM, no selective antiviral activity was observed for the following viruses: influenza A (H1N1 and H3N2) and influenza B virus (in

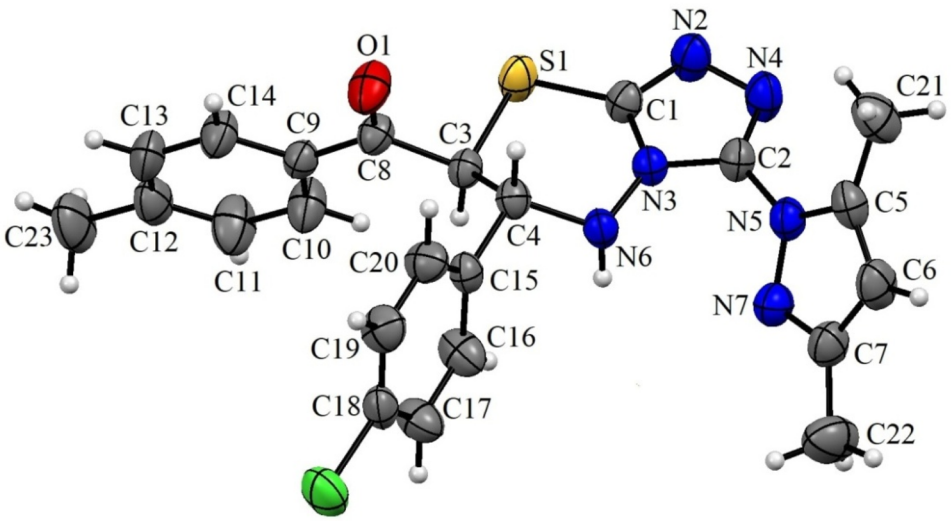


Fig. 2 ORTEP representation of compound (±)–5 h

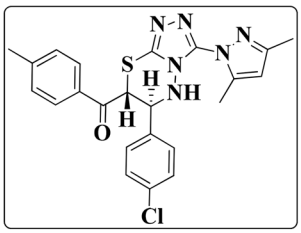


Table 4 Important crystallographic data for compound (±)–**5** h

Compound	(±)–5 h
Chemical formula	C_{23} H_{21} Cl N_6 O S
Formula weight	464.97
Crystal system	Monoclinic
Space group	$P2_1/n$
a (Å)	14.2063(18)
b (Å)	8.4877(11)
c (Å)	20.022(3)
α (°)	90
β (°)	107.576(5)
γ (°)	90
V (Å^3)	2301.6(5)
Z	4
ρ (g cm^{-3})	1.342
μ (mm^{-1})	0.285
Reflections collected	34,696
Reflections unique	4077
Reflections [$I \geq 2\sigma(I)$]	4077
Parameters	289
*R*1, *wR*2 [$I \geq 2\sigma(I)$]	0.0471, 0.1330
*R*1, *wR*2 [all data]	0.0537, 0.1387
GOF on F^2	1.136
Max./Min. $\Delta\rho$ (e Å^{-3})	−0.710

MDCK cells), respiratory syncytial virus (in HEp-2cells), yellow fever virus (in Huh7 cells), herpes simplex virus type 1 and 2 (in HEL 299 cells). However, a number of derivatives did show antiviral activity against the human corona virus 229E (hCoV-229E) in HEL 299 cells (Table 5). Especially compounds (±)–5b and (±)–5f displayed promising activity with EC_{50} values of 4.7 and 3.2 μM, respectively. In addition, both derivatives lacked cytotoxicity for the HEL cells giving rise to favorable selectivity indexes.

In vitro antitumoral screening

To investigate their anti-cancer potential, compounds 5a-t were tested in vitro for their anti-proliferative properties, using a real-time IncuCyteproliferation assay against an array of solid and hematological cancers including LN-229 (glioblastoma), Capan-1 (pancreatic adenocarcinoma), HCT-116 (colorectal carcinoma), NCI-H460 (lung carcinoma), DND-41 (acute lymphoblastic leukemia), HL-60 (acute myeloid leukemia), K-562 (chronic myeloid leukemia) and Z-138 (non-Hodgkin lymphoma) cell lines. Docetaxel (a microtubule depolymerisation inhibitor) and staurosporine (STS, a pan-kinase inhibitor) were used as positive controls. From this screening campaign, two derivatives (compounds 5j and 5q) emerged that showed low μM activity against the different cell lines (Table 6).

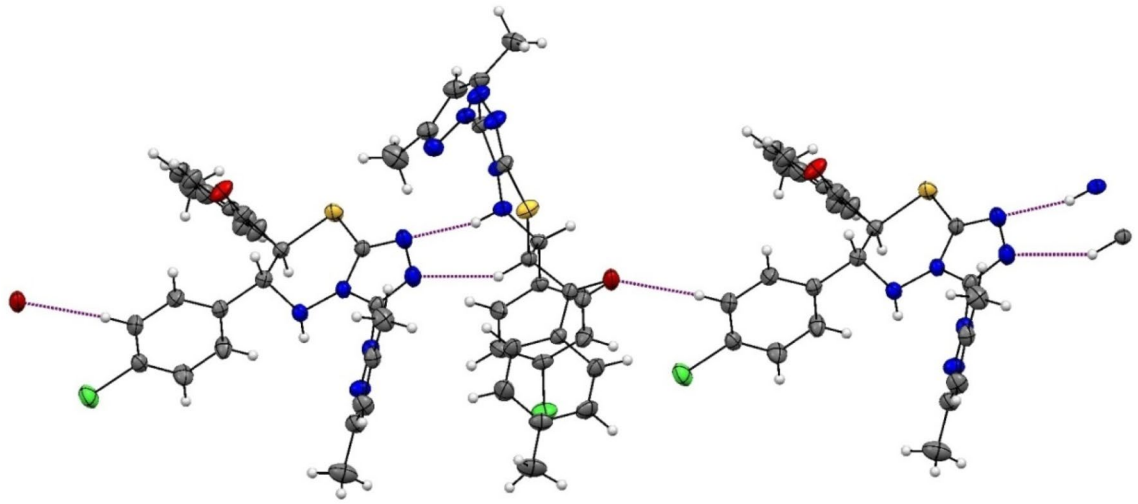


Fig. 3 Intermolecular Hydrogen bonding interactions of compound (±)–5 h in crystal lattice

Table 5 Antiviral evaluation of compounds (±)–**5**a–t against hCoV-229E

Compound	Conc. unit	hCoV-229E (HEL cells)	
		CC_{50}	EC_{50}
5b	µM	81.5	4.7 ± 0.5 (*)
5c	µM	> 100	24.4
5e	µM	> 100	> 100
5f	µM	> 100	3.2 ± 1.8 (*)
5 g	µM	> 100	> 100
5 h	µM	> 100	38.0
5j	µM	23.8	> 100
5 k	µM	> 100	> 100
5 m	µM	> 100	95.7
5n	µM	> 100	> 100
5p	µM	> 100	> 100
5q	µM	< 0.8	> 100
5r	µM	> 100	> 100
5 s	µM	> 100	> 100
5t	µM	> 100	> 100
UDA	µg/ml	> 100	2.1

(*)Mean value of three independent experiments ± SEM

Because of the promising antitumoral profile of compounds (±)–5j and (±)–5q, their apoptogenic potential in non-cancerous peripheral blood mononuclear cells (PBMCs) was determined as counter screening. The activation of the executioner caspases-3 and -7 normally precedes the manifestation of apoptosis as massive DNA fragmentation. Therefore, the caspase-3/7 Green reagent was added to the PBMCs, which are also treated with different concentrations of compounds (±)–5j and (±)–5q. When activated caspase 3 or 7 are intracellularly present, they will cleave the Caspase-3/7 Green Reagent at the DEVD motif. This results in the release of a DNA binding dye that fluorescently labels nuclear DNA of apoptic cells. In addition, in order to distinguish dead cells from live cells, a propidium iodide (PI) staining was carried out. As can be derived from Fig. 4, only very high concentrations of compounds (±)–5j and (±)–5q (100 µM) give rise to a small increase in the number of apoptotic and dead cells. Overall, these data indicate that compounds (±)–5j and (±)–5q did not inhibit the viability of normal PBMCs and demonstrate selectivity toward cancer cells over normal cells (Fig. 4).

Despite their promising antitumoral profile, the exact molecular target of compounds (±)-5j and (±)-5q remained elusive. In order to assess whether they interact with tubulin, an immune fluorescence analysis of tubulin in HEp-2 cells treated for 3 h with compounds (±)-5j and (±)-5q was performed, and compared to DMSO (vehicle control) and to vincristine (a known tubulin polymerization inhibitor, used as positive control). It can be clearly observed that both compounds (±)-5j and (±)-5q inhibit the polymerization of tubulin in a dose-dependent manner (Fig. 5).

Conclusion

The synthesis of a new series of (±)-3-(1*H*-pyrazol-1-yl)-6,7-dihydro-5*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine derivatives was carried out in an excellent yields via a one-pot, four-component method using readily available starting materials. The reactions proceeds in such a way with high atom economy, leading to the formation of one C=N, two C–N, one C–C, and one C–S bonds in a single operation, giving multi-annulated products. All the final compounds were tested for their antiviral and antitumoral activity. It

Table 6 Antitumoral evaluation of compounds from (±)–5a-t**.** IC_{50}

Compound	IC_{50} (μM)							
	LN-229	Capan-1	HCT-116	NCI-H460	DND-41	HL-60	K-562	Z-138
5b	47.1	57.5	67.8	> 100	39.3	50.9	10.4	48.4
5c	> 100	> 100	> 100	> 100	> 100	> 100	> 100	> 100
5e	> 100	> 100	> 100	> 100	> 100	> 100	> 100	> 100
5f	> 100	> 100	> 100	> 100	> 100	> 100	> 100	> 100
5 g	> 100	> 100	> 100	> 100	> 100	> 100	> 100	> 100
5 h	> 100	> 100	> 100	> 100	> 100	> 100	> 100	> 100
5j*	2.7 ± 0.2	2.3 ± 0.2	2.5 ± 0.09	56.0	2.4 ± 0.4	13.0 ± 2.8	3.4 ± 0.2	1.9 ± 0.03
5 k	> 100	> 100	> 100	> 100	> 100	> 100	> 100	> 100
5 m	> 100	> 100	> 100	> 100	> 100	> 100	> 100	> 100
5n	68.3	63.1	> 100	> 100	91.7	71.2	53.2	53.9
5p	> 100	> 100	> 100	> 100	> 100	> 100	> 100	> 100
5q*	0.7 ± 0.09	1.1 ± 0.7	1.0 ± 0.4	2.5 ± 0.2	0.6 ± 0.2	2.0 ± 0.4	2.3 ± 1.6	0.4 ± 0.005
5r	43.9	54.3	69.0	47.0	70.2	54.0	23.5	50.2
5 s	> 100	> 100	> 100	> 100	> 100	> 100	> 100	> 100
5t	62.7	> 100	> 100	> 100	> 100	74.5	79.3	49.5
Docetaxel*	0.0087 ± 0.0004	0.0042 ± 0.0021	0.0009 ± 0.0008	0.0038 ± 0.0029	0.0033 ± 0.0014	0.0023 ± 0.0003	0.0037 ± 0.0003	0.0011 ± 0.0008
STS*	0.0229 ± 0.0021	0.0007 ± 0.0002	0.0004 ± 0.0001	0.00010 ± 0.0000	0.0015 ± 0.0004	0.0043 ± 0.0022	0.0074 ± 0.0017	0.0224 ± 0.0074

*Mean value of two independent experiments ± SEM

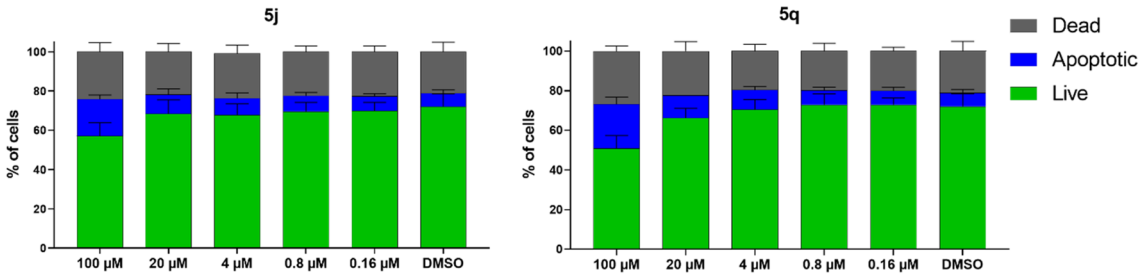


Fig. 4 Analysis of apoptosis induction by compound–5j (left) and (±)–5q (right) in PBMC originating from two healthy donors

was demonstrated that subtle structural modifications on the phenyl moieties allowed to tune the biological properties of the compounds. Among the newly synthesized compounds, a number of derivatives show promising antiviral activity against the hCoV-229E, whereas other derivatives exhibited cytotoxicity in various cancer cell lines. In addition, it was demonstrated that the antitumoral activity of these compounds is caused by inhibition of tubulin polymerization.

Experimental

General

All the reactants, reagents and solvents were pure, purchased from commercial sources and used without further purification. All the synthesized compounds were preliminarily confirmed by monitoring using TLC plates (E, Merck, Mumbai, India) in the UV-light chamber. A "Stuart SMP30" programmable melting point instrument (Bibby Scientific Ltd. U.K.) was used to record the melting points of the synthesized compounds. FT-IR spectra of the newly synthesized compounds in KBr-pellets were recorded on a PerkinElmer 100S FT-IR spectrophotometer. The ^{1}H- and the ^{13}C-NMR chemical shift values were determined for the compounds on Avance-III Bruker WM-400 MHz spectrometer in δ ppm. Tetramethylsilane (TMS) acts as reference standard for the chemical shifts. Suitable deuterated solvents like $CDCl_3$ and DMSO-d_6 were used as solvent for the various compounds to record ^{1}H- and ^{13}C-NMR spectra. Molecular ion peaks were recorded as *m/z,* ESI-Mass spectra on a PerkinElmer spectrometer performing at 12.5 eV. Carlo Erba EA 1108 CHNS-O automatic analyzer was used for the elemental analysis.

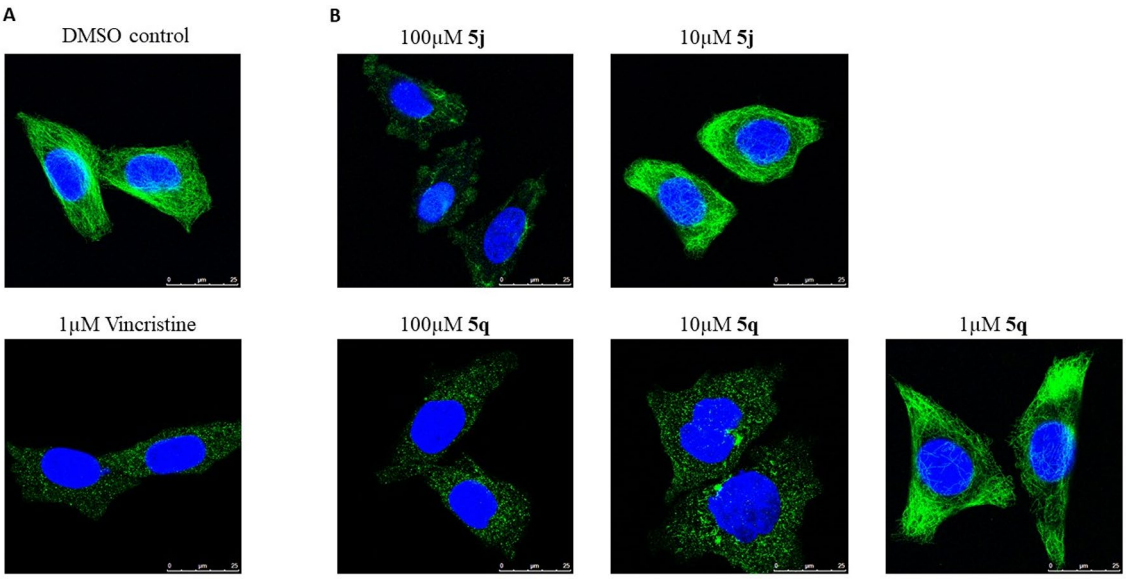


Fig. 5 Immune fluorescence staining of alpha-tubulin in HEp-2 cells: **a** Representative images of normal alpha-tubulin after treatment with DMSO (top) or typical phenotype after treatment with vincristine (bottom), **b** Treatment with compounds (±)–5j and (±)–5q. Green: alpha-tubulin, blue: DAPI. Scale bar: 25 μM

General procedure for the synthesis of (±)-(3-(3,5-dimethyl-1*H*-pyrazol-1-yl)-6-phenyl-6,7-dihydro-5*H*-[1,2,4]triazolo[3,4-*b*][1,3,4] thiadiazin-7-yl)(phenyl)methanones (5a-t).

A mixture of 4-amino-5-hydrazino-4*H*-[1, 2, 4] triazole-3-thiol 1 (1 mmol), acetyl acetone (ACAC) 2 (1 mmol) and appropriate aromatic aldehydes/heterocyclic aldehydes 3 (1 mmol) was taken sequentially in 5 mL of dry ethanol containing drop of Conc. HCl. The reaction mixture was refluxed for 5–7 h by monitoring TLC. After completion of reaction, to the reaction mixture substituted phenacyl bromides 4 (1 mmol) and triethylamine (TEA) (3 mmol) were added and one drop of HCl was neutralized by one mole of TEA. Then the reaction was continued under the reflux for 6–8 h by monitoring TLC ($CHCl_3$:CH_3OH = 95:5). The reaction mixture was cooled to room temperature, diluted with water and the solid separated was filtered. The final products were recrystallized from 6–8 mL ethanol.

(±)-(6-(2,3-Dimethoxyphenyl)-3-(3,5-dimethyl-1H-pyrazol-1-yl)-6,7-dihydro-5H[1,2,4]triazole [3,4-b][1,3,4]thiadiazin-7-yl)(4-methoxyphenyl) methanone (5a)

Light yellow color solid; yield 92%; m.p.: 192–194 °C; IR (KBr, υ_{max}/cm^{-1}): 3211 (NH), 1668 (C=O); ^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm): 2.24 (*s*, 3H, CH_3), 2.40 (*s*, 3H, CH_3), 3.87 (*s*, 6H, OCH_3), 3.90 (*s*, 3H, OCH_3), 5.28 (unresolved doublet, 2H, CH), 6.00 (*s*, 1H, CH of pyrazole ring), 6.68 (d, 1H, *J* = 7.6 Hz, Ar–H), 6.88 *(d*, 1H, *J* = 8.0 Hz, Ar–H), 6.94 (*s*, 1H, NH), 6.97 *(d*, 2H, *J* = 8.4 Hz, Ar–H), 7.11 *(d*, 1H, *J* = 8.0 Hz, Ar–H), 7.94 *(d*, 2H, *J* = 8.8 Hz, Ar–H); ^{13}C-NMR (100 MHz, $CDCl_3$, δ ppm): 11.7, 13.7, 42.6, 54.9, 55.7, 55.8, 61.0, 107.7, 112.9, 114.3, 119.7, 124.4, 127.4, 129.4, 130.3, 130.8, 131.2, 142.9, 146.1, 151.8, 152.6, 164.6, 193.2; ESI–MS *m/z*: 507 $[M+H]^+$; Analytical calculated formulae $C_{25}H_{26}N_6O_4S$: C, 59.27; H, 5.17; N, 16.59; S, 6.33; Found: C, 59.22; H, 5.22; N, 16.53; S, 6.30.

(±)-(3-(3,5-Dimethyl-1H-pyrazol-1-yl)-6-(p-tolyl)-6,7-dihydro-5H-[1,2,4] triazolo[3,4-b][1,3,4] thiadiazin-7-yl)(p-tolyl)methanone (5b)

White solid; yield 91%; m.p.: 194–196 °C; IR (KBr, υ_{max}/cm^{-1}): 3135 (NH), 1681 (C=O); ^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm): 2.22 (*s*, 3H, CH_3), 2.30 (*s*, 3H, CH_3), 2.38 (*s*, 3H, CH_3), 2.43 (*s*, 3H, CH_3), 5.05 (unresolved doublet, 1H, CH), 5.25 *(d*, 1H, *J* = 5.2 Hz, CH), 6.00 (*s*, 1H, CH of pyrazole ring), 7.11 *(d*, 2H, *J* = 8.0 Hz, Ar–H), 7.29 *(d*, 4H, *J* = 7.2 Hz, Ar–H), 7.42 (*s*, 1H, NH), 7.80 *(d*, 2H, *J* = 8.0 Hz, Ar–H); ^{13}C-NMR (100 MHz, $CDCl_3$, δ ppm): 11.9, 13.6, 21.1, 21.8, 44.2, 59.3, 107.8, 127.3, 128.8, 129.7, 129.8, 132.0, 132.7, 138.8, 141.3, 143.1, 145.6, 145.7, 151.8, 193.7; ESI–MS *m/z*: 445 $[M+H]^+$; Analytical calculated formulae $C_{24}H_{24}N_6OS$: C, 64.84; H, 5.44; N, 18.90; S, 7.21; Found: C, 64.89; H, 5.40; N, 18.85; S, 7.18.

(±)-(3-(3,5-Dimethyl-1H-pyrazol-1-yl)-6-(4-nitrophenyl)-6,7-dihydro-5H-[1,2,4]triazolo[3,4-b][1,3,4] thiadiazin-7-yl)(4-nitrophenyl) methanone (5c)

Yellow solid; yield 83%; m.p.: 242–244 °C; IR (KBr, υ_{max}/cm^{-1}): 3302 (NH), 1614 (–C=O); ^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm): 2.16 (*s*, 3H, CH_3), 2.44 (*s*, 3H, CH_3), 5.05 *(d*, 1H, *J* = 6.0 Hz, CH), 5.20 *(d*, 1H, *J* = 6.0 Hz, CH), 6.00 (*s*, 1H, CH of pyrazole ring), 7.30 *(d*, 2H, *J* = 8.4 Hz, Ar–H), 7.38 *(d*, 2H, *J* = 8.4 Hz, Ar–H), 7.65 *(d*, 2H, *J* = 8.1 Hz, Ar–H), 7.73 (*s*, 1H, NH), 7.77 *(d*, 2H, *J* = 8.4 Hz, Ar–H); ^{13}C-NMR (100 MHz, $CDCl_3$, δ ppm): 12.0, 13.5, 44.1, 59.1, 107.9, 128.9, 129.0, 129.2, 129.9, 131.9, 134.3, 134.9, 141.0, 143.1, 145.5, 146.0, 151.8, 193.5; ESI–MS *m/z*: 507 $[M+H]^+$; Analytical calculated formulae $C_{22}H_{18}N_8O_5S$: C, 52.17; H, 3.58; N, 22.12; S, 6.33; Found: C, 52.23; H, 3.54; N, 22.17; S, 6.30.

(±)-(4-Chlorophenyl)(3-(3,5-dimethyl-1H-pyrazol-1-yl)-6-(3-methoxyphenyl)-6,7-dihydro-5H-[1,2,4]triazolo[3,4-b][1,3,4][1,3,4]thiadiazin-7-yl)methanone (5d)

Cream color solid; yield 86%; m.p.: 188–190 °C; IR (KBr, υ_{max}/cm^{-1}): 3138 (NH), 1692 (C=O); ^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm): 2.19 (*s*, 3H, CH_3), 2.41 (*s*, 3H, CH_3), 3.74 (*s*, 3H, OCH_3), 5.04 (t, 1H, *J* = 4.0 Hz, CH), 5.25 *(d*, 1H, *J* = 4.4 Hz, CH), 6.00 (*s*, 1H, CH of pyrazole ring), 6.83 *(d*, 1H, *J* = 6.8 Hz, Ar–H), 6.96 (*s*, 1H, Ar–H), 6.98 *(d*, 1H, *J* = 6.4 Hz, Ar–H), 7.23 (t, 1H, *J* = 6.4 Hz, Ar–H), 7.47 *(d*, 2H, *J* = 6.4 Hz, Ar–H), 7.58 (*s*, 1H, NH), 7.84 *(d*, 2H, *J* = 6.8 Hz, Ar–H); ^{13}C-NMR (100 MHz, $CDCl_3$, δ ppm): 12.0, 13.6, 44.9, 55.3, 59.8, 107.9, 113.3, 114.4, 119.4, 129.5, 130.1, 130.2, 132.9, 137.1, 140.9, 141.2, 143.2, 145.5, 151.8, 160.0 192.9; ESI–MS *m/z*: 481 $[M+H]^+$; Analytical calculated formulae $C_{23}H_{21}ClN_6O_2S$: C, 57.44; H, 4.40; N, 17.47; S, 6.67; Found: C, 57.48; H, 4.45; N, 17.42; S, 6.62.

(±)-(6-(2-Bromophenyl)-3-(3,5-dimethyl-1H-pyrazol-1-yl)-6,7-dihydro-5H-[1,2,4]triazolo[3,4-b][1,3,4] thiadiazin-7-yl)(4-fluorophenyl)methanone (5e)

Golden yellow color solid; yield 90%; m.p.: 195–197 °C; IR (KBr, υ_{max}/cm^{-1}): 3138 (NH), 1692 (C=O); ^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm): 2.15 (*s*, 3H, CH_3), 2.48 (*s*, 3H, CH_3), 5.22 *(d*, 1H, *J* = 4.0 Hz, CH), 5.50 (t, 1H, *J* = 4.8 Hz, CH), 5.99 (*s*, 1H, CH of pyrazole ring), 7.17 (*s*, 1H, NH), 7.20 *(d*, 2H, *J* = 8.4 Hz, Ar–H), 7.24 *(d*, 1H, *J* = 2.0 Hz, Ar–H), 7.59 *(d*, 1H, *J* = 7.6 Hz, Ar–H), 7.78 *(d*, 1H, *J* = 5.6 Hz, Ar–H), 8.01 *(d*d, 2H, *J* = 8.8 Hz, *J* = 5,2 Hz, Ar–H); ^{13}C-NMR (100 MHz, $CDCl_3$, δ ppm): 11.9, 13.3, 43.1, 58.3, 107.8, 116.3, 116.5, 123.2, 128.1, 128.6, 130.2, 131.7, 131.8, 133.4, 136.4, 140.0, 142.9, 145.5, 151.7, 166.2, 167.8 192.5; ESI–MS *m/z*: 515 $[M+2]^+$; Analytical calculated formulae $C_{22}H_{18}BrFN_6OS$: C, 51.47; H, 3.53; N, 16.37; S, 6.25; Found: C, 51.42; H, 3.57; N, 16.32; S, 6.20.

(±)-(6-(2-Bromophenyl)-3-(3,5-dimethyl-1H-pyrazol-1-yl)-6,7-dihydro-5H-[1,2,4]triazolo[3,4-b][1,3,4] thiadiazin-7-yl)(p-tolyl)methanone (5f)

Lemon yellow color solid; yield 92%; m.p.: 201–203 °C; IR (KBr, υ_{max}/cm^{-1}): 3148 (NH), 1673 (C=O); ^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm): 2.20 (*s*, 3H, CH_3), 2.44 (*s*, 3H, CH_3), 2.46 (*s*, 3H, CH_3), 5.22 *(d*, 1H, *J* = 4.0 Hz, CH-), 5.49 (t, 1H, *J* = 4.8 Hz, CH), 6.00 (*s*, 1H, CH of pyrazole ring), 7.19 (t, 2H, *J* = 8.0 Hz, Ar–H), 7.23 (*s*, 1H, NH), 7.31 *(d*, 2H, *J* = 8.0 Hz, Ar–H), 7.58 *(d*, 1H, *J* = 7.6 Hz, Ar–H), 7.65 *(d*, 1H, *J* = 5.2 Hz, Ar–H), 7.86 *(d*, 2H, *J* = 8.0 Hz, Ar–H); ^{13}C-NMR (100 MHz, $CDCl_3$, δ ppm): 11.9, 13.5, 21.8, 42.9, 57.8, 107.8, 123.0, 128.1, 128.6, 128.9, 129.9, 130.2, 131.7, 133.4, 136.6 140.1, 142.9, 145.6, 145.7, 151.8, 193.7; ESI–MS *m/z*: 511 $[M+2]^+$; Analytical calculated formulae $C_{23}H_{21}BrN_6OS$: C, 54.23; H, 4.16; N, 16.50; S, 6.29; Found: C, 54.28; H, 4.21; N, 16.44; S, 6.33.

(±)-(4-Bromophenyl) (6-(4-chlorophenyl)-3-(3,5-dimethyl-1H-pyrazol-1-yl)-6,7-dihydro-5H- triazolo[3,4-b][1,3,4] thiadiazin-7-yl)methanone (5g)

White solid; yield 90%; m.p.: 205–207 °C; IR (KBr, υ_{max}/cm^{-1}): 3291 (NH), 1688 (C=O); ^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm): 2.16 *(s*, 3H, $–CH_3$), 2.44 *(s*, 3H, CH_3), 5.05 *(d*d, 1H, *J* = 6.0 Hz, *J* = 3.6 Hz, CH–), 5.2 *(d*, 1H, *J* = 6.0 Hz, CH), 6.00 *(s*, 1H, CH of pyrazole ring), 7.30 *(d*, 2H, *J* = 8.4 Hz, Ar–H), 7.38 *(d*, 2H, *J* = 8.4 Hz, Ar–H), 7.65 *(d*, 2H, *J* = 8.1 Hz, Ar–H), 7.72 *(s*, 1H, NH), 7.77 *(d*, 2H, *J* = 8.4 Hz, Ar–H); ^{13}C-NMR (100 MHz, $CDCl_3$, δ ppm): 12.0, 13.5, 44.9, 59.5, 107.9, 129.0, 129.3, 132.1, 130.2 132.6, 133.2, 134.2, 135.1, 140.6, 143.1, 145.3, 151.8, 192.8; ESI–MS *m/z*: 531 $[M+2]^+$; Analytical calculated formulae $C_{22}H_{18}BrClN_6OS$: C, 49.87; H, 3.42; N, 15.86; S, 6.05; Found: C, 49.84; H, 3.48; N, 15.83; S, 6.12.

(±)-(6-(4-Chlorophenyl)-3-(3,5-dimethyl-1H-pyrazol-1-yl)-6,7-dihydro-5H-[1,2,4]triazolo[3,4-b] [1,3,4]thiadiazin-7-yl)(p-tolyl)methanone (5 h)

White solid; yield 93%; m.p.: 214–216 °C; IR (KBr, υ_{max}/cm^{-1}): 3219 (NH), 1675 (C=O); ^{1}H-NMR (400 MHz, $CDCl_3$ + DMSO-d_6, δ ppm): 2.25 *(s*, 3H, CH_3), 2.31 *(s*, 3H, CH_3), 2.44 *(s*, 3H, CH_3), 3.21 *(s*, 1H, NH), 4.99 (unresolved singlet, 1H, CH), 5.69 *(d*, 1H, *J* = 5.2 Hz, CH), 6.06 *(s*, 1H,

CH of pyrazole ring), 7.19 *(d*, 1H, *J* = 7.2 Hz, Ar–H), 7.28 *(d*, 1H, *J* = 6.4 Hz, Ar–H), 7.33 *(d*, 2H, *J* = 7.6 Hz, Ar–H), 7.47 *(s*, 2H, Ar–H), 7.90 *(s*, 2H, Ar–H); ^{13}C-NMR (100 MHz, $CDCl_3$ + DMSO-d_6, δ ppm): 11.4, 13.7, 21.8, 42.5, 58.2, 107.6, 128.9, 129.1, 129.3, 129.8, 132.2, 133.9, 135.2, 141.8, 142.8, 145.6, 146.6, 151.4, 194.3; ESI–MS *m/z*: 465 $[M+H]^+$; Analytical calculated formulae $C_{23}H_{21}ClN_6OS$: C, 59.41; H, 4.55; N, 18.07; S, 6.90; Found: C, 59.45; H, 4.51; N, 18.10; S, 6.85.

(±)-(3-(3,5-Dimethyl-1H-pyrazol-1-yl)-6-(4-hydroxy-3,5-dimethoxyphenyl)-6,7-dihydro-5H- triazolo[3,4-b][1,3,4]thiadiazin-7-yl) (phenyl)methanone (5i)

Green solid; yield 89%; m.p.: 196–198 °C; IR (KBr, υ_{max}/cm^{-1}): 3435 (OH), 3134 (NH), 1653 (C=O); ^{1}H-NMR (400 MHz, $CDCl_3$ + DMSO-d_6, δ ppm): 2.21 *(s*, 3H, CH_3), 2.25 *(s*, 3H, CH_3), 3.71 *(s*, 6H, OCH_3), 4.80 (t, 1H, *J* = 6.8 Hz, CH), 5.86 *(d*, 1H, *J* = 6.0 Hz, CH), 6.11 *(s*, 1H, CH of pyrazole ring), 6.35 *(s*, 1H, OH), 6.77 *(s*, 2H, Ar–H), 7.07 *(s*, 1H, NH), 7.54 (t, 2H, *J* = 8.0 Hz, Ar–H), 7.67 (t, 1H, *J* = 7.2 Hz, Ar–H), 8.00 *(d*, 2H, *J* = 7.2 Hz, Ar–H); ^{13}C-NMR (100 MHz, $CDCl_3$, δ ppm): 11.9, 13.5, 45.4, 56.2, 60.8, 104.8, 107.8, 128.7, 129.1, 131.0, 134.5, 134.7, 138.4, 141.5, 143.2, 145.4, 151.7, 153.5, 194.1; ESI–MS *m/z*: 493 $[M+H]^+$; Analytical calculated formulae $C_{24}H_{24}N_6O_4S$: C, 58.52; H, 4.91; N, 17.06; S, 6.51; Found: C, 58.57; H, 4.94; N, 17.10; S, 6.47.

(±)-(3-(3,5-Dimethyl-1H-pyrazol-1-yl)-6-(3,4,5-trifluorophenyl)-6,7-dihydro-5H-[1,2,4]triazole [3,4-b][1,3,4]thiadiazin-7-yl) (p-tolyl)methanone (5j)

White solid; yield 92%; m.p.: 215–217 °C; IR (KBr, υ_{max}/cm^{-1}): 3219 (NH), 1674 (C=O); ^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm): 2.19 *(s*, 3H, CH_3), 2.43 *(s*, 3H, CH_3), 2.50 *(s*, 3H, CH_3), 3.48 *(s*, 1H, NH), 5.035 (t, 1H, *J* = 8.0 Hz, CH), 5.48 *(d*, 1H, *J* = 8.0 Hz, CH), 6.00 *(s*, 1H, CH of pyrazole ring), 6.67 (t, 2H, *J* = 8.4 Hz, Ar–H), 7.30 *(d*, 2H, *J* = 8.4 Hz, Ar–H), 7.82 *(d*, 2H, *J* = 8.0 Hz, Ar–H); ^{13}C-NMR (100 MHz, $CDCl_3$, δ ppm): 11.9, 13.5, 21.8, 44.1, 53.1, 101.3, 107.9, 127.5, 128.9, 129.9, 129.8, 131.6, 141.3, 143.2, 145.6, 146.1, 151.8, 160.0, 192.2; ESI–MS *m/z*: 485 $[M+H]^+$; Analytical calculated formulae $C_{23}H_{19}F_3N_6OS$: C, 57.02; H, 3.95; N, 17.35; S, 6.62; Found: C, 57.17; H, 3.99; N, 17.39; S, 6.62.

(±)-(3-(3,5-Dimethyl-1H-pyrazol-1-yl)-6-(3,4,5-trifluorophenyl)-6,7-dihydro-5H-[1,2,4]triazole [3,4-b][1,3,4]thiadiazin-7-yl) (phenyl)methanone (5 k)

Light yellow color solid; yield 90%; m.p.: 182–184 °C; IR (KBr, υ_{max}/cm^{-1}): 3207 (NH), 1681 (C=O); ^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm): 2.15 *(s*, 3H, CH_3), 2.49 *(s*, 3H, CH_3), 5.34 (t, 1H, *J* = 8.0 Hz, CH–), 5.56 *(d*, 1H, *J* = 8.4 Hz, CH), 5.99 *(s*, 1H, CH of pyrazole ring), 6.67 (t, 2H, *J* = 8.4 Hz, Ar–H), 7.15 *(s*, 1H, NH), 7.51 (t, 2H, *J* = 7.6 Hz, Ar–H), 7.64 (t, 1H, *J* = 7.2 Hz, Ar–H), 7.94 *(d*, 2H, *J* = 7.6 Hz, Ar–H); ^{13}C-NMR (100 MHz, $CDCl_3$, δ ppm): 11.9, 13.4, 44.3, 53.2, 101.3, 107.9, 127.5, 128.9, 129.1, 129.2, 130.4, 134.8, 134.9, 141.2, 143.2, 145.6, 151.8, 192.7; ESI–MS *m/z*: 471 $[M+H]^+$; Analytical calculated formulae $C_{22}H_{17}F_3N_6OS$: C, 56.16; H, 3.64; N, 17.86; S, 6.82; Found: C, 56.12; H, 3.60; N, 17.90; S, 6.87.

(±)-(3-(3,5-Dimethyl-1H-pyrazol-1-yl)-6-(3,4,5-trimethoxyphenyl)-6,7-dihydro-5H-triazole[3,4-b][1,3,4]thiadiazin-7-yl)(4-fluorophenyl)methanone (5 l)

White solid; yield 88%; m.p.: 196–198 °C; IR (KBr, υ_{max}/cm^{-1}): 3211 (NH), 1668 (C = O); ^{1}H-NMR (400 MHz, $CDCl_3$ + DMSO-d_6, δ ppm): 2.18 *(s*, 3H, CH_3), 2.22 *(s*, 3H, CH_3), 3.69 *(s*, 3H, OCH_3), 3.70 *(s*, 3H, OCH_3), 3.87 *(s*, 3H, OCH_3), 4.45 (t, 1H, *J* = 6.8 Hz, CH), 5.83 *(d*, 1H, *J* = 6.4 Hz, CH), 6.15 *(s*, 1H, CH of pyrazole ring), 6.87 *(s*, 1H, Ar–H), 6.97 *(s*, 1H, Ar–H), 7.07 *(s*, 1H, NH), 7.12 *(d*, 2H, *J* = 7.2 Hz, Ar–H), 8.01 *(d*, 2H, *J* = 8.4 Hz, Ar–H); ^{13}C-NMR (100 MHz, $CDCl_3$, δ ppm): 11.7, 13.7, 42.5, 54.9, 55.7, 55.8, 61.0, 107.7, 112.9, 114.3, 119.7, 124.4, 127.4, 129.4, 131.2, 142.9, 151.7, 152.6, 164.6, 193.2;ESI–MS *m/z*: 525 $[M+H]^+$; Analytical calculated formulae $C_{25}H_{25}FN_6O_4S$: C, 57.24; H, 4.80; N, 16.02; S, 6.11; Found: C, 57.20; H, 4.85; N, 16.17; S, 6.15.

(±)-(3-(3,5-Dimethyl-1H-pyrazol-1-yl)-6-(3,4,5-trimethoxyphenyl)-6,7-dihydro-5H-[1,2,4]triazole [3,4-b][1,3,4]thiadiazin-7-yl) (phenyl)methanone (5m)

Golden yellow color solid; yield 94%; m.p.: 192–194 °C; IR (KBr, υ_{max}/cm^{-1}): 3129 (NH), 1680 (C=O); ^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm): 2.19 *(s*, 3H, CH_3), 2.39 *(s*, 3H, CH_3), 3.48 *(s*, 6H, OCH_3), 3.78 *(s*, 3H, OCH_3), 5.00 (t, 1H, *J* = 5.2 Hz, CH), 5.31 *(d*, 1H, *J* = 5.6 Hz, CH), 6.00 *(s*, 1H, CH of pyrazole ring), 6.66 *(s*, 2H, Ar–H), 7.50 (t, 2H, *J* = 7.6 Hz, Ar–H), 7.59 *(s*, 1H, NH), 7.63 (t, 1H, *J* = 7.6 Hz, Ar–H), 7.90 *(d*, 2H, *J* = 7.6 Hz, Ar–H); ^{13}C-NMR (100 MHz, $CDCl_3$, δ ppm): 11.9, 13.5, 45.4, 56.2, 60.6,

60.8, 104.8, 107.8, 128.7, 129.1, 131.0, 134.5, 134.7, 138.4, 141.5, 143.2, 145.4, 151.7, 153.5, 194.1; ESI–MS *m/z*: 507 $[M+H]^+$; Analytical calculated formulae $C_{25}H_{26}N_6O_4S$: C, 59.27; H, 5.17; N, 16.59; S, 6.33; Found: C, 59.24; H, 5.20; N, 16.54; S, 6.38.

(±)-(6-(2-Chlorophenyl)-3-(3,5-dimethyl-1H-pyrazol-1-yl)-6,7-dihydro-5H-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazin-7-yl)(4-methoxyphenyl)methanone (5n)

White solid; yield 86%; m.p.: 198–200 °C; IR (KBr, υ_{max}/cm^{-1}): 3143 (NH), 1671 (C=O); ^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm): 2.21 *(s*, 3H, CH_3), 2.45 *(s*, 3H, CH_3), 3.90 *(s*, 3H, OCH_3), 5.18 *(d*, 1H, *J* = 4.0 Hz, CH), 5.50 (t, 1H, *J* = 4.4 Hz, CH), 6.00 *(s*, 1H, CH of pyrazole ring), 6.98 *(d*, 2H, *J* = 8.8 Hz, Ar–H), 7.16–7.23 (m, 2H, Ar–H), 7.29 *(s*, 1H, NH), 7.40 *(d*, 1H, *J* = 8.0 Hz, Ar–H), 7.60 *(d*, 1H, *J* = 4.8 Hz, Ar–H), 7.94 *(d*, 2H, *J* = 8.4 Hz, Ar–H); ^{13}C-NMR (100 MHz, $CDCl_3$, δ ppm): 12.0, 13.5, 21.8, 44.1, 59.1, 107.9, 128.9, 129.0, 129.2, 129.9, 131.9, 134.3, 134.9, 141.0, 143.1, 145.5, 145.9, 151.8, 193.5; ESI–MS *m/z*: 481 $[M+H]^+$; Analytical calculated formulae $C_{23}H_{21}ClN_6O_2S$: C, 57.44; H, 4.40; N, 17.47; S, 6.67; Found: C, 57.40; H, 4.45; N, 17.1; S, 6.62.

(±)-(6-(2,4-Dimethoxyphenyl)-3-(3,5-dimethyl-1H-pyrazol-1-yl)-6,7-dihydro-5H-[1,2,4]triazole[3,4-b][1,3,4]thiadiazin-7-yl)(4-methoxyphenyl)methanone (5o)

Yellow solid; yield 94%; m.p.: 150–152 °C; IR (KBr, υ_{max}/cm^{-1}): 3129 (NH), 1680 (C=O); ^{1}H-NMR (400 MHz, DMSO-d_6, δ ppm): 2.19 *(s*, 3H, CH_3), 2.22 *(s*, 3H, CH_3), 3.69 *(s*, 3H, OCH_3), 3.70 *(s*, 3H, OCH_3), 3.87 *(s*, 3H, OCH_3), 4.45 (t, 1H, *J* = 6.8 Hz, CH), 5.83 *(d*, 1H, *J* = 6.4 Hz, CH), 6.16 *(s*, 1H, CH of pyrazole ring), 6.86 *(d*, 1H, *J* = 8.4 Hz, Ar–H), 6.98 *(d*, 1H, *J* = 8.4 Hz, Ar–H), 7.07 *(s*, 1H, NH), 7.10 *(d*, 2H, *J* = 8.0 Hz, Ar–H), 7.12 *(s*, 1H, Ar–H), 8.01 *(d*, 2H, *J* = 8.4 Hz, Ar–H); ^{13}C-NMR (100 MHz, $CDCl_3$, δ ppm): 11.7, 13.7, 42.6, 54.9, 55.7, 55.8, 61.0, 107.7, 112.9, 114.3, 119.7, 124.4, 127.4, 129.4, 130.3, 130.8, 131.2, 142.9, 146.1, 151.8, 152.6, 164.6, 193.2; ESI–MS *m/z*: 507 $[M+H]^+$; Analytical calculated formulae $C_{25}H_{26}N_6O_4S$: C, 59.27; H, 5.17; N, 16.59; S, 6.33; Found: C, 59.24; H, 5.14; N, 16.63; S, 6.30.

(±)-(6-(2,4-dimethoxyphenyl)-3-(3,5-dimethyl-1H-pyrazol-1-yl)-5H-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazin-7-yl)(4-nitrophenyl)methanone (5p)

Yellow solid; yield 88%; m.p.: 236–238 °C; IR (KBr, υ_{max}/cm^{-1}): 3135 (NH), 1681 (C=O); ^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm): 2.35 *(s*, 3H, CH_3), 2.42 *(s*, 3H, CH_3), 3.79 *(s*, 3H, OCH_3), 3.88 *(s*, 3H, OCH_3), 6.08 *(s*, 1H, CH of pyrazole ring), 6.48 *(s*, 1H, Ar–H), 6.62 *(d*d, 1H, *J* = 8.4 Hz, *J* = 6.4 Hz, Ar–H), 7.27 *(s*, 1H, NH), 7.43 *(d*, 1H, *J* = 8.8 Hz, Ar–H), 7.95 *(d*, 2H, *J* = 8.8 Hz, Ar–H), 8.31 *(d*, 2H, *J* = 8.8 Hz, Ar–H); ^{13}C-NMR (100 MHz, $CDCl_3$, δ ppm): 11.7, 13.7, 55.6, 55.7, 98.5, 104.7, 108.1, 112.9, 114.6, 123.9, 131.0, 131.2, 138.3, 141.2, 143.6, 146.5, 149.4, 152.4, 16.2, 159.1, 163.3, 196.0; Analytical calculated formulae $C_{24}H_{21}N_7O_5S$: C, 55.48; H, 4.07; N, 18.87; S, 6.17; Found: C, 55.43; H, 4.02; N, 18.92; S, 6.21.

(±)-(3-(3,5-Dimethyl-1H-pyrazol-1-yl)-6-(furan-2-yl)-6,7-dihydro-5H-[1,2,4]triazolo[3,4-b][1,3,4] thiadiazin-7-yl)(4-methoxyphenyl)methanone (5q)

Brown solid; yield 87%; m.p.: 152–154°C; IR (KBr, υ_{max}/cm^{-1}): 3143 (NH), 1671 (C = O); ^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm): 2.30 *(s*, 3H, CH_3), 2.34 *(s*, 3H, CH_3), 3.92 *(s*, 3H, OCH_3), 5.23 (unresolved singlet, 2H, CH and CH), 6.03 *(s*, 1H, CH of pyrazole ring), 6.30 *(s*, 1H, CH-), 6.32 *(s*, 1H, CH), 7.02 *(d*, 3H, *J* = 8.8 Hz, Ar–H), 7.35 *(s*, 1H, NH), 7.94 *(d*, 2H, *J* = 8.4 Hz, Ar–H); ESI–MS *m/z* 437 $[M+H]^+$; Analytical calculated formulae $C_{21}H_{20}N_6O_3S$: C, 57.79; H, 4.62; N, 19.25; S, 7.35; Found: C, 57.83; H, 4.66; N, 19.21; S, 7.31.

(±)-(3-(3,5-Dimethyl-1H-pyrazol-1-yl)-6-(furan-2-yl)-6,7-dihydro-5H-[1,2,4]triazolo[3,4-b] [1,3,4]thiadiazin-7-yl)(p-tolyl)methanone (5r)

Brown solid; yield 85%; m.p.: 149–151°C; IR (KBr, υ_{max}/cm^{-1}): 3204 (NH), 1666 (C = O); ^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm): 2.30 *(s*, 3H, CH_3), 2.34 *(s*, 3H, CH_3), 2.46 *(s*, 3H, CH_3), 5.26 (unresolved singlet, 2H, CH-), 6.03 *(s*, 1H, CH of pyrazole ring), 6.31 *(d*, 2H, *J* = 8.0 Hz, Ar–H), 7.03 *(s*, 1H, NH), 7.35 *(d*, 3H, *J* = 8.8 Hz, Ar–H), 7.85 *(d*, 2H, *J* = 8.0 Hz, Ar–H); ^{13}C-NMR (100 MHz, $CDCl_3$, δ ppm): 11.6, 13.7, 21.9, 39.8, 53.0, 107.7, 109.2, 111.0, 128.9, 130.0, 131.6, 140.6, 142.7, 143.1, 146.1, 146.7, 148.3, 152.0, 194.4; ESI–MS *m/z*: 421 $[M+H]^+$; Analytical calculated formulae $C_{21}H_{20}N_6O_2S$: C, 59.98; H, 4.79; N, 19.99; S, 7.63; Found: C, 59.94; H, 4.7; N, 19.94; S, 7.68.

(±)-(3-(3,5-Dimethyl-1H-pyrazol-1-yl)-6-(thiophen-2-yl)-6,7-dihydro-5H-[1,2,4]triazolo[3,4-b][1,3,4] thiadiazin-7-yl)(4-nitrophenyl)methanone (5s)

Golden color solid; yield 89%; m.p.: 204–206°C; IR (KBr, υ_{max}/cm^{-1}): 3281(NH), 1696 (C=O); ^{1}H-NMR (400 MHz, $CDCl_3$ + DMSO-d_6, δ ppm): 2.26 *(s*, 3H, CH_3), 2.27 *(s*, 3H,

CH_3), 5.47 (t, 1H, $J = 3.6$ Hz, CH), 5.88 (*d*, 1H, $J = 3.2$ Hz, CH), 6.10 (*s*, 1H, CH of pyrazole ring), 6.97 (t, 1H, $J = 4.4$ Hz, Ar–H), 7.17 (*d*, 1H, $J = 4.4$ Hz, Ar–H), 7.31 (*d*, 1H, $J = 4.8$ Hz, Ar–H), 7.35 (s, 1H, NH), 8.37 (s, 4H, Ar–H); ^{13}C-NMR (100 MHz, $CDCl_3$ + DMSO-d_6, δ ppm): 11.4, 13.8, 42.9, 53.4, 107.5, 124.1, 126.3, 126.5, 127.4, 129.3, 130.8, 139.9, 142.9, 146.9, 149.6, 150.7, 151.3, 194.5; ESI–MS *m/z*: 468 $[M+H]^+$; Analytical calculated formulae $C_{20}H_{17}N_7O_3S$: C, 51.38; H, 3.67; N, 20.97; S, 13.72; Found: C, 51.34; H, 3.62; N, 20.94; S, 13.76.

(±)-(3-(3,5-Dimethyl-1H-pyrazol-1-yl)-6-(furan-2-yl)-6,7-dihydro-5H-[1,2,4]triazolo[3,4-b][1,3,4] thiadiazin-7-yl)(4-nitrophenyl) methanone (5t)

White solid; yield 92%; m.p.: 201–203°C; IR (KBr, υ_{max}/cm^{-1}): 3278 (NH), 1698 (C = O); ^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm): 2.25 (*s*, 3H, CH_3), 2.27 (*s*, 3H, CH_3), 5.28–5.32 (m, 1H, CH), 5.78 (*d*, 1H, $J = 4.0$ Hz, CH), 6.08 (*s*, 1H, CH of pyrazole ring), 6.45 (*s*, 1H, NH), 7.14 (*d*, 1H, $J = 4.0$ Hz, Ar–H), 7.48 (*d*, 1H, $J = 4.0$ Hz, Ar–H), 7.85 (t, 1H, $J = 8.4$ Hz, Ar–H), 8.29 (*d*, 2H $J = 8.4$ Hz, Ar–H), 8.33 (*d*, 2H, $J = 7.2$ Hz, Ar–H); ^{13}C-NMR (100 MHz, $CDCl_3$, δ ppm): 11.2, 13.8, 49.8, 52.5, 107.5, 109.2, 111.0, 124.1, 124.3, 130.4, 130.6, 142.9, 143.0, 148.1, 149.1, 150.7 151.3, 194.0; ESI–MS *m/z*: 452 $[M+H]^+$; Analytical calculated formulae $C_{20}H_{17}N_7O_4S$: C, 53.21; H, 3.80; N, 21.72; S, 7.10; Found: C, 53.25; H, 3.85; N, 21.7; S, 7.15.

X-ray crystallography

The diffraction data was collected on Bruker APEX2 single crystal X-ray diffractometere quipped with a CCD area detector system, graphite mono chromator and a Mo-K_α fine focus sealed tube ($\lambda = 0.71073$ Å). Bruker SAINT PLUS was used for data reduction, SHELXT-2014 [49] was used for structure solution and SHELXL-2018 [50] was used for full-matrix least-squares refinement. Mercury 3.3 [51] was used for molecular graphics. All non-hydrogen atoms were refined using anisotropic thermal parameters. All hydrogen atoms bound to carbons were positioned geometrically and refined using a riding model. Important crystallographic data and table for bond distances and bond angles were provided in supporting information.

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