Molecular Diversity
https://doi.org/10.1007/s11030-018-9845-0

ORIGINAL ARTICLE

One-pot synthesis, biological evaluation and molecular docking studies of fused thiazolo[2,3-*b*]pyrimidinone-pyrazolylcoumarin hybrids

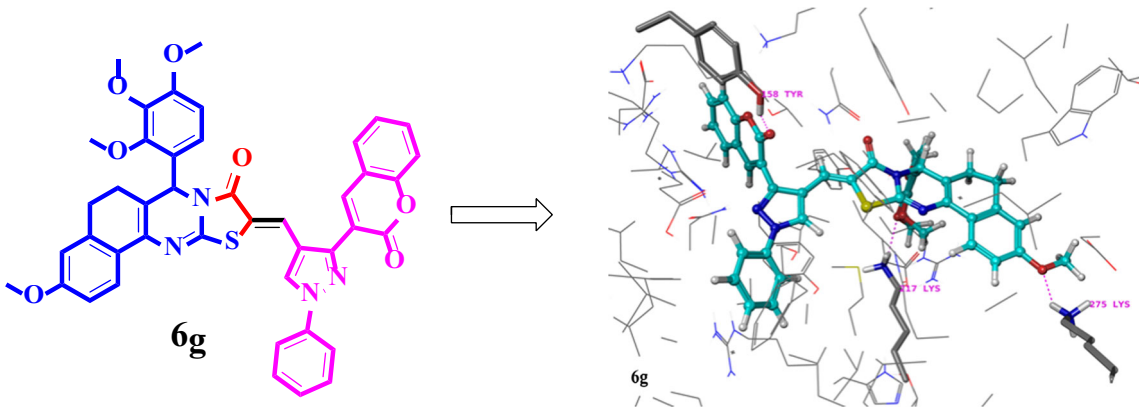
Ramesh Gondru[1] · Saikiran Reddy Peddi[2] · Vijjulatha Manga[2] · Manjulatha Khanapur[3] · Rajitha Gali[1] · Narsimha Sirassu[4] · Rajitha Bavantula[1]

Received: 8 September 2017 / Accepted: 14 June 2018

Abstract

As a part of our endeavor toward the synthesis of a new class of biologically potent heterocyclic hybrids, a series of newly fused thiazolo[2,3-*b*]pyrimidinones bearing a pyrazolylcoumarin moiety (**6a**–**p**) were synthesized in acceptable yields. Anticipated structures of all titled compounds were in agreement with spectral and analytical (C, H and N) analyses. The compounds were screened for in vitro antibacterial activity against both G^+ and G^- bacterial strains and antiproliferative activity against K562 (chronic myelogenous leukemia), MCF-7 (breast cancer), MDA-MB-231 (breast cancer), COLO 205 (colorectal adenocarcinoma), HepG2 (hepatocellular carcinoma) cell lines. Further, potent antibacterial compounds were subjected to molecular docking studies in order to gain insight into their plausible binding modes and mechanism of action against MurB. The modeling results were in agreement with the experimental data.

Graphical abstract



Keywords Antibacterial activity · Molecular hybrid · Molecular docking · MurB · Thiazolo[2,3-*b*]pyrimidinones

Introduction

After cardiovascular diseases, cancer is the second most death causing multifactorial disease [1–3] resulting from a combined influence of genetic (inherited genes, genetic mutations and DNA damages) and environmental factors (exposure to UV radiations, chemical agents and tobacco consumption). Malignancy is characterized by uncontrolled

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s11030-018-9845-0) contains supplementary material, which is available to authorized users.

Extended author information available on the last page of the article

Published online: 02 July 2018

cell proliferation and differentiation [4]. The high risk of toxicity and lack of specificity (over non-cancerous cells) were limiting the efficacy of most of the currently using chemotherapeutic in cancer therapy. Multi-drug resistance (MDR) developed by the tumor cells becomes pandemic and is making paucity of chemotherapeutic drugs. Hence, there is an urgency to design and develop alternative chemical entities with the multi-target mechanism of action in disease progression pathway or which can modulate more than one biological target with high specificity.

Also, antimicrobial drug resistance (AMDR) [5] in microorganisms is rampant and also emerged as one of the principal causes of mortality over the world. Intemperate and inappropriate use of antibiotics (prolonged drug exposure), emerging of intrinsically or acquired antibiotic resistance traits and resistance mechanisms adopted by the microbes (by changing the principal targets, or by activating the efflux mechanisms) leading to antibiotic resistance and limiting the efficacy of the pre-existing medication. Hence, the drug development process becomes a formidable challenge for the development of new and effective drug candidates with a novel mode of action [6].

Multi-component reactions (MCRs) [7, 8] are one of the frequently used strategies in modern synthetic organic chemistry [9] that involve more than two easily accessible reactants join through covalent bonds to give multi-functionalized complex structures in a single synthetic operation [10, 11]. MCRs can offer significant advantages [12] such as high atom efficiency, fewer by-product production because of the reduced number of synthetic steps, operational simplicity (workup, extraction and purification) under mild reaction conditions, cost-effective, and also it offers a target- and diversity-oriented synthesis. Therefore, the development of new MCRs using green reaction conditions is inevitable at present, especially in the areas of drug discovery, organic synthesis and combinatorial chemistry [13, 14].

A broad spectrum of pharmacological properties of thiazolo[2,3-*b*]pyrimidinones has gained much attention as a lead molecule from the synthetic and medicinal chemists. The biological properties include antibacterial [15], antiviral [16], antitumor [17, 18], antioxidant [19], antinociceptive [20], antiparkinsonian [21], antimitotic [22, 23], anti-inflammatory [24, 25], anticonvulsant [26], analgesic [27] and antibiofilm modulators [28]. Some of the dihydropyrimidine-based compounds have also been reported as calcium channel modulators [29, 30] and 5-HT_2 receptor antagonists [31, 32] and also serve as inhibitors of xanthine oxidase [33], CDC25B phosphatase enzymes and Bcl-2 family proteins [34].

Also, pyrazoles [35, 36] and coumarin [37–39] derivatives are known as bioactive pharmacophores associated with various biological activities [40]. On the other hand, chalcones and their derivatives are also significant structural motifs with a broad spectrum of biological activities [41].

In the course of our long-standing research endeavor toward the development of new bioactive heterocycles [42–44], from the molecular design point of view and also by relying on the aforementioned biological data, herein we designed and synthesized novel heterocyclic molecular frameworks (**6a–j**) embedding thiazolo[2,3-*b*]pyrimidinone and pyrazolyl chromenone pharmacophores in their structural framework, hoping the synergistic influence of this combination on antibacterial and anticancer activity. All the synthesized compounds were assessed for their in vitro antibacterial and anticancer activity studies. Figure 1 represents a few of the literature reported and commercially important heterocyclic-based drugs and bioactive molecules.

Molecular docking studies were also performed for the synthesized molecules in order to explore the possible binding modes and understand the mode of action of these compounds through their interactions with *E. coli* MurB enzyme, a key enzyme in peptidoglycan biosynthesis. The peptidoglycan layer of bacterial cell wall has been an important target in antibacterial chemotherapy for a long time. MurB catalyzes the reduction of enolpyruvate moiety to a lactyl ether yielding UDP-*N*-acetylmuramate (UDP-MurNAc), a precursor of the cell wall [45, 46]. Subsequently, this UDP-MurNAc is added with three amino acids and a dipeptide, resulting in a pentapeptide. This pentapeptide when activated permits the cross-linking that gives cell wall its rigidity [47]. Further, MurB along with other Mur proteins (Mur A-F, Y, and G) catalyzes various biosynthetic transformations, which are essential in the formation of the peptidoglycan layer of the bacterial cell wall [48]. Furthermore, from the literature, we came to know that Andres et al. [49] synthesized the substituted 4-thiazolidinone derivatives and demonstrated their ability to inhibit MurB enzyme by acting as diphosphate mimics at low micromolar levels. Also, they have performed docking studies on the MurB enzyme for 4-thiazolidinones. Yang and his co-workers [50] identified 4-chlorophenyl-3,5-dioxopyrazolidine derivatives as novel inhibitors of MurB of *Escherichia coli*, *Staphylococcus aureus* in the micromolar range. Previously, our group [44] and Bhat et al. [51] have reported MurB as an interesting target to exhibit antimicrobial activity for pyrazolylcoumarin-bearing aryl thiazoles and 1,2,3-triazolyl pyrazole derivatives. Since the compounds reported in this manuscript also possessed similar pharmacophore sub-units, herein we selected MurB as a potential target to authenticate ours in vitro results.

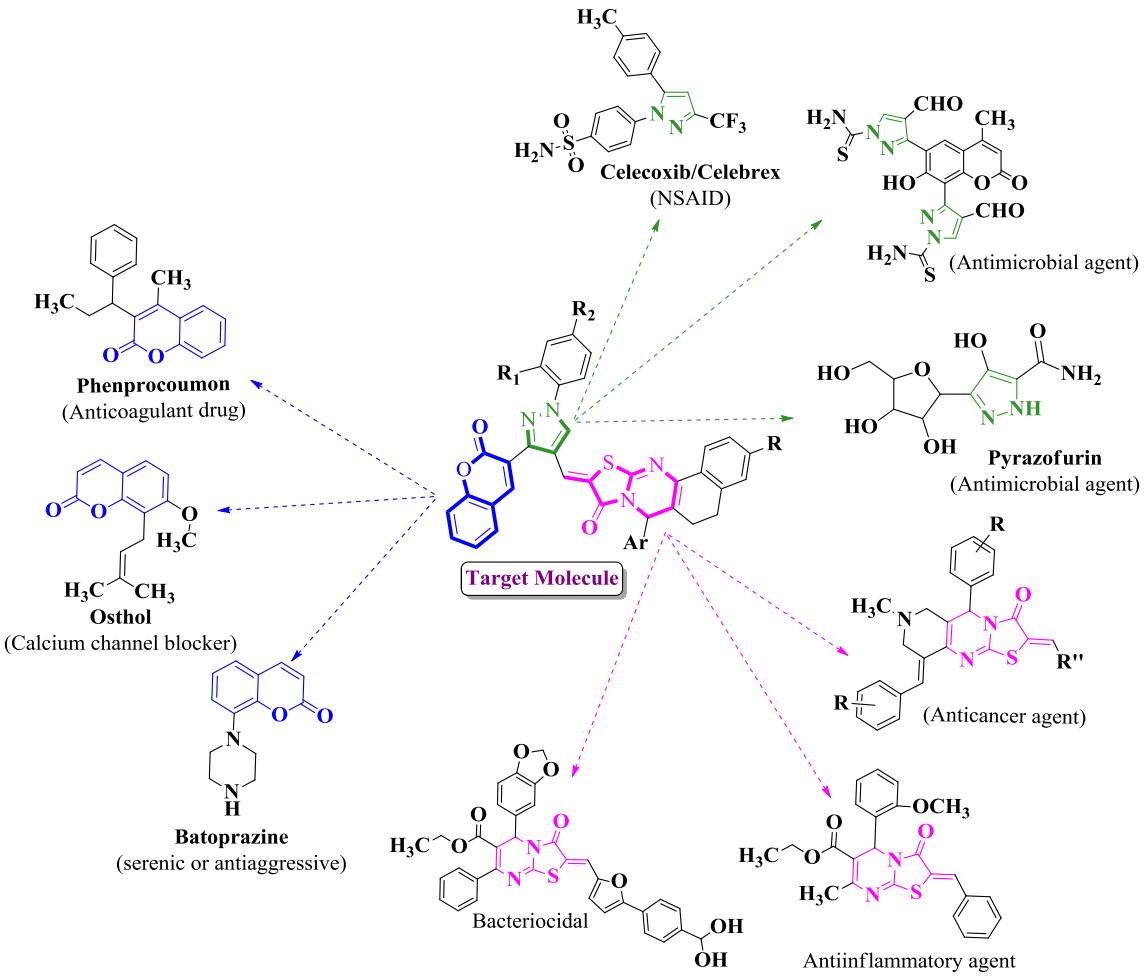
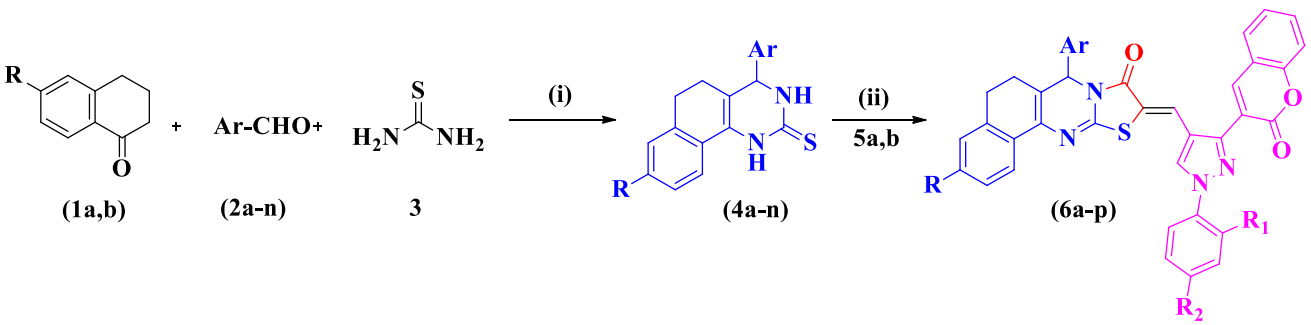


Fig. 1 Representative examples of biologically active heterocyclic molecules possessing coumarin, pyrazole and thiazolo[2,3-*b*]pyrimidinones moieties

Results and discussion

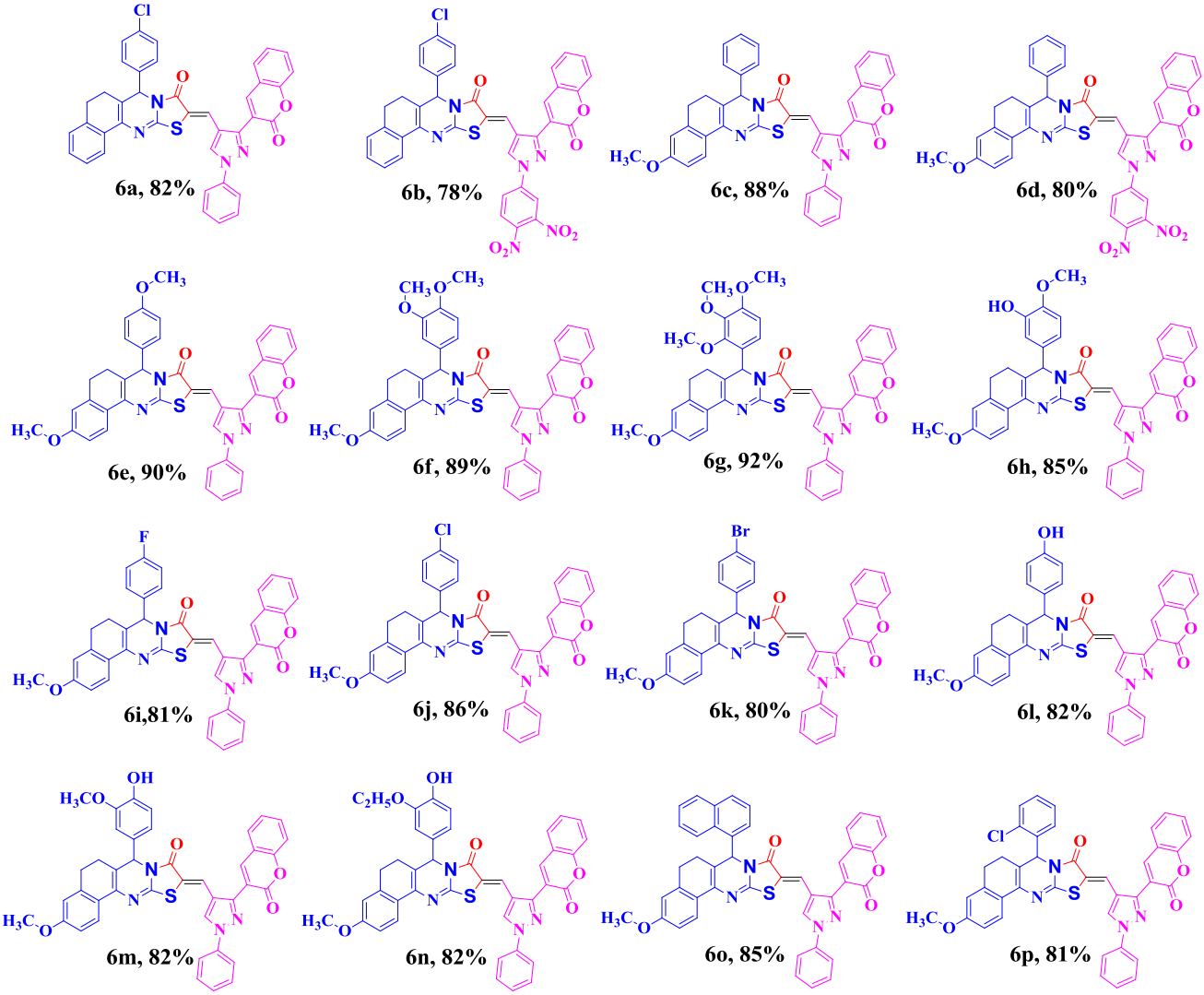
Chemistry

The synthetic strategy adopted to obtain the titled compounds (**6a–p**) is outlined in Scheme 1. The target compounds were achieved in good yields by one-pot three-component condensation of modified Biginelli product, fused 3,4-dihydropyrimidin-2(1*H*)-thiones (**4a–n**), monochloroacetic acid and 3-(2-oxo-2*H*-chromen-3-yl)-1-aryl-1*H*-pyrazole-4-carbaldehyde (**5a**,**b**) in refluxing AcOH in the presence of Ac_2O and NaOAc. The structure



Scheme 1 Reagents and conditions: (i) MeOH, cat. H_2SO_4, reflux, 4 h (yield: 80–95%); (ii) chloroacetic acid, NaOAc, $AcOH/Ac_2O$, **5a**, **b**, reflux, 4–6 h (yield: 79–90%). Structures of all the synthesized compounds were in agreement with their spectral and analytical analyses. Isolated yields after filtration

elucidation of newly synthesized compounds was well established by FTIR, NMR and mass spectral studies as well as elemental analyses (C, H and N).



Biological activity

Antiproliferative activity

In vitro antiproliferative activity was performed against five cancer lines (Colo205, K562, MCF-7, MDA-MB-231 and Hep G2) and normal cell line (HEK293) by MTT assay [52] using doxorubicin as a positive control, and the results are tabulated in Table 1.

The anticancer results revealed that most of the tested samples were inactive against the tested cell lines. However, the derivatives **6a**, **6h**, **6k**, **6m** and **6n** have shown moderate antiproliferative potency against the HepG2 tumor cell line with an average percentage of inhibition (Avg % inhibition) ranging from 39.09 to 40.35 when compared with remaining derivatives. Compound **6g** was the only compound which showed bit reasonable antiproliferative activity against both Colo 205 and Hep G2 tumor cell lines (Table 1). On overall comparison, compounds derived from 4-chlorophenyl (**6a**) and 4-hydroxy-3-ethoxy phenyl (**6n**) substitutions have exhibited moderate anticancer activity against HepG2 when compared with the others. Hence, further optimization of these two compounds (**6a** and **6n**) is required to enhance their antiproliferative efficacy, and they can be considered as a lead molecule for the development of new antineoplastic drugs.

Antibacterial Activity

The title compounds (**6a–p**) were assessed for their in vitro antibacterial activity against both gram-positive (G^+) and gram-negative (G^-) bacterial strains by the standard broth microdilution technique [53, 54] by using penicillin and

streptomycin as positive controls. The minimum inhibitory concentrations (MICs) for all the synthesized compounds were reported in μg/mL, and the results are illustrated in Table 2.

It is evident from Table 2 that the majority of the tested compounds (**6b**, **6e**–**6h**, **6j** and **6l**–**6n**) exerted significant in vitro antibacterial activity against almost all the tested bacterial strains with MICs ranging from 1.56 to 12.5 μg/mL. Among the tested series, compound **6g** was found to be efficient and displayed equipotent inhibitory efficacies and broader antibacterial spectrum than that of the reference drugs. Compound **6g** exhibited excellent inhibiting activity than the standard streptomycin (MIC = 6.25 μg/mL) and equipotent to that of penicillin (MIC = 1.562 μg/mL) against *S. aureus* and *B. subtilis* with MIC values 1.56 μg/mL, exerted nearly as active as positive control drugs (MIC = 3.12 μg/mL) against gram-positive *S. epidermidis* (MIC = 3.12 μg/mL). Also, compound **6g** effectively inhibited the gram-negative *E. coli* and *K. pneumonia* (MIC = 6.25 μg/mL) and also demonstrated inhibitory potency against *P. aeruginosa* (MIC = 12.5 μg/mL) equal to that of the standard penicillin. Compounds **6f** and **6h** could effectively inhibit the growth of *S. aureus* with MIC values (MIC = 1.56 and 3.12 μg/mL, respectively) and *P. aeruginosa* (MIC = 6.25 μg/mL). Compounds **6b**, **6e**, **6f** and **6h** have shown bioactivity against *P. aeruginosa* (MIC = 6.25 μg/mL), which was better than penicillin. The compounds **6h** and **6j** have shown equipotent activity than that of standards streptomycin and penicillin, respectively, against *B. subtilis* and *P. aeruginosa* (MIC = 6.25 and 12.5 μg/mL). Compounds **6m** and **6n** showed significant activity against *S. aureus* (MIC = 3.12 μg/mL). Compound **6n** showed premising inhibition against *B. subtilis*, *E. coli* and *P. aeruginosa* with MICs = 6.25 μg/mL. Finally, the compound **6l** also showed very good activity against *S. aureus* and *B. subtilis* with MICs = 6.25 μg/mL, while the rest of the compounds (**6a**, **6c**, **6d**, **6i**, **6k**, **6o** and **6p**) have shown modest activity against all the tested strains with MIC values ranging from 12.5 to 50 μg/mL.

Structure–activity relationship (SAR)

Interestingly, it was observed from experimental data (Table 2) that most of the analogs displayed potent bioactivity against gram-positive bacterial strains, *i.e.*, *B. subtilis*, *S. aureus* and *S. epidermidis* with MIC values ranging from 1.56 to 6.25 μg/mL and also displayed

Table 1 Antiproliferative activity (Avg. % of inhibition ± SD) of compounds **6a**–**p** and reference doxorubicin (DOX) against a panel of tumor cell lines

Analogs	Cancer cell lines					
	Colo 205	K562	MCF-7	MDA-MB-231	Hep G2	HEK 293
6a	NA	11.76 ± 2.65	18.38 ± 1.50	15.26 ± 1.70	40.35 ± 1.55	− 2.60 ± 1.50[a]
6b	7.29 ± 1.75	17.73 ± 1.32	14.90 ± 0.90	20.86 ± 1.27	21.67 ± 3.33	− 11.17 ± 0.64
6c	7.94 ± 1.65	15.78 ± 1.50	15.39 ± 1.14	15.46 ± 1.36	15.23 ± 2.96	− 0.25 ± 6.14
6d	9.31 ± 1.87	22.22 ± 1.65	10.31 ± 1.84	15.22 ± 2.43	14.29 ± 2.07	− 1.60 ± 1.31
6e	13.25 ± 1.51	11.17 ± 0.97	11.00 ± 1.43	17.98 ± 6.62	13.40 ± 1.98	− 1.99 ± 1.63
6f	14.88 ± 3.78	12.63 ± 2.47	19.78 ± 2.65	21.75 ± 1.56	22.46 ± 2.21	− 1.06 ± 2.68
6g	35.54 ± 1.21	7.12 ± 2.13	15.32 ± 3.16	20.37 ± 1.39	36.18 ± 1.88	− 5.14 ± 3.39
6h	3.41 ± 3.53	15.19 ± 2.66	18.11 ± 1.75	NA	39.70 ± 3.04	− 4.05 ± 1.82
6i	11.70 ± 1.47	NA	10.65 ± 2.27	NA	19.95 ± 2.14	− 10.78 ± 3.07
6j	25.50 ± 1.85	NA	28.48 ± 0.91	NA	36.32 ± 2.63	− 12.49 ± 3.80
6k	NA	3.33 ± 1.28	22.68 ± 1.34	17.62 ± 1.07	39.89 ± 1.88	− 2.05 ± 1.76
6l	4.54 ± 1.22	15.22 ± 0.89	26.71 ± 2.12	20.11 ± 1.98	21.02 ± 2.56	− 1.77 ± 1.36
6m	3.11 ± 2.49	13.49 ± 1.39	16.17 ± 1.11	NA	39.09 ± 2.04	− 4.11 ± 1.80
6n	5.39 ± 1.62	17.62 ± 1.07	20.41 ± 1.62	NA	40.11 ± 2.67	− 3.79 ± 2.69
6o	NA	20.12 ± 1.77	11.36 ± 1.34	15.38 ± 5.12	10.21 ± 1.44	− 1.66 ± 2.36
6p	11.89 ± 1.93	10.67 ± 1.55	4.54 ± 1.22	NA	35.21 ± 1.38	− 1.87 ± 3.10
DOX[b]	91.55 ± 1.87	95.57 ± 2.22	97.61 ± 2.19	98.66 ± 3.26	92.35 ± 1.57	5.68 ± 1.56

Values are mean ± SD of three replicates

NA not active

[a]Negative values indicate the growth of normal cell line HEK 293. Hence, the samples were not toxic to non-cancerous cells

[b]DOX—doxorubicin (positive control) and DMSO (negative control)

Table 2 *In vitro* antibacterial activity data for test compounds (**6a–j**)

Analogs	MIC (μg/mL)					
	S. aureus	*B. subtilis*	*S. epidermidis*	*E. coli*	*K. pneumonia*	*P. aeruginosa*
6a	25 ± 0.11	–	25 ± 0.15	–	50 ± 0.56	50 ± 0.29
6b	–	–	50 ± 0.22	–	50 ± 0.63	6.25 ± 0.21
6c	–	50 ± 0.45	25 ± 0.36	12.5 ± 0.25	12.5 ± 0.61	–
6d	50 ± 0.35	–	–	–	12.5 ± 0.23	25 ± 0.17
6e	25 ± 0.62	25 ± 0.46	12.5 ± 0.90	50 ± 0.32	50 ± 0.79	6.25 ± 0.79
6f	1.56 ± 0.22	12.5 ± 0.71	12.5 ± 0.3	12.5 ± 0.44	12.5 ± 0.58	6.25 ± 0.15
6g	1.56 ± 0.35	1.56 ± 0.45	3.12 ± 0.66	6.25 ± 0.70	6.25 ± 0.4	12.5 ± 0.23
6h	3.12 ± 0.28	6.25 ± 0.19	12.5 ± 0.37	50 ± 0.68	25 ± 0.30	6.25 ± 0.16
6i	–	50 ± 0.82	–	25 ± 0.15	12.5 ± 0.33	–
6j	12.5 ± 0.19	25 ± 0.30	25 ± 0.36	–	25 ± 0.39	12.5 ± 0.66
6k	–	50 ± 0.33	–	50 ± 0.39	50 ± 0.28	–
6l	6.25 ± 0.49	6.25 ± 0.33	12.5 ± 0.38	50 ± 0.42	12.5 ± 0.22	12.5 ± 0.50
6m	3.12 ± 0.28	12.5 ± 0.42	12.5 ± 0.31	25 ± 0.20	50 ± 0.40	12.5 ± 0.36
6n	3.12 ± 0.19	6.25 ± 0.20	12.5 ± 0.45	6.25 ± 0.43	12.5 ± 0.22	6.25 ± 0.38
6o	–	–	–	12.5 ± 0.25	–	25 ± 0.55
6p	12.5 ± 0.36	–	12.5 ± 0.27	12.5 ± 0.32	–	–
Streptomycin	6.25 ± 0.25	6.25 ± 0.70	3.125 ± 0.45	6.25 ± 0.82	3.125 ± 0.96	1.562 ± 0.69
Penicillin	1.562 ± 0.21	1.562 ± 0.65	3.125 ± 0.22	12.5 ± 0.35	6.25 ± 0.88	12.5 ± 0.74

MIC (μg/mL), minimum inhibitory concentration, i.e., the lowest concentration of the test compound to inhibit the growth of bacteria completely

"–" Indicates concentration > 100 μg/mL

moderate-to-good inhibiting activity against gram-negative strains, *i.e.*, *E. coli*, *P. aeruginosa* and *K. pneumonia* with MICs ranging from 6.25 to 12.5 μg/mL. On the whole from the above in vitro results, we can conclude that the derivatives bearing 4-chlorophenyl, 3,4-dimethoxyphenyl, 2,3,4-trimethoxyphenyl, 4-hydroxyphenyl, 4-hydroxy-3-methoxyphenyl and 4-hydroxy-3-methoxyphenyl moieties on the thiazolo-quinazoline scaffold were found to be potent antibacterial agents.

Molecular docking study

Molecular docking was performed using Schrodinger suite 2010. Initially, the crystal structure of target enzyme MurB (PDB id: 1MBB) was obtained from Protein Data Bank (http://www.rcsb.org/pdb). It was prepared, refined and minimized using protein preparation wizard available in the Schrodinger suite 2010. Later receptor grid was generated around the active site of the enzyme using GLIDE 5.6 ((Schrödinger LLC, 2010), Glide, version 5.6. New

Table 3 Dock scores and hydrogen bond interactions of ligands with *E. coli* (PDB id: 1MBB) obtained from docking studies

Compound	MIC (μg/mL)	Dock score (kcal/mol)	Residues involved in hydrogen bonding
6c	12.5 ± 0.25	− 5.005	Lys 217, Gln 288
6e	50 ± 0.32	− 2.968	–
6f	12.5 ± 0.44	− 5.248	Ser 229, Tyr 254, Lys 262,
6g	6.25 ± 0.70	− 6.098	Tyr 158, Lys 217, Lys 275
6h	50 ± 0.68	− 3.656	Gln 287
6i	25 ± 0.15	− 4.294	Gln 288
6k	50 ± 0.39	− 3.890	Gln 288
6l	50 ± 0.42	− 4.811	Tyr 125, Asp 270, Lys 275
6m	25 ± 0.20	− 4.957	Gln 287
6n	6.25 ± 0.43	− 6.107	Lys 275, Gln 287, Gln 288
6o	12.5 ± 0.25	− 5.480	–
6p	12.5 ± 0.32	− 5.327	–

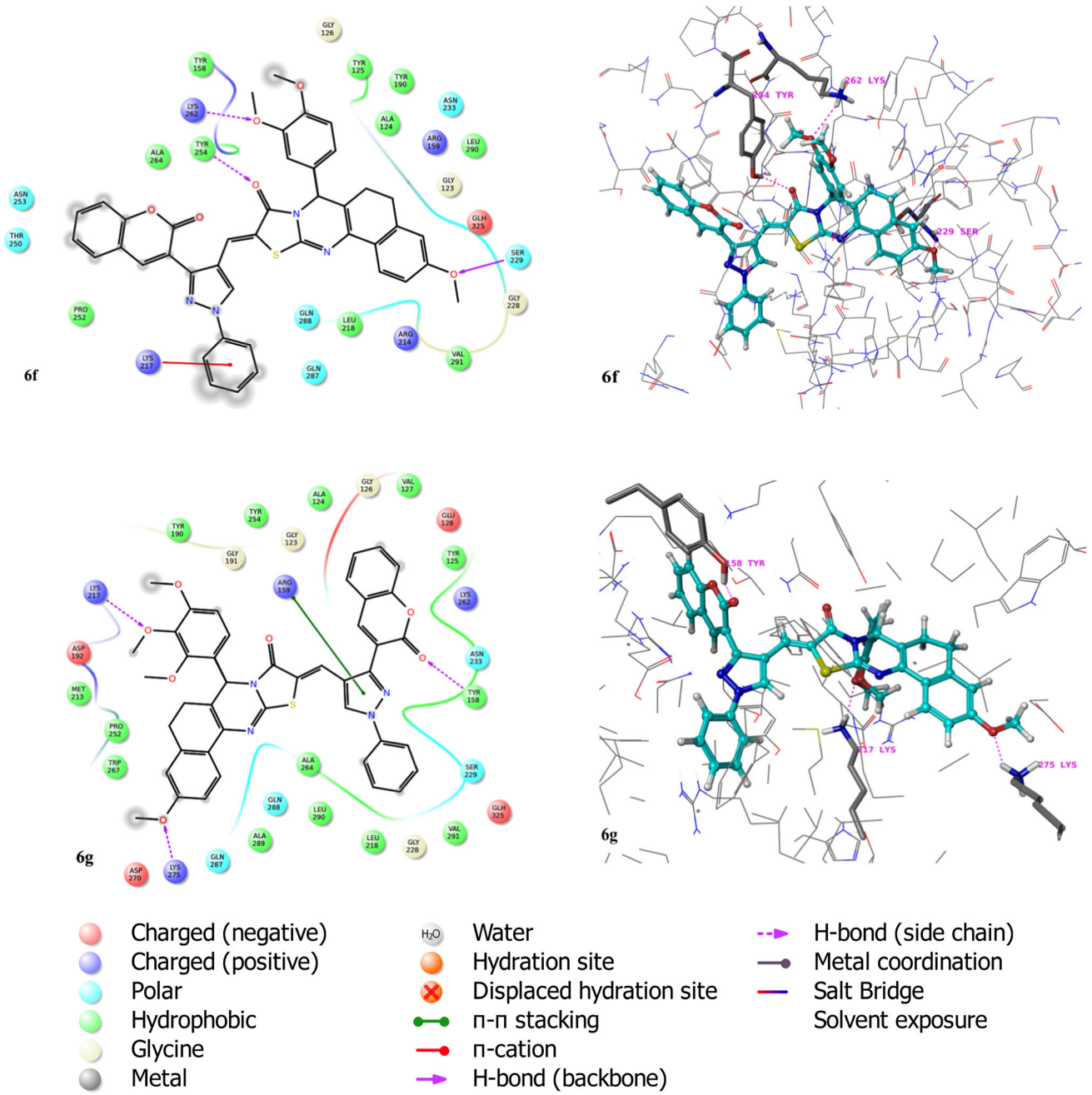


Fig. 2 Ligand interaction diagram of compounds **6f** and **6g** showing hydrogen bond interactions (pink dotted and thick lines), π–π stacking interactions (green) and π-cationic interactions (red)

York). During grid generation, the receptor van der Waals scaling was set to 0.9 [55]. Meanwhile, the ligands were drawn in Maestro build panel and prepared by LigPrep module available in the same suite. Finally, the low energy conformers of the prepared ligands were docked into the active site of the MurB enzyme. Docking results are tabulated in Table 3; energetically most favored dock pose of each ligand was analyzed for interactions with the target receptor.

The docking studies clearly showed that the best active compounds in the series (**6g** and **6n**) could act as good antibacterial agents which is evident from their high dock scores (− 6.107 and − 6.098 kcal/mol, respectively). Compound **6n** showed three hydrogen bond interactions with amino acid residues Lys 275, Gln 287, Gln 288, three π–π stacking interactions with Tyr 190, Tyr 254 and two π-cationic interactions with residues Lys 217 and Lys 262 (Fig. 2). On the other hand, compound **6g** showed three

hydrogen bond interactions with Tyr158, Lys 217, Lys 275 (Fig. 2) and a π–π stacking interaction with Arg 159 (Fig. 2). Compounds **6o**, **6p**, **6f,** and **6c** which possessed good activity values next to compounds **6n** and **6g** in the series showed dock scores of − 5.480, − 5.327, − 5.248 and − 5.005 kcal/mol, respectively (Table 3). Compound **6f** showed three hydrogen bonds with Ser 229, Tyr 254, Lys 262 and a π-cationic interaction with Lys 217, whereas compound **6c** showed two hydrogen bonds with Lys 217 and Gln 288. Surprisingly, compounds **6o** and **6p** showed only π–π stacking and π-cationic interactions. Compound **6o** showed π–π stacking interactions with Tyr 254 and π-cationic interactions with Lys 262, whereas compound **6p** showed π–π stacking interactions with Tyr 125 and π-cationic interactions with Lys 217 and Lys 262. Another noteworthy thing is that compounds which exhibited poor biological activities (**6k**, **6h** and **6e**) showed poor dock scores of − 3.890, − 3.656 and − 2.968 kcal/mol, respectively. Compound **6k** showed hydrogen bond interaction with Gln 288, π–π stacking interactions with Tyr254 and π-cationic interactions with Lys 262, whereas compound **6h** showed only one hydrogen bond interaction with Gln 287 and hydrogen bond interactions were utterly absent in the case of compound **6e**. Interestingly, compounds **6m**, **6l** and **6i** which exhibited relatively better activity compared to **6k**, **6h** and **6e** showed dock scores of − 4.957, − 4.811 and − 4.294 kcal/mol. Compound **6l** showed three hydrogen bond interactions with Tyr 125, Asp 270, Lys 275, two π-cationic interactions with Lys 217, Lys 262 and a π–π stacking interaction with Tyr 254. Both compounds **6m** and **6i** showed π-cationic interactions with Lys 262 apart from hydrogen bond interactions with Gln 287 and Gln 288, respectively. Furthermore, compound **6m** also showed π–π stacking interactions with Tyr 254. On the whole, it was observed that the docking results well corroborated with in vitro antibacterial studies, indicating that these compounds can be further optimized and developed as lead compounds.

Conclusion

In summary, a series of novel heterocyclic hybrids (**6a**–**p**) were designed and synthesized by the one-pot three-component approach with the hope of discovering new bioactive molecular frameworks with an enhanced broad spectrum of pharmacological activities. All the newly synthesized compounds were well characterized by spectral and elemental analyses. The compounds were investigated for their in vitro antiproliferative and antibacterial activities by MTT and broth microdilution technique, respectively. From the experimental studies, it was revealed that among the synthesized compounds (**6a**–**p**), derivatives **6a** and **6n** had better antiproliferative activity against Hep G2 cell line when compared with other compounds. Regarding antibacterial studies, compounds **6b**, **6e**–**6h**, **6j** and **6l**–**6n** showed broad and excellent antibacterial efficacy against both G^+ and G^- strains comparable to that of the standards. These in vitro antibacterial studies were further supported by molecular docking. Overall, from the in vitro anticancer and antibacterial studies, we can conclude that the presence of positive mesomeric groups on phenyl ring has been suggested to be responsible for the promising in vitro antibacterial activities of the title compounds. Based on the above results, the synthesized series of compounds could be potential candidates for further development of novel antimicrobial agents.

Experimental

General

All chemical reagents and solvents were purchased from commercial sources and used without further purification. Melting points were determined in open capillaries using electrothermal digital apparatus model Stuart SMP30 and were uncorrected. Reactions were monitored by TLC on silica gel-coated aluminum sheets, and the developed chromatogram was visualized under UV light and iodine vapors. IR spectra were recorded on PerkinElmer 100S spectrophotometer using KBr disks. NMR spectra (^{1}H and ^{13}C) were recorded on a Bruker 400 MHz spectrometer using chloroform-D and DMSO-d_6 as solvents and TMS as an internal standard. Chemical shift values were reported in ppm (δ), and coupling constants (*J*) in Hertz (Hz). Standard abbreviations indicating a splitting pattern (multiplicity) were designated as follows: singlet (s), doublet (d), triplet (t) and multiplet (m). Elemental analyses were performed on a Carlo Erba model EA1108 analytical unit, and the values are ± 0.4% of theoretical values. Mass spectra were recorded on a Jeol JMSD-300 spectrometer.

Biological protocols

Tested cancer cell lines and antiproliferative activity

In vitro cytotoxi*c* activity was carried out against human colorectal adenocarcinoma (Colo 205), chronic myelogenous leukemia (K562), breast adenocarcinoma (MCF-7), breast adenocarcinoma (MDA-MB-231), hepatocellular carcinoma chronic myelogenous (Hep G2), and human embryonic kidney 293 cells (HEK293). One of the most effective anticancer agents, doxorubicin (DOX), was used as a positive control (reference), and the results are summarized in Table 1. The cell lines were obtained from the

National Centre for Cell Sciences, Pune, India, and were cultured at a seeding density of 0.2 × 106 in DMEM/RPMI medium supplemented with 10% FBS, 100 Um/L penicillin, and 100 µgm/L streptomycin, respectively, and maintained in a humidified atmosphere with of 5% CO_2 at 37 ± 1 °C. The samples were dissolved in dimethylsulfoxide (DMSO, not exceeding the final concentration of 0.01%) and further diluted in cell culture medium. The antiproliferative response of the extract was assessed by the quantitative colorimetric 3-(4,5-dimethythiazol-2-yl)-2,5-diphenyl tetrazolium bromide (MTT) assay. Cells (∼ 10,000) were plated in 200 µL growth medium in the presence or absence of test sample (10 µM concentration) in 96-well culture plates for 24 h. Then, the culture plates (inserted in the swing bucket rotors of the A-2-DWP) were centrifuged at 2000 rpm for 10 min at room temperature using Eppendorf 5810R centrifuge. 100 µL of the supernatant discarded, and 20 µL of MTT (5 mg/mL in PBS) was added to each well and incubated for 4 h at 37 ± 1 °C. The viability of the cells was determined using a spectrophotometer at 570 nm. HEK 293 cells were screened to evaluate the toxicity of the samples. The response parameter was expressed in the average percentage of inhibition of samples at 10 µM concentrations. The experiment was performed in triplicate, and the results were taken as a mean ± SD and are given in Table 1.

Tested microbial strains and antibacterial activity

The title compounds (**6a**–**p**) were assessed for their in vitro antibacterial activity against both gram-positive (*Staphylococcus aureus* (MTCC 121), *Bacillus subtilis* (MTCC 96) and *Staphylococcus epidermidis* (MTCC 2639)) and gram-negative bacterial strains (*Escherichia coli* (MTCC 40), *Klebsiella pneumonia* (MTCC 109) and *Pseudomonas aeruginosa* (MTCC 2453)). Standard pathogenic microbial cultures were procured from the Microbial Type Culture Collection and Gene Bank (MTCC), Chandigarh, India, which was recognized by the World Intellectual Property Organization (WIPO). The experiments were carried out in triplicate, and the results were taken as a mean ± SD. The minimum inhibitory concentrations (MICs) of all the synthesized compounds are reported in μg/mL after 24 h at 37 ± 1, and the results are tabulated in Table 2. Antibacterial activity was assessed by the standard broth microdilution technique. The antibiotics, penicillin and streptomycin were used as positive controls (standards), and DMSO was used as a negative control (solvent control), and they were also screened under identical conditions for the comparison of activity results.

General procedure for the synthesis of 4-aryl-3,4,5,6-tetrahydrobenzo[h]quinazoline-2(1H)-thiones (4a–n)

Equimolar concentrations of tetralones **1** (1 mmol), aromatic aldehydes **2** (1 mmol) and thiourea **3** (1 mmol) were refluxed (without stirring) in a clean round-bottomed flask containing absolute ethanol at refluxing temperature for 4 h in the presence of catalytic amount of concentrated sulfuric acid. After the completion of reaction (monitored by TLC), the separated crystalline solid was filtered under suction, washed with water, dried to afford pure product.

General procedure for the synthesis of 3-(2-oxo-2H-chromen-3-yl)-1-aryl-1H-pyrazole-4-carbaldehyde (5a* and *5b) Starting materials carbaldehydes (**5a** and **5b)** were synthesized according to the literature method [56].

General procedure for the synthesis of 10-((3-(2-oxo-2H-chromen-3-yl)-1-aryl-1H-pyrazol-4-yl)methylene)-7-aryl-7,10-dihydro-5H-benzo[h]thiazolo[2,3-b]quinazolin-9(6H)-ones (6a–p) A mixture of compound **4a**–**n** (1 mmol), monochloroacetic acid (1.5 mmol), anhydrous sodium acetate (2 mmol), glacial acetic acid (2 mL), acetic anhydride (1.5 mL) and carbaldehydes (**5a**,**b**) (1 mmol) was refluxed with stirring at 60 °C for 4–6 h. The progress of the reaction was monitored by TLC. Upon completion of the reaction, the reaction mixture was cooled to room temperature and poured on to crushed ice under vigorous stirring. The precipitate was filtered under suction, washed with cold water and recrystallized from glacial acetic acid to afford analytically pure products (**6a**–**p)** in excellent yields.

Characterization data of the products

7-(4-chlorophenyl)-10-((3-(2-oxo-2H-chromen-3-yl)-1-phenyl-1H-pyrazol-4-yl)methylene)-7,10-dihydro-5H-benzo[h]thiazolo[2,3-b]quinazolin-9(6H)-one (6a) Yellow solid; M.P.: 273–275 °C; IR (KBr, cm^{-1}) υ_{max}: 1720 cm^{-1} (coumarin C=O), 1709 cm^{-1} (thiazole C=O), 1631 cm^{-1} (pyrimidine C=N), 1596 cm^{-1} (pyrazole C=N), 1532 cm^{-1} (C=C of α, β-unsaturated carbonyl); ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.90–2.33 (m, 2H), 2.63–2.78 (m, 2H), 5.86 (s, 1H), 7.14 (d, 1H, J = 6.8 Hz), 7.19–7.27 (m, 2H), 7.42–7.50 (m, 7H), 7.54–7.61 (m, 3H), 7.69 (d, 1H, J = 6.8 Hz), 7.80 (d, 2H, J = 7.2 Hz), 7.85 (d, 2H, J = 8.0 Hz), 8.05 (d, 1H, J = 8.0 Hz), 8.78 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.02, 159.81, 154.21, 150.22, 148.79, 144.02, 139.15, 137.51, 135.28, 134.78, 134.64, 132.52, 132.43, 129.75, 129.04, 128.48, 128.01, 127.89, 127.37, 127.22, 126.75, 124.77, 123.32, 121.64, 120.25, 119.72, 119.63, 118.91, 118.41, 116.78, 115.64, 59.35, 27.43, 24.99;MS (ESI) *m/z*: 665 $[M]^+$;Anal. calcd. for $C_{39}H_{25}ClN_4O_3S$: C, 70.42; H, 3.79; N, 8.42. Found: C, 70.71; H, 3.93; N, 8.72.

7-(4-chlorophenyl)-10-((1-(3,4-dinitrophenyl)-3-(2-oxo-2H-chromen-3-yl)-1H-pyrazol-4-yl)methylene)-7,10-dihydro-5H-benzo[h]thiazolo[2,3-b]quinazolin-9(6H)-one (6b) Orange solid; M.P.: 236–238 °C; IR (KBr, cm^{-1}) υ_{max}: 1719 cm^{-1} (coumarin C=O), 1706 cm^{-1} (thiazole C=O), 1633 cm^{-1} (pyrimidine C=N), 1597 cm^{-1} (pyrazole C=N), 1538 cm^{-1} (C=C of α, β-unsaturated carbonyl); ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.88–2.34 (m, 2H), 2.61–2.79 (m, 2H), 5.88 (s, 1H), 7.13–7.50 (m, 10H), 7.68–7.72 (m, 1H), 7.79–7.85 (m, 2H), 8.21 (s, 1H), 8.39 (d, 1H, *J* = 9.2 Hz), 8.72–8.74 (m, 1H); 8.93–8.95 (m, 2H); MS (ESI) *m/z*: 755 $[M]^{+\cdot}$;Anal. calcd. for $C_{39}H_{23}ClN_6O_7S$: C, 62.03; H, 3.07; N, 11.13. Found: C, 61.86; H, 3.22; N, 10.82.

3-methoxy-10-((3-(2-oxo-2H-chromen-3-yl)-1-phenyl-1H-pyrazol-4-yl)methylene)-7-phenyl-7,10-dihydro-5H-benzo[h]thiazolo[2,3-b]quinazolin-9(6H)-one (6c) Yellow solid; M.P.: 268–270 °C; IR (KBr, cm^{-1}) υ_{max}: 1717 cm^{-1} (coumarin C=O), 1711 cm^{-1} (thiazole C=O), 1635 cm^{-1} (pyrimidine C=N), 1606 cm^{-1} (pyrazole C=N), 1537 cm^{-1} (C=C of α, β-unsaturated carbonyl); ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.86–1.93 (m, 1H), 2.27–2.32 (m, 1H), 2.56–2.67 (m, 1H), 2.71–2.77 (m, 1H), 3.75 (s, 3H), 5.80 (s, 1H), 6.74–6.84 (m, 2H), 7.29–7.36 (m, 5H), 7.41–7.72 (m, 8H), 7.84 (d, 1H, *J* = 6.8 Hz), 8.05 (d, 2H, *J* = 8.4 Hz), 8.41 (s, 1H), 8.78 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.05, 159.42, 154.20, 148.73, 144.00, 139.24, 137.17, 134.09, 132.48, 129.74, 128.76, 128.46, 128.27, 127.84, 127.16, 125.70, 124.74, 124.60, 121.10, 120.29, 120.00, 119.72, 118.91, 118.51, 116.77, 113.79, 113.58, 111.23, 60.03, 55.32, 27.90, 24.99; MS (ESI) *m/z*: 662 $[M + H]^+$; Anal. calcd. for $C_{40}H_{28}N_4O_4S$: C, 72.71; H, 4.27; N, 8.48. Found: C, 72.50; H, 4.55; N, 8.71.

10-((1-(3,4-dinitrophenyl)-3-(2-oxo-2H-chromen-3-yl)-1H-pyrazol-4-yl)methylene)-3-methoxy-7-phenyl-7,10-dihydro-5H-benzo[h]thiazolo[2,3-b]quinazolin-9(6H)-one (6d) Orange solid; M.P.: 233–235 °C; IR (KBr, cm^{-1}) υ_{max}: 1720 cm^{-1} (coumarin C=O), 1709 cm^{-1} (thiazole C=O), 1634 cm^{-1} (pyrimidine C=N), 1605 cm^{-1} (pyrazole C=N), 1539 cm^{-1} (C=C of α, β-unsaturated carbonyl); ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.90–1.93 (m, 1H), 2.27–2.31 (m, 1H), 2.57–2.61 (m, 1H), 2.71–2.76 (m, 1H), 3.74 (s, 3H), 5.79 (s, 1H), 6.73–6.83 (m, 2H), 7.29–7.40 (m, 6H), 7.49 (t, 2H, *J* = 8.4 Hz), 7.67–7.84 (m, 3H), 8.21 (s, 1H), 8.38 (d, 1H, *J* = 8.8 Hz), 8.71–8.95 (m, 3H); MS (ESI) *m/z*: 785 $[M + H]^+$; Anal. calcd. for $C_{40}H_{26}N_6O_8S$: C, 63.99; H, 3.49; N, 11.19. Found: C, 64.29; H, 3.78; N, 11.32.

3-methoxy-7-(4-methoxyphenyl)-10-((3-(2-oxo-2H-chromen-3-yl)-1-phenyl-1H-pyrazol-4-yl)methylene)-7,10-dihydro-5H-benzo[h]thiazolo[2,3-b]quinazolin-9(6H)-one (6e) Yellow solid; M.P.: 254–256 °C; IR (KBr, cm^{-1}) υ_{max}: 1729 cm^{-1} (coumarin C=O), 1704 cm^{-1} (thiazole C=O), 1634 cm^{-1} (pyrimidine C=N), 1598 cm^{-1} (pyrazole C=N), 1535 cm^{-1} (C=C of α, β-unsaturated carbonyl); ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.85–1.94 (m, 1H), 2.22–2.29 (m, 1H), 2.56–2.67 (m, 1H), 2.70–2.76 (m, 1H), 3.71 (s, 3H), 3.75 (s, 3H), 5.72 (s, 1H), 6.70 (s, 1H), 6.81–6.91 (m, 3H), 7.27 (d, 2H, *J* = 8.4 Hz), 7.39-7.60 (m, 6H), 7.70 (t, 2H, *J* = 8.4 Hz), 7.84 (d, 1H, *J* = 7.6 Hz), 8.04 (d, 2H, *J* = 8.0 Hz), 8.40 (s, 1H), 8.75 (s, 1H); MS (ESI) *m/z*: 490 $[M + H]^+$; Anal. calcd. for $C_{41}H_{30}N_4O_5S$: C, 71.29; H, 4.38; N, 8.11. Found: C, 71.48; H, 4.69; N, 7.85.

7-(3,4-dimethoxyphenyl)-3-methoxy-10-((3-(2-oxo-2H-chromen-3-yl)-1-phenyl-1H-pyrazol-4-yl)methylene)-7,10-dihydro-5H-benzo[h]thiazolo[2,3-b]quinazolin-9(6H)-one (6f) Yellow solid; M.P.: 262–264 °C; IR (KBr, cm^{-1}) υ_{max}: 1728 cm^{-1} (coumarin C=O), 1705 cm^{-1} (thiazole C=O), 1634 cm^{-1} (pyrimidine C=N), 1599 cm^{-1} (pyrazole C=N), 1533 cm^{-1} (C=C of α, β-unsaturated carbonyl); ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.94–2.32 (m, 2H), 2.60–2.74 (m, 2H), 3.70 (s, 3H), 3.75 (s, 3H), 3.79 (s, 3H), 5.73 (s, 1H), 6.75–6.97 (m, 5H), 7.42–7.59 (m, 6H), 7.71 (d, 2H, *J* = 7.6 Hz), 7.85 (d, 1H, *J* = 6.0 Hz), 8.05 (d, 2H, *J* = 7.2 Hz), 8.41 (s, 1H), 8.77 (s, 1H); MS (ESI) *m/z*: 721 $[M]^+$; Anal. calcd. for $C_{42}H_{32}N_4O_6S$: C, 69.99; H, 4.47; N, 7.77. Found: C, 70.23; H, 4.22; N, 7.58.

3-methoxy-10-((3-(2-oxo-2H-chromen-3-yl)-1-phenyl-1H-pyrazol-4-yl)methylene)-7-(2,3,4-trimethoxyphenyl)-7,10-dihydro-5H-benzo[h]thiazolo[2,3-b]quinazolin-9(6H)-one (6g) Yellow solid; M.P.: 266–268 °C; IR (KBr, cm^{-1}) υ_{max}: 1728 cm^{-1} (coumarin C=O), 1703 cm^{-1} (thiazole C=O), 1633 cm^{-1} (pyrimidine C=N), 1597 cm^{-1} (pyrazole C=N), 1532 cm^{-1} (C=C of α, β-unsaturated carbonyl); ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.86–2.25 (m, 2H), 2.55–2.74 (m, 2H), 3.71 (s, 3H), 3.74 (s, 3H), 3.75 (s, 6H), 5.85 (s, 1H), 6.72–6.81 (m, 3H), 6.97 (d, 1H, *J* = 8.0 Hz), 7.41–7.49 (m, 4H), 7.59 (t, 2H, *J* = 8.0 Hz), 7.69 (t, 2H, *J* = 8.0 Hz), 7.84 (d, 1H, *J* = 7.6 Hz), 8.05 (d, 2H, *J* = 7.6 Hz), 8.40 (s, 1H), 8.76 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.09, 159.85, 159.49, 154.20, 150.08, 148.77, 144.05, 139.16, 137.15, 134.33, 132.54, 130.26, 130.18, 129.76, 128.47, 127.88, 127.20, 125.55, 124.78, 124.66, 121.37, 120.25, 119.78, 119.72, 118.90, 118.44, 116.78, 115.83, 115.61, 113.61, 113.37, 111.27, 60.07, 59.21, 55.32, 55.09, 52.46, 27.88, 24.98; MS (ESI) *m/z*: 751 $[M]^+$; Anal. calcd. for $C_{43}H_{34}N_4O_7S$: C, 68.79; H, 4.56; N, 7.46. Found: C, 68.48; H, 4.32; N, 7.22.

7-(3-hydroxy-4-methoxyphenyl)-3-methoxy-10-((3-(2-oxo-2H-chromen-3-yl)-1-phenyl-1H-pyrazol-4-yl)methylene)-7,10-dihydro-5H-benzo[h]thiazolo[2,3-b]quinazolin-9(6H)-one (6h) Yellow solid; M.P.: 244–246 °C; IR (KBr, cm^{-1}) υ_{max}: 3516 cm^{-1} (OH), 1729 cm^{-1} (coumarin C=O), 1702 cm^{-1} (thiazole C=O), 1634 cm^{-1} (pyrimidine C=N),

1596 cm^{-1} (pyrazole C=N), 1535 cm^{-1} (C=C of α, β-unsaturated carbonyl); ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.90–1.99 (m, 1H), 2.23–2.31 (m, 1H), 2.58–2.66 (m, 1H), 2.70–2.79 (m, 1H), 3.71 (s, 3H), 3.75 (s, 3H), 5.66 (s, 1H), 6.73–6.83 (m, 4H), 6.93 (s, 1H), 7.39–7.71 (m, 8H), 7.84 (d, 1H, *J* = 7.6 Hz), 8.04 (d, 2H, *J* = 8.4 Hz), 8.40 (s, 1H), 8.75 (s, 1H), 9.09 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.15, 159.82, 159.40, 154.20, 150.05, 148.71, 146.57, 146.05, 144.02, 139.18, 137.21, 134.10, 132.49, 131.22, 129.74, 128.47, 127.84, 127.17, 125.73, 124.75, 124.56, 121.61, 121.07, 120.30, 120.11, 119.70, 118.92, 118.53, 116.76, 114.49, 113.98, 113.59, 111.24, 110.98, 59.80, 56.06, 55.32, 28.01, 24.98; MS (ESI) *m/z*: 707 $[M]^+$; Anal. calcd. for $C_{41}H_{30}N_4O_6S$: C, 69.68; H, 4.28; N, 7.93. Found: C, 69.48; H, 3.99; N, 8.27.

7-(4-fluorophenyl)-3-methoxy-10-((3-(2-oxo-2H-chromen-3-yl)-1-phenyl-1H-pyrazol-4-yl)methylene)-7,10-dihydro-5H-benzo[h]thiazolo[2,3-b]quinazolin-9(6H)-one (6i) Yellow solid; M.P.: 254–256 °C; IR (KBr, cm^{-1}) υ_{max}: 1718 cm^{-1} (coumarin C=O), 1706 cm^{-1} (thiazole C=O), 1633 cm^{-1} (pyrimidine C=N), 1601 cm^{-1} (pyrazole C=N), 1539 cm^{-1} (C=C of α, β-unsaturated carbonyl); ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.86–1.92 (m, 1H), 2.26–2.32 (m, 1H), 2.59–2.75 (m, 2H), 3.75 (s, 3H), 5.83 (s, 1H), 6.75 (s, 1H), 6.82 (d, 1H, *J* = 8.4 Hz), 7.18 (t, 2H, *J* = 8.8 Hz), 7.40–7.61 (m, 8H), 7.70 (t, 2H, *J* = 8.8 Hz), 7.85 (d, 1H, *J* = 7.6 Hz), 8.05 (d, 2H, *J* = 8.4 Hz), 8.41 (s, 1H), 8.77 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.97, 159.86, 159.20, 154.18, 153.90, 151.83, 150.36, 148.69, 144.02, 139.22, 137.09, 133.14, 132.48, 129.76, 128.46, 127.82, 127.18, 126.01, 124.75, 124.34, 120.48, 120.34, 120.25, 119.71, 118.91, 118.62, 116.76, 113.50, 111.15, 107.34, 55.91, 55.29, 27.90, 24.51; MS (ESI) *m/z*: 679 $[M]^+$; Anal. calcd. for $C_{40}H_{27}FN_4O_4S$: C, 70.78; H, 4.01; N, 8.25. Found: C, 71.06; H, 3.87; N, 8.58.

7-(4-chlorophenyl)-3-methoxy-10-((3-(2-oxo-2H-chromen-3-yl)-1-phenyl-1H-pyrazol-4-yl)methylene)-7,10-dihydro-5H-benzo[h]thiazolo[2,3-b]quinazolin-9(6H)-one (6j) Yellow solid; M.P.: 251–253 °C; IR (KBr, cm^{-1}) υ_{max}: 1720 cm^{-1} (coumarin C=O), 1709 cm^{-1} (thiazole C=O), 1631 cm^{-1} (pyrimidine C=N), 1596 cm^{-1} (pyrazole C=N), 1532 cm^{-1} (C=C of α, β-unsaturated carbonyl); ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.90–2.33 (m, 2H), 2.61–2.78 (m, 2H), 3.75 (s, 3H), 5.86 (s, 1H), 7.15–7.27 (m, 3H), 7.42–7.59 (m, 9H), 7.69 (s, 1H), 7.79–7.86 (m, 2H), 8.05 (d, 2H, *J* = 7.2 Hz), 8.41 (s, 1H), 8.78 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.04, 159.84, 154.20, 150.22, 148.79, 144.05, 139.15, 137.48, 135.28, 134.79, 134.63, 132.54, 132.42, 129.77, 129.04, 128.48, 128.01, 127.91, 127.37, 127.23, 126.76, 124.79, 123.31, 121.63, 120.23, 119.74, 119.62, 118.90, 118.40, 116.79, 115.65, 59.35, 59.10, 27.43, 24.99; MS (ESI) *m/z*: 695 $[M]^+$; Anal. calcd. for $C_{40}H_{27}ClN_4O_4S$: C, 69.11; H, 3.91; N, 8.06. Found: C, 69.41; H, 4.19; N, 8.31.

7-(4-bromophenyl)-3-methoxy-10-((3-(2-oxo-2H-chromen-3-yl)-1-phenyl-1H-pyrazol-4-yl)methylene)-7,10-dihydro-5H-benzo[h]thiazolo[2,3-b]quinazolin-9(6H)-one (6k) Yellow solid; Yield: 80%; M.P.: 268–270 °C; IR (KBr, cm^{-1}) υ_{max}: 1722 cm^{-1} (coumarin C=O), 1709 cm^{-1} (thiazole C=O), 1633 cm^{-1} (pyrimidine C=N), 1596 cm^{-1} (pyrazole C=N), 1538 cm^{-1} (C=C of α, β-unsaturated carbonyl); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.02–2.10 (m, 1H), 2.19–2.27 (m, 1H), 2.69–2.74 (m, 1H), 2.78–2.84 (m, 1H), 3.84 (s, 3H), 5.66 (s, 1H), 6.70 (s, 1H), 6.84 (d, 1H, *J* = 8.8 Hz), 7.34 (t, 3H, *J* = 8.0 Hz), 7.40–7.47 (m, 4H), 7.53–7.59 (m, 3H), 7.62 (d, 2H, *J* = 6.8 Hz), 7.88 (d, 2H, *J* = 8.0 Hz), 7.89 (d, 1H, *J* = 8.8 Hz), 8.05 (s, 1H), 8.23 (s, 1H); MS (ESI) *m/z*: 740 $[M]^+$; Anal. calcd. for $C_{40}H_{27}BrN_4O_4S$: C, 64.95; H, 3.68; N, 7.57. Found: C, 64.72; H, 91; N, 7.27.

7-(4-hydroxyphenyl)-3-methoxy-10-((3-(2-oxo-2*H*-chromen-3-yl)-1-phenyl-1*H*-pyrazol-4-yl)methylene)-7,10-dihydro-5*H*-benzo[*h*]thiazolo[2,3-*b*]quinazolin-9(6*H*)-one *(6l)* Yellow solid; M.P.: 242–244 °C; IR (KBr, cm^{-1}) υ_{max}: 3511 cm^{-1} (OH), 1720 cm^{-1} (coumarin C=O), 1708 cm^{-1} (thiazole C=O), 1632 cm^{-1} (pyrimidine C=N), 1596 cm^{-1} (pyrazole C=N), 1535 cm^{-1} (C=C of α, β-unsaturated carbonyl); ^{1}H NMR (400 MHz, $CDCl_3$ + DMSO-d_6): δ 1.96–2.04 (m, 1H), 2.09–2.17 (m, 1H), 2.57–2.75 (m, 2H), 3.73 (s, 3H), 5.50 (s, 1H), 6.59 (s, 1H), 6.66–6.72 (m, 3H), 7.14 (d, 2H, *J* = 8.0 Hz), 7.28–7.34 (m, 2H), 7.46 (t, 4H, *J* = 8.8 Hz), 7.54 (t, 2H, *J* = 7.2 Hz), 7.73 (d, 3H, *J* = 7.6 Hz), 8.04 (s, 1H), 8.21 (s, 1H), 8.98 (s, 1H); MS (ESI) *m/z*: 677 $[M]^+$; Anal. calcd. for $C_{40}H_{28}N_4O_5S$: C, 70.99; H, 4.17; N, 8.28. Found: C, 71.32; H, 4.39; N, 8.07.

7-(4-hydroxy-3-methoxyphenyl)-3-methoxy-10-((3-(2-oxo-2H-chromen-3-yl)-1-phenyl-1H-pyrazol-4-yl)methylene)-7,10-dihydro-5H-benzo[h]thiazolo[2,3-b]quinazolin-9(6H)-one (6m) Yellow solid; Yield: 80%; M.P.: 245–247 °C; IR (KBr, cm^{-1}) υ_{max}: 3518 cm^{-1} (OH), 1726 cm^{-1} (coumarin C=O), 1700 cm^{-1} (thiazole C=O), 1638 cm^{-1} (pyrimidine C=N), 1601 cm^{-1} (pyrazole C=N), 1540 cm^{-1} (C=C of α, β-unsaturated carbonyl); ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.04–2.12 (m, 1H), 2.18–27 (m, 1H), 2.64–2.82 (m, 2H), 3.13 (s, 6H), 5.56 (s, 1H), 6.67 (t, 1H, *J* = 8.0 Hz), 6.75–6.84 (m, 3H), 6.88 (d, 1H, *J* = 9.2 Hz), 7.35–7.42 (m, 3H), 7.53 (t, 2H, *J* = 7.6 Hz), 7.64 (t, 2H, *J* = 7.6 Hz), 7.70 (s, 1H), 7.79 (t, 1H, *J* = 8.0 Hz), 7.85 (t, 2H, *J* = 7.2 Hz), 8.26 (d, 2H, *J* = 8.0 Hz), 8.82 (s, 1H); MS (ESI) *m/z*: 707 $[M]^+$; Anal. calcd. for $C_{41}H_{30}N_4O_6S$: C, 69.68; H, 4.28; N, 7.93. Found: C, 69.40; H, 4.03; N, 7.70.

7-(3-ethoxy-4-hydroxyphenyl)-3-methoxy-10-((3-(2-oxo-2H-chromen-3-yl)-1-phenyl-1H-pyrazol-4-yl)methylene)-7,10-dihydro-5H-benzo[h]thiazolo[2,3-b]quinazolin-9(6H)-one

(6n) Yellow solid; M.P.: 264–266 °C; IR (KBr, cm^{-1}) υ_{max}: 3520 cm^{-1} (OH), 1726 cm^{-1} (coumarin C=O), 1701 cm^{-1} (thiazole C=O), 1633 cm^{-1} (pyrimidine C=N), 1592 cm^{-1} (pyrazole C=N), 1539 cm^{-1} (C=C of α, β-unsaturated carbonyl) ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.41 (t, 3H, *J* = 6.8 Hz), 2.10–2.25 (m, 2H), 2.68–2.84 (m, 2H), 3.84 (s, 3H), 4.09 (q, 2H, *J* = 6.8 Hz), 5.61 (s, 1H), 5.70 (s, 1H), 6.71 (s, 1H), 6.80–6.88 (m, 2H), 6.95 (d, 2H, *J* = 8.0 Hz), 7.34 (t, 1H, *J* = 7.2 Hz), 7.41–7.45 (m, 2H), 7.53–7.63 (m, 5H), 7.78 (d, 2H, *J* = 8.0 Hz), 7.88 (d, 1H, *J* = 8.0 Hz), 8.05 (s, 1H), 8.23 (s, 1H); MS (ESI) *m/z*: 721 $[M]^+$; Anal. calcd. for $C_{42}H_{32}N_4O_6S$: C, 69.99; H, 4.47; N, 7.77. Found: C, 70.21; H, 4.23; N, 7.98.

3-methoxy-7-(naphthalen-1-yl)-10-((3-(2-oxo-2H-chromen-3-yl)-1-phenyl-1H-pyrazol-4-yl)methylene)-7,10-dihydro-5H-benzo[h]thiazolo[2,3-b]quinazolin-9(6H)-one (6o) Yellow solid; M.P.: 242–244 °C; IR (KBr, cm^{-1}) υ_{max}: 1718 cm^{-1} (coumarin C=O), 1710 cm^{-1} (thiazole C=O), 1639 cm^{-1} (pyrimidine C=N), 1600 cm^{-1} (pyrazole C=N), 1539 cm^{-1} (C=C of α, β-unsaturated carbonyl); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.88–2.01 (m, 1H), 2.28–2.33 (m, 1H), 2.59–2.90 (m, 2H), 3.83 (s, 3H), 5.58 (s, 1H), 6.70–6.76 (m, 3H), 7.36–7.45 (m, 6H), 7.52–7.77 (m, 8H), 7.81 (d, 1H, *J* = 7.2 Hz), 8.01 (d, 2H, *J* = 8.0 Hz), 8.39 (s, 1H), 8.77 (s, 1H); MS (ESI) *m/z*: 711 $[M]^+$; Anal. calcd. for $C_{44}H_{30}N_4O_4S$: C, 74.35; H, 4.25; N, 7.88. Found: C, 74.11; H, 4.01; N, 8.02.

7-(2-chlorophenyl)-3-methoxy-10-((3-(2-oxo-2H-chromen-3-yl)-1-phenyl-1H-pyrazol-4-yl)methylene)-7,10-dihydro-5H-benzo[h]thiazolo[2,3-b]quinazolin-9(6H)-one (6p) Yellow solid; M.P.: 255–257 °C; IR (KBr, cm^{-1}) υ_{max}: 1722 cm^{-1} (coumarin C=O), 1707 cm^{-1} (thiazole C=O), 1639 cm^{-1} (pyrimidine C=N), 1601 cm^{-1} (pyrazole C=N), 1538 cm^{-1} (C=C of α, β-unsaturated carbonyl); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.90–1.95 (m, 1H), 2.28–2.36 (m, 1H), 2.61–2.81 (m, 2H), 3.73 (s, 3H), 5.88 (s, 1H), 7.13–7.25 (m, 3H), 7.49–7.52 (m, 9H), 7.66 (s, 1H), 7.77–7.90 (m, 2H), 8.01 (d, 2H, *J* = 7.6 Hz), 8.39 (s, 1H), 8.76 (s, 1H); MS (ESI) *m/z*: 695 $[M]^+$; Anal. calcd. for $C_{40}H_{27}ClN_4O_4S$: C, 69.11; H, 3.91; N, 8.06. Found: C, 69.38; H, 3.70; N, 8.33.

Acknowledgements We greatly acknowledge Tripos Inc., USA, and Schrödinger LLC, New York, for providing the software. The authors thank the Director, National Institute of Technology, Warangal, for providing research facilities and one of the authors RG gratefully acknowledges MHRD for financial assistance. The author Saikiran Reddy Peddi (IF150172) would like to thank DST for a research fellowship.

References

1. Xie W, Xie S, Zhou Y et al (2014) Design and synthesis of novel 5,6-disubstituted pyridine-2,3-dione-3-thiosemicarbazone derivatives as potential anticancer agents. Eur J Med Chem 81:22–27. https://doi.org/10.1016/j.ejmech.2014.05.001
2. Tzanetou E, Liekens S, Kasiotis KM et al (2014) Antiproliferative novel isoxazoles: modeling, virtual screening, synthesis, and bioactivity evaluation. Eur J Med Chem 81:139–149. https://doi.org/10.1016/j.ejmech.2014.05.011
3. George RF, Fouad MA, Gomaa IEO (2016) Synthesis and cytotoxic activities of some pyrazoline derivatives bearing phenyl pyridazine core as new apoptosis inducers. Eur J Med Chem 112:48–59. https://doi.org/10.1016/j.ejmech.2016.01.048
4. Alanazi AM, Abdel-Aziz AAM, Al-Suwaidan IA et al (2014) Design, synthesis and biological evaluation of some novel substituted quinazolines as antitumor agents. Eur J Med Chem 79:446–454. https://doi.org/10.1016/j.ejmech.2014.04.029
5. Bielenica A, Stefańska J, Stępień K et al (2015) Synthesis, cytotoxicity and antimicrobial activity of thiourea derivatives incorporating 3-(trifluoromethyl)phenyl moiety. Eur J Med Chem 101:111–125. https://doi.org/10.1016/j.ejmech.2015.06.027
6. Krátký M, Vinšová J (2016) Salicylanilide *N*-monosubstituted carbamates: synthesis and in vitro antimicrobial activity. Bioorg Med Chem 24:1322–1330. https://doi.org/10.1016/j.bmc.2016.02.004
7. Gu Y (2012) Multicomponent reactions in unconventional solvents: state of the art. Green Chem 14:2091. https://doi.org/10.1039/c2gc35635j
8. José Climent M, Corma A, Iborra S (2012) Homogeneous and heterogeneous catalysts for multicomponent reactions. RSC Adv 2:16–58. https://doi.org/10.1039/C1RA00807B
9. El-borai MA, Rizk HF, Abd-Aal MF, El-Deeb IY (2012) Synthesis of pyrazolo[3,4-b]pyridines under microwave irradiation in multi-component reactions and their antitumor and antimicrobial activities—Part 1. Eur J Med Chem 48:92–96. https://doi.org/10.1016/j.ejmech.2011.11.038
10. Rajanarendar E, Raju S, Reddy MN et al (2012) Multi-component synthesis and in vitro and in vivo anticancer activity of novel arylmethylene bis-isoxazolo[4,5-b]pyridine-*N*-oxides. Eur J Med Chem 50:274–279. https://doi.org/10.1016/j.ejmech.2012.02.004
11. Dömling A, Ugi I (2000) Multicomponent reactions with isocyanides. Angew. Chemie 39:3168–3210. https://doi.org/10.1002/1521-3773(20000915)39:18%3C3168::AID-ANIE3168%3E3.0.CO;2-U
12. Fayol A, Zhu J (2005) Three-Component Synthesis of Polysubstituted 6-Azaindolines and Its Tricyclic Derivatives. Org Lett 7:239–242. https://doi.org/10.1021/ol0477881
13. Bienaymé H, Hulme C, Oddon G, Schmitt P (2000) Maximizing synthetic efficiency: multi-component transformations lead the way. Chem–A Eur J 6:3321–3329. https://doi.org/10.1002/1521-3765(20000915)6:18%3C3321::AID-CHEM3321%3E3.0.CO;2-A
14. Shaabani A, Maleki A, Rezayan AH, Sarvary A (2011) Recent progress of isocyanide-based multicomponent reactions in Iran. Mol Divers 15:41–68. https://doi.org/10.1007/s11030-010-9258-1
15. Zhao D, Chen C, Liu H et al (2014) Biological evaluation of halogenated thiazolo[3,2-a]pyrimidin-3-one carboxylic acid derivatives targeting the YycG histidine kinase. Eur J Med Chem 87:500–507. https://doi.org/10.1016/j.ejmech.2014.09.096
16. Mohamed SF, Flefel EM, Amr AE-GE, Abd El-Shafy DN (2010) Anti-HSV-1 activity and mechanism of action of some new synthesized substituted pyrimidine, thiopyrimidine and thiazolopyrimidine derivatives. Eur J Med Chem 45:1494–1501. https://doi.org/10.1016/j.ejmech.2009.12.057
17. Holla BS, Rao BS, Sarojini BK, Akberali PM (2004) One pot synthesis of thiazolodihydropyrimidinones and evaluation of their anticancer activity. Eur J Med Chem 39:777–783. https://doi.org/10.1016/j.ejmech.2004.06.001
18. Flefel EE, Salama MA, El-Shahat M et al (2007) A novel synthesis of some new pyrimidine and thiazolopyrimidine derivatives for anticancer evaluation. Phosphorus, Sulfur Silicon Relat Elem 182:1739–1756. https://doi.org/10.1080/10426500701313912

19. Maddila S, Damu GLV, Oseghe EO et al (2012) Synthesis and biological studies of novel biphenyl-3,5-dihydro-2H-thiazolopyrimidines derivatives. J Korean Chem Soc 56:334–340. https://doi.org/10.5012/jkcs.2012.56.3.334
20. Alam O, Khan SA, Siddiqui N, Ahsan W (2010) Synthesis and pharmacological evaluation of newer thiazolo[3,2-a]pyrimidines for anti-inflammatory and antinociceptive activity. Med Chem Res 19:1245–1258. https://doi.org/10.1007/s00044-009-9267-8
21. Amr AE-GE, Maigali SS, Abdulla MM (2008) Synthesis, and analgesic and antiparkinsonian activities of thiopyrimidine, pyrane, pyrazoline, and thiazolopyrimidine derivatives from 2-chloro-6-ethoxy-4-acetylpyridine. Monatshefte für Chemie–Chem Mon 139:1409–1415. https://doi.org/10.1007/s00706-008-0937-x
22. Mayer TU (1999) Small molecule inhibitor of mitotic spindle bipolarity identified in a phenotype-based screen. Science 286:971–974. https://doi.org/10.1126/science.286.5441.971
23. Hurst EW, Hull R (1961) Two new synthetic substances active against viruses of the psittacosis-lymphogranuloma-trachoma group. J Med Pharm Chem 3:215–229. https://doi.org/10.1021/jm50015a002
24. Sawant RL, Bansode CA, Wadekar JB (2013) In vitro anti-inflammatory potential and QSAR analysis of oxazolo/thiazolo pyrimidine derivatives. Med Chem Res 22:1884–1892. https://doi.org/10.1007/s00044-012-0189-5
25. Tozkoparan B, Ertan M, Kelicen P, Demirdamar R (1999) Synthesis and anti-inflammatory activities of some thiazolo[3,2-a]pyrimidine derivatives. Farm 54:588–593. https://doi.org/10.1016/S0014-827X(99)00068-3
26. Abd El-Latif NA, Amr AE-GE, Ibrahiem AA (2007) Synthesis, reactions, and pharmacological screening of heterocyclic derivatives using nicotinic acid as a natural synthon. Monatshefte für Chemie–Chem Mon 138:559–567. https://doi.org/10.1007/s00706-007-0628-z
27. Amr AE-GE, Sabrry NM, Abdalla MM, Abdel-Wahab BF (2009) Synthesis, antiarrhythmic and anticoagulant activities of novel thiazolo derivatives from methyl 2-(thiazol-2-ylcarbamoyl)acetate. Eur J Med Chem 44:725–735. https://doi.org/10.1016/j.ejmech.2008.05.004
28. Pan B, Huang R, Zheng L et al (2011) Thiazolidione derivatives as novel antibiofilm agents: design, synthesis, biological evaluation, and structure–activity relationships. Eur J Med Chem 46:819–824. https://doi.org/10.1016/j.ejmech.2010.12.014
29. Atwal KS, Swanson BN, Unger SE et al (1991) Dihydropyrimidine calcium channel blockers. 3. 3-Carbamoyl-4-aryl-1,2,3,4-tetrahydro-6-methyl-5-pyrimidinecarboxylic acid esters as orally effective antihypertensive agents. J Med Chem 34:806–811. https://doi.org/10.1021/jm00106a048
30. Rovnyak GC, Atwal KS, Kimball SD et al (1992) Dihydropyrimidine calcium channel blockers. 4. Basic 3-Substituted-4-aryl-1,4-dihydropyrimidine-5-carboxylic acid esters. Potent antihypertensive agents. J Med Chem 35:3254–3263. https://doi.org/10.1021/jm00095a023
31. Ruiu S, Marchese G, Saba PL et al (2000) The 5-HT2 antagonist ritanserin blocks dopamine re-uptake in the rat frontal cortex. Mol Psychiatry 5:673–677. https://doi.org/10.1038/sj.mp.4000804
32. Awadallah FM (2008) Synthesis, pharmacophore modeling, and biological evaluation of novel 5H-Thiazolo[3,2-a]pyrimidin-5-one Derivatives as 5-HT2A receptor antagonists. Sci Pharm 76:415–438. https://doi.org/10.3797/scipharm.0804-20
33. Khobragade CN, Bodade RG, Dawane BS et al (2010) Synthesis and biological activity of pyrazolo[3,4-*d*]thiazolo[3,2-*a*]pyrimidin-4-one derivatives: in silico approach. J Enzyme Inhib Med Chem 25:615–621. https://doi.org/10.3109/14756360903389849
34. Xu Y, Zhou M, Li Y et al (2013) Characterization of the Stereochemical Structures of 2 H–Thiazolo [3,2-*a*]pyrimidine Compounds and their binding affinities for anti-apoptotic Bcl-2 family proteins. ChemMedChem 8:1345–1352. https://doi.org/10.1002/cmdc.201300159
35. Küçükgüzel ŞG, Şenkardeş S (2015) Recent advances in bioactive pyrazoles. Eur J Med Chem 97:786–815. https://doi.org/10.1016/j.ejmech.2014.11.059
36. Harikrishna N, Isloor AM, Ananda K et al (2015) 1,3,4-Trisubstituted pyrazole bearing a 4-(chromen-2-one) thiazole: synthesis, characterization and its biological studies. RSC Adv 5:43648–43659. https://doi.org/10.1039/C5RA04995D
37. Kontogiorgis C, Detsi A, Hadjipavlou-Litina D (2012) Coumarin-based drugs: a patent review (2008-present). Expert Opin Ther Pat 22:437–454. https://doi.org/10.1517/13543776.2012.678835
38. Srivastava P, Vyas VK, Variya B et al (2016) Synthesis, anti-inflammatory, analgesic, 5-lipoxygenase (5-LOX) inhibition activities, and molecular docking study of 7-substituted coumarin derivatives. Bioorg Chem 67:130–138. https://doi.org/10.1016/j.bioorg.2016.06.004
39. Musa M, Cooperwood J, Khan MO (2008) A review of coumarin derivatives in pharmacotherapy of breast cancer. Curr Med Chem 15:2664–2679. https://doi.org/10.2174/092986708786242877
40. Nagamallu R, Srinivasan B, Ningappa MB, Kariyappa AK (2016) Synthesis of novel coumarin appended bis(formylpyrazole) derivatives: studies on their antimicrobial and antioxidant activities. Bioorg Med Chem Lett 26:690–694. https://doi.org/10.1016/j.bmcl.2015.11.038
41. Kant R, Kumar D, Agarwal D et al (2016) Synthesis of newer 1,2,3-triazole linked chalcone and flavone hybrid compounds and evaluation of their antimicrobial and cytotoxic activities. Eur J Med Chem 113:34–49. https://doi.org/10.1016/j.ejmech.2016.02.041
42. Banothu J, Khanapur M, Basavoju S et al (2014) Synthesis, characterization and biological evaluation of fused thiazolo [3,2-a]pyrimidine derivatives. RSC Adv 4:22866–22874. https://doi.org/10.1039/c4ra02514h
43. Gali R, Banothu J, Porika M et al (2014) Synthesis and in vitro cytotoxic activity of novel coumarinylimidazo [2,1-*b*]thiazole derivatives. RSC Adv 4:53812–53819. https://doi.org/10.1039/C4RA11428K
44. Gondru R, Banothu J, Thatipamula RK et al (2015) 3-(1-Phenyl-4-((2-(4-arylthiazol-2-yl)hydrazono)methyl)-1H-pyrazol-3-yl)-2H-chromen-2-ones: one-pot three component condensation, in vitro antimicrobial, antioxidant and molecular docking studies. RSC Adv 5:33562–33569. https://doi.org/10.1039/C5RA04196A
45. Benson TE, Walsh CT, Hogle JM (1996) The structure of the substrate-free form of MurB, an essential enzyme for the synthesis of bacterial cell walls. Structure 4:47–54. https://doi.org/10.1016/S0969-2126(96)00008-1
46. Lees WJ, Benson TE, Hogle JM, Walsh CT (1996) (E)-Enolbutyryl-UDP-*N*-acetylglucosamine as a Mechanistic Probe of UDP-*N*-acetylenolpyruvylglucosamine Reductase (MurB). Biochemistry 35:1342–1351. https://doi.org/10.1021/bi952287w
47. Bugg TDH, Walsh CT (1992) Intracellular steps of bacterial cell wall peptidoglycan biosynthesis: enzymology, antibiotics, and antibiotic resistance. Nat Prod Rep 9:199. https://doi.org/10.1039/np9920900199
48. El Zoeiby A, Sanschagrin F, Levesque RC (2002) Structure and function of the Mur enzymes: development of novel inhibitors. Mol Microbiol 47:1–12. https://doi.org/10.1046/j.1365-2958.2003.03289.x
49. Andres CJ, Bronson JJ, D'Andrea SV et al (2000) 4-Thiazolidinones: novel inhibitors of the bacterial enzyme murB. Bioorg Med Chem Lett 10:715–717. https://doi.org/10.1016/S0960-894X(00)00073-1
50. Yang Y, Severin A, Chopra R et al (2006) 3,5-dioxopyrazolidines, novel inhibitors of UDP-*N*-acetylenolpyruvylglucosamine reductase (MurB) with activity against gram-positive bacteria.

Antimicrob Agents Chemother 50:556–564. https://doi.org/10.1128/AAC.50.2.556-564.2006
51. Bhat M, Kayarmar GKNR et al (2016) Design, synthesis and characterization of new 1,2,3-triazolyl pyrazole derivatives as potential antimicrobial agents via a Vilsmeier-Haack reaction approach. RSC Adv 6:59375–59388. https://doi.org/10.1039/C6RA06093E
52. Mosmann T (1983) Rapid colorimetric assay for cellular growth and survival: application to proliferation and cytotoxicity assays. J Immunol Methods 65:55–63. https://doi.org/10.1016/0022-1759(83)90303-4
53. Mallié M, Bastide JM, Blancard A et al (2005) In vitro susceptibility testing of Candida and Aspergillus spp. to voriconazole and other antifungal agents using Etest®: results of a French multicentre study. Int J Antimicrob Agents 25:321–328. https://doi.org/10.1016/j.ijantimicag.2004.11.010
54. Subramaniam P, Nandan N (2011) Effect of xylitol, sodium fluoride and triclosan containing mouth rinse on Streptococcus mutans. Contemp Clin Dent 2:287. https://doi.org/10.4103/0976-237X.91790
55. Friesner RA, Banks JL, Murphy RB et al (2004) Glide: a new approach for rapid, accurate docking and scoring. 1. Method and assessment of docking accuracy. J Med Chem 47:1739–1749. https://doi.org/10.1021/jm0306430
56. Alegaon SG, Hirpara MB, Alagawadi KR et al (2014) Synthesis of novel pyrazole–thiadiazole hybrid as potential potent and selective cyclooxygenase-2 (COX-2) inhibitors. Bioorg Med Chem Lett 24:5324–5329. https://doi.org/10.1016/j.bmcl.2014.08.062

Affiliations

Ramesh Gondru[1] · Saikiran Reddy Peddi[2] · Vijjulatha Manga[2] · Manjulatha Khanapur[3] · Rajitha Gali[1] · Narsimha Sirassu[4] · Rajitha Bavantula[1]

✉ Rajitha Bavantula
rajitabhargavi@yahoo.com

[1] Department of Chemistry, National Institute of Technology, Warangal, Telangana State 506004, India

[2] Department of Chemistry, Osmania University, Hyderabad, Telangana State 500007, India

[3] Department of Biochemistry, School of Life Sciences, University of Hyderabad, Hyderabad, Telangana State 500046, India

[4] Department of Chemistry, Kakatiya University, Warangal, Telangana State 506 009, India