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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Synthesis and anti-bacterial activities of some novel pyrazolobenzothiazine-based chalcones and their pyrimidine derivatives

Mujahid Hussain Bukhari · Hamid Latif Siddiqui · Matloob Ahmad · Tanvir Hussain · Mark G. Moloney

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Abstract A novel series of fifteen pyrimidine derivatives was prepared from pyrazolobenzothiazine-based chalcones by refluxing with guanidine hydrochloride. The starting materials 4-(3,4-dimethyl-5,5-dioxidobenzo[4,3-c][1,2]thiazin-2(4-H)yl)phenyl)ethanone (**2**) or 4-(3,4-dimethyl-5,5-dioxidobenzo[4,3-c][1,2]thiazin-2(4-H)yl)benzaldehyde (**3**) were obtained by *N*-arylation of 3,4-dimethyl-2,4-dihydrobenzo[e]pyrazolo[4,3-c][1,2]thiazine 5,5-dioxide (**1**) with 4-fluoroacetophenone or 4-fluorobenzaldehyde, respectively, using phase transfer catalyst, hexadecyl-tri-*n*-butylphsophonium bromide. The *N*-arylated product (**2**) or (**3**) was reacted in MeONa/MeOH with diversified aromatic aldehydes or ketones to furnish two series of new chalcones **4** and **5**. Refluxing of **4** or **5** with guanidine hydrochloride in $KOH_{(aq)}$ and H_2O_2/EtOH yielded the 2-(4-(2-amino-6-arylpyrimidin-4-yl)phenyl)3,4-dimethyl-2,4-dihydrobenzo[e]pyrazolo[4,3-c][1,2]thiazine-5,5-dioxide (**6**). The structures of chalcones (**4** or **5**) and corresponding pyrimidines (**6**) were confirmed with spectral data and elemental analysis. Several chalcones as well as pyrimidines showed marked activity against *E. coli* and *S. aureus*.

Keywords Pyrazolobenzothiazine · Chalcones · Pyrimidines · Anti-bacterial

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Introduction

Pyrimidine and its derivatives are most important nitrogen based heterocycles which play a vital role in many life processes. The ring system is present in nucleic acids and their derivatives (willardiine, tingitanine) (Bell and Foster, 1962), several vitamins (vitamin B1) (Jansen and Donath, 1926), antibiotics (bacimethrin, sparsomycin, bleomycin) (Tanaka *et al.,* 1961), alkaloids (heteromines, crambescins, manzacidins, variolins, meridianins, psammopemmins) (Berlinck *et al.,* 1993; Lin *et al.,* 1997), toxins (Banker *et al.,* 2000; Ohtani *et al.,* 1992), coenzymes, uric acid, and purines. Many synthetic members of the group are also important as drugs including barbituric acid derivatives and chemotherapeutic agents including sulfadiazine (Petersen and Schmidt 2003), Gleevec (imatinib mesilate) (Nadal and Olavarria, 2004), and Xeloda (capecitabine) (Blum, 2001). Trimethoprim, Iclaprim, and metronidazole are well known synthetic antibacterial remedies based on pyrimidine scaffold (Joffe *et al.,* 1989). Some pyrimidine derivatives are recently reported as inhibitors of CDK (Chu *et al.,* 2006; Moravec *et al.,* 2003), MK2 (Argiriadi *et al.,* 2010), CB2 (Sullivan *et al.,* 1998), VEGFR (Munchhof *et al.,* 2004), and Adenosine A1/A2a/A3 (Baraldi *et al.,* 2001; Chang *et al.,* 2004) (Fig. 1).

The current investigations reveal that pyrimidine analogs exhibit potential biological activities such as anticancer (Baraldi *et al.*, 2002), antiviral (Chern *et al.,* 2004), antimycobacterial (Ballell *et al.,* 2007), anti-inflammatory and analgesic (Sondhi *et al.,* 2005), antiallergic (Ban *et al.,* 1998), and anti-HIV (Malik *et al.,* 2006). Pyrrolo-pyrimidine nucleoside derivatives act as potential anti-HCV (Hepatitis C Virus) agents (Chamakura *et al.,* 2007; Coelmont *et al.,* 2006).

On the other hand, 1,2-benzothiazine-1,1-dioxides are also known as potentially biologically active molecules

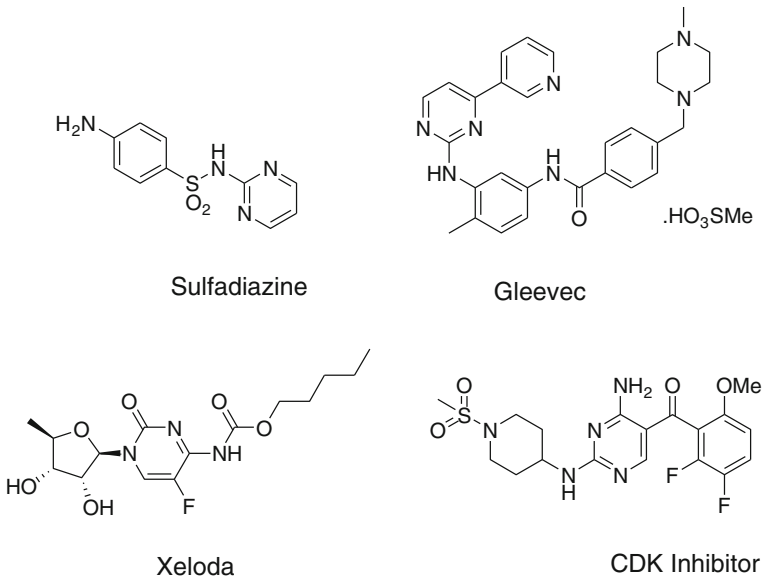


Fig. 1 Structures of well known bioactive molecules containing pyrimidine scaffold

e.g., 1,2-benzothiazine-3-carboxamide-1,1-dioxide derivatives belonging to oxicams, i.e., piroxicam, meloxicam, ampiroxicam, and isoxicam are well known as analgesic and anti-inflammatory compounds (Lee *et al.,* 2008) (Fig. 2).

Moreover, benzothiazine derivatives are known as potent calpain I inhibitors (Xu, 2007) while its 3-aryl-quinazolin-4-one derivatives showed marked antimicrobial (Ahmad *et al.,* 2011) activity. We have already reported N′-aryl-methylidene-2-(3,4-dimethyl-5,5-dioxidopyrazolo[4,3-c][1,2]benzothiazin-2(4*H*)-yl)acetohydrazides as potent anti-oxidant and anti-bacterial agents (Ahmad *et al.,* 2010).

Keeping in view the long-lasting interest of the synthetic community in pyrimidines as well as 1,2-benzothiazine-1,1-dioxides as potential drugs, we planned to synthesize both the heterocyclic moieties in a single nucleus and study their synergic effect which may result some biologically more potent molecules.

Results and discussion

Chemistry

3,4-Dimethyl-2,4-dihydropyrazolo[4,3-c][1,2]benzothiazine-5,5-dioxide **1** was synthesized by our own method (Ahmad *et al.,* 2010) starting from commercially available sodium saccharin. *N*-arylation of **1** was carried out with 4-fluoro-acetophenone or 4-fluorobenzaldehyde in the presence of phase transfer catalyst hexadecyl-tri-*n*-butylphosphonium bromide yielding 4-(3,4-dimethyl-5,5-dioxidobenzo[4,3-c][1,2]thiazin-2(4-H)yl)phenyl)ethanone **2** or 4-(3,4-dimethyl-5,5-dioxidobenzo[4,3-c][1,2]thiazin-2(4-H)yl)benzaldehyde **3**, respectively. Further reaction of **2** or **3** with corresponding aromatic aldehyde or acetophenone (Scheme 1) gave two series of chalcones i.e., **4a–k** and **5a–f**, respectively (Table 1). For this reaction, stronger base NaOMe, in MeOH instead of NaOH was used.

Each chalcone was treated with guanidine hydrochloride in the presence of 50% aqueous KOH solution in absolute ethanol followed by portion wise addition of 30% H_2O_2 solution at reflux temperature (Varga *et al.,* 2003). This crucial step resulted in a novel series of pyrimidines (**6a–o**) by ring closure (Table 1). Spectral data IR, ^{1}H- and ^{13}C-NMR, and MS of all the synthesized compounds were recorded and found in full agreement with the proposed structures. The elemental analysis results were within ±0.4% of the theoretical values.

Antibacterial studies

Bioassay of synthesized compounds summarized in Table 2 indicated that bioactivity of pyrimidines was somewhat greater than their corresponding chalcones. It seems that pyrimidine ring may have enhanced the activity against pathogens. Moreover, it was observed that all the compounds were active against *E. coli* (gram negative) but only two compounds, i.e., pyrimidines **6e** and **6h** showed activity against both pathogens. The results indicated that compound **6h** showed high activity against both pathogens which may be attributed by 2-MeO-phenyl group of the compound which was also higher than its corresponding chalcone **4g**. However, interestingly, compound **6j** showing highest activity against *E. coli* was inactive against *S. aureus.* It may be considered that two methoxy functionalities at 3 and 4 positions of 6-phenyl group enhanced its activity against *E. coli* but these groups inactivated the compound against *S. aureus.* Bromo-chalcones **4c**, **4f**, and

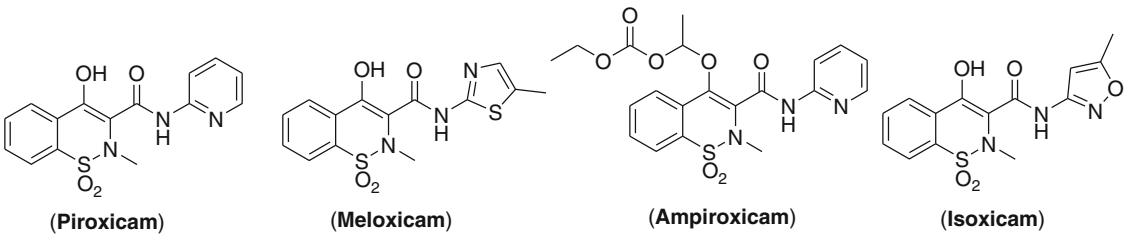
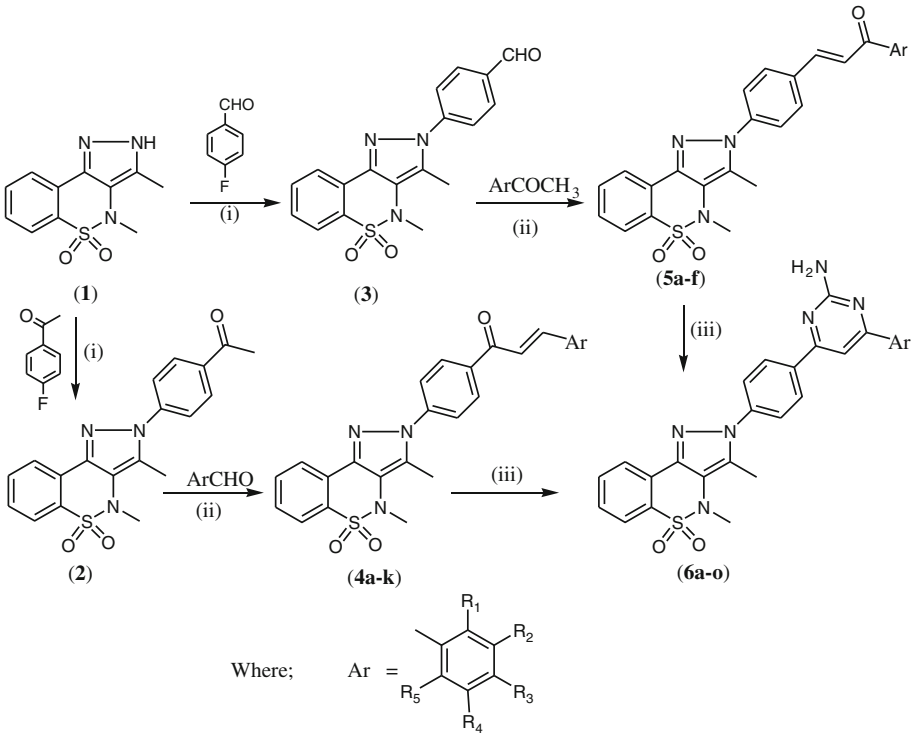


Fig. 2 Structures of well known oxicam drugs

Scheme 1 Synthetic route to 2-(4-(2-amino-6-arylpyrimidin-4-yl)phenyl)-3,4-dimethyl-2,4-dihydrobenzo[e]pyrazolo[4,3-c][1,2]thiazine-5,5-dioxides (**6a–o**)



(i) K_2CO_3 (anhydrous); Hexadecyl-tri-n-butylphosphonium bromide; DMF, 120°C (ii) NaOMe/MeOH, RT

(iii) $(NH_2)_2C{=}NH.HCl$; 50% KOH/EtOH, reflux; 30%H_2O_2, reflux

5b showed marked activity against *E. coli,* while bromo-pyrimidine **6e** exhibited significant activity against both pathogens. The results are summarized in Table 2.

Conclusion

We have synthesized series of pyrazolobenzothiazine based chalcones and their pyrimidine derivatives which were found to possess anti-bacterial activity. It was observed that all the chalcones as well as pyrimidines except **4j** and **5d** showed activity against gram negative bacteria i.e., *E. coli.* On the other hand, no activity was observed against gram positive bacteria i.e., *S. aureus* except two pyrimidines i.e., **6e** and **6h**. Compound **6h** containing 2-methoxyphenyl group at position 6 exhibited highest activity against both pathogens. Bromo derivatives showed more activity against the pathogens, in general. Moreover, pyrimidines showed more activity than chalcones and could be a suitable template for further manipulation leading to novel anti-bacterial agents. The new moieties may also possess other biological activities of the parent ring systems.

Experimental

General

All the chemicals were purchased from E. Merck, Sigma Aldrich or Wako and used without purification. However,

Table 1 Characterization of the synthesized compounds

Compounds	R1	R2	R3	R4	R5	Molecular formula	Yield %	mp °C	Analysis% calculated (found)		
									C	H	N
4a	H	H	F	H	H	$C_{26}H_{20}FN_3O_3S$	78	188–190	65.95 (65.94)	4.26 (4.27)	8.87 (8.88)
4b	H	H	Cl	H	H	$C_{26}H_{20}ClN_3O_3S$	68	235–236	63.73 (63.72)	4.11 (4.12)	8.58 (8.57)
4c	H	Cl	H	H	H	$C_{26}H_{20}ClN_3O_3S$	72	235–236	63.73 (63.72)	4.11 (4.12)	8.58 (8.57)
4d	Cl	H	Cl	H	H	$C_{26}H_{19}Cl_2N_3O_3S$	62	210–212	59.55 (59.56)	3.65 (3.64)	8.08 (8.00)
4e	H	H	Br	H	H	$C_{26}H_{20}BrN_3O_3S$	58	205–206	58.43 (58.42)	3.77 (3.78)	7.86 (7.85)
4f	H	Br	H	H	H	$C_{26}H_{20}BrN_3O_3S$	59	261–262	58.43 (58.42)	3.77 (3.78)	7.86 (7.85)
4g	MeO	H	H	H	H	$C_{27}H_{23}N_3O_4S$	66	178–179	66.79 (66.79)	4.77 (4.77)	8.65 (8.64)
4h	H	MeO	MeO	H	H	$C_{28}H_{25}N_3O_5S$	59	261–262	65.23 (65.22)	4.89 (4.88)	8.15 (8.16)
4i	MeO	MeO	MeO	H	H	$C_{29}H_{27}N_3O_6S$	81	185–186	63.84 (63.85)	4.99 (4.97)	7.70 (7.69)
4j	H	MeO	MeO	MeO	H	$C_{29}H_{27}N_3O_6S$	72	211–213	63.84 (63.85)	4.99 (4.97)	7.70 (7.69)
4k	H	H	NO_2	H	H	$C_{26}H_{20}N_4O_5S$	69	186–187	62.39 (62.38)	4.03 (4.03)	11.19 (11.20)
5a	H	H	Cl	H	H	$C_{26}H_{20}ClN_3O_3S$	70	178–179	63.73 (63.74)	4.11 (4.10)	8.58 (8.57)
5b	H	H	Br	H	H	$C_{26}H_{20}BrN_3O_3S$	63	216–217	58.43 (58.44)	3.77 (3.76)	7.86 (7.86)
5c	H	H	MeO	H	H	$C_{27}H_{23}N_3O_4S$	76	207–209	66.79 (66.79)	4.77 (4.77)	8.65 (8.65)
5d	H	H	H	H	H	$C_{26}H_{21}N_3O_4S$	58	231–232	68.55 (58.57	4.65 (4.65)	9.22 (9.21)
5e	H	H	CH_3	H	H	$C_{27}H_{23}N_3O_3S$	65	172–174	69.06 (69.07)	4.94 (4.93)	8.95 (8.94)
5f	CH_3	H	CH_3	H	CH_3	$C_{29}H_{27}N_3O_3S$	79	244–246	70.00 (70.02)	5.47 (5.46)	8.95 (8.97)
6a	H	H	F	H	H	$C_{27}H_{21}FN_6O_2S$	80	238–240	63.27 (63.9)	4.13 (4.12)	16.40 (16.41)
6b	H	H	Cl	H	H	$C_{27}H_{21}ClN_6O_2S$	69	233–234	61.30 (61.30)	4.00 (4.01)	15.89 (15.88)
6c	H	Cl	H	H	H	$C_{27}H_{21}ClN_6O_2S$	58	220–221	61.30 (61.29)	4.00 (4.02)	15.89 (15.87)
6d	Cl	H	Cl	H	H	$C_{27}H_{20}Cl_2N_6O_2S$	60	265–267	57.55 (57.54)	3.58 (3.57)	14.92 (14.95)
6e	H	H	Br	H	H	$C_{27}H_{21}BrN_6O_2S$	65	179–180	56.55 (56.56)	3.69 (3.71)	14.65 (14.63)
6f	H	Br	H	H	H	$C_{27}H_{21}BrN_6O_2S$	60	245–246	56.55 (56.53)	3.69 (3.68)	14.65 (14.68)
6g	H	H	MeO	H	H	$C_{29}H_{26}N_6O_4S$	57	187–188	64.11 (64.13)	4.61 (4.59)	16.02 (16.00)
6h	MeO	H	H	H	H	$C_{28}H_{24}N_6O_3S$	76	180–182	64.11 (64.12)	4.61 (4.58)	16.02 (16.03)
6i	H	MeO	MeO	H	H	$C_{29}H_{26}N_6O_4S$	69	241–242	62.80 (62.78)	4.73 (4.73)	15.15 (15.16)
6j	MeO	MeO	MeO	H	H	$C_{30}H_{28}N_6O_5S$	72	203–204	61.63 (61.62)	4.83 (4.84)	14.37 (14.36)
6k	H	MeO	MeO	MeO	H	$C_{30}H_{28}N_6O_5S$	66	172–174	61.63 (61.61)	4.83 (4.85)	14.37 (14.37)
6l	H	H	NO_3	H	H	$C_{27}H_{21}N_7O_4S$;	70	185–187	60.10 (60.12)	3.92 (3.92)	18.17 (18.16)
6m	H	H	H	H	H	$C_{27}H_{22}N_6O_2S$	61	211–212	65.57 (65.60)	4.48 (4.45)	16.99 (16.97)
6n	H	H	CH_3	H	H	$C_{28}H_{24}N_6O_2S$	57	173–175	66.12 (66.13)	4.76 (4.76)	16.52 (16.50)
6o	CH_3	H	CH_3	H	CH_3	$C_{30}H_{28}N_6O_2S$	79	209–210	67.14 (67.12)	5.26 (5.25)	15.66 (15.67)

solvents were purified through distillation. ^{1}H NMR spectra were recorded on a Bruker DPX-400 instrument at 400 MHz. Chemical shifts are reported in ppm referenced to the residual solvent signal. Mass spectra were recorded on Agilent 5973N instrument using EI mode. Melting points were recorded on a Gallenkamp melting point apparatus and are uncorrected. Elemental analysis was carried out using a Perkin Elmer 2400-CHN Analyser. X-ray crystallography was carried out on Bruker Nonius Kappa CCD diffractometer with graphite monochromated Mo-Kα radiation and the data were corrected for Lorentz and polarization effects and for absorption using multi-scan method [25, 26].

*Synthesis of 4-(3,4-dimethyl-5,5-dioxidobenzo[e]pyrazolo[4,3-c][1,2]thiazin-2(4H)-yl)ethanone (**2**)*

A mixture of 3,4-dimethyl-2,4-dihydropyrazolo[4,3-*c*][1,2]benzothiazine 5,5-dioxide (**1**) (6.25 g; 25.0 mmol), 4-fluoroacetophenone (4.14 g; 30.0 mmol), anhydrous K_2CO_3 (4.15 g; 30.0 mmol), and hexadecyl-*n*-tributyl-phosphonium bromide (1.27 g; 2.5 mmol) was refluxed in DMF (100 mL) for a period of 2 h under nitrogen atmosphere. The precipitates formed after adding ice cold water were collected, dried, and recrystallized from EtOH. Pale yellow crystals. Yield: 6.88 g; (75%). mp 230–232 °C. ^{1}H

Table 2 Bioactivities of the synthesized compounds

Compounds	Inhibition zone (mm) *E. coli* X580	Bioactivity	Inhibition zone (mm) *S. aureus* N.C.T.C. 6571	Bioactivity
4a	14	4.13	–	–
4b	13	3.55	–	–
4c	15	4.81	–	–
4d	16	5.61	–	–
4e	15	4.81	–	–
4f	17	6.53	–	–
4g	16	5.61	–	–
4h	15	4.81	–	–
4i	14	4.13	–	–
4j	–	–	–	–
4k	15	4.81	–	–
5a	14	4.13	–	–
5b	16	5.61	–	–
5c	15	4.81	–	–
5d	–	–	–	–
5e	13	3.55	–	–
5f	15	4.81	–	–
6a	15	4.81	–	–
6b	16	5.61	–	–
6c	16	5.61	–	–
6d	–	–	–	–
6e	19	8.87	17	508
6f	14	4.13	–	–
6g	–	–	–	–
6h	20	10.34	22	1390
6i	14	4.13	–	–
6j	24	19.06	–	–
6k	13	3.55	–	–
6l	14	4.13	–	–
6m	14	4.13	–	–
6n	14	4.13	–	–
6o	15	4.81	–	–

2 mg/mL solution in DMSO

Equivalent inhibition to that of nmoles Cephalosporin C in well volume of 100 μL

NMR (400 MHz, $CDCl_3$) δ: 2.50 (3H, s, CH_3), 2.68 (3H, s, $COCH_3$), 3.13 (3H, s, NCH_3), 7.57–7.61 (1H, m, ArH), 7.64–7.67 (2H, m, ArH), 7.69–7.73 (1H, m, ArH), 7.97 (2H, d, $J = 7.7$ Hz, ArH), 8.10 (1H, m., ArH), 8.11–8.13 (1H, m, ArH). ^{13}C NMR: 10.9, 26.7, 40.0, 124.2, 124.4, 124.7, 124.9, 125.2 (2C), 127.9, 129.2, 129.6, 132.5, 132.9, 133.5, 136.4, 139.5, 142.9, 196.9. MS *m/z*: 390.09 $(M + Na)^+$. Anal. calc. for $C_{19}H_{17}N_3O_3S$; C, 62.11; H, 4.66; N, 11.44; Found: C, 62.10; H, 4.67; N, 11.43.

*General procedure for the synthesis of 3-aryl-1-(4-(3,4-dimethyl-5,5-dioxidobenzo[e]pyrazolo[4,3-c][1,2]thiazin-2(4H) yl)phenyl)prop-2-en-1-ones (**4a–k**)*

All chalcones were prepared according to the literature procedure (Furniss *et al.,* 1989). A mixture of 4-(3,4-dimethyl-5,5-dioxidobenzo[e]pyrazolo[4,3-c][1,2]thiazin-2(4H)-yl)acetophenone (**2**) (20.0 mmol), corresponding aromatic aldehyde (20.0 mmol), MeONa (20.0 mmol) in MeOH (100 mL) was stirred at room temperature for a period of 2–4 h. The resulted precipitates were collected and washed with MeOH followed by cold water. The products were purified by flash chromatography by eluting with MeOH/$CHCl_3$ (1:4).

*1-(4-(3,4-dimethyl-5,5-dioxidobenzo[e]pyrazolo[4,3-c][1,2]thiazin-2(4H)-yl)phenyl)-3-(4-fluorophenyl)prop-2-en-1-one (**4a**)* Yellowish white powder; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.51 (3H, s, CH_3), 3.13 (3H, s, NCH_3), 7.14 (2H, t, $J = 8.5$ Hz, ArH), 7.49 (1H, d, $J = 15.7$ Hz, Hα), 7.54–7.62 (2H, m, ArH), 7.66 (1H, d, $J = 8.0$ Hz. ArH), 7.70 (4H, d, $J = 8.5$ Hz, ArH), 7.83 (1H, d, $J = 15.7$ Hz, Hβ), 7.97 (1H, d, $J = 7.8$ Hz, ArH), 8.12 (1H, d, $J = 7.4$ Hz, ArH), 8.19 (1H, d, $J = 8.5$ Hz, ArH). ^{13}C NMR: 10.9, 40.0, 116.2, 116.4, 121.3, 124.2, 124.5, 124.9, 125.2, 127.9, 129.3, 129.6, 129.7, 130.5, 130.6, 130.9, 132.5, 133.0, 133.6, 137.5, 139.5, 142.7, 144.3, 162.9, 165.4, 189.0. MS *m/z*: 496.11 $(M + Na)^+$.

*3-(4-chlorophenyl)-1-(4-(3,4-dimethyl-5,5-dioxidobenzo[e]pyrazolo[4,3-c] [1,2]thiazine-2(4H)-yl)phenyl)prop-2-en-1-one (**4b**)* Pale yellow powder; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.52 (3H, s, CH_3), 3.14 (3H, s, NCH_3), 7.43 (2H, m, ArH), 7.54 (1H, d, $J = 15.8$ Hz, Hα), 7.60–7.63 (3H, m, ArH), 7.71 (3H, d, $J = 8.6$ Hz, ArH), 7.82 (1H, d, $J = 15.8$ Hz, Hβ), 7.98 (1H, d, $J = 7.8$ Hz, ArH), 8.12 (1H, d, $J = 7.7$ Hz, ArH), 8.19 (2H, m, $J = 8.6$ Hz, ArH). ^{13}C NMR: 10.9, 40.0, 121.9, 124.2, 124.5, 127.9, 129.2, 129.4, 129.6, 129.8, 130.1, 130.5, 131.0, 131.6, 132.1, 132.5, 132.9, 133.1, 133.5, 135.5, 136.8, 137.4, 139.5, 142.7, 144.1, 188.9. MS *m/z*: 512.08 $(M + Na)^+$.

*3-(3-chlorophenyl)-1-(4-(3,4-dimethyl-5,5-dioxidobenzo[e]pyrazolo[4,3-c][1,2]thiazin-2(4H)-yl)phenyl)prop-2-en-1-one (**4c**)* Yellow powder; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.53 (3H, s, CH_3), 3.15 (3H, s, NCH_3), 7.42 (1H, m, ArH), 7.52 (1H, d, $J = 15.8$ Hz, Hα), 7.57–7.60 (2H, m, ArH), 7.64 (1H, d, $J = 15.8$ Hz, Hβ), 7.69–7.73 (3H, m, ArH), 7.76 (2H, d, $J = 5.1$ Hz, ArH), 7.99 (1H, d, $J = 6.7$ Hz, ArH), 8.13 (1H, d, $J = 7.0$ Hz, ArH), 8.20–8.23 (2H, m, ArH). ^{13}C NMR: 10.6, 40.2, 121.7, 124.0, 124.5, 127.4, 128.8, 129.4, 129.7, 129.9, 130.2, 130.5, 131.4, 131.7, 132.3, 132.6, 133.1, 133.4, 133.7, 135.3, 136.1, 138.4, 139.8, 141.6, 143.2, 188.6. MS *m/z*: 512.08 $(M + Na)^+$.

3-(2,4-dichlorophenyl)-1-(4-(3,4-dimethyl-5,5-dioxidobenzo[e]pyrazolo[4,3-c][1,2]thiazin-2(4H)-yl)phenyl)prop-2-en-1-one (***4d***) Yellow amorphous solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.52 (3H, s, CH_3), 3.15 (3H, s, NCH_3), 7.51 (1H, m, ArH), 7.57 (1H, d, $J = 15.6$ Hz, Hα), 7.58 (2H, m, ArH), 7.64 (1H, d, $J = 15.6$ Hz, Hβ), 7.70 (3H, t, $J = 8.0$ Hz, ArH), 7.76–7.80 (1H, m, ArH), 7.95–8.01 (1H, m, ArH), 8.10–8.15 (1H, m, ArH), 8.18 (1H, $J = 5.1$ Hz, ArH). ^{13}C NMR: 10.8, 40.2, 121.9, 124.2, 124.5, 127.9, 129.2, 129.4, 129.6, 129.8, 130.1, 130.5, 131.0, 131.6, 132.1, 132.5, 132.9, 133.1, 133.5, 135.5, 136.8, 137.4, 140.5, 143.7, 144.9, 187.6. MS *m/z*: 546.04 $(M + Na)^+$.

3-(4-bromophenyl)-1-(4-(3,4-dimethyl-5,5-dioxidobenzo[e]pyrazolo[4,3-c][1,2]thiazin-2(4H)-yl)phenyl)prop-2-en-1-one (***4e***) Yellow powder; Yield: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.53 (3H, s, CH_3), 3.15 (3H, s, NCH_3), 7.32 (1H, d, $J = 15.7$ Hz, Hα,), 7.36 (1H, d, $J = 1.9$ Hz, ArH), 7.49 (1H, m, ArH), 7.55 (1H, d, $J = 3.5$ Hz, ArH), 7.62 (1H, d, $J = 15.7$ Hz, Hβ), 7.68–7.73 (4H, m, ArH), 7.79 (1H, m, ArH), 7.99 (1H, d, $J = 6.5$ Hz, ArH), 8.12–8.17 (2H, m, ArH), 8.22 (1H, m, ArH). ^{13}C NMR: 10.8, 40.1, 121.7, 124.0, 124.5, 127.4, 128.8, 129.4, 129.7, 129.9, 130.2, 130.5, 131.4, 131.7, 132.3, 132.6, 132.9, 133.2, 133.9, 135.5, 136.5, 138.4, 139.2, 142.3, 144.0, 187.6. MS *m/z*: 556.03 $(M + Na)^+$.

3-(3-bromophenyl)-1-(4-(3,4-dimethyl-5,5-dioxidobenzo[e]pyrazolo[4,3-c][1,2]thiazin-2(4H)-yl)phenyl)prop-2-en-1-one (***4f***) Yellow crystals; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.53 (3H, s, CH_3), 3.15 (3H, s, NCH_3), 7.31–7.33 (1H, m, ArH), 7.36–7.39 (1H, m, ArH), 7.49 (1H, d, J = 16.9 Hz, Hα), 7.55–7.58 (1H, m, ArH), 7.62 (1H, d, $J = 16.9$ Hz, Hβ), 7.69–7.72 (4H, m, ArH), 7.79 (1H, m., ArH), 7.99 (1H, d, $J = 6.5$ Hz, ArH), 8.12–8.14 (1H, m, ArH), 8.18 (1H, d, $J = 6.3$ Hz, ArH), 8.22 (1H, d, $J = 5.5$ Hz, ArH). ^{13}C NMR: 10.8, 40.1, 121.7, 124.0, 124.5, 127.4, 128.8, 129.4, 129.7, 129.9, 130.2, 130.5, 131.4, 131.7, 132.3, 132.6, 132.9, 133.2, 133.9, 135.5, 136.5, 138.4, 139.2, 142.3, 144.0, 187.6. MS *m/z*: 556.03 $(M + Na)^+$.

1-(4-(3,4-dimethyl-5,5-dioxidobenzo[e]pyrazolo[4,3-c][1,2]thiazin-2(4H)-yl)phenyl)-3-(2-methoxyphenyl)prop-2-en-1-one (***4g***) Yellow powder; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.49 (3H, s, CH_3), 3.03 (3H, s, NCH_3), 3.90 (3H, s, OCH_3), 6.91 (1H, d, $J = 16.7$ Hz, Hα), 7.37 (2H, m, ArH), 7.61 (1H, d, $J = 16.7$ Hz, Hβ), 7.65 (1H, m, ArH), 7.70–7.73 (1H, m, ArH), 7.78 (1H, d, $J = 6.1$ Hz, ArH), 7.82 (2H, d, $J = 2.7$ Hz, ArH), 7.89 (1H, m, ArH), 7.97 (1H, d, $J = 5.8$ Hz, ArH), 8.03–8.06 (1H, m, ArH), 8.10–8.14 (2H, m, ArH). ^{13}C NMR: 10.8, 40.1, 60.8 121.2, 121.8, 124.6, 124.8, 126.8, 128.4, 129.7, 130.5, 130.8, 131.1, 131.4, 131.7, 132.3, 132.6, 132.9, 133.2, 133.9, 135.5, 136.2, 138.4, 139.3, 141.9, 142.9, 189.7. MS *m/z*: 508.13 $(M + Na)^+$.

3-(3,4-dimethoxyphenyl)-1-(4-(3,4-dimethyl-5,5-dioxidobenzo[e]pyrazolo[4,3-c][1,2]thiazin-2(4H)-yl)phenyl)prop-2-en-1-one (***4h***) Yellow solid; Yield; 59%; mp 261–262 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.52 (3H, s, CH_3), 3.14 (3H, s, NCH_3), 3.93 (3H, s, OCH_3), 3.95 (3H, s, OCH_3), 6.87–6.91 (2H, m, ArH), 7.40 (1H, d, $J = 5.5$ Hz, ArH), 7.44 (1H, d, $J = 15.6$ Hz, Hα), 7.58–7.62 (1H, m, ArH), 7.71 (3H, d, $J = 5.6$ Hz, ArH), 7.78 (1H, d, $J = 15.6$ Hz, Hβ), 7.99 (1H, d, $J = 7.8$ Hz, ArH), 8.12 (1H, d, $J = 7.7$ Hz, ArH), 8.19 (2H, d, $J = 8.5$ Hz, ArH). ^{13}C NMR: 10.9, 40.0, 56.2, 61.0, 105.8, 120.9, 121.6, 124.6, 124.8, 124.8, 125.2, 127.9, 129.2, 129.8, 130.1, 132.4, 132.9, 133.5, 133.9, 135.5, 136.2, 137.6, 139.3, 140.6, 142.5, 145.8, 153.5 189.4. MS *m/z*: 538.14 $(M + Na)^+$.

1-(4-(3,4-dimethyl-5,5-dioxidobenzo[e]pyrazolo[4,3-c][1,2]thiazin-2(4H)-yl)phenyl)-3-(2,3,4-trimethoxyphenyl)prop-2-en-1-one (***4i***) Pale yellow powder; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.67 (3H, s, CH_3), 3.13 (3H, s, NCH_3), 3.91 (3H, s, OCH_3), 3.93 (3H, s, OCH_3), 3.98 (3H, s, OCH_3), 6.75 (1H, d, $J = 15.8$ Hz, Hα), 7.42 (1H, d, $J = 15.8$ Hz, Hβ), 7.58 (2H, d, $J = 7.2$ Hz, ArH), 7.65–7.69 (2H, m, ArH), 7.96–7.99 (1H, m, ArH), 8.13 (3H, d, $J = 8.7$ Hz, ArH), 8.18 (2H, d, $J = 8.5$ Hz, ArH). ^{13}C NMR: 10.9, 40.0, 56.1, 60.9, 61.4, 107.6, 120.8, 121.7, 124.1, 124.5, 127.9, 129.2, 129.4, 129.6, 129.7, 131.5, 131.9, 132.5, 132.9, 133.5, 136.3, 138.0, 139.4, 141.0, 142.3, 142.5, 152.9, 156.1, 189.7. MS *m/z*: 568.15 $(M + Na)^+$.

1-(4-(3,4-dimethyl-5,5-dioxidobenzo[e]pyrazolo[4,3-c][1,2]thiazin-2(4H)-yl)phenyl)-3-(3,4,5-trimethoxyphenyl)prop-2-en-1-one (***4j***) Yellow amorphous solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.47 (3H, s, CH_3), 3.13 (3H, s, NCH_3), 3.91 (3H, s, OCH_3), 3.94 (6H, s, 2xOCH_3), 6.75 (2H, d, $J = 8.8$ Hz, ArH), 7.42 (1H, d, $J = 15.8$ Hz, Hα), 7.58 (1H, d, $J = 15.8$ Hz, Hβ), 7.65–7.68 (2H, m, ArH), 7.94–7.98 (1H, m, ArH), 8.13 (3H, d, $J = 8.7$ Hz, ArH), 8.18 (2H, d, $J = 8.5$ Hz, ArH). ^{13}C NMR: 10.9, 40.0, 56.1, 60.9, 61.4, 107.6, 120.8, 121.7, 124.1, 124.5, 127.9, 129.2, 129.4, 129.6, 129.7, 132.5, 132.9, 133.5, 133.9, 134.5, 136.3, 138.0, 139.4, 141.0, 142.4, 142.5, 152.9, 156.1, 189.7. MS *m/z*: 568.15 $(M + Na)^+$.

1-(4-(3,4-dimethyl-5,5-dioxidobenzo[e]pyrazolo[4,3-c][1,2]thiazin-2(4H)-yl)phenyl)-3-(4-nitrophenyl)prop-2-en-1-one (***4k***) Yellow powder; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.53 (3H, s, CH_3), 3.14 (3H, s, NCH_3), 7.59 (1H, d, $J = 15.6$ Hz, Hα), 7.66 (1H, d, $J = 15.6$ Hz, Hβ), 7.72 (2H, d, $J = 1.7$ Hz, ArH), 7.76–7.79 (1H, m, ArH), 7.81 (1H, d,

$J = 5.2$ Hz, ArH), 7.85-7.88 (1H, m, ArH), 7.98 (1H, d, $J = 7.7$ Hz, ArH), 8.12 (2H, d, $J = 6.8$ Hz, ArH), 8.20 (2H, m, ArH), 8.24 (1H, m, ArH), 8.31 (1H, d, $J = 8.7$ Hz, ArH). ^{13}C NMR: 10.9, 40.0, 121.9, 124.1, 124.6, 127.6, 128.7, 129.3, 129.6, 129.9, 130.2, 130.4, 131.5, 131.8, 132.3, 132.6, 132.9, 133.2, 133.9, 135.5, 136.5, 138.4, 139.2, 143.3, 145.4, 188.5. MS *m/z*: 523.1 $(M + Na)^+$.

*Synthesis of 4-(3,4-dimethyl-5,5-dioxidobenzo[e]pyrazolo[4,3-c][1,2]thiazin-2(4H)-yl)benzaldehyde (**3**)*

A mixture of 3,4-dimethyl-2,4-dihydropyrazolo[4,3-*c*][1,2] benzothiazine 5,5-dioxide (**1**) (6.25 g, 25.0 mmol), 4-fluorobenzaldehyde (3.72 g, 30.0 mmol), anhydrous K_2CO_3 (4.15 g, 30.0 mmol), and hexadecyl-*n*-tributylphosphonium bromide (1.27 g, 2.5 mmol) was refluxed in DMF (100 mL) for a period of 2 h under nitrogen atmosphere. The precipitates formed after adding ice cold water were collected, dried, and recrystallized from EtOH. Yellow crystals. Yield: 7.15 g, (81%); mp 230–232 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.52 (3H, s, CH_3), 3.13 (3H, s, NCH_3), 7.57–7.60 (1H, m, ArH), 7.68–7.72 (1H, m, ArH), 7.73–7.76 (2H, m, ArH), 7.97 (1H, d, $J = 7.7$ Hz, ArH), 8.06–8.09 (2H, m, ArH), 8.11 (1H, d, $J = 7.7$ Hz, ArH), 10.10 (1H, s, CHO). ^{13}C NMR: 11.0, 40.0, 124.2, 124.7, 124.9(2C), 125.5, 127.8, 129.3(2C), 130.8, 132.6, 133.0, 133.6, 135.4, 139.7, 143.9, 190.9; MS *m/z*: 376.1 $(M + Na)^+$. Anal. calc. for $C_{18}H_{15}N_3O_3S$; C, 61.18; H, 4.28; N, 11.89; Found: C, 61.18; H, 4.28; N, 11.88.

*General procedure for the synthesis of 1-aryl-3-(4-(3,4-dimethyl-5,5-dioxidobenzo[e]pyrazolo[4,3-c][1,2]thiazin-2(4H) yl)phenyl)prop-2-en-1-ones (**5a–f**)*

A mixture of 1-(4-(3,4-dimethyl-5,5-dioxidobenzo[*e*]pyrazolo[4,3-*c*][1,2]thiazin-2(4*H*)-yl)phenyl)benzaldehyde (**3**) (20.0 mmol), corresponding acetophenone (20.0 mmol), MeONa (20.0 mmol) in MeOH (100 mL) was stirred at room temperature for a period of 2–4 h. The resulted ppt were collected and washed with MeOH followed by cold water. The products were purified by flash chromatography by eluting with $CHCl_3$/MeOH (4:1).

*1-(4-chlorophenyl)-3-(4-(3,4-dimethyl-5,5-dioxidobenzo[e]pyrazolo[4,3-c][1,2]thiazin-2(4H)-yl)phenyl)prop-2-en-1-one (**5a**)* Yellow amorphous solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.48 (3H, s, CH_3), 3.12 (3H, s, NCH_3), 7.50 (2H, d, $J = 8.6$ Hz, ArH), 7.52 (1H, d, $J = 14.2$ Hz, Hα), 7.60 (2H, d, $J = 8.3$ Hz, ArH), 7.64 (1H, d, $J = 14.2$ Hz, Hβ), 7.74–7.89 (4H, m, ArH), 7.94–8.02 (3H, m, ArH), 8.10 (1H, d, $J = 7.7$ Hz, ArH). ^{13}C NMR: 10.8, 40.0, 122.5, 124.2, 124.8, 125.0, 127.9, 129.0, 129.4, 129.9, 130.1, 130.5, 131.0, 131.6, 132.4, 132.9, 133.1, 133.4, 133.5, 134.5, 136.2, 137.4, 139.2, 140.8, 143.6, 188.7. MS *m/z*: 512.08 $(M + Na)^+$.

*1-(4-bromophenyl)-3-(4-(3,4-dimethyl-5,5-dioxidobenzo[e]pyrazolo[4,3-c][1,2]thiazin-2(4H)-yl)phenyl)prop-2-en-1-one (**5b**)* Pale yellow crystals; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.50 (3H, s, CH_3), 3.14 (3H, s, NCH_3), 7.48–7.59 (4H, m, ArH), 7.62 (1H, d, $J = 14.4$ Hz, Hα), 7.68–7.73 (3H, m, ArH), 7.82 (1H, d, $J = 14.5$ Hz, Hβ), 7.87 (1H, d, $J = 7.1$ Hz, ArH), 7.96–8.03 (3H, m, ArH), 8.11 (1H, d, $J = 7.7$ Hz, ArH). ^{13}C NMR: 10.8, 40.0, 122.8, 124.1, 124.7, 125.0, 128.0, 128.7, 129.1, 129.3, 130.5, 130.8, 132.4, 132.9, 133.0, 133.4, 134.8, 137.9, 138.4, 139.0, 139.2, 140.6, 142.3, 143.1, 144.0, 190.1. MS *m/z*: 556.03 $(M + Na)^+$.

*3-(4-(3,4-dimethyl-5,5-dioxidobenzo[e]pyrazolo[4,3-c][1,2]thiazin-2(4H)-yl)phenyl)-1-(4-methoxyphenyl)prop-2-en-1-one (**5c**)* Yellow amorphous solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.48 (3H, s, CH_3), 3.13 (3H, s, NCH_3), 3.90 (3H, s, OCH_3), 7.01 (1H, d, $J = 15.2$ Hz, Hα), 7.57–7.61 (2H, m, ArH), 7.64–7.67 (2H, m, ArH), 7.74 (1H, d, $J = 15.2$ Hz, Hβ), 7.75–7.79 (1H, m, ArH), 7.82 (2H, d, $J = 2.7$ Hz, ArH), 7.86–7.89 (1H, m, ArH), 7.97 (1H, d, $J = 6.8$ Hz, ArH), 8.05–8.14 (3H, m, ArH). ^{13}C NMR: 10.8, 40.1, 57.8, 121.2, 121.8, 124.6, 124.8, 126.8, 128.4, 129.7, 130.5, 130.8, 131.1, 131.4, 131.7, 132.3, 132.6, 132.9, 133.2, 133.9, 135.5, 136.2, 138.4, 139.3, 141.9, 142.9, 189.7. MS *m/z*: 508.13 $(M + Na)^+$.

*3-(4-(3,4-dimethyl-5,5-dioxidobenzo[e]pyrazolo[4,3-c][1,2]thiazin-2(4H)-yl)phenyl)-1-phenylprop-2-en-1-one (**5d**)* Yellowish white solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.49 (3H, s, CH_3), 3.13 (3H, s, NCH_3), 7.52-7.57 (2H, m, ArH), 7.59–7.62 (4H, m, ArH), 7.65 (1H, d, $J = 15.$ 7 Hz, Hα), 7.70 (1H, t, $J = 8.2$ Hz, ArH), 7.81 (2H, d, $J = 8.5$ Hz, ArH), 7.86 (1H, d, $J = 15.7$ Hz, Hβ), 7.97 (1H, d, $J = 7.7$ Hz, ArH), 8.06 (2H, d, $J = 7.2$ Hz, ArH), 8.11 (1H, d, $J = 7.7$ Hz, ArH). ^{13}C NMR: 10.8, 40.0, 123.1, 124.2, 124.7, 124.9, 125.1, 125.2, 128.8, 128.5, 128.7(2C), 129.1, 130.5, 130.8, 132.4(2C), 132.9, 133.1, 133.4, 134.8, 138.0, 139.2, 140.6, 143.1, 190.1. MS *m/z*: 478.12 $(M + Na)^+$.

*3-(4-(3,4-dimethyl-5,5-dioxidobenzo[e]pyrazolo[4,3-c][1,2]thiazin-2(4H)-yl)phenyl)-1-(p-tolyl)prop-2-en-1-one (**5e**)* Pale yellow crystalline solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.46 (3H, s, CH_3), 2.49 (3H, s, CH_3), 3.14 (3H, s, NCH_3), 7.34 (1H, d, $J = 14.8$ Hz, Hα), 7.60 (1H, $J = 14.8$ Hz, Hβ), 7.63 (2H, d, $J = 5.4$ Hz, ArH), 7.70 (2H, t, ArH), 7.79–7.84 (4H, m, ArH), 7.98 (3H, d, $J = 8.0$ Hz, ArH), 8.11 (1H, d, $J = 7.7$ Hz, ArH). ^{13}C NMR: 10.8, 21.7, 40.1, 121.2, 121.8, 124.6, 124.8, 126.8,

128.4, 129.7, 130.5, 130.8, 131.1, 131.4, 131.7, 132.3, 132.6, 132.9, 133.2, 133.9, 135.5, 136.2, 138.4, 139.3, 141.9, 142.9, 189.7. MS *m/z*: 492.14 $(M + Na)^+$.

*3-(4-(3,4-dimethyl-5,5-dioxidobenzo[e]pyrazolo[4,3-c][1,2]thiazin-2(4H)-yl)phenyl)-1-mesitylprop-2-en-1-one (**5f**)* Yellow crystals; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.22 (6H, s, 2xCH_3), 2.34 (3H, s, CH_3), 2.47 (3H, s, CH_3), 3.12 (3H, s, NCH_3), 6.94 (2H, d, $J = 6.2$ Hz, ArH), 6.98 (1H, d, $J = 16.2$ Hz, Hα), 7.19–7.22 (1H, m, ArH), 7.56 (1H, d, $J = 16.2$ Hz, Hβ), 7.58–7.61 (2H, m, ArH), 7.65–7.70 (3H, m, ArH), 7.96 (1H, d, $J = 7.8$ Hz, ArH), 8.08 (1H, m, ArH). ^{13}C NMR: 10.8, 19.4, 21.2, 40.0, 56.1, 107.6, 120.8, 121.7, 124.1, 124.8, 125.0, 128.5, 129.4, 129.6, 129.7, 131.4, 131.9, 132.5, 132.9, 133.5, 134.1, 138.0, 139.4, 141.0, 142.4, 144.8, 152.9, 156.1, 188.9. MS *m/z*: 520.17 $(M + Na)^+$.

*General procedure for the synthesis of 2-(4-(2-amino-6-arylpyrimidin-4-yl)phenyl)-3,4-dimethyl-2,4-dihydrobenzo[e]pyrazolo[4,3-c][1,2]thiazine-5,5-dioxides (**6a–o**)*

All compounds were prepared according to the literature procedure (Varga *et al.,* 2003). A mixture of corresponding chalcone (9.1 mmol), guanidine hydrochloride (13.6 mmol) and 50% aqueous KOH solution (4.0 mL) was stirred at reflux temperature for a period of 1 h in EtOH (20.0 mL) followed by portion wise addition of 30% H_2O_2 (30.3 mmol, 3.1 mL) over 1 h under the same conditions. The precipitates thus formed were thoroughly washed with EtOH and then with pure water. Recrystallization from a suitable solvent resulted pure compounds.

*2-(4-(2-amino-6-(4-fluorophenyl)pyrimidin-4-yl)phenyl)-3,4-dimethyl-2,4-dihydrobenzo[e]pyrazolo[4,3-c][1,2]thiazine 5,5-dioxide (**6a**)* Yellowish white powder; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.50 (3H, s, CH_3), 3.15 (3H, s, NCH_3), 5.21 (2H, br. s, NH_2), 7.21 (2H, t, $J = 8.5$ Hz, ArH), 7.45–7.48 (1H, m, ArH), 7.57–7.61 (1H, m, ArH), 7.66–7.75 (3H, m, ArH), 7.99 (1H, d, $J = 7.8$ Hz, ArH), 8.07–8.16 (3H, m, ArH), 8.25 (2H, d, $J = 8.3$ Hz, ArH). ^{13}C NMR: 10.8, 40.0, 103.8, 115.7, 124.2, 124.8 (2C), 125.0, 128.2 (2C), 129.1, 129.4, 132.4, 132.9, 133.0, 133.5, 136.4, 137.5, 137.6, 139.1, 143.2, 153.5, 162.0, 162.9, 163.8, 164.6, 165.5. MS *m/z*: 535.14 $(M + Na)^+$.

*2-(4-(2-amino-6-(4-chlorophenyl)pyrimidin-4-yl)phenyl)-3,4-dimethyl-2,4-dihydrobenzo[e]pyrazolo[4,3-c][1,2]thiazine 5,5-dioxide (**6b**)* Pale yellow powder; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.48 (3H, s, CH_3), 3.09 (3H, s, NCH_3), 5.25 (2H, br. s, NH_2), 7.38 (2H, m, ArH), 7.56–7.60 (3H, m, ArH), 7.67 (2H, d, $J = 8.7$ Hz, ArH), 7.87 (2H, d, $J = 7.6$ Hz, ArH), 7.93 (1H, d, $J = 8.0$ Hz, ArH), 8.07 (2H, d, $J = 8.0$ Hz, ArH), 8.12–8.16 (1H, m, ArH). ^{13}C NMR: 10.8, 40.0, 104.0, 104.5, 105.4, 124.2, 124.4, 124.8, 125.0, 127.8, 128.2, 129.2, 129.6, 130.4, 132.4, 132.9, 133.0, 133.3, 134.3, 136.4, 138.8, 137.6, 139.1, 143.9, 163.5, 163.9, 165.7. MS *m/z*: 551.10 $(M + Na)^+$.

*2-(4-(2-amino-6-(3-chlorophenyl)pyrimidin-4-yl)phenyl)-3,4-dimethyl-2,4-dihydrobenzo[e]pyrazolo[4,3-c][1,2]thiazine 5,5-dioxide (**6c**)* Light brown amorphous powder; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.50 (3H, s, CH_3), 3.14 (3H, s, N CH_3), 5.27 (2H, br. s, NH_2), 7.04 (1H, m, ArH), 7.29–7.40 (4H, m, ArH), 7.48 (1H, s, ArH), 7.67 (3H, d, $J = 7.3$ Hz, ArH), 7.98 (2H, d, $J = 7.3$ Hz, ArH), 8.11 (1H, d, $J = 2.4$ Hz, ArH), 8.24 (1H, d, $J = 8.5$ Hz, ArH). ^{13}C NMR: 10.8, 39.9, 48.8, 49.0, 49.2, 49.4, 49.7, 121.9, 124.2, 124.6, 124.8, 125.5, 127.7, 129.3, 129.7, 129.8, 130.2, 130.6, 132.4, 133.1, 133.8, 135.8, 136.4, 137.5, 163.3, 163.9, 165.5. MS *m/z*: 551.10 $(M + Na)^+$.

*2-(4-(2-amino-6-(2,4-dichlorophenyl)pyrimidin-4-yl)phenyl)-3,4-dimethyl-2,4-dihydrobenzo[e]pyrazolo[4,3-c][1,2]thiazine 5,5-dioxide (**6d**)* Yellow powder; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.47 (3H, s, CH_3), 3.09 (3H, s, NCH_3), 5.25 (2H, br. s, NH_2), 7.35–7.38 (2H, m, ArH), 7.56–7.60 (2H, m, ArH), 7.67 (3H, d, $J = 8.7$ Hz,,ArH), 7.77 (1H, d, $J = 7.7$ Hz, ArH), 7.93 (1H, d, $J = 8.0$ Hz, ArH), 8.07 (1H, d, $J = 9.0$ Hz, ArH), 8.15–8.18 (2H, m, $J = 8.7$ Hz, ArH). ^{13}C NMR: 10.8, 40.0, 104.0, 104.5, 105.4, 124.2, 124.4, 124.8, 125.0, 127.8, 128.2, 129.2, 129.6, 130.4, 132.4, 132.9, 133.0, 133.3, 134.3, 136.4, 138.8, 137.6, 139.1, 143.9, 163.5, 163.9, 165.7. MS *m/z*: 585.06 $(M + Na)^+$.

*2-(4-(2-amino-6-(4-bromophenyl)pyrimidin-4-yl)phenyl)-3,4-dimethyl-2,4-dihydrobenzo[e]pyrazolo[4,3-c][1,2]thiazine 5,5-dioxide (**6e**)* Dirty white crystals; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.50 (3H, s, CH_3), 3.14 (3H, s, NCH_3), 5.29 (2H, br. s, NH_2), 7.49 (1H, s, ArH), 7.54–7.64 (3H, m, ArH), 7.69 (4H, d, $J = 5.6$ Hz, ArH), 7.99 (3H, d, $J = 8.2$ Hz, ArH), 8.13 (1H, d, $J = 7.7$ Hz, ArH), 8.25 (1H, d, $J = 8.4$ Hz, ArH). ^{13}C NMR: 10.9, 40.0, 124.2, 124.4, 124.9, 125.2, 127.9, 129.2, 129.6, 132.5, 132.9, 133.5, 136.4(2C), 136.7, 136.9, 137.2, 137.5, 137.7(2C), 137.9, 139.5, 142.9(2C), 162.3, 162.5, 164.3. MS *m/z*: 595.05 $(M + Na)^+$.

*2-(4-(2-amino-6-(3-bromophenyl)pyrimidin-4-yl)phenyl)-3,4-dimethyl-2,4-dihydrobenzo[e]pyrazolo[4,3-c][1,2]thiazine 5,5-dioxide (**6f**)* White amorphous powder; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.50 (3H, s, CH_3), 3.15 (3H, s, NCH_3), 5.32 (2H, br. s, NH_2), 7.42 (2H, d, $J = 7.8$ Hz, ArH), 7.49 (1H, s, ArH), 7.65 (3H, d, $J = 7.5$ Hz, ArH), 8.00 (3H, t, $J = 7.2$ Hz, ArH), 8.10–8.13 (1H, m, ArH), 8.24–8.27 (2H, m, ArH). ^{13}C NMR: 10.9, 40.0, 124.2,

124.4, 124.9, 125.4, 127.8, 129.3, 129.8, 132.5, 132.9, 133.5, 134.4(2C), 136.7, 136.9, 137.2, 137.5, 137.4(2C), 137.9, 139.5, 142.2(2C), 162.3, 162.5, 164.3. MS *m/z*: 571.06 $(M\text{-}H)^+$.

*2-(4-(2-amino-6-(4-methoxyphenyl)pyrimidin-4-yl)phenyl)-3,4-dimethyl-2,4-dihydrobenzo[e]pyrazolo[4,3-c][1,2]thiazine 5,5-dioxide (**6g**)* Yellow powder; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.48 (3H, s, CH_3), 3.13 (3H, s, NCH_3), 3.63 (3H, s, OCH_3), 5.24 (2H, br. s, NH_2), 6.82 (1H, d, $J = 8.8$ Hz, ArH), 7.55–7.60 (2H, m, ArH), 7.64–7.72 (4H, m, ArH), 7.74 (1H, s, ArH), 7.97 (1H, d, $J = 7.8$ Hz, ArH), 8.02 (1H, d, $J = 7.7$ Hz, ArH), 8.14 (2H, d, $J = 8.2$ Hz, ArH), 8.27(1H, d, $J = 8.1$ Hz, ArH). ^{13}C NMR: 10.8, 40.0, 60.0, 104.0, 104.5, 105.4, 118.2, 120.7, 124.8, 125.0, 126.9, 128.2, 129.2, 129.6, 130.4, 132.4, 132.9, 133.0, 133.5, 136.4, 138.8, 137.6, 139.1, 140.9, 153.6, 157.8, 163.2, 164.5. MS *m/z*: 525.17 $(M + H)^+$.

*2-(4-(2-amino-6-(2-methoxyphenyl)pyrimidin-4-yl)phenyl)-3,4-dimethyl-2,4-dihydrobenzo[e]pyrazolo[4,3-c][1,2]thiazine 5,5-dioxide (**6h**)* Dark yellow powder; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.49 (3H, s, CH_3), 3.18 (3H, s, NCH_3), 3.93 (3H, s, OCH_3), 5.24 (2H, br. s, NH_2), 6.87 (1H, d, $J = 8.6$ Hz, ArH), 7.35–7.40 (2H, m, ArH), 7.64–7.68 (4H, m, ArH), 7.72 (1H, s, ArH), 7.95 (1H, d, $J = 6.8$ Hz, ArH), 8.10 (1H, d, $J = 8.0$ Hz, ArH), 8.22 (2H, d, $J = 8.1$ Hz, ArH), 8.29(1H, d, $J = 7.7$ Hz, ArH). ^{13}C NMR: 10.8, 40.0, 60.0, 104.0, 104.5, 105.4, 118.2, 120.7, 124.8, 125.0, 127.8, 128.2, 129.2, 129.6, 130.4, 132.4, 132.9, 133.0, 133.5, 136.4, 138.8, 137.6, 139.1, 140.9, 153.5, 158.2, 163.5, 164.8. MS *m/z*: 526.17 $(M + H)^+$.

*2-(4-(2-amino-6-(3,4-dimethoxyphenyl)pyrimidin-4-yl)phenyl)-3,4-dimethyl-2,4-dihydrobenzo[e]pyrazolo[4,3-c][1,2]thiazine 5,5-dioxide (**6i**)* Pale yellow crystals; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.49 (3H, s, CH_3), 3.14 (3H, s, NCH_3), 3.97 (3H, s, OCH_3), 4.03 (3H, s, OCH_3), 5.25 (2H, br. s, NH_2), 6.99 (1H, d, $J = 8.4$ Hz, ArH), 7.47 (1H, s, ArH), 7.64–7.74 (6H, m, ArH), 7.98 (1H, d, $J = 7.7$ Hz, ArH), 8.13 (1H, d, $J = 7.5$ Hz, ArH), 8.23 (2H, d, $J = 8.5$ Hz, ArH). ^{13}C NMR: 10.2, 40.1, 56.1, 56.4, 101.5, 109.0, 111.5, 124.2, 124.4, 124.8, 125.0, 127.8, 128.2, 129.2, 129.6, 130.4, 132.4, 132.9, 133.0, 133.5, 136.4, 136.8, 137.6, 139.1, 143.9, 153.5, 163.5, 164.8, 166.2. MS *m/z*: 555.18 $(M + H)^+$.

*2-(4-(2-amino-6-(2,3,4-trimethoxyphenyl)pyrimidin-4-yl)phenyl)-3,4-dimethyl-2,4-dihydrobenzo[e]pyrazolo[4,3-c][1,2]thiazine 5,5-dioxide (**6j**)* Yellow powder; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.48 (3H, s, CH_3), 3.13 (3H, s, NCH_3), 3.87 (3H,s, OCH_3), 3.93 (3H, s, OCH_3), 3.95 (3H, s, OCH_3), 5.24 (2H, br. s, NH_2), 6.82 (1H, d, $J = 8.8$ Hz, ArH), 7.55–7.60 (1H, m, ArH), 7.64–7.72 (4H, m, ArH), 7.74 (1H, s, ArH), 7.97 (1H, d, $J = 7.8$ Hz, ArH), 8.12 (1H, d, $J = 7.7$ Hz, ArH), 8.22 (2H, d, $J = 8.2$ Hz, ArH). ^{13}C NMR: 10.8, 40.0, 56.1, 56.4, 61.0, 104.0, 104.5, 105.4, 124.2, 124.4, 124.8, 125.0, 127.8, 128.2, 129.2, 129.6, 130.4, 132.4, 132.9, 133.0, 133.5, 136.4, 136.8, 137.6, 139.1, 140.9, 153.5, 163.5, 163.8, 167.0. MS *m/z*: 585.19 $(M + H)^+$.

*2-(4-(2-amino-6-(3,4,5-trimethoxyphenyl)pyrimidin-4-yl)phenyl)-3,4-dimethyl-2,4-dihydrobenzo[e]pyrazolo[4,3-c][1,2]thiazine 5,5-dioxide (**6k**)* Light brown powder; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.49 (3H, s, CH_3), 3.14 (3H, s, NCH_3), 3.87 (3H, s, OCH_3), 3.94 (3H, s, OCH_3), 4.00 (3H, s, OCH_3), 5.24 (2H, s, NH_2), 6.49 (1H, m, ArH), 7.33 (1H, d, $J = 7.0$ Hz, ArH), 7.44 (1H, d, $J = 7.0$ Hz, ArH), 7.56–7.59 (2H, m, ArH), 7.65–7.74 (3H, m, ArH), 7.98 (1H, d, $J = 7.7$ Hz, ArH), 8.13 (2H, d, $J = 7.4$ Hz, ArH). ^{13}C NMR: 10.8, 40.0, 56.1, 56.4, 61.0, 104.0, 104.5, 105.4, 124.2, 124.4, 124.8, 125.0, 127.8, 128.2, 129.2, 129.6, 130.4, 132.4, 132.9, 133.0, 133.5, 136.4, 138.8, 137.6, 139.1, 140.9, 153.5, 163.5, 164.8, 166.2. MS *m/z*: 607.17 $((M + Na)^+$.

*2-(4-(2-amino-6-(4-nitrophenyl)pyrimidin-4-yl)phenyl)-3,4-dimethyl-2,4-dihydrobenzo[e]pyrazolo[4,3-c][1,2]thiazine 5,5-dioxide (**6l**)* Yellow powder; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.51 (3H, s, CH_3), 3.15 (3H, s, NCH_3), 5.49 (2H, br. s, NH_2), 7.57 (1H, m, ArH), 7.64 (1H, s, ArH), 7.69–7.75 (3H, m, ArH), 7.91–8.03 (4H, m, ArH), 8.13 (2H, d, $J = 7.2$ Hz, ArH), 8.27–8.37 (2H, m, ArH). ^{13}C NMR: 10.8, 40.0, 104.0, 104.5, 105.4, 121.9, 124.2, 124.6, 124.8, 125.5, 127.7, 129.3, 129.7, 129.8, 130.2, 130.6, 132.4, 133.1, 133.8, 134.8, 135.4, 136.5, 141.9, 147.8, 163.3, 163.8, 165,6. MS *m/z*: 562.14 $((M + Na)^+$.

*2-(4-(2-amino-6-phenylpyrimidin-4-yl)phenyl)-3,4-dimethyl-2,4-dihydrobenzo[e]pyrazolo[4,3-c][1,2]thiazine 5,5-dioxide (**6m**)* Yellow powder; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.49 (3H, s, CH_3), 3.14 (3H, s, NCH_3), 5.22 (2H, br. s,, NH_2), 7.51–7.56 (4H, m, ArH), 7.58 (1H, t, $J = 7.6$ Hz, ArH), 7.66–7.72 (3H, m, ArH), 7.98 (1H, d, $J = 7.7$ Hz, ArH), 8.08–8.10 (2H, m, ArH), 8.13 (1H, d, $J = 7.7$ Hz, ArH), 8.25 (2H, d, $J = 8.5$ Hz, ArH). ^{13}C NMR: 10.5, 40.0, 104.2, 124.2, 124.8, 124.9, 125.2, 127.1, 128.0, 128.2, 128.7, 129.02, 129.4, 130.6, 130.9 132.4, 132.9, 133.2, 133.5, 134.0, 137.5, 137.6, 139.1, 140.8, 163.6, 164.7, 166.6. MS *m/z*: 517.14 $(M + Na)^+$.

*2-(4-(2-amino-6-(p-tolyl)pyrimidin-4-yl)phenyl)-3,4-dimethyl-2,4-dihydrobenzo[e]pyrazolo[4,3-c][1,2]thiazine 5,5-dioxide (**6n**)* Yellow powder; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.46 (3H, s, CH_3), 2.49 (3H, s, CH_3), 3.14 (3H,

s, CH_3), 5.25 (2H, br. s, NH_2), 7.34 (2H, d, $J = 8.0$ Hz, ArH), 7.56–7.61 (2H, m, ArH), 7.64 (2H, d, $J = 3.8$ Hz, ArH), 7.79 (1H, s, ArH), 7.83 (2H, d, $J = 3.8$ Hz, ArH), 7.98 (3H, d, $J = 7.9$ Hz, ArH), 8.12 (1H, d, $J = 7.6$ Hz, ArH). ^{13}C NMR: 10.7, 20.4, 40.0, 104.0, 104.5, 105.4, 124.2, 124.4, 124.8, 125.0, 127.8, 128.2, 129.2, 129.6, 130.4, 132.4, 132.9, 133.2, 133.5, 136.4, 138.8, 137.6, 139.1, 140.9, 153.5, 163.8, 164.6, 166.5. MS *m/z*: 509.18 $(M + H)^+$.

*2-(4-(2-amino-6-mesitylpyrimidin-4-yl)phenyl)-3,4-dimethyl-2,4-dihydrobenzo[e]pyrazolo[4,3-c][1,2]thiazine 5,5-dioxide (**6o**)* Yellow powder; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.20 (6 H, s, 2xCH_3), 2.37 (3H, s, CH_3), 2.45 (3H, s, CH_3), 3.12 (3H, s, NCH_3), 6.12 (2H, br. s, NH_2), 7.07–7.26 (3H, m, ArH), 7.53 (2H, d, $J = 8.3$ Hz, ArH), 7.69 (2H, t, $J = 7.6$ Hz, ArH), 7.94–7.99 (2H, m, ArH), 8.10 (2H, d, $J = 7.7$ Hz, ArH). ^{13}C NMR: 10.7, 19.3 (3C), 40.0, 104.0, 104.5, 105.4, 124.2, 124.4, 124.8, 125.0, 127.8, 128.2, 129.2, 129.6, 130.4, 132.4, 132.9, 133.0, 133.5, 136.4, 138.8, 137.6, 139.1, 140.9, 153.5, 163.5, 164.8, 166.2. MS *m/z*: 536.20 (M^+).

Anti-bacterial testing

Anti-bacterial assays were performed by the hole-plate method (Baldwin *et al.,* 1989; Baldwin *et al.,* 1987; Smith *et al.,* 1967) with the test organisms *Staphylococcus aureus* N.C.T.C. 6571 and *E. coli* X580. Solutions (100 µl) of the compounds to be tested (2 mg/mL) were loaded into wells in bioassay plates and incubated overnight at 37 °C. The diameters of the resultant inhibition zones were measured, and amounts of product were estimated by reference to standards prepared with Cephalosporin C. The results are summarized in Table 2.

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