

Supporting Information

for

Synthesis, characterization, antimicrobial, cytotoxic and carbonic anhydrase inhibition activities of multifunctional pyrazolo-1,2-benzothiazine acetamides

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Experimental procedures, spectra (NMR, HRMS) and graphs of antimicrobial and cytotoxic assays

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1. Experimental procedures

1.1 Synthesis of methyl 2-(1,1-dioxido-3-oxo-1,2-benzisothiazol-2(3*H*)yl)acetate (2)

Saccharine sodium (5.125 g, 25 mmol) was dissolved in DMF (30 mL) and methyl chloroacetate (2.712 g, 25 mmol) was added after the complete dissolution of saccharine sodium. The reaction mixture was stirred at 90–110 °C for 3–4 hours. After the completion of the reaction, the reaction mixture was allowed to cool to room temperature. Now the flask contents were poured into ice-cold water. White precipitates of methyl 2-(1,1-dioxido-3-oxobenzo[*d*]isothiazol-2(*3H*)-yl)acetate (**2**) were formed which were filtered, washed with excess of water and then recrystallized from ethanol [1,2]. M.P: 116-117°C, Yield: 5.487 g (86%).

1.2 Synthesis of methyl 4-hydroxy-2*H*-benzo[*e*][1,2]thiazine-3-carboxylate 1,1dioxide (3)

Fresh sodium methoxide (1.350 g, 25 mmol) was prepared using sodium metal and dry methanol (30 mL) as solvent. A solution of compound **2** (2.550 g, 10 mmol) in dry DMSO was prepared separately. Both of these solutions were prepared under moisture-free conditions. Then these two solutions were mixed at room temperature and swirled well until a dark orange red color was obtained. Then, the contents of the reaction mixture were poured over the mixture of ice and concentrated hydrochloric acid having pH 3. Keep on stirring while pouring the reaction mixture. White colored precipitates of methyl 4-hydroxy-2*H*-benzo[*e*][1,2]thiazine-3-carboxylate 1,1-dioxide (**3**) were formed, which were then filtered, washed with excess water, dried and recrystallized using ethanol [1,2]. M.P: 171-172°C, Yield: 1.531 g (60%).

1.3 Synthesis of methyl 4-hydroxy-2-methyl-2*H*-benzo[e][1,2]thiazine-3carboxylate 1,1-dioxide (4)

Compound **3** (5.100 g, 20 mmoles) was dissolved in acetone (20 mL) and sodium hydroxide (2 N) was added slowly while stirring at room temperature to set the pH at 10–11. The reaction mixture was stirred for 5 minutes. Then, dimethyl sulfate (2.520 g, 20 mmol) was added drop-wise. This reaction mixture was further stirred for 40 minutes. After the completion of the reaction, it was acidified with dilute hydrochloric acid until the appearance of white precipitates of methyl 4-hydroxy-2-methyl-*2H*-benzo[*e*][1,2]thiazine-3-carboxylate 1,1-dioxide (**4**). These were filtered, washed with water, dried and recrystallized with ethanol [3]. M.P 161-162°C, Yield: 3.822 g (71%).

1.4 Synthesis of 2-chloro-N-aryl/benzyl/cyclohexylacetamides 6a-n

Aryl/benzyl/cyclohexylamines (5 mmol) were dissolved in DCM and Na₂CO₃ solution (7%) was added dropwise to set the pH at 9.0. This reaction mixture was stirred for 30 minutes at room temperature. Then, chloroacetyl chloride (847 mg, 7.5 mmol) in 2 mL DCM was added drop-wise in about 10–15 min with vigorous stirring. Stirring was continued until the precipitation of solid 2-chloro-*N*-aryl/benzyl/cyclohexylacetamides **6a**–**n**. After the completion of the reaction, precipitates were filtered, washed with chilled distilled water, and dried to produce the desired alkylating agents [4].



2. Spectra of pyrazolo-1,2-benzothiazine acetamides 7a-n

Figure S1. ¹H NMR of compound 7a in DMSO-d₆ at 300 MHz.



Figure S2. ¹³C NMR of compound 7a in DMSO-d₆ at 75 MHz.



Figure S3. HRMS of compound 7a.



Figure S4. ¹H NMR of compound **7b** in DMSO-d₆ at 300 MHz.



Figure S5. ¹³C NMR of compound **7b** in DMSO-d₆ at 75 MHz.

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Figure S6. HRMS of compound 7b.



Figure S7. ¹H NMR of compound 7c in DMSO-d₆ at 300 MHz.



Figure S8. ¹³C NMR of compound 7c in DMSO-d₆ at 75 MHz.



Figure S9. HRMS of compound 7c.



Figure S10. ¹H NMR of compound 7d in DMSO-d₆ at 300 MHz.



Figure S11. ¹³C NMR of compound 7d in DMSO-d₆ at 75 MHz.

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Figure S12. HRMS of compound 7d.



Figure S13. ¹H NMR of compound 7e in DMSO-d₆ at 300 MHz.



Figure S14. ¹³C NMR of compound 7e in DMSO-d₆ at 75 MHz.



Figure S15. HRMS of compound 7e.



Figure S16. ¹H NMR of compound 7f in DMSO-d₆ at 300 MHz.



Figure S17. ¹³C NMR of compound **7f** in DMSO-d₆ at 75 MHz.



Figure S18. HRMS of compound 7f.



Figure S19. ¹H NMR of compound **7g** in DMSO-d₆ at 300 MHz.



Figure S20. ¹³C NMR of compound **7g** in DMSO-d₆ at 75 MHz.



Figure S21. HRMS of compound 7g.



Figure S22. ¹H NMR of compound **7h** in DMSO-d₆ at 300 MHz.



Figure S23. ¹³C NMR of compound **7h** in DMSO-d₆ at 75 MHz.



Figure S24. HRMS of compound 7h.



Figure S25. ¹H NMR of compound 7i in DMSO-d₆ at 300 MHz.



Figure S26. ¹³C NMR of compound 7i in DMSO-d₆ at 75 MHz.



Figure S27. HRMS of compound 7i in DMSO-d₆ at 75 MHz.



Figure S28. ¹H NMR of compound 7j in DMSO-d₆ at 300 MHz.



Figure S29. ¹³C NMR of compound 7j in DMSO-d₆ at 75 MHz.



Figure S30. HRMS of compound 7j.



Figure S31. ¹H NMR of compound 7k in DMSO-d₆ at 300 MHz.



Figure S32. ¹³C NMR of compound 7k in DMSO-d₆ at 75 MHz.



Figure S33. HRMS of compound 7k.



Figure S34. ¹H NMR of compound 7I in DMSO-d₆ at 300 MHz.



Figure S35. ¹³C NMR of compound 7I in DMSO-d₆ at 75 MHz.

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Figure S36. HRMS of compound 7I.



Figure S37. ¹H NMR of compound **7m** in DMSO-d₆ at 300 MHz.



Figure S38. ¹³C NMR of compound **7m** in DMSO-d₆ at 75 MHz.



Figure S39. HRMS of compound 7m.



Figure S40. ¹H NMR of compound 7n in DMSO-d₆ at 300 MHz.



Figure S41. ¹³C NMR of compound **7n** in DMSO-d₆ at 75 MHz.

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Figure S42. HRMS of compound 7n.



Figure S43: Graph showing results of antimicrobial single-dose microbroth assays of compounds **7a–n**, dose of tested compounds = 125 μ g/mL, control antibiotics used: kanamycin = 50 μ g/mL (*Staphylococcus aureus* ATCC 25923), ampicillin = 50 μ g/mL (*Escherichia coli* ATCC 8739), and amphotericin B = 25 μ g/mL (*Candida albicans* ATCC 90027). Dimethylsulfoxide (DMSO) was used as the negative control at 1.25% v/v.

Table S1: Results of single-dose antimicrobial and cytotoxic assays for compounds **7a–n**; dosage of tested compounds = 125 μ g/mL; antibiotic control dosage (kanamycin = 50 μ g/mL (*Staphylococcus aureus* ATCC 25923), ampicillin = 50 μ g/mL (*Escherichia coli* ATCC 8739), and amphotericin B = 25 μ g/mL (*Candida albicans* ATCC 90027). For cytotoxic assays, dosage of tested compounds = 10 μ M; dosage of mensacarcin = 10 μ M.

	Percent survival / % Cell viability												
Samples	S. aureus	E coli (SD)	Calbicans (SD)	HCT-116									
	(SD)			(SD)									
7a	71.75 (21)	>100	96.68 (12)	85.40 (3)									
7b	37.17 (13)	95.34 (16)	86.98 (6)	88.90 (3)									
7c	>100	>100	>100	81.40 (2)									
7d	>100	92.68 (2)	>100	>100									
7e	>100	>100	>100	>100									
7f	>100	>100	>100	>100									
7g	>100	95.01 (1)	71.75 (0)	>100									
7h	16.73 (3)	>100	65.10 (5)	>100									
7i	>100	>100	84.21 (5)	87.30 (6)									
7j	>100	>100	99.45 (6)	>100									
7k	>100	94.18 (0.1)	>100	90.70 (4)									
71	>100	>100	>100	63.60 (1)									
7m	>100	>100	>100	>100									
7n	>100	92.35 (1)	>100	>100									
Kanamycin	0.37 (0.7)	-	_	_									
Ampicillin	_	4.16 (3)	_	_									
Amphotericin	_		4 71 (1)										
В	_		7.7 1 (1)										
Mensacarcin	_	_	_	11.50 (1)									



Figure S44: Graph showing cell viability of compounds **7a–n** against human colon carcinoma cell line (HCT-116, ATCC CCL-247), dose of tested compounds = 10 μ M, dose of positive control (mensacarcin) = 10 μ M.

3. Characterization data of compounds 7a-n

All the synthesized compounds in DMSO-d₆ were scanned for their ¹H NMR spectra at 300 MHz and ¹³C NMR at 75 MHz.

N-(4-Chlorophenyl)-2-(3-hydroxy-4-methyl-5,5-dioxidobenzo[e]pyrazolo [4,3-*c*] [1,2] thiazine-1(4*H*)-yl)acetamide (7a)

Off white solid, Yield 335 mg (80%), m.p 156-158 °C, FT-IR: 1537 (C=O), 1335, 1171 (SO₂), 1239 (C–N); ¹H NMR (δ): *N*-CH₃ (linked with thiazine ring) = 3.08 (s, 3H), *N*-CH₂ (linked with pyrazole ring) = 4.95 (s, 2H), N-H (amide) = 10.36 (s, 1H), O-H (linked with pyrazole ring) = 13.12 (s, 1H); Aromatic protons: 7.37 (d, 2H, J = 8.8 Hz), 7.65 (d, 2H, J = 8.7 Hz), 7.71 (d, 1H, J = 6.0 Hz), 7.86 (t, 1H, J = 7.5 Hz), 7.92 (t, 2H, J = 7.6 Hz); ¹³C NMR (δ): 38.1, 67.8, 109.2, 121.3, 123.7, 124.4, 124.8, 127.5, 129.2, 130.0, 130.2, 130.6, 133.8, 138.0, 154.3, 166.9; HR-MS: Mass to charge ratio calculated from theoretical formula C₁₈H₁₅CIN₄O₄S [M+H]⁺ 419.0575, observed 419.0578, Δppm 0.71.

N-(3-Chlorophenyl)-2-(3-hydroxy-4-methyl-5,5-dioxidobenzo[e] pyrazolo [4,3-*c*] [1,2] thiazine-1(4*H*)-yl)acetamide (7b)

Peach colored solid, Yield 331 mg (79%), m.p 170-172 °C, FT-IR: 1592 (C=O), 1335, 1179 (SO₂), 1298 (C–N); ¹H NMR (δ): *N*-CH₃ (linked with thiazine ring) = 3.08 (s,3H), *N*-CH₂ (linked with pyrazole ring) = 4.96 (s, 2H), N-H (amide) = 10.45 (s, 1H), O-H (linked with pyrazole ring) = 13.21 (s, 1H); Aromatic protons: 7.13 (d, 1H, J = 6.9 Hz), 7.35 (t, 1H, J = 8.1 Hz), 7.48 (d, 1H, J = 8.4 Hz), 7.61 (t, 1H, J = 7.7 Hz), 7.70 (t, 1H, J = 6.8 Hz), 7.83 (1H, s), 7.93 (d, 2H, J = 8.1 Hz); ¹³C NMR (δ): 38.1, 67.8, 109.1, 118.1, 119.2, 123.4, 123.7, 124.5, 124.7, 124.8, 130.2, 130.6, 131.0, 133.6, 133.7, 140.5, 154.2, 167.1; HR-MS: Mass to charge ratio calculated from theoretical formula C₁₈H₁₅CIN₄O₄S [M+H]⁺ 419.0575 and observed 419.0578, Δppm 0.71.

N-(3,5-Dimethylphenyl)-2-(3-hydroxy-4-methyl-5,5-dioxidobenzo[e]pyrazolo[4,3c][1,2]thiazine-1(4*H*)-yl)acetamide (7c)

Light brown solid, Yield 341 mg (83%), m.p 152-154 °C, FT-IR: 1510 (C=O), 1339, 1158 (SO₂), 1266 (C–N); ¹H NMR (δ): Ar-CH₃ (linked with *N*-aryl-acetamide) = 2.23 (s, 6H), *N*-CH₃ (linked with thiazine ring) = 3.09 (s, 3H), *N*-CH₂ (linked with pyrazole ring) = 4.92 (s, 2H), N-H (amide) = 10.04 (s, 1H), O-H (linked with pyrazole ring) = 13.10 (s,

1H); Aromatic protons: 6.70 (s, 1H), 7.24 (s, 2H), 7.69 (t, 1H, J = 7.5 Hz), 7.86 (t, 1H, J = 7.4 Hz), 7.89 – 7.96 (m, 2H); ¹³C NMR (δ): 21.5, 38.1, 67.7, 109.2, 117.5, 123.7, 124.4, 124.8, 125.5, 129.9, 130.2, 130.6, 133.7, 138.2, 138.9, 154.4, 166.5; HR-MS: Mass to charge ratio calculated from theoretical formula C₂₀H₂₀N₄O₄S [M+H]⁺ 413.1278 and observed 413.1289, Δ ppm 2.66.

2-(3-Hydroxy-4-methyl-5,5-dioxidobenzo[e]pyrazolo[4,3-c][1,2] thiazine-1(4*H*)yl)-*N*-(*m*-tolyl)acetamide (7d)

Light orange solid, Yield 322 g (81%), m.p 155-156 °C, FT-IR: 1537 (C=O), 1336, 1155 (SO₂), 1260 (C–N); ¹H NMR (δ): Ar-CH₃ (linked with *N*-aryl-acetamide) = 2.27 (s, 3H), *N*-CH₃ (linked with thiazine ring) = 3.09 (s, 3H), *N*-CH₂ (linked with pyrazole ring) = 4.94 (s, 2H), N-H (amide) = 10.14 (s, 1H), O-H (linked with pyrazole ring) = 13.14 (s, 1H); Aromatic protons: 6.88 (d, 1H, *J* = 7.5 Hz), 7.19 (t, 1H, *J* = 7.8 Hz), 7.39 (d, 1H, *J* = 8.3 Hz), 7.48 (s, 1H), 7.70 (t, 1H, *J* = 7.5 Hz), 7.80 – 8.04 (m, 3H); ¹³C NMR (δ): 21.6, 38.1, 67.8, 109.1, 117.0, 120.2, 123.7, 124.5, 124.6, 124.8, 129.1, 130.0, 130.2, 130.6, 133.7, 138.5, 139.0, 154.3, 166.6.; HR-MS: Mass to charge ratio calculated from theoretical formula C₁₉H₁₈N₄O₄S [M+H]⁺ 399.1122 and observed 399.1128, Δppm 1.50.

2-(3-Hydroxy-4-methyl-5,5-dioxidobenzo[e]pyrazolo[4,3-c][1,2] thiazine-1(*4H*)yl)-*N*-(2-nitrophenyl)acetamide (7e)

Yellow solid, Yield 334 g (78%), m.p 151-153 °C, FT-IR: 1494 (C=O), 1335, 1155 (SO₂), 1248 (C–N); ¹H NMR (δ): *N*-CH₃ (linked with thiazine ring) = 3.11 (s, 3H), *N*-CH₂ (linked with pyrazole ring) = 5.00 (s, 2H), N-H (amide) = 10.75 (s, 1H), O-H (linked with pyrazole ring) = 13.23 (s, 1H); Aromatic protons: 7.38 (t, 1H, *J* = 7.8 Hz), 7.71 (t, 1H, *J* = 7.5 Hz), 7.77 (t, 1H, *J* = 7.8 Hz), 7.87 (t, 1H, *J* = 7.4 Hz), 7.93 (t, 2H, *J* = 6.5 Hz), 8.10 (t, 2H, *J* = 8.9 Hz); ¹³C NMR (δ): 38.2, 68.0, 109.1, 123.8, 124.4, 124.5, 124.8, 125.5, 125.8, 130.2, 130.3, 130.7, 132.0, 133.8, 135.4, 140.6, 153.9, 167.30; HR-MS: Mass to charge ratio calculated from theoretical formula C₁₈H₁₅N₅O₆S [M+H]⁺ 430.0816 and observed 430.0821, Δ ppm 1.16.

N-Benzyl-2-(3-hydroxy-4-methyl-5,5-dioxidobenzo[e]pyrazolo[4,3-c][1,2] thiazine-1 (4*H*)-yl)acetamide (7f)

White solid, Yield 308 mg (77%), m.p 154-156 °C, FT-IR: 1536 (C=O), 1336, 1153 (SO₂), 1228 (C–N); ¹H NMR (δ): *N*-CH₃ (linked with thiazine ring) = 3.06 (s, 3H), Ar-CH₂ (benzyl) = 4.35 (d, J = 2.9 Hz, 2H), *N*-CH₂ (linked with pyrazole ring) = 4.80 (s, 2H), N-H (amide) = 8.65 (s, 1H), O-H (linked with pyrazole ring) = 13.14 (s, 1H); Aromatic protons: 7.13 – 7.48 (m, 5H), 7.70 (t, 1H, J = 7.2 Hz), 7.90 (t, 3H, J = 11.4 Hz); ¹³C NMR (δ): 38.1, 42.2, 67.9, 109.1, 123.7, 124.5, 124.7, 127.2, 127.6, 128.7, 129.9, 130.2, 130.6, 133.7, 139.7, 154.3, 167.91; HR-MS: Mass to charge ratio calculated from theoretical formula C₁₉H₁₈N₄O₄S [M+H]⁺ 399.1122 and observed 399.1131, Δppm 2.25.

2-(3-Hydroxy-4-methyl-5,5-dioxidobenzo[e]pyrazolo[4,3-c][1,2] thiazine-1(4*H*)yl)-*N*-(naphthalen-1-yl)acetamide (7g)

Light orange solid, Yield 351 mg (81%), m.p 161-163 °C, FT-IR: 1502 (C=O), 1338, 1157 (SO₂), 1252 (C–N); ¹H NMR (δ): *N*-CH₃ (linked with thiazine ring) = 3.11 (s, 3H), *N*-CH₂ (linked with pyrazole ring) = 5.13 (s, 2H), N-H (amide) = 10.22 (s, 1H), O-H (linked with pyrazole ring) = 13.20 (s, 1H); Aromatic protons: 7.50 (d, 1H, *J* = 7.8 Hz), 7.51 – 7.60 (m, 2H), 7.63 – 7.76 (m, 2H), 7.80 (d, 1H, *J* = 8.2 Hz), 7.87 (t, 1H, *J* = 7.6 Hz), 7.95 (d, 3H, *J* = 8.0 Hz), 8.08 – 8.13 (m, 1H); ¹³C NMR (δ): 38.1, 68.0, 109.2, 122.6, 123.4, 123.7, 124.5, 124.8, 126.0, 126.2, 126.4, 126.6, 128.6, 130.0, 130.2, 130.7, 133.4, 133.8, 134.2, 143.4, 154.5, 167.6; HR-MS: Mass to charge ratio calculated from theoretical formula $C_{22}H_{18}N_4O_4S$ [M+H]⁺ 435.1122 and observed 435.1128, Δppm 1.37.

N-(4-Bromophenyl)-2-(3-hydroxy-4-methyl-5, 5-dioxidobenzo [e] pyrazolo[4,3c][1,2] thiazine-1(4*H*)-yl)acetamide (7h)

Light yellow solid, Yield 378 mg (82%), m.p 185-186 °C, FT-IR: 1538 (C=O), 1349, 1172 (SO₂), 1270 (C–N); ¹H NMR (δ): *N*-CH₃ (linked with thiazine ring) = 3.08 (s, 3H), *N*-CH₂ (linked with pyrazole ring) = 4.95 (s, 2H), N-H (amide) = 10.40 (s, 1H), O-H (linked with pyrazole ring) = 13.03 (s, 1H); Aromatic protons: 7.50 (d, 2H, *J* = 8.9 Hz), 7.60 (d, 2H, *J* = 8.9 Hz), 7.69 (t, 1H, *J* = 7.5 Hz), 7.85 (t, 1H, *J* = 7.7 Hz), 7.93 (d, 2H, *J* = 9.0 Hz); ¹³C NMR (δ): 38.2, 67.8, 109.1, 115.5, 121.7, 123.7, 124.6, 124.8, 130.1,

130.6, 132.1, 133.7, 138.4, 154.3, 166.9; HR-MS: Mass to charge ratio calculated from theoretical formula $C_{18}H_{15}BrN_4O_4S [M+H]^+$ 463.0078 and observed 463.0070, $\Delta ppm - 1.72$.

2-((4-Methyl-1-(2-((4-nitrophenyl)amino)-2-oxoethyl)-5,5-dioxido-1,4-dihydro benzo[e] pyrazolo[4,3-c][1,2]thiazine-3-yl)oxy)-*N*-(4-nitrophenyl) acetamide (7i)

Light orange brown solid, Yield 475 mg (78%), m.p 185-187 °C, FT-IR: 1602, 1504 (C=O), 1328, 1175 (SO₂), 1253 (C–N); ¹H NMR (δ): *N*-CH₃ (linked with thiazine ring) = 3.08 (s, 3H), *N*-CH₂ (linked with pyrazole ring) = 5.01 (s, 2H), *O*-CH₂ (linked with pyrazole ring) = 5.31 (s, 2H), N-H (amide) = 10.82 (s, 1H), N-H (amide) = 11.07 (s, 1H); Aromatic protons: 7.82-8.20 (m, 12H); ¹³C NMR (δ): 37.9, 55.0, 68.2, 112.6, 119.5, 125.5, 127.6, 129.1, 130.5, 131.8, 133.7, 134.7, 143.3, 145.1, 166.7, 166.7; HR-MS: Mass to charge ratio calculated from theoretical formula $C_{26}H_{21}N_7O_9S$ [M+H]⁺ 608.1194 and observed 608.1202, Δppm 1.31.

N-(4-Methoxyphenyl)-2-(3-(2-((4-methoxyphenyl)amino)-2-oxoethoxy)-4-methyl-5,5-dioxidobenzo[e]pyrazolo[4,3-c][1,2]thiazine-1(4*H*)-yl)acetamide (7j)

Light orange solid, Yield 442 mg (77%), m.p 180-182 °C, FT-IR: 1610, 1506 (C=O), 1334, 1170 (SO₂), 1232 (C–N); ¹H NMR (δ): *N*-CH₃ (linked with thiazine ring) = 3.08 (s, 3H), *O*-CH₃ (linked with *N*-aryl-acetamide) = 3.72 (s, 6H), *N*-CH₂ (linked with pyrazole ring) = 4.91(s, 2H), *O*-CH₂ (linked with pyrazole ring) = 5.22 (s, 2H), N-H (amide) = 10.06 (s, 1H), N-H (amide) = 10.40 (s, 1H); Aromatic protons: 6.82-6.93 (m, 4H), 7.49-7.54 (m, 4H), 7.75 (d, 1H, *J* = 7.8 Hz), 7.87 (d, 1H, *J* = 6.8 Hz), 7.98-8.08 (m, 2H); ¹³C NMR (δ): 38.0, 54.8, 55.6, 55.6, 67.9, 109.9, 114.3, 114.4, 121.3, 121.6, 124.3, 125.3, 128.4, 130.2, 131.4, 132.0, 133.7, 135.4, 137.1, 153.8, 155.9, 156.0, 165.2, 165.8; HR-MS: Mass to charge ratio calculated from theoretical formula C₂₈H₂₇N₅O₇S [M+H]⁺ 578.1704 and observed 578.1710, Δppm 1.03.

N-(2,3-Dimethylphenyl)-2-(3-(2-((2,3-dimethylphenyl)amino)-2-oxoethoxy)-4methyl-5,5-dioxidobenzo[e]pyrazolo[4,3-c][1,2]thiazine-1(4*H*)-yl)acetamide (7k)

Light pink solid, Yield 482 mg (84%), m.p 198-199 °C, FT-IR: 1670, 1536 (C=O), 1348, 1155 (SO₂), 1268 (C–N); ¹H NMR (δ): Ar-CH₃ (linked with *N*-aryl-acetamide) = 2.07 (s, 3H), Ar-CH₃ (linked with *N*-aryl-acetamide) = 2.11 (s, 3H), Ar-CH₃ (linked with *N*-aryl-acetamide) = 2.22 (s, 3H), Ar-CH₃ (linked with *N*-aryl-acetamide) = 2.24 (s, 3H), *N*-

CH₃ (linked with thiazine ring) = 3.09 (s, 3H), *N*-CH₂ (linked with pyrazole ring) = 4.96 (s, 2H), *O*-CH₂ (linked with pyrazole ring) = 5.32 (s, 2H), N-H (amide) = 9.62 (s, 1H), N-H (amide) = 9.86 (s, 1H); Aromatic protons: 7.00 – 7.10 (m, 4H), 7.18 (ddd, 2H, *J* = 14.2, 6.3, 2.8 Hz), 7.75 (t, 1H, *J* = 7.7 Hz), 7.88 (t, 1H, *J* = 7.4 Hz), 8.00 (td, 2H, *J* = 6.3, 3.2 Hz); ¹³C NMR (δ): 14.4, 14.5, 20.6, 20.6, 37.9, 54.6, 68.1, 109.9, 123.8, 124.2, 124.3, 125.2, 125.2, 125.6, 125.7, 127.7, 130.2, 131.2, 131.4, 131.5, 132.2, 133.6, 135.8, 135.8, 137.4, 137.6, 153.7, 165.9, 166.6; HR-MS: Mass to charge ratio calculated from theoretical formula $C_{30}H_{31}N_5O_5S$ [M+H]⁺ 574.2119 and observed 574.2126, Δppm 1.21.

2-((4-Methyl-5,5-dioxido-1-(2-oxo-2-(*o*-tolylamino)ethyl)-1,4-dihydrobenzo [e]pyrazolo [4,3-c][1,2]thiazine-3-yl)oxy)-*N*-(*o*-tolyl)acetamide (7l)

Light yellow solid , Yield 438 mg (80%), m.p 202-203 °C, FT-IR: 1610, 1513 (C=O), 1339, 1177 (SO₂), 1260 (C–N); ¹H NMR (δ): Ar-CH₃ (linked with *N*-aryl-acetamide) = 2.20 (s, 3H), Ar-CH₃ (linked with *N*-aryl-acetamide) = 2.24 (s, 3H), *N*-CH₃ (linked with thiazine ring) = 3.09 (s, 3H), *N*-CH₂ (linked with pyrazole ring) = 4.97 (s, 2H), *O*-CH₂ (linked with pyrazole ring) = 5.33 (s, 2H), N-H (amide) = 9.54 (s, 1H), N-H (amide) = 9.78 (s, 1H); Aromatic protons: 7.08 – 7.21 (m, 4H), 7.22 (t, 2H, *J* = 5.4 Hz), 7.43 (t, 2H, *J* = 7.1 Hz), 7.75 (t, 1H, *J* = 7.6 Hz), 7.88 (t, 1H, *J* = 7.8 Hz), 7.99 (d, 2H, *J* = 7.9 Hz); ¹³C NMR (δ): 18.2, 18.3, 38.0, 54.7, 68.0, 109.9, 124.3, 125.2, 125.3, 125.7, 126.0, 126.4, 126.5, 130.2, 130.8, 130.9, 131.2, 131.4, 132.1, 132.6, 133.6, 136.0, 153.7, 165.9, 166.5; HR-MS: Mass to charge ratio calculated from theoretical formula C₂₈H₂₇N₅O₅S [M+H]⁺ 546.1806 and observed 546.181, Δppm 0.91.

2-((4-Methyl-5,5-dioxido-1-(2-oxo-2-(*p*-tolylamino)ethyl)-1,4-dihydrobenzo [e]pyrazolo [4,3-c][1,2]thiazine-3-yl)oxy)-*N*-(*p*-tolyl)acetamide (7m)

Light yellow solid, Yield 431 mg (79%), m.p 205-207 °C, FT-IR: 1653, 1537 (C=O), 1341, 1180 (SO₂), 1262 (C–N); ¹H NMR (δ): Ar-CH₃ (linked with *N*-aryl-acetamide) = 2.24 (s, 3H), Ar-CH₃ (linked with *N*-aryl-acetamide) = 2.25 (s, 3H), *N*-CH₃ (linked with thiazine ring) = 3.07 (s, 3H), *N*-CH₂ (linked with pyrazole ring) = 4.92 (s, 2H), *O*-CH₂ (linked with pyrazole ring) = 5.23 (s, 2H), N-H (amide) = 10.09 (s, 1H), N-H (amide) = 10.40 (s, 1H); Aromatic protons: 7.05 – 7.17 (m, 4H), 7.48 (d, 2H, *J* = 8.4 Hz), 7.74 (t, 1H, *J* = 8.0 Hz), 7.86 (t, 1H, *J* = 7.7 Hz), 7.99 (d, 2H, *J* = 9.1 Hz); ¹³C NMR (δ): 21.0, 38.0, 54.8, 67.8, 109.8, 119.7, 119.9, 124.3, 125.2, 125.3, 129.6, 129.7, 130.2, 131.4,

132.9, 133.2, 133.7, 136.4, 136.4, 153.8, 165.5, 166.0; HR-MS: Mass to charge ratio calculated from theoretical formula $C_{28}H_{27}N_5O_5S$ [M+H]⁺ 546.1806 and observed 546.1812, Δppm 1.09.

N-Cyclohexyl-2-(3-(2-(cyclohexylamino)-2-oxoethoxy)-4-methyl-5,5 dioxido benzo[e] pyrazolo[4,3-c][1,2]thiazine-1(4*H*)-yl)acetamide (7n)

Light orange solid, Yield 417 mg (79%), m.p 196-198 °C, FT-IR: 1657, 1511 (C=O), 1341, 1152 (SO₂), 1252 (C–N); ¹H NMR (δ): CH₂ (cyclohexyl) = 1.26 - 1.19 (m, 10H), CH₂ (cyclohexyl) = 1.76 - 1.64 (m, 10H), *N*-CH₃ (linked with thiazine ring) = 3.03 (s, 3H), CH (cyclohexyl) = 3.61 - 3.53 (m, 2H), *N*-CH₂ (linked with pyrazole ring) = 4.66 (s, 2H), *O*-CH₂ (linked with pyrazole ring) = 4.95 (s, 2H), N-H (amide) = 7.74 (d, *J* = 7.8 Hz, 1H), N-H (amide) = 8.23 (d, *J* = 7.8 Hz, 1H); Aromatic protons: 7.91 (m, 4H); ¹³C NMR (δ): 24.9, 25.1, 25.2, 25.6, 26.8, 31.4, 32.8, 37.9, 47.9, 48.3, 54.3, 67.8, 109.7, 124.3, 125.1, 125.2, 130.1, 131.0, 131.4, 133.5, 153.6, 165.8, 166.3; HR-MS: Mass to charge ratio calculated from theoretical formula C₂₆H₃₅N₅O₅S [M+H]⁺ 530.2432 and observed 529.2340, Δppm 1.51.

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