Electronic supplementary information for

Design, synthesis and molecular modelling of novel methyl[4-oxo-2-(aroylimino)-3-(substituted phenyl)thiazolidin-5-ylidene]acetates as potent and selective aldose reductase inhibitors

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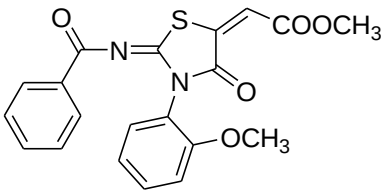
Contents

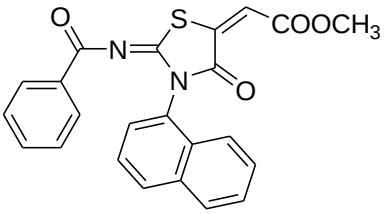
1. Chemistry S-2

Methyl[4-oxo-2-(benzoylimino)-3-(2-methoxyphenyl)thiazolidin-5-ylidene]acetate



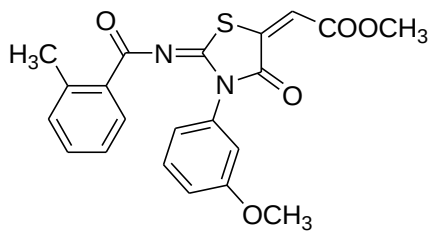
(2a). Yield: 84%; R_f^*: 0.22; m.p. 121-123ºC; **IR**: 2953 (CH_3), 1724, 1692, 1652 (3C=O), 1538 (N=C), 1254 (C–S) cm^{-1}. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.89-7.76 (m, 1H, ArH), 7.65-7.63 (m, 2H, ArH), 7.54-7.48 (m, 1H, ArH), 7.35-7.21 (m, 2H, ArH) 7.20-7.19 (m, 3H, ArH), 7.14 (s, 1H, C=CH-C), 3.78, 3.75 ($2OCH_3$); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 176.7, 165.9, 165.0, 163.7, 141.8, 138.8, 135.4, 134.5, 135.2, 133.4, 132.9, 131.5, 128.4, 127.9, 122.0, 121.8, 53.1, 53.0.**EIMS***m/z* (%): 369 [M^+] (15), 105 (100%), 107 (19), 59 (26).**Anal**. Calcd. for $C_{20}H_{16}N_2O_5S$: C, 60.60; H, 4.07; N, 7.07; S, 8.09. found: C, 60.67; H, 4.19; N, 7.25; S, 8.24.

Methyl[4-oxo-2-(benzoylimino)-3-(1-naphthalenyl)thiazolidin-5-ylidene]acetate (2b). Yield:



81%; R_f^*: 0.23; m.p. 244-246ºC; **IR**: 2949 (CH_3), 1727, 1699, 1643 (3C=O), 1525 (N=C), 1260 (C–S) cm^{-1}. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 8.20-8.02 (m, 2H, ArH), 7.83-7.81 (m, 3H, ArH), 7.64-7.4.9 (m, 2H, ArH), 7.57-7.41 (m, 3H, ArH), 7.45-7.32 (m, 2H, ArH), 7.13 (s, 1H, C=CH-C), 3.91 (CH_3); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 176.6, 165.7, 164.2, 163.7, 140.8, 135.1, 134.8, 133.6, 132.7, 132.4, 132.0, 131.9, 131.3, 130.3, 129.6, 129.5, 128.2, 127.4, 125.9, 120.5, 53.4. **EIMS***m/z* (%): 416 [M^+] (14), 127 (57), 105 (100%), 31 (25). **Anal**. Calcd. for $C_{23}H_{16}N_2O_4S$: C, 66.33; H, 3.87; N, 6.73; S, 7.70. found: C, 66.41; H, 3.72; N, 6.77; S, 7.92.

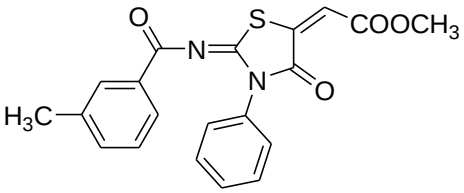
Methyl[4-oxo-2-(2-methybenzoylimino)-3-(3-methoxyphenyl)thiazolidin-5-ylidene] acetate



(2c). Yield: 79%; R_f^*: 0.34; m.p. 204-206ºC; **IR**: 2949 (CH_3), 1731, 1691, 1643 (3C=O), 1562 (N=C), 1252 (C–S) cm^{-1}. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.87-7.81 (m, 1H, ArH), 7.78-

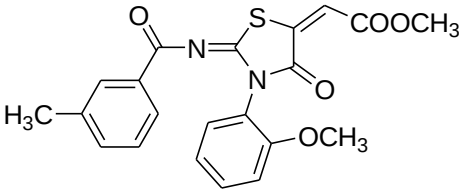
7.72 (m, 1H, ArH), 7.66-7.54 (m, 1H, ArH), 7.41-7.39 (m, 2H, ArH), 7.38-7.26 (m, 1H, ArH), 7.22-7.11 (m, 2H, ArH), 7.04 (s, 1H, C=CH-C), 3.88, 3.72 ($2OCH_3$), 2.40, 2.34 (CH_3); **^{13}C NMR** (75 MHz, $CDCl_3$,): δ 176.4, 165.7, 165.0, 163.6, 140.2, 135.9, 134.7, 133.9, 133.0, 132.8, 132.2, 131.5, 128.5, 127.8, 127.7, 124.8, 121.9, 121.6, 51,3, 53.2, 23.9. **EIMS***m/z* (%): 410 [M^+] (19), 266 (14), 119 (100%), 107 (20). **Anal**. Calcd. for $C_{21}H_{18}N_2O_5S$: C, 61.45; H, 4.42; N, 6.83; S, 7.81. found: C, 61.58; H, 4.61; N, 6.90; S, 7.96.

Methyl[4-oxo-2-(3-methylbenzoylimino)-3-phenylthiazolidin-5-ylidene]acetate (2d). Yield:



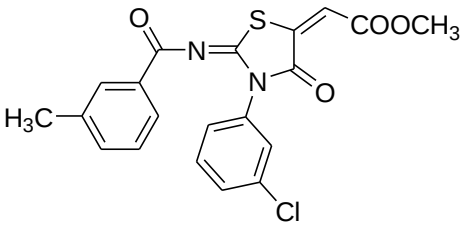
86%; R_f^*: 0.45; m.p. 202-203ºC; **IR**: 2950 (CH_3), 1722, 1708, 1645 (3C=O), 1520 (N=C), 1277 (C–S) cm^{-1}. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.80-7.75 (m, 2H, ArH), 7.64-7.61 (m, 3H, ArH), 7.49-7.41 (m, 1H, ArH), 7.38-7.23 (m, 3H, ArH), 7.14 (s, 1H, C=C*H*-C), 3.93 (OCH_3), 2.64 (CH_3); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 176.6, 165.7, 165.1, 163.5, 140.1, 137.9, 136.5, 134.7, 133.5, 132.4, 131.1, 129.4, 127.6, 125.8, 124.2, 122.2, 53.0, 24.6.**EIMS***m/z* (%): 380 [M^+] (17), 119 (100%), 85 (20), 59 (33) **Anal**. Calcd. for $C_{20}H_{16}N_2O_4S$: C, 63.14; H, 4.24; N, 7.36; S, 8.43. found: C, 63.30; H, 4.34; N, 7.49; S, 8.60.

Methyl[4-oxo-2-(3-methybenzoylimino)-3-(2-methoxyphenyl)thiazolidin-5-ylidene] acetate



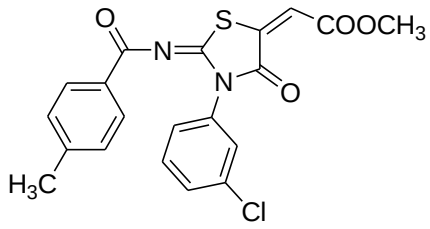
(2e). Yield: 82%; R_f^*: 0.28; m.p. 160-161ºC; **IR**: 2949 (CH_3), 1692, 1646, 1604 (3C=O), 1533 (N=C), 1253 (C–S) cm^{-1}. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.82-7.80 (m, 1H, ArH), 7.75-7.73 (m, 1H, ArH), 7.51-7.47 (m, 1H, ArH), 7.31-7.28 (m, 2H, ArH), 7.24-7.20 (m, 1H, ArH), 7.13-7.07 (m, 2H, ArH), 7.04 (s, 1H, C=CH-C), 3.87, 3.78 ($2OCH_3$), 2.31 (s, 3H, CH_3); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 176.6, 165.9, 165.3, 163.8, 141.4, 138.8, 134.1, 133.8, 133.3, 132.9, 132.0, 131.9, 130.0, 128.5, 126.1, 127.4, 123.7, 120.1, 53.3, 53.0, 21.3. **EIMS***m/z* (%): 410 [M^+] (19), 266 (15), 119 (100%), 107 (60) **Anal**. Calcd. for $C_{21}H_{18}N_2O_5S$: C, 61.45; H, 4.42; N, 6.83; S, 7.81, found: C, 61.41; H, 4.50; N, 6.91; S, 7.93.

Methyl[4-oxo-2-(3-methybenzoylimino)-3-(3-chlorophenyl)thiazolidin-5-ylidene] acetate



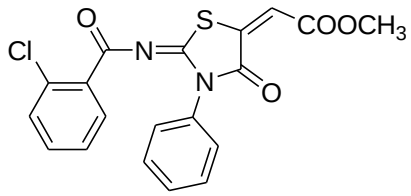
(2f). Yield: 81%; R_f^*: 0.35; m.p. 193-195ºC; **IR**: 2919 (CH_3), 1724, 1698, 1650 (3C=O), 1530 (N=C), 1273 (C–S) cm^{-1}. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.77-7.72 (m, 2H, ArH), 7.64-7.56 (m, 3H, ArH), 7.40-7.39 (m, 2H, ArH), 7.38-7.24 (m, 1H, ArH), 7.14 (s, 1H, C=CH-C), 3.93 (OCH_3), 2.61 (CH_3); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 176.6, 165.5, 165.2, 163.5, 140.2, 137.8, 136.2, 135.6, 131.8, 131.1, 130.4, 128.3, 127.8, 124.5, 123.8, 121.3, 53.4, 24.5**. EIMS***m/z* (%): 414 [M^+] (21), 270 (26), 119 (100%), 111 (57), 59 (43). **Anal**. Calcd. for $C_{20}H_{15}ClN_2O_4S$: C, 57.90; H, 3.64; N, 6.75; S, 7.73. found: C, 57.82; H, 3.51; N, 6.65; S, 7.56.

Methyl[4-oxo-2-(4-methybenzoylimino)-3-(3-chlorophenyl)thiazolidin-5-ylidene] acetate



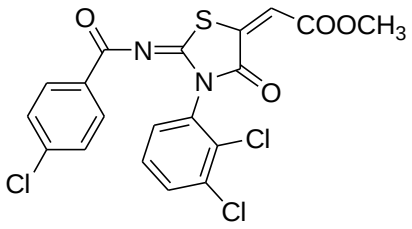
(2g). Yield: 82%; R_f^*: 0.16; m.p. 223-226ºC; **IR**: 2950 (CH_3), 1746, 1738, 1658 (3C=O), 1555 (N=C), 1273 (C–S) cm^{-1}.**^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.81-7.74 (m, 2H, ArH), 7.65-7.59 (m, 3H, ArH), 7.41 (d, 2H, *J* = 7.5 Hz, ArH), 7.34-7.23 (m, 1H, ArH), 7.14 (s, 1H, C=CH-C), 3.93 (OCH_3), 2.61 (CH_3); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 176.6, 165.5, 165.2, 163.6, 140.1, 137.8, 136.4, 135.1, 130.8, 131.1, 130.5, 128.6, 127.9, 124.4, 123.6, 121.7, 53.4, 24.5. **EIMS***m/z* (%): 414 [M^+] (20), 270 (21), 119 (100%), 111 (50), 59 (41). **Anal**. Calcd. for $C_{20}H_{15}ClN_2O_4S$: C, 57.90; H, 3.64; N, 6.75; S, 7.73. found: C, 57.70; H, 3.49; N, 6.85; S, 7.91.

Methyl[4-oxo-2-(2-chlorobenzoylimino)-3-phenyl)thiazolidin-5-ylidene]acetate (2h). Yield:



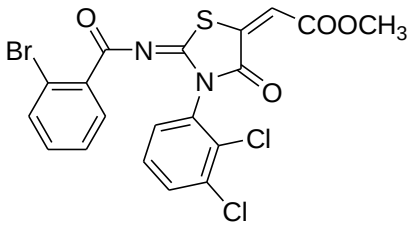
78%; R_f^*: 0.34; m.p. 198-200ºC; **IR**: 2955 (CH_3), 1716, 1702, 1661 (3C=O), 1532 (N=C), 1301 (C–S) cm^{-1}. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.78-7.76 (m, 2H, ArH), 7.69-7.57 (m, 1H, ArH), 7.50-7.42 (m, 2H, ArH), 7.34-7.27 (m, 3H, ArH), 7.26-7.19 (m, 1H, ArH), 7.15 (s, 1H, C=CH-C), 3.90 (OCH_3); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 175.4, 165.0, 164.9, 163.5, 140.1, 136.4, 135.1, 133.7, 132.6, 131.6, 129.6, 127.4, 125.2, 124.9, 122.1, 121.8, 53.1. **EIMS***m/z* (%): 340 [M^+] (21), 138 (100%), 77 (41), 59 (60). **Anal**. Calcd. for $C_{19}H_{13}ClN_2O_4S$: C, 56.93; H, 3.27; N, 6.99; S, 8.00. found: C, 56.81; H, 3.36; N, 6.70; S, 8.16.

Methyl[4-oxo-2-(4-chlorobenzoylimino)-3-(2,3-dichlorophenyl)thiazolidin-5-ylidene]



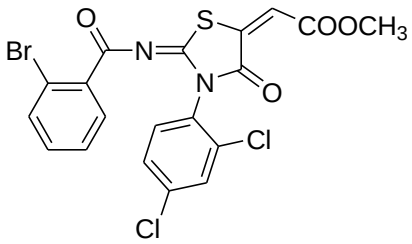
acetate (2i). Yield: 84%; R_f^*: 0.41; m.p. 244-245ºC; **IR**: 2952 (CH_3), 1742, 1709, 1643 (3C=O), 1589 (N=C), 1266 (C–S) cm^{-1}. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.78-7.74 (m, 1H, ArH), 7.67 (d, 2H, *J* = 7.5 Hz, ArH), 7.44-7.36 (m, 3H, ArH), 7.26-7.21 (m, 1H, ArH), 7.13 (s, 1H, C=CH-C), 3.91 (OCH_3); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 175.4, 165.5, 165.0, 163.6, 140.1, 137.8, 133.7, 132.1, 131.5, 130.6, 129.4, 126.9, 126.1, 125.2, 123.6, 122.4, 53.5. **EIMS***m/z* (%): 467 [M^+] (19), 138 (100%), 144 (40). **Anal**. Calcd. for $C_{19}H_{11}Cl_3N_2O_4S$: C, 48.58; H, 2.36; N, 5.96; S, 6.83. found: C, 48.63; H, 2.46; N, 6.04; S, 6.73.

Methyl[4-oxo-2-(2-bromobenzoylimino)-3-(2,3-dichlorophenyl)thiazolidin-5-ylidene]



acetate (2j). Yield: 83%; R_f^*: 0.38; m.p. 179-182ºC; **IR**: 2957 (CH_3), 1741, 1706, 1644(3C=O), 1529 (N=C), 1266 (C–S) cm^{-1}. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.82-7.78 (m, 1H, ArH), 7.68-7.61 (m, 2H, ArH), 7.45-7.40 (m, 1H, ArH), 7.35-7.28 (m, 3H, ArH), 7.14 (s, 1H, C=CH-C), 3.93 (OCH_3);**^{13}C NMR** (75 MHz, $CDCl_3$): δ 176.5, 165.9, 165.3, 163.8, 140.0, 134.8, 134.4, 133.5, 133.2, 132.8, 132.0, 131.6, 130.3, 128.4, 127.9, 127.8, 122.7, 121.6, 53.0. **EIMS***m/z* (%): 514 [M^++2] (14), 367 (15), 144 (41), 182 (100%), 59 (32).**Anal**. Calcd. for $C_{19}H_{11}BrCl_2N_2O_4S$: C, 44.38; H, 2.16; N, 5.45; S, 6.24. found: C, 44.35; H, 2.25; N, 5.58; S, 6.34.

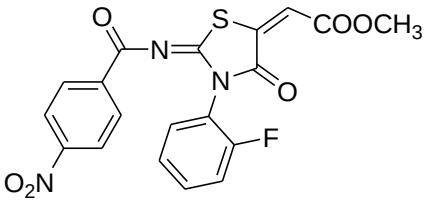
Methyl[4-oxo-2-(2-bromobenzoylimino)-3-(2,4-dichlorophenyl)thiazolidin-5-ylidene] acetae



(2k). Yield: 79%; R_f^*: 0.34; m.p. 200-203ºC; **IR**: 2949 (CH_3), 1741, 1692, 1656 (3C=O), 1538 (N=C), 1255 (C–S) cm^{-1}. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.78-7.76 (m, 2H, ArH), 7.58-7.50 (m, 2H, ArH), 7.45 (s, 1H, ArH), 7.36-7.29 (m, 2H, ArH), 7.14 (s, 1H, C=CH-C), 3.92 (OCH_3); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 176.8, 165.7, 165.5, 163.9, 140.1, 135.7, 134.9, 133.4, 133.1, 132.5, 132.2, 131.5, 131.3, 128.4, 127.2, 127.1, 123.7, 120.6, 53.3.**EIMS***m/z* (%): 514 [M^++2] (14), 144 (30), 182

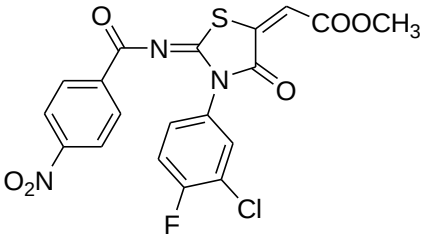
(100%), 72 (10). **Anal**. Calcd. for $C_{19}H_{11}BrCl_2N_2O_4S$: C, 44.38; H, 2.16; N, 5.45; S, 6.24. found: C, 44.40; H, 2.15; N, 5.45; S, 6.22.

Methyl[4-oxo-2-(4-nitrobenzoylimino)-3-(2-fluorophenyl)thiazolidin-5-ylidene] acetate (2l).



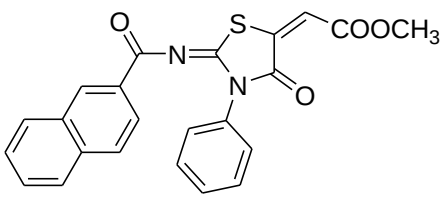
Yield: 76%; R_f^*: 0.28; m.p. 204-206ºC; **IR**: 2950 (CH_3), 1743, 1707, 1660 (3C=O), 1539 (N=C), 1242 (C–S) cm^{-1}. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 8.74 (d, 2H, *J* = 7.5 Hz, ArH), 7.94-7.78 (m, 2H, ArH), 7.41-7.30 (m, 4H, ArH), 7.15 (s, 1H, C=CH-C), 3.93 (OCH_3); **^{13}C NMR** (75 MHz, $CDCl_3$): 179.7, 167.5, 166.6, 164.9, 150.9, 150.4 (d, ^1J = 249.7 Hz, ArC), 148.4, 131.9, 130.5, 129.6, 128.9 (d, ^2J = 22.4 Hz, ArC), 126.7, 124.6 (d, ^3J = 9.1 Hz, C), 124.2, 123.5, 122.0, 53.8.**EIMS***m/z* (%): 429 [M^+] (17), 285 (11), 150 (100%), 95 (68), 59 (29).**Anal**. Calcd. for $C_{19}H_{12}FN_3O_6S$: C, 53.15; H, 2.82; N, 9.79; S, 7.47. found: C, 53.01; H, 2.63; N, 9.61; S, 7.33.

Methyl[4-oxo-2-(4-nitrobenzoylimino)-3-(3-chloro-4-fluorophenyl)thiazolidin-5-ylidene]acetate (2m).



Yield: 74%; R_f^*: 0.44; m.p. 260-262ºC; **IR**: 3064 (CH_3), 1726, 1710, 1662 (3C=O), 1520 (N=C), 1247 (C–S) cm^{-1}. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 8.83 (d, 2H, *J* = 7.5 Hz, ArH), 8.35 (d, 2H, *J* = 7.5 Hz, ArH) 7.98-7.71 (m, 3H, ArH), 7.16 (s, 1H, C=CH-C), 3.91 (OCH_3); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 179.8, 167.7, 166.6, 164.9, 150.8, 149.9 (d, ^1J = 249.7 Hz, ArC), 148.6, 131.9, 130.5 (d, ^2J = 22.4 Hz, ArC), 129.2, 128.7, 126.1, 124.4 (d, ^3J = 9.2 Hz, C), 124.0, 122.5, 122.3, 53.8.**EIMS***m/z* (%): 463 [M^+] (11), 319 (10), 150 (100%), 128 (71), 59 (66). **Anal**. Calcd. for $C_{19}H_{11}ClFN_3O_6S$: C, 49.20; H, 2.39; N, 9.06; S, 6.91. found: C, 49.18; H, 2.30; N, 9.10; S, 6.81.

Methyl[4-oxo-2-(2-naphthoylimino)-3-phenylthiazolidin-5-ylidene]acetate (2n).



Yield: 83%; R_f^*: 0.34; m.p. 211-212ºC; **IR**: 2950 (CH_3), 1737, 1715, 1690 (3C=O), 1531 (N=C), 1271 (C–S) cm^{-1}. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 8.04-8.01 (m, 1H, ArH), 7.83-7.80 (m, 4H, ArH), 7.57-7.53 (m, 2H, ArH), 7.50-7.44 (m, 3H,

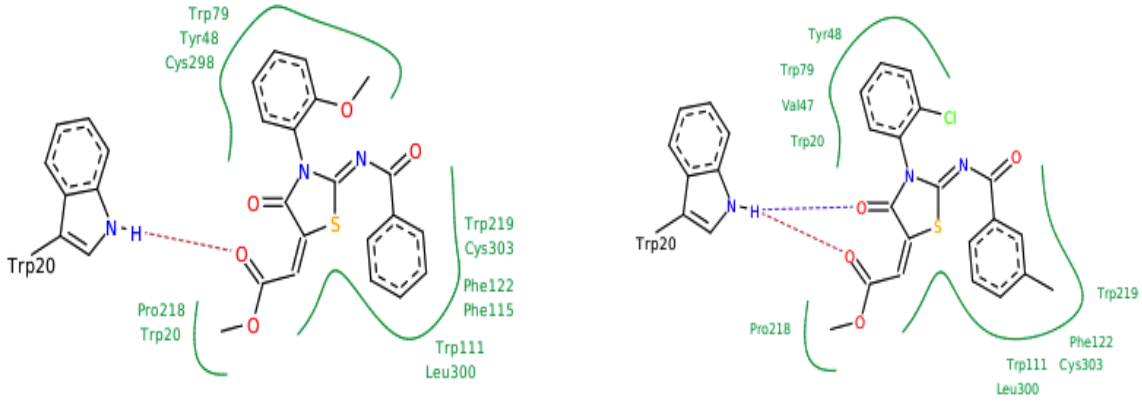
ArH), 7.40-7.34 (m, 2H, ArH), 7.10 (s, 1H, C=CH-C), 3.90 (s, 3H, OCH_3); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 176.6, 165.9, 164.2, 163.8, 140.9, 135.9, 134.5, 133.5, 132.4, 132.2, 132.1, 131.9, 131.0, 130.0, 129.5, 129.0, 128.2, 127.6, 125.2, 120.5, 53.4.**EIMS***m/z* (%): 416 [M^+] (21), 155 (100%), 127 (84), 77 (64), 29 (47), **Anal**. Calcd. for $C_{23}H_{16}N_2O_4S$: C, 66.33; H, 3.87; N, 6.73; S, 7.70. found: C, 66.30; H, 3.89; N, 6.75; S, 7.75.

*(Petroleum ether : Ethyl acetate, 4:1)

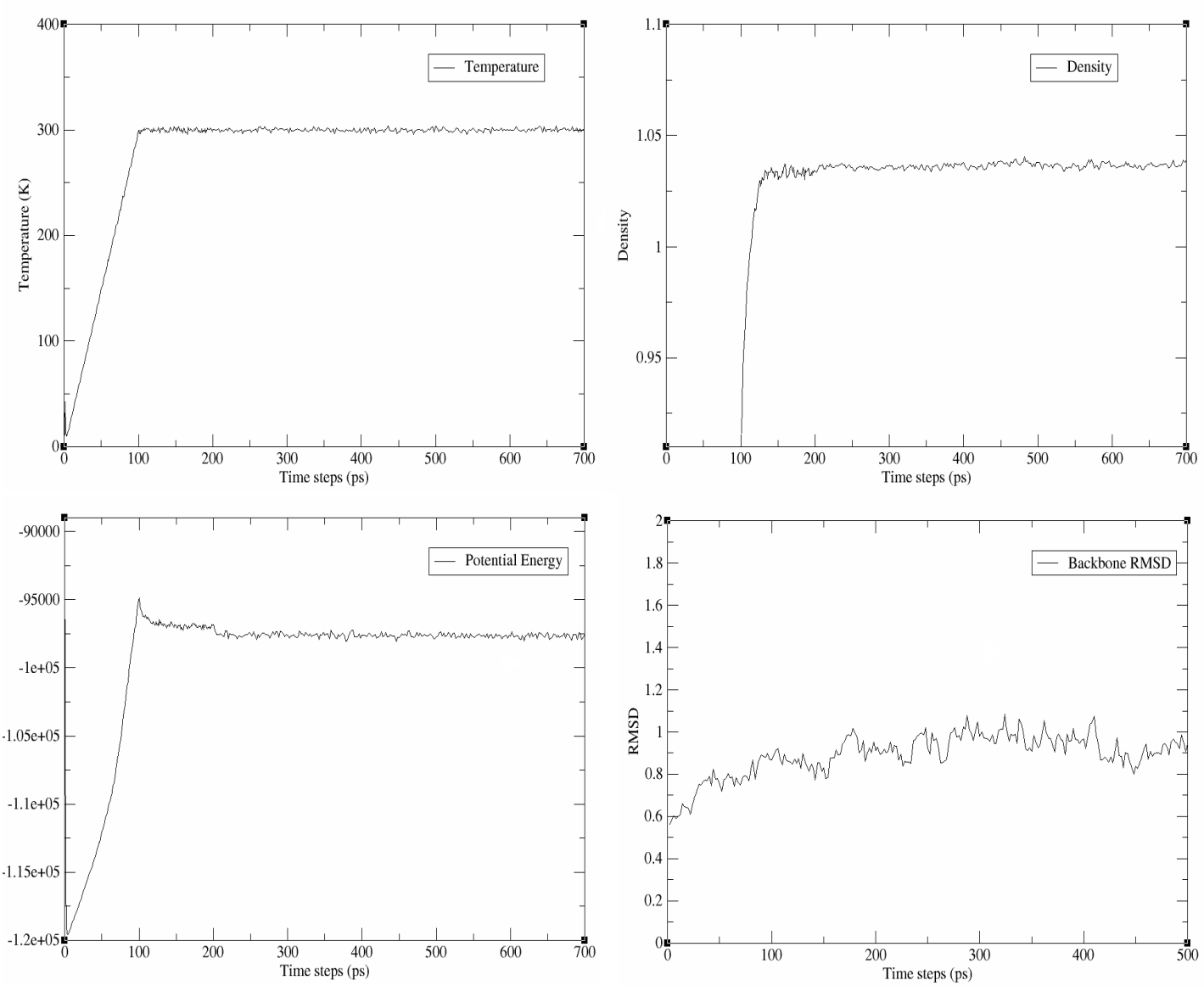
2. Table S1 Physical data of methyl[4-oxo-2-(aroylimino)-3-(substituted phenyl)thiazolidin-5-ylidene]acetates

Comp	R_1	R_2	Yield (%)	R_f[a]	m.p °C
2a	C_6H_5	*o*-OCH_3-C_6H_4	84	0.22	121-123
2b	C_6H_5	1-Naphthyl	81	0.23	224-246
2c	*o*-CH_3- C_6H_4	*m*-OCH_3-C_6H_4	79	0.34	204-206
2d	*m*-CH_3-C_6H_4	C_6H_5	86	0.45	202-203
2e	*m*-CH_3-C_6H_4	*o*-OCH_3-C_6H_4	82	0.28	160-161
2f	*m*-CH_3-C_6H_4	*m*-Cl-C_6H_4	81	0.35	193-195
2g	*p*-CH_3-C_6H_4	*m*-Cl-C_6H_4	82	0.16	223-226
2h	*o*-Cl-C_6H_4	C_6H_5	78	0.34	198-200
2i	*p*-Cl-C_6H_4	*o,m*-di-Cl-C_6H_3	84	0.41	244-245
2j	*o*-Br-C_6H_4	*o,m*-di-Cl-C_6H_3	83	0.38	179-182
2k	*o*-Br-C_6H_4	*o,p*-di-Cl-C_6H_3	79	0.34	200-203
2l	*p*-NO_2-C_6H_4	*o*-F-C_6H_4	76	0.28	204-206
2m	*p*-NO_2-C_6H_4	*m*-Cl, *p*-F-C_6H_3	74	0.44	260-262
2n	2-naphthyl	C_6H_5	83	0.34	211-212

[a](Petroleum ether : acetone) = 4:1

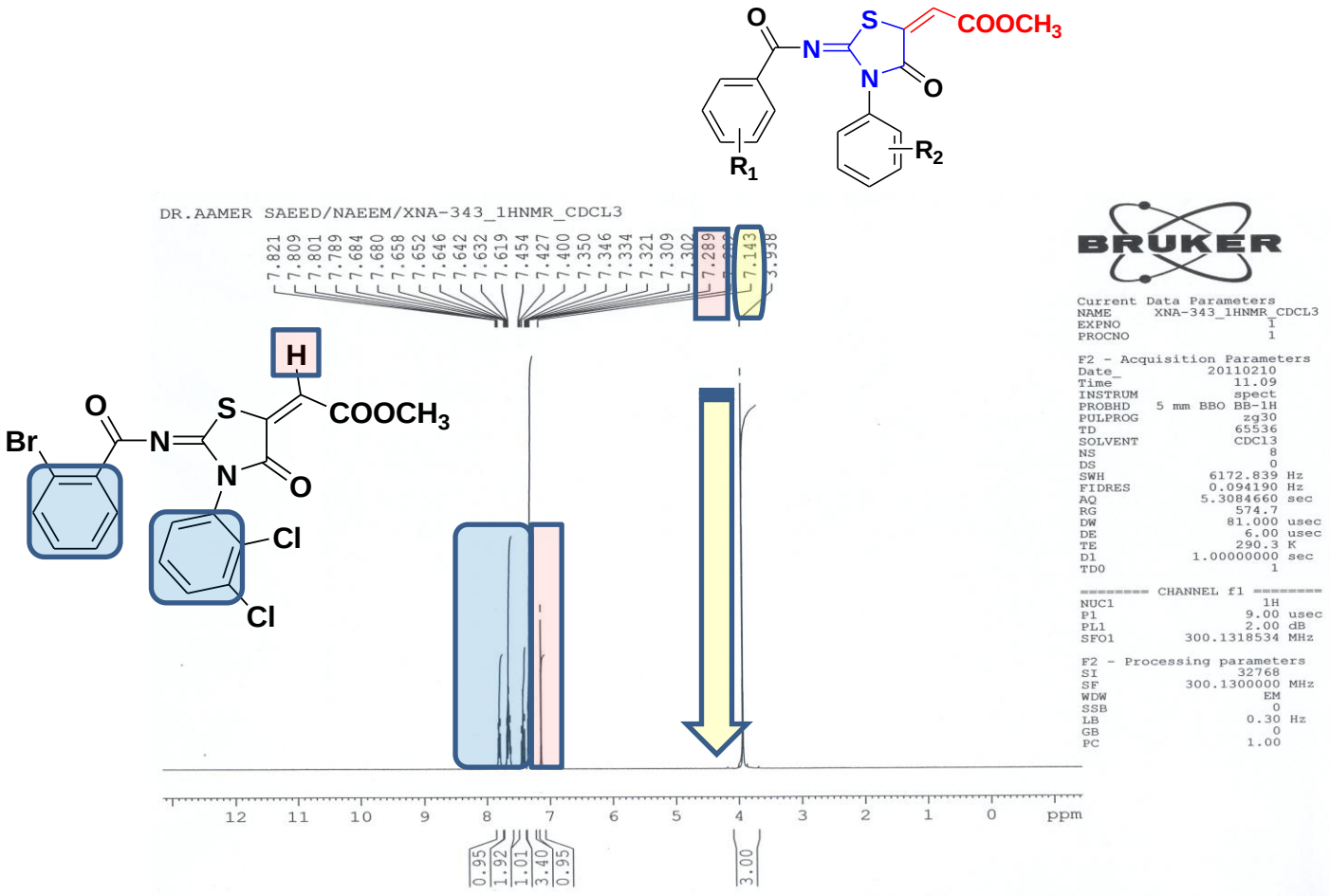


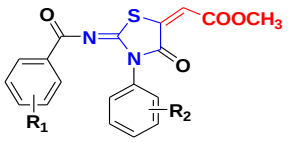
3. Figure S1 Interaction diagrams of compounds **2a** (left) and **2f** (right). The dotted lines indicate hydrogen-bonding interactions with the side-chain of Trp20. The green lines surrounding the aromatic rings of the compounds show the list of hydrophobic interacting residues of the active site pocket of the enzyme.

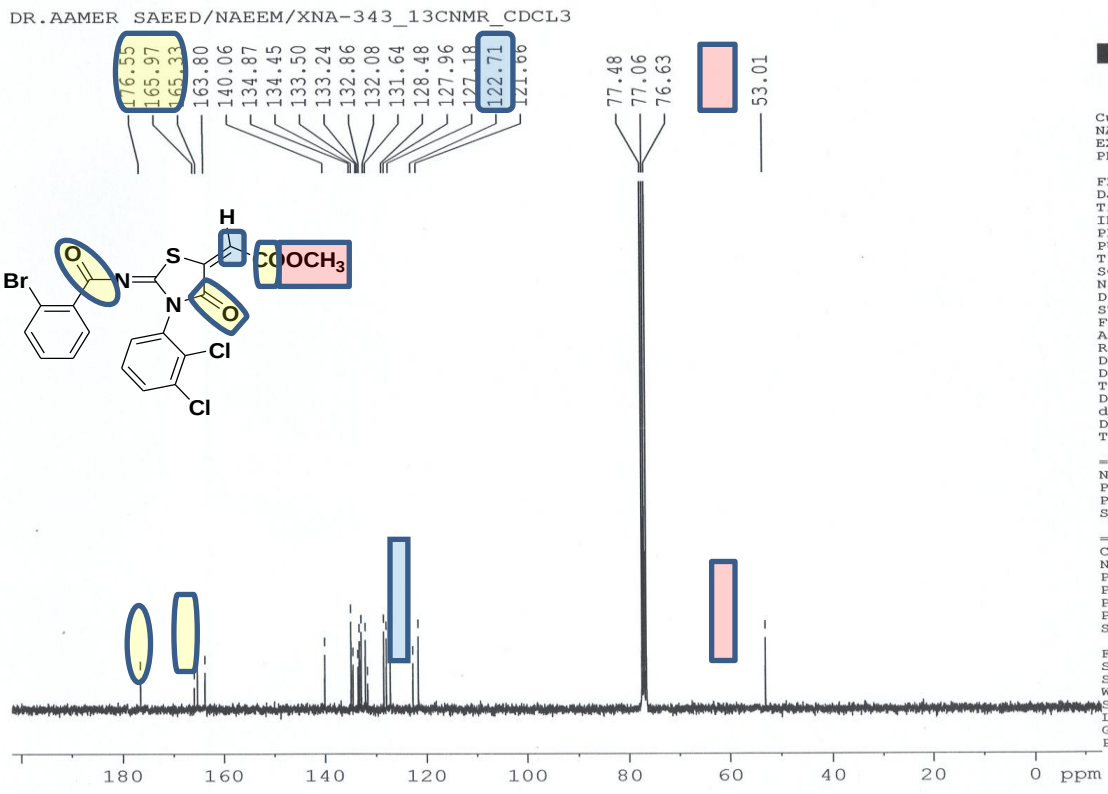


4. **Figure S2** Equilibration steps showing density, temperature, potential energy and backbone RMSD plots of the equilibrated complex.

5. NMR of representative compounds







BRUKER

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PROCNO                           1

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PULPROG                   zgpg30
TD                         65536
SOLVENT                    CDCl3
NS                           861
DS                             0
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FIDRES                0.274439 Hz
AQ                    1.8219508 sec
RG                        18390.4
DW                       27.800 usec
DE                        6.00 usec
TE                       290.0 K
D1                    2.00000000 sec
d11                   0.03000000 sec
DELTA                 1.89999998 sec
TD0                              1

========== CHANNEL f1 ==========
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P1                         6.00 usec
PL1                       -5.00 dB
SFO1                 75.4752953 MHz

========== CHANNEL f2 ==========
CPDPRG2                  waltz16
NUC2                          1H
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PL2                        2.00 dB
PL12                      20.98 dB
PL13                      20.00 dB
SFO2                300.1312005 MHz

F2 - Processing parameters
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GB                               0
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