Tetrahedron 65 (2009) 344–350

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Three-component one-pot synthetic route to 2-amino-5-alkylidene-thiazol-4-ones

Marko Anderluh *, Marko Jukič, Rok Petrič

University of Ljubljana, Department of Medicinal Chemistry, Faculty of Pharmacy, Aškerčeva 7, 1000 Ljubljana, Slovenia

ARTICLE INFO

Article history:
Received 3 June 2008
Received in revised form 1 October 2008
Accepted 16 October 2008
Available online 1 November 2008

Keywords:
2-Amino-5-alkylidene-thiazol-4-one
Rhodanine
Knoevenagel condensation
Multi-component reaction
Parallel synthesis
Microwave-assisted organic synthesis

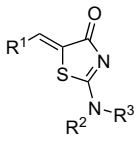
ABSTRACT

A fast and straightforward three-component reaction to 2-amino-5-alkylidene-thiazol-4-ones is described. The one-pot methodology, reported for the first time, involves Knoevenagel condensation of aromatic aldehydes and rhodanine followed by displacement of the thiocarbonyl sulfur with primary or secondary amines in the same reaction mixture. The reactions were performed using a dedicated microwave reactor, which enabled short reaction times and easy work-up.

1. Introduction

Thiazolidinone derivatives have been extensively used in drug discovery.[1] In particular, the biological activities of various 2-amino-5-alkylidene-thiazol-4-ones (**1**, Fig. 1) have been reported in approximately 150 publications, including 80 patents.[2] Not surprisingly, numerous synthetic routes have been developed in order to obtain this heterocyclic core, many of which were recently reviewed.[2]

These procedures involve cyclocondensations from acyclic precursors, and step-wise functionalization of thiazolones or, most conveniently, from rhodanine (**2**). We were particularly interested in synthesis from the latter, where three routes are possible (Fig. 2).



1

Figure 1. 2-Amino-5-alkylidene-thiazol-4-one core.

In the first route the rhodanine thiocarbonyl sulfur is substituted with the amine, either immediately (**3**, Route 1) or after activation via alkyl thioether (**4**, Route 2), the resulting aminothiazolone being condensed with aldehyde via Knoevenagel condensation.[2,3]

Alternatively, rhodanine is first condensed with an aldehyde and the resulting alkylidene rhodanine (**5**) reacted with an amine (Route 3).[3a–c,4] These two procedures involve at least two subsequent steps with lengthy reaction times and sometimes laborious work-up, which is hardly convenient for a parallel synthesis. This was partly overcome by Pulici et al. by a traceless two-step solid-phase synthesis that, however, requires a rather expensive solid support and still suffers from lengthy reaction times.[2] During the course of our work, Bourahla et al. reported a quite attractive microwave-assisted synthesis of 2-amino-5-alkylidene-thiazol-4-ones, which, however, comprises a rather complicated sequence of reaction steps.[4d]

We are interested in the inhibition of the enzymes involved in peptidoglycan biosynthesis (see Acknowledgements). The title compounds and their derivatives have already been reported to inhibit bacterial growth and/or enzymes involved in this process.[1b,5–7] To produce a library of 2-amino-5-alkylidene-thiazol-4-ones for subsequent screening, we sought a rapid and convenient synthetic route toward 2-amino-5-alkylidene-thiazol-4-ones. As noted above, none of the previously reported methods appeared to meet our requirements.

We have therefore developed a novel, fast, and straightforward three-component reaction to 2-amino-5-alkylidene-thiazol-4-ones

* Corresponding author. Tel.: +386 1 47 69 639; fax: +386 1 42 58 031.
E-mail address: marko.anderluh@ffa.uni-lj.si (M. Anderluh).

0040-4020/$ – see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2008.10.045

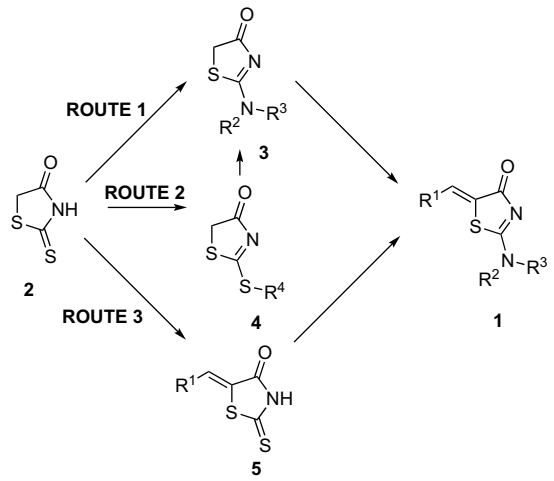
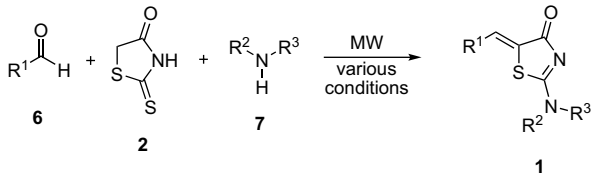


Figure 2. 2-Amino-5-alkylidene-thiazol-4-one synthesis starting from rhodanine.

(Scheme 1). The one-pot methodology involves Knoevenagel condensation of aromatic aldehyde (**6**) and rhodanine (**2**) followed by displacement of the thiocarbonyl sulfur with primary or secondary amines (**7**) in the same reaction mixture. The amine acts as the catalyst in the Knoevenagel condensation and as a nucleophile in the second step. The reactions were performed using a dedicated microwave reactor, which enabled short reaction times and easy work-up, as well as conventional heating. Such a synthesis has not been published before.



Scheme 1. One-pot 2-amino-5-alkylidene-thiazol-4-one microwave-assisted synthesis.

2. Results and discussion

The one-pot synthesis (Scheme 1) was optimized on a model reaction involving benzaldehyde (**6a**), rhodanine (**2**), and piperidine (**7a**) under a variety of conditions (Table 1). The reaction was first tried with a large excess (2 equiv) of benzaldehyde in the microwave reactor for 45 min at various temperatures. Knoevenagel condensation proceeded quantitatively in a few minutes, as concluded from the ^{1}H NMR spectra of the precipitate formed after a few minutes in the reaction mixture at room temperature (data not included). This led us to conclude that the first step of the reaction is a Knoevenagel condensation followed by addition of the amine. The one-pot reaction was sufficiently robust to withstand high temperatures (up to 150 °C). As expected, higher temperatures led to higher yields. Interestingly, microwave heating for 45 min at 80 °C led to far higher yield than the conventional heating for the same time at temperature of reflux (approx. 80 °C), and practically the same yield was obtained only after 5 h. This may be explained by the specific non-thermal microwave effect, which could accelerate thiocarbonyl sulfur displacement.[8,9] Thus, the addition–elimination mechanism proceeds via the bipolar intermediate, which could selectively absorb microwaves by dielectric heating.

Decreasing the reaction time to 20 min had no influence on the yield, but after 10 min the conversion was incomplete. The reaction time was thus reduced to only 20 min. It may be concluded that the large excess of piperidine that acts as a catalyst in the Knoevenagel condensation leads to significant reduction of time compared to the previously reported methods.[2,3a–c,4] The maximum yield obtained by this protocol (**8e**) was 83%, but other yields were significantly lower in some cases. We might speculate that the low yields are also due to the precipitation method of isolation.

The choice of the solvent had a crucial effect on the yield and ethanol was chosen as the best of those used. However, it should be noted that the yields relate to the products crystallized from the reaction mixture and the lower yield may be simply due to higher solubility of the compounds in some solvents. Interesting yields were obtained under solvent-free conditions, but the products obtained were proven, by ^{1}H NMR, not to be sufficiently pure. Since this solvent-free procedure required additional crystallization, it was concluded that the use of small quantities of solvent is necessary to obtain pure compounds and that the reaction conditions of the entry 5 (Table 1) are optimal. In this manner, the work-up was optimized to a single step of filtration.

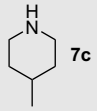
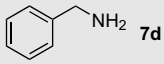
Reagent quantities were optimized (Table 2). Surprisingly, the larger excess of piperidine (2 molar equivalents) was detrimental to the yield, as was also observed with the other amines. In contrast, the same excess of the aldehyde led to higher yields. The latter could be explained by a competitive Cannizzaro reaction, a typical reaction for aromatic aldehydes in the basic media that yields aromatic acids and consumes aldehydes in the reaction mixture.[10] Another possible cause could be the oxidation of aromatic adehydes to their corresponding acids. Both were shown to be possible, proven by ^{1}H NMR and also by mass spectra of the crude product

Table 1
Optimization of the model one-pot synthesis with benzaldehyde (**6a**) and piperidine (**7a**) under different conditions according to the general procedure in Section 4.2.1

Entry	**7a** (equiv)	**6a** (equiv)	Heating conditions	Solvent	Reaction time	Temperature (°C)	Yield %[a]
1	1.1	2.0	MW	EtOH	45 min	80	61
2	1.1	2.0	MW	EtOH	45 min	100	69
3	1.1	2.0	MW	EtOH	45 min	120	73
4	1.1	2.0	MW	EtOH	45 min	150	79
5	1.1	2.0	MW	EtOH	20 min	150	83
6	1.1	2.0	MW	EtOH	10 min	150	73
7	1.1	2.0	Conventional heating	EtOH	45 min	Reflux	21
8	1.1	2.0	Conventional heating	EtOH	5 h	Reflux	66
9	1.1	1.2	MW	EtOH	20 min	150	23
10	2.0	1.1	MW	EtOH	20 min	150	24
11	1.1	2.0	MW	AcOH	20 min	150	25
12	1.1	2.0	MW	THF	20 min	150	67
13[b]	1.1	2.0	MW	—	20 min	150	52
14[b]	2.0	1.1	MW	—	20 min	150	92

[a] Yields relate to the products crystallized from the solvents in the reaction mixture and are calculated relative to the effective loading of rhodanine.
[b] Yields relate to crude compounds.

Table 2
One-pot synthesis via Scheme 1 according to the optimized procedure in Section 4.2.2 with benzaldehyde (**6a**) and different amines

Entry	Amine	Amine equivalents	**6a** (equiv)	Yield %[a]
1	 **7a**	1.1	2.0	83
2		2.0	1.1	24
3		1.1	1.2	23
4	 **7b**	1.1	2.0	55
5		2.0	1.1	27
6		1.1	1.2	61
7	 **7c**	1.1	2.0	56
8		2.0	1.1	14
9		1.1	1.2	37
10	 **7d**	1.1	2.0	41
11		2.0	1.1	11
12		1.1	1.2	27

[a] Yields relate to the products crystallized from the solvents in the reaction mixture and are calculated relative to the effective loading of rhodanine.

(Table 1, entry 13), which showed the characteristic peak for benzoic acid (m/z 122 M^+).

Further reactions were performed according to the optimized conditions (Table 1, entry 5) with a variety of amines and aromatic aldehydes. Thus we obtained a focused library of 2-amino-5-alkylidene-thiazol-4-ones (Table 3). The described protocol worked well with the majority of the substrates. In only one case (**15**) was flash chromatography necessary to obtain pure product.

The described synthesis could lead to two isomers, *E* and *Z*. In all cases, the ^{1}H NMR spectra revealed only one type of methine proton at 7.55–7.93 ppm, at lower field values than those expected for the *E*-isomers.[5] Thus we may conclude that the Knoevenagel condensation proceeds in a completely regioselective way to give the thermodynamically more stable *Z*-isomer, as noted.[2,4d,5]

3. Conclusion

This paper describes for the first time a one-pot, three-component reaction to 2-amino-5-alkylidene-thiazol-4-ones, involving conventional heating or microwave irradiation. The one-pot methodology was proved to work well with different amines and aromatic aldehydes and has numerous advantages over the previously reported methods: a robust reaction that withstands high temperatures that significantly shorten reaction times, easy work-up (reactions and work-up performed in one vial, simple filtration to obtain pure products), no solid support is needed, and reactions performed well even in solvent-free conditions (shown in a model reaction). The protocol is thus particularly useful for parallel synthesis with automated microwave synthesis systems. By its use, a wide variety of target compounds could be reached in a matter of days.

4. Experimental

4.1. General methods and materials

Chemicals from Aldrich Chemical Co., Fluka, and Acros Organics were used without further purification. Analytical TLC was performed on Merck silica gel (60 GF_{254}) plates (0.25 mm) and components were visualized with ultraviolet light (254 nm wavelength) and ninhydrin charring. Flash column chromatography was carried out on Merck silica gel 60 (particle size 0.040–0.063 mm). Melting points were determined on a Reichert hot stage microscope and are uncorrected. ^{1}H NMR spectra were recorded on a Bruker AVANCE DPX300 spectrometer in $CDCl_3$ or DMSO-d_6 solution with TMS as the internal standard. Coupling constants (J) are given in hertz. IR spectra were obtained on a Perkin–Elmer 1600 FT-IR spectrometer. Mass spectra were obtained using a VG-Analytical Autospec Q mass spectrometer.

Microwave-assisted reactions were performed using a focused microwave reactor (Discover™, CEM Corporation, Matthews, NC). The reactor uses a continuous, focused microwave power-delivery system with an operator-selectable power output of up to 300 W. Reactions were performed in glass vials (10 mL) sealed with a septum. The pressure was monitored by a load cell connected to the septum. The temperature of the reaction mixture was monitored using a calibrated infrared temperature controller mounted under the reaction vessel.

4.2. Synthesis

4.2.1. General procedure for microwave-assisted synthesis of 2-amino-5-alkylidene-thiazol-4-ones

To a suspension of rhodanine (1.0 equiv) in dry solvent (3 mL), aldehyde (1.1–2.0 equiv), amine (1.1–2.0 equiv), and glacial acetic acid (0.1 equiv) were added. The reactions were also performed under solvent-free conditions. The reaction mixture was stirred for half a minute in order to prevent aggregation of solid substances and then heated with microwave irradiation (20 W of max. power) to the desired temperature. The pressure limit was set at 20 bar. Once the desired temperature was reached, heating was continued for a further period (Table 1) to maintain the temperature. The reaction vessel was then cooled in an ice bath, the precipitated crystalline solid was filtered off, washed with ice-cooled solvent, and dried under vacuum. If performed under solvent-free conditions, additional recrystallization was needed to obtain pure product.

4.2.2. The optimized procedure for microwave-assisted synthesis of 2-amino-5-alkylidene-thiazol-4-ones

To a suspension of rhodanine (0.500 g, 3.75 mmol, 1.0 equiv) in dry ethanol (3 mL), aldehyde (7.50 mmol, 2.0 equiv), amine (4.13 mmol, 1.1 equiv), and glacial acetic acid (21 μL, 0.375 mmol, 0.1 equiv) were added. The reaction mixture was stirred before heating for half a minute and then heated with microwave irradiation (20 W of max. power) to reach 150 °C, the rate not exceeding 2 °C/s. The pressure limit was set to 20 bar, since H_2S developed during the reaction. Once the desired temperature was reached, the mixture was heated for a further 20 min at the same temperature. The reaction vessel was then cooled in an ice bath, the precipitated crystalline solid was filtered off, washed with ice-cooled ethanol, and dried under vacuum.

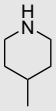
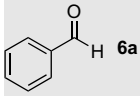
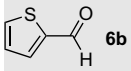
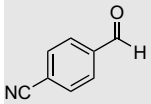
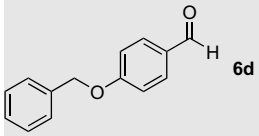
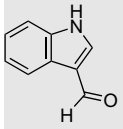
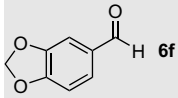
4.2.3. The reaction performed using conventional heating

To a suspension of rhodanine (0.500 g, 3.75 mmol, 1.0 equiv) in dry ethanol (3 mL), benzaldehyde (1.042 mL, 7.50 mmol, 2.0 equiv), piperidine (0.408 mL, 4.13 mmol, 1.1 equiv), and glacial acetic acid (21 μL, 0.375 mmol, 0.1 equiv) were added. The reaction mixture was stirred under reflux in an oil bath for 5 h. The reaction vessel was then cooled in an ice bath, the precipitated crystalline solid was filtered off, washed with ice-cooled ethanol, and dried under vacuum.

4.3. Analytical and spectroscopic data of the products

All compounds included were synthesized according to the optimized procedure for microwave-assisted synthesis of 2-amino-5-alkylidene-thiazol-4-ones (see Section 4.2.2).

Table 3
The one-pot synthesis via Scheme 1 according to the optimized procedure in Section 4.2.2

Compound, yield %[a]	 **7a**	 **7b**	 **7c**	 **7d**	 **7e**
 **6a**	**8**, 83%	**9**, 55%	**10**, 56%	**11**, 41%	**12**, 68%
 **6b**	**13**, 53%	**14**, 57%	**15**,[b] 37%	**16**, 55%	**17**, 81%
 **6c**	**18**, 64%	**19**, 70%	**20**, 62%	**21**, 53%	**22**, 99%
 **6d**	**23**, 56%	**24**, 80%	**25**, 63%	**26**, 57%	**27**, 95%
 **6e**	**28**, 90%	**29**, 89%	**30**, 80%	**31**, 57%	**32**, 96%
 **6f**	**33**, 94%	**34**, 82%	**35**, 70%	**36**, 66%	**37**, 88%

[a] Yields relate to the products crystallized from the solvents in the reaction mixture (except **15**) and are calculated relative to the effective loading of **2**.
[b] The pure compound was obtained after purification with flash chromatography.

4.3.1. 5-Benzylidene-2-(piperidin-1-yl)thiazol-4(5H)-one (**8**)[2]

Yellow crystalline solid (0.849 g, 83% yield). Mp=213–215 °C. IR ν_{max} (KBr): 2939, 1700, 1673, 1612, 1560 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ=1.78 (6H, br s, $-CH_2-CH_2-CH_2-$), 3.60 (2H, br s, $-CH_{ax}H_{eq}-N-CH_{ax}H_{eq}-$), 4.03–4.06 (2H, m, $-CH_{ax}H_{eq}-N-CH_{ax}H_{eq}-$), 7.39–7.49 (3H, m, CH_{Ar}), 7.56 (dd, 2H, dd, J=1.2, 8.3 Hz, CH_{Ar}), 7.82 (1H, s, CH) ppm. MS (ESI): m/z 273 (MH^+, 100). HRMS (ESI): calcd for $C_{15}H_{17}N_2OS$ 273.1062, found 273.1056.

4.3.2. 5-Benzylidene-2-morpholinothiazol-4(5H)-one (**9**)[11]

Yellow crystalline solid (0.571 g, 55%). Mp=194–195 °C. IR ν_{max} (KBr): 3049, 2856, 1630, 1589 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ=3.09 (4H, t, J=4.7 Hz, CH_2-N-CH_2), 3.82 (4H, t, J=4.7 Hz, CH_2-O-CH_2), 7.48–7.50 (5H, m, CH_{Ar}), 7.60 (1H, s, CH) ppm. MS (EI): m/z 274 (M^+, 13%), 134 (100). HRMS (EI): calcd for $C_{14}H_{14}N_2O_2S$ 274.077600, found 274.078250.

4.3.3. 5-Benzylidene-2-(4-methylpiperidin-1-yl)thiazol-4(5H)-one (**10**)

Light yellow crystalline solid (0.598 g, 56%). Mp=171 °C. IR ν_{max} (KBr): 2933, 2364, 1677, 1607, 1577, 1560 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ=0.95 (3H, d, J=6.3 Hz, CH_3), 1.12–1.29 (2H, m, CH_2), 1.75–1.85 (3H, m, $CH_2-CH-CH_3$), 3.25 (1H, dt, J=2.7, 13.5 Hz, $N-CH_{ax2}H_{eq2}$), 3.45 (1H, dt, J=2.1, 13.5 Hz, $N-CH_{ax1}H_{eq1}$), 3.80 (1H, br d, J=13.5 Hz, $N-CH_{ax2}H_{eq2}$), 4.60 (1H, br d, J=13.5 Hz, $-N-CH_{ax1}H_{eq1}$), 7.44–7.55 (3H, m, CH_{Ar}), 7.63 (1H, s, CH), 7.62–7.65 (2H, m, $2CH_{Ar}$) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ=22.0, 30.7, 33.9, 34.5, 49.2, 50.0, 129.7, 130.4, 130.5, 134.8, 174.2, 180.2 ppm. MS (EI): m/z 286 (M^+, 73%), 134 (100). HRMS (ESI): calcd for $C_{16}H_{19}N_2OS$ 287.1218, found 287.1222.

4.3.4. 2-(Benzylamino)-5-benzylidenethiazol-4(5H)-one (**11**)[2,11]

Pale yellow crystalline solid (0.449 g, 41%). Mp=236–237 °C. IR ν_{max} (KBr): 3207, 3012, 2363, 1674, 1622, 1492 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ=4.75 (2H, d, J=5.6 Hz, CH_2NH), 7.29–7.64 (11H, m, CH_{Ar}, CH), 10.08 (1H, t, J=5.6 Hz, NH) ppm. MS (ESI) m/z 295 (MH^+). HRMS (ESI) calcd for $C_{17}H_{15}N_2OS$ 295.0905, found 295.0908.

4.3.5. 5-Benzylidene-2-(pyrrolidin-1-yl)thiazol-4(5H)-one (**12**)[12]

Yellow crystalline solid (0.661 g, 68%). Mp=219–220 °C. IR ν_{max} (KBr): 2361, 1682, 1616, 1558 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ=1.96–2.06 (4H, m, $-CH_2-CH_2-$), 3.63 (2H, t, J=6.5 Hz, $-CH'H''-N-CH'H''-$), 3.71 (2H, t, J=6.5 Hz, $-CH'H''-N-CH'H''-$), 7.42–7.54 (3H, m, CH_{Ar}), 7.61–7.64 (3H, m, CH_{Ar}, CH) ppm. MS (ESI): m/z 259 (MH^+, 100). HRMS (ESI): calcd for $C_{14}H_{15}N_2OS$ 259.0905, found 259.0910.

4.3.6. 2-(Piperidin-1-yl)-5-((thiophen-2-yl)methylene)thiazol-4(5H)-one (**13**)[13]

Yellow-green crystalline solid (0.551 g, 53%). Mp=203 °C. IR ν_{max} (KBr): 3015, 2938, 2861, 1718, 1700, 1670, 1606, 1560 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ=1.63–1.68 (6H, m, $-CH_2-CH_2-CH_2-$), 3.61

(2H, s, –C*H*$_{ax}$H$_{eq}$–N–C*H*$_{ax}$H$_{eq}$–), 3.88–3.92 (2H, m, –CH$_{ax}$*H*$_{eq}$–N–CH$_{ax}$*H*$_{eq}$–), 7.26 (1H, dd, *J*=1.2, 3.9 Hz, CH$_{Ar}$), 7.59 (1H, d, *J*=3.3 Hz, CH$_{Ar}$), 7.85 (1H, s, CH), 7.90 (1H, d, *J*=5.1 Hz, CH$_{Ar}$) ppm. MS (ESI): *m*/*z* 279 (MH$^+$, 100). HRMS (ESI): calcd for $C_{13}H_{18}N_2OS_2$ 279.0626, found 279.0630.

4.3.7. 2-Morpholino-5-((thiophen-2-yl)methylene)thiazol-4(5H)-one (**14**)[13]

Dark yellow crystalline solid (0.599 g, 57%). Mp=193 °C. IR ν_{max} (KBr): 3014, 2857, 1700, 1672, 1602, 1559 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6): δ=3.60 (2H, t, *J*=4.7 Hz, C*H*$_{ax}$H$_{eq}$–N–C*H*$_{ax}$H$_{eq}$), 3.71–3.78 (4H, m, CH$_2$–O–CH$_2$), 3.90 (2H, t, *J*=4.7 Hz, –CH$_{ax}$*H*$_{eq}$–N–CH$_{ax}$*H*$_{eq}$–), 7.26 (1H, dd, *J*=3.6, 5.1 Hz, CH$_{Ar}$), 7.60 (1H, AA′, *J*=3.6 Hz, CH$_{Ar}$), 7.88 (1H, s, CH), 7.91 (1H, BB′, *J*=5.1 Hz, CH$_{Ar}$) ppm. MS (EI): *m*/*z* 280 (M$^+$, 40%), 140 (100). HRMS (EI): calcd for $C_{12}H_{12}N_2O_2S_2$ 280.034021, found 280.035000.

4.3.8. 2-(4-Methylpiperidin-1-yl)-5-((thiophen-2-yl)methylene)thiazol-4(5H)-one (**15**)

Yellow solid (0.402 g, 37%). Mp=164–166 °C. IR ν_{max} (KBr): 2951, 2360, 1677, 1602, 1570 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6): δ=0.94 (3H, d, *J*=6.0 Hz, CH$_3$), 1.12–1.29 (2H, m, –CH$_2$–), 1.74–1.89 (3H, m, CH$_2$–CH–), 3.24 (1H, br t, *J*=12.3 Hz, –N–C*H*$_{ax2}$H$_{eq2}$–), 3.44 (1H, br t, *J*=12.6, –N–C*H*$_{ax1}$H$_{eq1}$), 3.78 (1H, br d, *J*=12.5 Hz, –N–CH$_{ax2}$*H*$_{eq2}$), 4.56 (1H, br d, *J*=12.5 Hz, –N–CH$_{ax1}$*H*$_{eq1}$–), 7.24–7.27 (1H, m, CH$_{Ar}$), 7.59 (1H, d, *J*=2.4 Hz, CH$_{Ar}$), 7.85 (1H, s, CH), 7.89 (1H, d, *J*=4.8 Hz, CH$_{Ar}$) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ=22.0, 30.7, 33.9, 34.5, 49.2, 50.0, 123.5, 127.9, 129.7, 131.9, 133.7, 139.5, 173.2, 179.9 ppm. MS (ESI): *m*/*z* 293 (MH$^+$). HRMS (ESI): calcd for $C_{14}H_{16}N_2OS_2$ 293.0782, found 293.0791.

4.3.9. 2-(Benzylamino)-5-((thiophen-2-yl)methylene)thiazol-4(5H)-one (**16**)

Yellow-green crystalline solid (0.449 g, 55%). Mp=195–196 °C. IR ν_{max} (KBr): 2365, 1684, 1616, 1589 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6): δ=4.74 (2H, d, *J*=5.9 Hz, *CH*$_2$NH), 7.24–7.27 (1H, m, CH$_{Ar}$), 7.29–7.39 (5H, m, CH$_{Ar}$), 7.57 (1H, d, *J*=3.6 Hz, CH$_{Ar}$), 7.85 (1H, s, CH), 7.89 (1H, d, *J*=4.8 Hz, CH$_{Ar}$), 10.04 (1H, t, *J*=5.9 Hz, NH) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ=48.7, 123.3, 127.9, 128.3, 128.5, 128.6, 129.5, 129.5, 129.7, 131.9, 133.7, 138.0, 139.7, 173.7, 180.2 ppm. MS (ESI): *m*/*z* 301 (MH$^+$, 100). HRMS (ESI): calcd for $C_{15}H_{12}N_2OS_2$ 301.0469, found 301.0475.

4.3.10. 2-(Pyrrolidin-1-yl)-5-((thiophen-2-yl)methylene)thiazol-4(5H)-one (**17**)

Red crystalline solid (0.799 g, 81%). Mp=184–186 °C. IR ν_{max} (KBr): 3062, 1682, 1603, 1560 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6): δ=1.96–2.06 (4H, m, –CH$_2$–CH$_2$–), 3.63 (2H, t, *J*=6.3 Hz, –C*H*′H″–N–C*H*′H″–), 3.70 (2H, t, *J*=6.6 Hz, –CH′*H*″–N–CH′*H*″–), 7.24–7.27 (1H, m, CH$_{Ar}$), 7.58 (1H, d, *J*=3.6 Hz, CH$_{Ar}$), 7.84 (1H, s, CH), 7.89 (1H, d, *J*=5.1 Hz, CH$_{Ar}$) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ=25.4, 25.6, 49.7, 51.5, 123.6, 128.1, 131.9, 133.8, 139.5, 171.0, 179.3 ppm. MS (ESI) *m*/*z* 265 (MH$^+$, 100). HRMS (ESI): calcd for $C_{12}H_{13}N_2OS_2$ 265.0469, found 265.0470.

4.3.11. 4-((4-Oxo-2-(piperidin-1-yl)thiazol-5(4H)-ylidene)-methyl)benzonitrile (**18**)

Yellow crystalline solid (0.717 g, 64% yield). Mp=192 °C. IR ν_{max} (KBr): 2929, 2219, 1687, 1560 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6): δ=1.68 (6H, br s, –CH$_2$–CH$_2$–CH$_2$–), 3.64 (2H, br s, –C*H*$_{ax}$H$_{eq}$–N–C*H*$_{ax}$H$_{eq}$–), 3.91–3.94 (2H, m, –CH$_{ax}$*H*$_{eq}$–N–CH$_{ax}$*H*$_{eq}$–), 7.68 (1H, s, CH), 7.81 (2H, AA′, *J*=8.4 Hz, CH$_{Ar}$), 7.96 (2H, BB′, *J*=8.4 Hz, CH$_{Ar}$) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ=24.2, 26.0, 26.6, 50.3, 50.9, 112.2, 119.4, 128.3, 130.8, 133.2, 133.7, 139.4, 173.8, 179.8 ppm. MS (ESI): *m*/*z* 298 (MH$^+$, 100). HRMS (ESI): calcd for $C_{16}H_{16}N_3OS$ 298.1014, found 298.1025.

4.3.12. 4-((2-Morpholino-4-oxothiazol-5(4H)-ylidene)-methyl)benzonitrile (**19**)

Yellow crystalline solid (0.778 g, 70%). Mp=271 °C. IR ν_{max} (KBr)=2934, 2227, 1701, 1576 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6): δ=3.69 (2H, t, *J*=3.6 Hz, C*H*$_{ax}$H$_{eq}$–N–C*H*$_{ax}$H$_{eq}$), 3.74–3.78 (4H, m, –CH$_2$–O–CH$_2$–), 3.95 (2H, t, *J*=4.8 Hz, CH$_{ax}$*H*$_{eq}$–N–CH$_{ax}$*H*$_{eq}$), 7.72 (1H, s, CH), 7.81 (2H, AA′, *J*=8.3 Hz, CH$_{Ar}$), 7.98 (2H, BB′, *J*=8.3 Hz, CH$_{Ar}$) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ=49.7, 66.4, 66.5, 112.4, 119.4, 128.8, 130.9, 132.7, 133.8, 139.3, 174.9, 179.6 ppm. MS (EI): *m*/*z* 299 (M$^+$, 35%), 159 (100). HRMS (EI): calcd for $C_{15}H_{13}N_3O_2S$ 299.072849, found 299.073500.

4.3.13. 4-((2-(4-Methylpiperidin-1-yl)-4-oxothiazol-5(4H)-ylidene)-methyl)benzonitrile (**20**)

Yellow crystalline solid (0.722 g, 62%). Mp=133–136 °C. IR ν_{max} (KBr): 3431, 3056, 2952, 2868, 2366, 2344, 2231, 1718, 1683, 1611, 1572 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6): δ=0.90 (3H, d, *J*=2.3 Hz, CH$_3$), 1.15–1.31 (2H, m, –CH$_2$–), 1.77–1.86 (3H, m, CH$_2$–CH), 3.24–3.40 (1H, m, –N–C*H*$_{ax2}$H$_{eq2}$–), 3.43–3.53 (1H, m, –N–C*H*$_{ax1}$H$_{eq1}$), 3.81–3.86 (1H, br d, *J*=13.5 Hz, –N–CH$_{ax2}$*H*$_{eq2}$–), 4.59 (1H, br d, *J*=13.5 Hz, –N–CH$_{ax1}$*H*$_{eq1}$–), 7.69 (1H, s, CH), 7.81 (2H, AA′, *J*=7.8 Hz, CH$_{Ar}$), 7.97 (2H, BB′, *J*=7.8 Hz, CH$_{Ar}$) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ=22.0, 30.7, 33.5, 34.5, 49.5, 50.1, 112.2, 119.4, 128.3, 130.8, 133.7, 139.4, 173.8, 179.8 ppm. MS (ESI): *m*/*z* 312 (MH$^+$). HRMS (ESI): calcd for $C_{17}H_{18}N_3OS$ 312.1171, found 312.1185.

4.3.14. 2-(Benzylamino)-5-benzylidenethiazol-4(5H)-one (**21**)

Orange crystalline solid (0.641 g, 53%). Mp=265–269 °C. IR ν_{max} (KBr): 2228, 1711, 1606, 1436, 1411, 1364, 1341, 1299, 1258, 1218, 1192, 1086, 1062 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6): δ=4.77 (2H, d, *J*=5.6 Hz, *CH*$_2$NH), 7.32–7.42 (5H, m, CH$_{Ar}$), 7.69 (1H, s, CH), 7.77 (2H, AA′, *J*=8.4 Hz, CH$_{Ar}$), 7.98 (2H, BB′, *J*=8.4 Hz, CH$_{Ar}$), 10.22 (1H, t, *J*=5.6 Hz, NH) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ=48.9, 112.1, 119.4, 128.1, 128.7, 129.5, 130.0, 131.6, 133.2, 133.8, 137.8, 138.2, 139.5, 174.3, 180.0 ppm. MS (ESI): *m*/*z* 320 (MH$^+$). HRMS (ESI): calcd for $C_{18}H_{14}N_3OS$ 320.0858, found 320.0870.

4.3.15. 4-((4-Oxo-2-(pyrrolidin-1-yl)thiazol-5(4H)-ylidene)-methyl)benzonitrile (**22**)

Orange crystalline solid (1.049 g, 99%). Mp=256–260 °C. IR ν_{max} (KBr): 2219, 1686, 1560 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6): δ=1.97–2.07 (4H, m, –CH$_2$–CH$_2$–), 3.66 (2H, t, *J*=6.6 Hz, –C*H*′H″–N–C*H*′H″–), 3.73 (2H, t, *J*=6.3 Hz, –CH′*H*″–N–CH′*H*″–), 7.68 (1H, s, CH), 7.78–7.83 (2H, m, CH$_{Ar}$), 7.96–7.99 (2H, m, CH$_{Ar}$) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ=25.4, 25.6, 49.7, 51.7, 113.1, 119.2, 127.4, 130.8, 133.2, 133.8, 139.4, 148.4, 171.6, 179.1 ppm. MS (ESI) *m*/*z* 284 (MH$^+$, 100). HRMS (ESI): calcd for $C_{15}H_{14}N_3OS$ 284.0858, found 284.0850.

4.3.16. 5-(4-(Benzyloxy)benzylidene)-2-(piperidin-1-yl)thiazol-4(5H)-one (**23**)

Dark yellow crystalline solid (0.795 g, 56%). Mp=175–177 °C. IR ν_{max} (KBr): 2363, 1675, 1560, 1508 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6): δ=1.67 (6H, br s, –CH$_2$–CH$_2$–CH$_2$–), 3.60 (2H, br s, –C*H*$_{ax}$H$_{eq}$–N–C*H*$_{ax}$H$_{eq}$–), 3.88–3.90 (2H, m, –CH$_{ax}$*H*$_{eq}$–N–CH$_{ax}$*H*$_{eq}$–), 5.19 (2H, s, –O–CH$_2$–), 7.15 (2H, AA′, *J*=8.7 Hz, CH$_{Ar}$), 7.36–7.40 (5H, m, CH$_{Ar}$), 7.57 (1H, s, CH), 7.58 (2H, BB′, *J*=8.7 Hz, CH$_{Ar}$) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ=24.3, 26.0, 26.6, 49.9, 50.7, 70.3, 116.4, 126.9, 127.4, 128.7, 128.9, 129.4, 130.3, 132.2, 137.5, 160.4, 174.1, 180.5 ppm. MS (ESI): *m*/*z* 379 (MH$^+$, 100). HRMS (ESI): calcd for $C_{22}H_{23}N_2O_2S$ 379.1480, found 379.1470.

4.3.17. 5-(4-(Benzyloxy)benzylidene)-2-morpholinothiazol-4(5H)-one (**24**)[12]

Yellow crystalline solid (1.14 g, 80%). Mp=169–171 °C. IR ν_{max} (KBr): 1676, 1559, 1508, 1387, 1350, 1240, 1162, 1111 cm^{-1}. ^{1}H

NMR (300 MHz, DMSO-d_6): δ=3.65–3.68 (2H, m, CH_{ax}H$_{eq}$–N–CH_{ax}H$_{eq}$), 3.71–3.77 (4H, m, CH$_2$–O–CH$_2$), 3.90–3.94 (2H, m, –CH$_{ax}H_{eq}$–N–CH$_{ax}H_{eq}$–), 6.12 (2H, s, CH$_2$), 5.19 (2H, s, –O–CH$_2$–), 7.16 (2H, AA′, J=8.9 Hz, CH$_{Ar}$), 7.34–7.49 (4H, m, CH$_{Ar}$), 7.59 (2H, BB′, J=8.9 Hz, CH$_{Ar}$), 7.62 (1H, s, CH) ppm. MS (EI): m/z 380 (M$^+$, 100%). HRMS (EI): calcd for $C_{21}H_{20}N_2O_3S$ 380.119465, found 380.120000.

4.3.18. 5-(4-(Benzyloxy)benzylidene)-2-(4-methylpiperidin-1-yl)thiazol-4(5H)-one (**25**)

Orange crystalline solid (0.929 g, 63%). Mp=165–166 °C. IR ν_{max} (KBr): 2926, 1674, 1598, 1558, 1508 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6): δ=0.94 (3H, d, J=6.2 Hz, CH$_3$), 1.15–1.28 (2H, m, –CH$_2$–), 1.74–1.84 (3H, m, CH$_2$–CH–), 3.19–3.27 (1H, m, –N–CH_{ax2}H$_{eq2}$–), 3.38–3.48 (1H, br d, J=13.4 Hz, –N–CH_{ax1}H$_{eq1}$), 3.81 (1H, br d, J=13.4 Hz, –N–CH$_{ax2}H_{eq2}$–), 4.60 (1H, d, J=13.3 Hz, –N–CH$_{ax1}H_{eq1}$–), 5.18 (2H, s, –O–CH$_2$–), 7.15 (2H, AA′, J=8.8 Hz, CH$_{Ar}$), 7.32–7.49 (5H, m, CH$_{Ar}$), 7.58 (1H, s, CH), 7.59 (2H, BB′, J=8.8 Hz, CH$_{Ar}$) ppm. ^{13}C NMR (75 MHz, CDCl$_3$): δ=21.8, 31.2, 33.9, 34.5, 49.3, 49.8, 70.5, 115.8, 126.3, 127.6, 127.9, 128.6, 129.1, 131.4, 131.9, 136.8, 160.3, 174.9, 181.7 ppm. MS (ESI): m/z 393 (MH$^+$, 100). HRMS (ESI): calcd for $C_{23}H_{25}N_2O_2S$ 393.1637, found 393.1656.

4.3.19. 5-(4-(Benzyloxy)benzylidene)-2-(benzylamino)thiazol-4(5H)-one (**26**)

Pale orange crystalline solid (0.849 g, 57%). Mp=182 °C. IR ν_{max} (KBr): 3007, 1685, 1586, 1507 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6): δ=4.74 (2H, d, J=5.4 Hz, CH_2NH), 5.15 (2H, d, –O–CH$_2$–), 7.17 (2H, AA′, J=9.0 Hz, CH$_{Ar}$), 7.31–7.61 (12H, m, CH$_{Ar}$, CH), 7.60 (1H, s, CH), 10.00 (1H, t, J=5.4 Hz, NH) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ=48.6, 70.5, 116.5, 123.3, 126.6, 127.5, 128.2, 128.6, 128.8, 129.3, 129.5, 132.6, 133.5, 137.5, 138.1, 160.3, 174.5, 180.7 ppm. MS (ESI): m/z 401 (MH$^+$, 100). HRMS (ESI): calcd for $C_{24}H_{20}N_2O_2S$ 401.1324, found 401.1323.

4.3.20. 5-(4-(Benzyloxy)benzylidene)-2-(pyrrolidin-1-yl)thiazol-4(5H)-one (**27**)

Yellow crystalline solid (1.304 g, 95%). Mp=203–209 °C. IR ν_{max} (KBr): 1676, 1554, 1508, 1455, 1416, 1371, 1346, 1328, 1287, 1240, 1173 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6): δ=1.99–2.04 (4H, m, –CH$_2$–CH$_2$–), 3.62 (2H, t, J=6.3 Hz, –CH′H″–N–CH′H″–), 3.70 (2H, t, J=6.3 Hz, –CH′H″–N–CH′H″–), 5.19 (2H, s, CH_2Ph), 7.17 (2H, AA′, J=8.9 Hz, CH$_{Ar}$), 7.34–7.48 (6H, m, CH$_{Ar}$), 7.58 (1H, s, CH), 7.58 (2H, BB′, J=8.9 Hz, CH$_{Ar}$) ppm. ^{13}C NMR (75 MHz, CDCl$_3$): δ=24.9, 25.2, 48.6, 50.6, 70.0, 115.3, 125.9, 127.0, 127.3, 128.1, 128.6, 131.2, 131.4, 136.3, 159.8, 172.3, 180.5 ppm. MS (ESI) m/z 365 (MH$^+$, 100). HRMS (ESI): calcd for $C_{21}H_{21}N_2O_2S$ 365.1324, found 365.1324.

4.3.21. 5-((1H-Indol-3-yl)methylene)-2-(piperidin-1-yl)thiazol-4(5H)-one (**28**)

Dark yellow crystalline solid (1.502 g, 90%). Mp=245 °C. IR ν_{max} (KBr): 3172, 2939, 1654, 1604, 1559 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6): δ=1.68 (6H, br s, –CH$_2$–CH$_2$–CH$_2$–), 3.62 (2H, br s, –CH_{ax}H$_{eq}$–N–CH_{ax}H$_{eq}$–), 3.87–3.91 (2H, m, –CH$_{ax}H_{eq}$–N–CH$_{ax}H_{eq}$–), 7.17–7.24 (2H, m, CH$_{Ar}$), 7.49 (1H, d, J=7.2 Hz, CH$_{Ar}$), 7.74 (1H, d, J=3.0 Hz, CH$_{Ar}$), 7.84 (1H, d, J=8.4 Hz, CH$_{Ar}$), 7.87 (1H, s, CH), 11.97 (1H, s, NH) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ=23.5, 25.1, 25.8, 48.7, 49.7, 111.1, 112.3, 118.3, 121.6, 122.7, 122.8, 126.8, 127.2, 136.4, 172.5, 179.8 ppm. MS (ESI): m/z 312 (MH$^+$). HRMS (ESI): calcd for $C_{17}H_{18}N_3OS$ 312.1171, found 312.1165.

4.3.22. 5-((1H-Indol-2-yl)methylene)-2-morpholinothiazol-4(5H)-one (**29**)

Yellow-green crystalline solid (1.05 g, 89%). Mp=310–314 °C. IR ν_{max} (KBr): 3204, 2363, 1661, 1602, 1544, 1458, 1437, 1385, 1351, 1280, 1223, 1180, 1114, 1020 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6): δ=3.66–3.67 (2H, m, CH_{ax}H$_{eq}$–N–CH_{ax}H$_{eq}$), 3.73–3.77 (4H, m, CH$_2$–O–CH$_2$), 3.90–3.91 (2H, m, –CH$_{ax}H_{eq}$–N–CH$_{ax}H_{eq}$–), 7.17–7.27 (2H, m, CH$_{Ar}$), 7.50 (1H, d, J=7.5 Hz, CH$_{Ar}$), 7.74 (1H, d, J=2.7 Hz, CH$_{Ar}$), 7.86 (1H, d, J=7.5 Hz, CH$_{Ar}$), 7.93 (1H, s, CH), 12.00 (1H, s, NH) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ=48.8, 49.3, 66.4, 66.5, 111.9, 113.2, 119.2, 121.6, 123.0, 123.1, 127.6, 128.2, 137.2, 174.3, 180.4 ppm. MS (EI): m/z 313 (M$^+$, 22%), 173 (100). HRMS (EI): calcd for $C_{16}H_{15}N_3O_2S$ 313.088499, found 313.089500.

4.3.23. 5-((1H-Indol-3-yl)methylene)-2-(4-methylpiperidin-1-yl)thiazol-4(5H)-one (**30**)

Light yellow crystalline solid (0.970 g, 80%). Mp=235–236 °C. IR ν_{max} (KBr): 3166, 2923, 2868, 2365, 1654, 1603, 1558 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6): δ=0.96 (3H, d, J=2.7 Hz, CH$_3$), 1.16–1.26 (2H, m, –CH$_2$–), 1.75–1.86 (3H, m, CH$_2$–CH), 3.17–3.27 (1H, m, –N–CH_{ax2}-H$_{eq2}$), 3.39–3.49 (1H, m, –N–CH_{ax1}H$_{eq1}$), 3.82 (1H, br d, J=13.3 Hz, –N–CH$_{ax2}H_{eq2}$–), 4.6 (1H, br d, J=13.3 Hz, –N–CH$_{ax1}H_{eq1}$–), 7.15–7.26 (2H, m, CH$_{Ar}$), 7.49 (1H, d, J=7.8 Hz, CH$_{Ar}$), 7.74 (1H, d, J=2.4 Hz, CH$_{Ar}$), 7.83 (1H, s, CH), 7.85 (1H, d, CH$_{Ar}$) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ=19.4, 22.1, 30.8, 34.0, 48.8, 49.7, 111.9, 113.1, 119.1, 121.5, 122.5, 123.6, 123.6, 127.7, 128.1, 137.2, 173.3, 180.6 ppm. MS (ESI): m/z 326 (MH$^+$, 100). HRMS (ESI) calcd for $C_{18}H_{20}N_3OS$ 326.1327, found 326.1329.

4.3.24. 5-((1H-Indol-2-yl)methylene)-2-(benzylamino)thiazol-4(5H)-one (**31**)

Orange crystalline solid (0.713 g, 57%). Mp=271 °C. IR ν_{max} (KBr): 3265, 3043, 2850, 1681, 1589, 1570, 1512, 1491, 1457, 1436, 1348, 1331, 1292, 1214, 1141, 1086, 1010 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6): δ=4.73 (2H, d, J=5.7 Hz, CH_2NH), 7.19–7.40 (7H, m, CH$_{Ar}$), 7.51 (1H, dd, J=5.0, 7.5 Hz, CH$_{Ar}$), 7.62 (1H, s, CH$_{Ar}$), 7.86 (1H, d, J=7.8 Hz, CH$_{Ar}$), 7.93 (1H, s, CH), 9.87 (1H, t, J=5.7 Hz, NH) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ=48.4, 112.0, 113.2, 119.2, 121.4, 122.3, 123.5, 127.6, 127.9, 128.4, 128.6, 129.5, 137.2, 138.4, 173.6, 180.8 ppm. MS (ESI): m/z 334 (MH$^+$). HRMS (ESI): calcd for $C_{19}H_{16}N_3OS$ 334.1014, found 334.1005.

4.3.25. 5-((1H-Indol-2-yl)methylene)-2-(pyrrolidin-1-yl)thiazol-4(5H)-one (**32**)

Orange crystalline solid (0.989 g, 96%). Mp=333–337 °C. IR ν_{max} (KBr): 3148, 1654, 1603, 1558, 1452, 1368, 1346, 1311, 1223, 1131, 1017 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6): δ=1.97–2.06 (4H, m, –CH$_2$–CH$_2$–), 3.61 (2H, t, J=6.6 Hz, –CH′H″–N–CH′H″–), 3.69 (2H, t, J=6.6 Hz, –CH′H″–N–CH′H″–), 7.17 (1H, dt, J_1=1.2 Hz, J_2=7.8 Hz, CH$_{Ar}$), 7.23 (1H, dt, J_1=1.5 Hz, J_2=7.4 Hz, CH$_{Ar}$), 7.50 (1H, d, J=7.8 Hz, CH$_{Ar}$), 7.72 (1H, s, CH$_{Ar}$), 7.85 (1H, d, J=7.4 Hz, CH$_{Ar}$), 7.87 (1H, s, CH), 11.96 (1H, s, NH) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ=25.4, 25.7, 49.5, 51.1, 111.9, 113.2, 119.1, 121.5, 122.6, 123.6, 127.6, 137.6, 171.1, 180.0 ppm. MS (ESI) m/z 298 (MH$^+$, 100). HRMS (ESI): calcd for $C_{16}H_{16}N_3OS$ 298.1014, found 298.0999.

4.3.26. 5-((Benzo[d][1,3]dioxol-6-yl)methylene)-2-(piperidin-1-yl)thiazol-4(5H)-one (**33**)[15]

Yellow crystalline solid (1.119 g, 94%). Mp=200 °C. IR ν_{max} (KBr): 3404, 2940, 1664, 1611, 1595, 1570, 1507 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6): δ=1.67 (6H, br s, –CH$_2$–CH$_2$–CH$_2$–), 3.62 (2H, br s, –CH_{ax}H$_{eq}$–N–CH_{ax}H$_{eq}$–), 3.88–3.91 (2H, m, –CH$_{ax}H_{eq}$–N–CH$_{ax}H_{eq}$–), 6.12 (2H, s, CH$_2$), 7.06 (1H, d, J=8.7 Hz, CH$_{Ar}$), 7.17–7.20 (2H, m, CH$_{Ar}$), 7.56 (1H, s, CH) ppm. MS (ESI): m/z 317 (MH$^+$, 100). HRMS (ESI): calcd for $C_{16}H_{17}N_2O_3S$ 317.0960, found 317.0970.

4.3.27. 5-((Benzo[d][1,3]dioxol-6-yl)methylene)-2-morpholinothiazol-4(5H)-one (**34**)[4d]

Yellow crystalline solid (0.973 g, 82%). Mp=268 °C. IR ν_{max} (KBr): 3152, 1734, 1684, 1612, 1564, 1501 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-

d_6): δ=3.67–3.69 (2H, m, CH_{ax}H$_{eq}$–N–CH_{ax}H$_{eq}$), 3.71–3.78 (4H, m, CH$_2$–O–CH$_2$), 3.90–3.92 (2H, m, –CH$_{ax}$$H_{eq}$–N–CH$_{ax}$$H_{eq}$–), 6.12 (2H, s, CH$_2$), 7.05–7.08 (1H, m, CH$_{Ar}$), 7.17–7.20 (2H, m, CH$_{Ar}$), 7.59 (1H, s, CH) ppm. MS (EI): m/z 318 (M$^+$, 22%), 178 (100). HRMS (EI): calcd for $C_{15}H_{14}N_2O_4S$ 318.067429, found 318.068400.

*4.3.28. 5-((Benzo[d][1,3]dioxol-6-yl)methylene)-2-(4-methylpiperidin-1-yl)thiazol-4(5H)-one (**35**)*

Yellow crystalline solid (0.871 g, 70%). Mp=162–167 °C. IR ν_{max} (KBr)=2928, 2865, 1677, 1611, 1560, 1500 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6): δ=0.95 (3H, d, J=5.7 Hz, CH$_3$), 1.15–1.28 (2H, m, –CH$_2$–), 1.74–1.84 (3H, m, CH$_2$–CH), 3.19–3.28 (1H, m, –N–CH_{ax2}H$_{eq2}$–), 3.39–3.48 (1H, m, –N–CH_{ax1}H$_{eq1}$), 3.83 (1H, br d, J=13.5 Hz, –N–CH$_{ax2}$$H_{eq2}$–), 4.57 (1H, br d, J=13.2 Hz, –N–CH$_{ax1}$$H_{eq1}$–), 6.11 (2H, s, –O–CH$_2$–O–), 7.06 (1H, d, J=8.7 Hz, CH$_{Ar}$), 7.17–7.20 (2H, m, CH$_{Ar}$), 7.56 (1H, s, CH) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ=22.0, 30.7, 33.9, 34.5, 49.1, 49.9, 102.7, 109.6, 109.8, 125.9, 127.4, 129.0, 130.5, 149.0, 149.5, 174.1, 180.4 ppm. MS (ESI): m/z 331 (MH$^+$). HRMS (ESI): calcd for $C_{17}H_{19}N_2O_3S$ 331.1116, found 331.1124.

*4.3.29. 5-(Benzo[d][1,3]dioxol-5-ylmethylene)-2-(benzylamino)thiazol-4(5H)-one (**36**)*[14]

Yellow-orange crystalline solid (0.841 g, 66%). Mp=245–246 °C. IR ν_{max} (KBr): 3243, 1662, 1602, 1542, 1458, 1436, 1385, 1351, 1281, 1223, 1180, 1115, 1020 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6): δ=4.73 (2H, d, J=4.8 Hz, CH_2NH), 6.13 (2H, s, CH$_2$), 7.08–7.18 (5H, m, CH$_{Ar}$), 7.34–7.39 (2H, m, CH$_{Ar}$), 7.57 (1H, s, CH), 10.01 (1H, t, J=4.8 Hz, NH) ppm. MS (ESI): m/z 339 (MH$^+$). HRMS (ESI): calcd for $C_{18}H_{15}N_2O_3S$ 339.0803, found 339.0804.

*4.3.30. 5-((Benzo[d][1,3]dioxol-6-yl)methylene)-2-(pyrrolidin-1-yl)thiazol-4(5H)-one (**37**)*

Yellow crystalline solid (0.989 g, 88%). Mp=277–279 °C. IR ν_{max} (KBr): 1687, 1610, 1558 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6): δ=1.97–2.06 (4H, m, –CH$_2$–CH$_2$–), 3.62 (2H, t, J=6.4 Hz, –CH'H″–N–CH'H″–), 3.70 (2H, t, J=6.4 Hz, –CH′H''–N–CH′H''–), 6.12 (2H, s, CH$_2$), 7.06–7.19 (3H, m, CH$_{Ar}$), 7.55 (1H, s, CH) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ=25.6, 51.4, 103.0, 110.2, 110.4, 123.8, 127.6, 128.1, 132.8, 149.2, 150.6, 170.3, 179.7 ppm. MS (ESI) m/z 303 (MH$^+$, 100). HRMS (ESI): calcd for $C_{15}H_{15}N_2O_3S$ 303.0803, found 303.0810.

Acknowledgements

This work was supported by the European Union FP6 Integrated Project EUR-INTAFAR (Project No. LSHM-CT 2004-512138) under the thematic priority of Life Sciences, Genomics, and Biotechnology for Health (http://www.cip.ulg.ac.be/EUR-INTAFAR). Dr. B. Kralj and Dr. D. Žigon (Center for Mass Spectrometry, Jožef Stefan Institute, Ljubljana, Slovenia) are gratefully acknowledged for the mass measurements. We thank Dr. Roger Pain and Dr. Jožko Cesar for careful reading of the manuscript and many useful suggestions.

References and notes

1. (a) Lee, C. L.; Sim, M. M. *Tetrahedron Lett.* **2000**, *41*, 5729–5732; (b) Andres, C. J.; Bronson, J. J.; D'Andrea, S. V.; Deshpande, M. S.; Falk, P. J.; Grant-Young, K. A.; Harte, W. E.; Ho, H.-T.; Misco, P. F.; Robertson, J. G.; Stock, D.; Sun, Y.; Walsh, A. W. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 715–717.
2. Pulici, M.; Quartieri, F. *Tetrahedron Lett.* **2005**, *46*, 2387–2391.
3. (a) Taylor, E. C., Jr.; Wolinski, J.; Lee, H.-H. *J. Am. Chem. Soc.* **1954**, *76*, 1870–1872; (b) Hu, B.; Malamas, M.; Ellingboe, J.; Largis, E.; Han, S.; Mulvey, R.; Tillett, J. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 981–984; (c) Hu, B.; Malamas, M.; Ellingboe, J. *Heterocycles* **2002**, *57*, 857–870; (d) Song, Y.; Connor, D. T.; Doubleday, R.; Sorenson, R. J.; Sercel, A. D.; Unangst, P. C.; Roth, B. D.; Gilbertsen, R. B.; Chan, K.; Schrier, D. J.; Guglietta, A.; Bornemeier, D. A.; Dyer, R. D. *J. Med. Chem.* **1999**, *42*, 1151–1160; (e) Janusz, J. M.; Young, P. A.; Ridgeway, J. M.; Scherz, M. W.; Enzweiler, K.; Wu, L. I.; Gan, L.; Chen, J.; Kellstein, D. E.; Green, S. A.; Tulich, J. L.; Rosario-Jansen, T.; Magrisso, I. J.; Wehmeyer, K. R.; Kuhlenbeck, D. L.; Eichhold, T. H.; Dobson, R. L. *J. Med. Chem.* **1998**, *41*, 3515–3529; (f) Unangst, P. C.; Connor, D. T.; Cetenko, W. A.; Sorenson, R. J.; Kostlan, C. R.; Sircar, J. C.; Wright, C. D.; Schrier, D. J.; Dyer, R. D. *J. Med. Chem.* **1994**, *37*, 322–328.
4. (a) Vachal, P.; Pihera, P.; Svoboda, J. *Collect. Czech. Chem. Commun.* **1997**, *62*, 1468–1480; (b) Tashima, T.; Kagechika, H.; Tsuji, M.; Fukasawa, H.; Kawachi, E.; Hashimoto, Y.; Sudo, K. *Chem. Pharm. Bull.* **1997**, *45*, 1805–1813; (c) Simpson, J.; Rathbone, D. L.; Billington, D. C. *Tetrahedron Lett.* **1999**, *40*, 7031–7033; (d) Bourahla, K.; Derdour, A.; Rahmouni, M.; Carreaux, F.; Bazureau, J. P. *Tetrahedron Lett.* **2007**, *48*, 5785–5789.
5. Vicini, P.; Geronikaki, A.; Anastasia, K.; Incerti, M.; Zaini, F. *Bioorg. Med. Chem.* **2006**, *14*, 3859–3864.
6. Sim, M. M.; Ng, S. B.; Buss, A. D.; Crasta, S. C.; Goh, K. L.; Lee, S. K. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 697–699.
7. (a) Helm, J. S.; Hu, Y.; Chen, L.; Gross, B.; Walker, S. *J. Am. Chem. Soc.* **2003**, *125*, 11168–11169; (b) Hu, Y.; Helm, J. S.; Chen, L.; Ginsberg, C.; Gross, B.; Kraybill, B.; Tiyanont, K.; Fang, X.; Wu, T.; Walker, S. *Chem. Biol.* **2004**, *11*, 703–711.
8. (a) *Microwaves in Organic Synthesis*; Loupy, A., Ed.; Wiley-VCH: Weinheim, 2002; (b) Hayes, B. L. *Microwave Synthesis: Chemistry at the Speed of Light*; CEM: Matthews, NC, 2002.
9. Kappe, O. *Angew. Chem., Int. Ed.* **2004**, *43*, 6250–6284.
10. Geissman, T. A. *Org. React.* **1944**, *2*, 94–113.
11. Kutschy, P.; Dzurilla, M.; Kristian, P.; Kutschyova, K. *Collect. Czech. Chem. Commun.* **1981**, *46*, 436–445.
12. Frank, R.; Kless, A.; Jostock, R. PCT Int. Appl. WO 2006122777 A2, 2006, 153 pp.
13. Moharram, H. H.; Tammam, G. H.; Mansour, S. A. *Egypt. J. Chem.* **1983**, *26*, 441–445.
14. Rueckle, T.; Shaw, J.; Church, D.; Covini, D. PCT Int. Appl. WO 2005011686 A1, 2005, 72 pp.
15. Raouf, A. R. A.; Omar, M. T.; Omran, S. M. A.; El-Bayoumy, K. E. *Acta Chim. Acad. Sci. Hung.* **1974**, *83*, 359–365.