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Journal Name

ARTICLE

Synthesis of 4,8-dihydro-1*H*-pyrazolo[3,4-*e*][1,4]thiazepin-7(6*H*)-one derivatives by solid acid-catalyzed multi-component reaction in water

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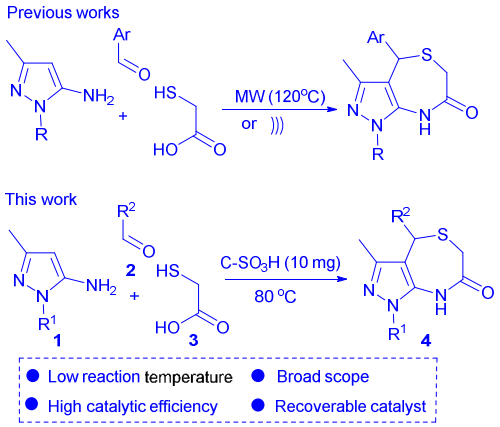
A solid acid functionalized with polyvinyl alcohol and hydroxyethylsulfuric acid is found to efficiently catalyze the one-pot three-component condensation of substituent-pyrazoles, aldehydes, and thioglycollic acid to afford a wide range of 4,8-dihydro-1*H*-pyrazolo[3,4-*e*][1,4]thiazepin-7(6*H*)-one derivatives with good to excellent yields. The using of recyclable heterogeneous solid acid catalyst makes this procedure mild, simple, efficient, and sustainable.

Introduction

The nitrogen-containing heterocycles comprising 1,4-oxazepines, 1,4-thiazepines, morpholines, and thiomorpholines are some of the most important pharmacophores,[1] which have been widely used for the synthesis of pharmaceutical agents and biologically active compounds.[2] Besides, pyrazole skeletons constitute the core structural element in both natural and synthetic bioactive compounds, which show many pharmacological properties such as anxiolytic,[3] inhibitors of A1 adenosine receptors,[4] inhibitors of xanthine oxidases,[5] treatment of Alz-heimer's disease,[6] kinase inhibitors,[7] inhibitors in immune and inflammatory cells.[8] In view of the versatile bioactivities of the above mentioned skeletons, we reasoned that the combination of pyrazole scaffold with 1,4-thiazepine segment might result in the discovery of unknown drug intermediates with enhanced or new bioactivities. However, compared with the vast attentions and numerous synthetic methods to 1,4-thiazepines and pyrazoles, the design and synthesis of 1,4-thiazepine compounds with pyrazole frameworks has been less recognized and only very few literatures involved the synthesis of such compounds.[9] The previous methods employing pyrazole were reported by Tu[9b] and Maheshwari[9d], respectively, but those procedures suffered from one or more shortcomings, such as particular conditions (microwave irradiation or sonication), high temperature, especially, the limited substrate scopes. Therefore, the development of a facile approach for 1,4-thiazepine derivatives implanted with pyrazole with structural diversity is still highly desirable and valuable for medicinal chemistry and drug discovery (Scheme 1).

Tackling the current increasing environmental concerns, sustainability has become a watchword for modern society.[10] Heterogeneous catalysis has a rich history of facilitating energy efficient selective molecular transformations and contributes to chemical manufacturing processes and industrial products.[11] As a traditional heterogeneous catalysis, solid acids are usually used in the transes-terification and esterification of oils.[12] Since some carbonaceous materials solid acids were found owned high catalysis activity in organic synthesis, more and more new solid acids were synthesized and used to induce organic synthesis reaction.[13] Liang group synthesized a series of novel sulfuric acid groups functionalized carbonaceous materials,[14] many of them showed high catalytic activities in organic synthesis reactions. As the continued effort of diversity synthesis of heterocyclic skeletons,[15] we would like to report a green chemistry approach for the synthesis 4,8-dihydro-1*H*-pyrazolo[3,4-*e*][1,4]thiazepin-7(6*H*)-one derivatives using sulfuric acid groups functionalized carbonaceous material (C-SO_3H)[14b] of polyvinyl alcohol and hydroxyethylsulfuric acid as heterogeneous catalysis.



Scheme 1 Strategies for the synthesis of pyrazolo[3,4-e][1,4] thiazepines.

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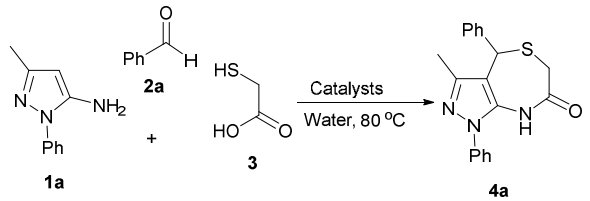
Results and discussion

The choice of a suitable catalyst is very important for successful preparation of target product. Firstly, we started from the reaction of 3-methyl-1-phenyl-1*H*-pyrazol-5-amine (**1a**), benzaldehyde (**2a**), and thioglycollic acid (**3**) with equimolar quantity for catalyst screening at 80 °C in water. As shown in Table 1, no goal product was given even after 24 h at 80 °C in the absence of catalyst (Table 1, entry 1). Then, zeolite (HY) and Amberlyst-15 were used as a catalyst for the model reaction respectively, yet the reaction did not occur and gave no target compound (Table 1, entries 2-3). However, when sulfonated solid acid[14a] synthesized with furaldehyde and hydroxyethylsulfonic acid was used, the goal product was obtained with 59% yield (Table 1, entry 4). Gratifyingly, when the sulfonated solid acid[14a] was replaced with C-SO_3H, the target product was obtained smoothly with even excellent yield (Table 1, entry 5). Subsequently, different Brønsted acid such as H_2SO_4, TFA, PTSA, and HOAc and Lewis acids such as $AlCl_3$, and $TiCl_4$ were used to catalyze the model reaction respectively. Unfortunately, only 10-56% yields of 3-methyl-1,4-diphenyl-4,8-dihydro-1*H*-pyrazolo[3,4-*e*][1,4]thiazepin-7(6*H*)-one were obtained (Table 1, entries 6-11). From above results it is obvious that C-SO_3H shows a superior catalytic advantage not only in promoting the reaction but also in isolation procedure, and the best yield was obtained (Table 1, entry 5). The subsequent results demonstrate C-SO_3H (10 mg) is enough to promote this reaction. Thus, C-SO_3H (10 mg) was employed as the catalyst for the following reactions.

Table 1 Screening of the catalyst for synthesis of compound **4**.[a]

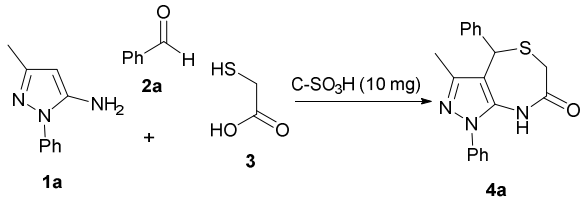


Entry	Catalyst (mg)	Time (h)	Yield (%)[b]
1	-	24	0
2	Zeolite (HY) (10)	24	0
3	Amberlyst-15 (10)	24	0
4	Sulfonated carbon (10)[c]	6	59
5	C-SO_3H (10)	6	87
6	H_2SO_4 (10)	6	56
7	TFA (10)	6	43
8	PTSA (10)	6	20
9	HOAc (10)	6	34
10	$AlCl_3$ (10)	6	21
11	$TiCl_4$ (10)	6	10
12	C-SO_3H (5)	6	63
13	C-SO_3H (20)	6	88

[a] Reaction conditions: **1a** (1.0 mmol), **2a** (1.0 mmol), **3** (1.0 mmol) and different catalyst at 80 °C in water. [b] Isolated yields. [c] The catalyst was synthesized according to the methods in refs [14a].

To search for the optimal reaction media, the model reaction was firstly carried out without using any solvent, only middle yield of product **4a** was obtained (Table 2, entry 1). To further choose the optimum solvent, the same reaction was performed at certain temperature catalyzed by C-SO_3H (10 mg) in different solvents including dichloromethane (CH_2Cl_2), trichloromethane ($CHCl_3$), acetonitrile (CH_3CN), tetrahydrofuran (THF), toluene, methanol (MeOH), ethanol (EtOH) and water (H_2O) (Table 2, entries 2-9). We found that the protonation ability of the solvents had an obvious impact on the yield of **4a**. The aprotic solvents with different polarity such as dichloromethane (CH_2Cl_2), trichloromethane ($CHCl_3$), acetonitrile (CH_3CN), tetrahydrofuran (THF), and toluene only gave poor yields of goal product (Table 2 entries 2-6). However, the protic solvents such as methanol (MeOH), ethanol (EtOH) and water (H_2O) gave obvious high yields of product (Table 2, entries 7-9). Taking into account economy, efficiency, as well as sustainability, we chose water as the optimum reaction medium. Then, to screen the optimum reaction temperature, the model reaction was carried out at a temperature ranging from 20 °C to 100 °C under above optimized reaction conditions. As can be seen from Table 2, we found that the yield of **4a** improved obviously as the temperature increased from 20 °C to 80 °C (Table 2, entries 9-12). However, the yield reached a plateau when the temperature was further increased from 80 °C to 100 °C (Table 2, entries 12-13). Therefore, 80 °C was chosen as reaction temperature for the following synthesis of compound **4**.

Table 2 Optimization of the solvent and temperature for the synthesis of compound **4**.[a]



Entry	Solvent	T (°C)	Yield (%)[b]
1	-	80	56
2	CH_2Cl_2	reflux	18
3	CH_2Cl_3	reflux	36
4	CH_3CN	80	47
5	THF	reflux	41
6	Toluene	80	53
7	EtOH	reflux	81
8	MeOH	reflux	61
9	H_2O	80	87
10	H_2O	20	0
11	H_2O	40	20
12	H_2O	60	45
13	H_2O	100	89

[a] Reaction conditions: **1a** (1.0 mmol), **2a** (1.0 mmol), **3** (1.0 mmol) and C-SO_3H (10 mg) at selected temperature in different solvents. [b] Isolated yields.

With the above optimized reaction conditions, we then used 3-methyl-1-phenyl-1*H*-pyrazol-5-amine (**1a**) and thioglycollic acid (**3**) as model substrates and invesgated the scope of aldehydes by using various aromatic aldehydes and aliphatic aldehydes. In all these cases, the multi-component reaction proceeded smoothly to give corresponding 3-methyl-1-phenyl-4,8-dihydro-1*H*-pyrazolo[3,4-*e*][1,4]thiazepin-7(6*H*)-one derivatives with good to excellent yields (Table 3, entries 1-14). Meanwhile, we also noted that the

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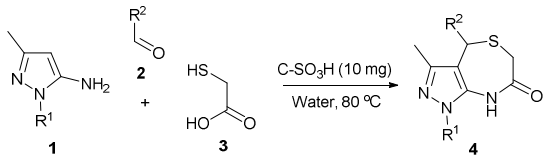
electronic nature and position of the substituents bearing the aromatic rings had slight effects on the yields. The strongly electron donating 4-methoxybenzaldehyde (**2f**) afforded the highest yield (Table 3, entry 6). However, the aldehydes with electron withdrawing group universally gave slight low yields of product, and the 4-nitrobenzaldehyde gave the lowest yield (Table 3, entry 5). At the same time, the position of substituents on the phenyl ring of **2** also affects the conversion of the reaction, *ortho*-substituted aromatic aldehydes only give corresponding product in 72-81% yield and the 2,6-dichlorobenzaldehyde (**2j**) gave the lowest yield of product in 72% (Table 3, entry 10). Furthermore, the 1-naphthaldehyde (**2k**) and the heterocyclic aldehydes such as thiophene-2-carbaldehyde (**2l**) still displayed high reactivities and gave desired products with 81-82% yield correspondingly (Table 3, entries 11-12). In addition, it is worth mentioning that the aliphatic aldehydes such as 3-methylbutanal and nonanal also proceeded this transformation and gave corresponding 3-methyl-4,8-dihydro-1*H*-pyrazolo[3,4-*e*][1,4]thiazepin-7(6*H*)-one derivatives (Table 3, entries 13-14).

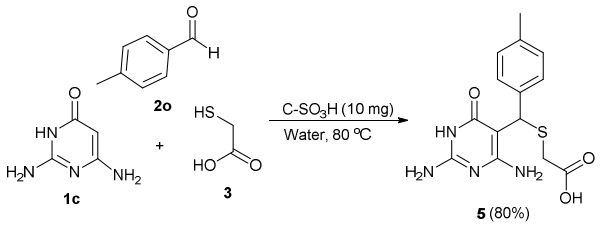
Table 3 Substrate scope of the multi-component reaction.[a]



Entry	R^1	R^2	4	Time (h)	Yield (%)[b]
1	C_6H_5 (**1a**)	C_6H_5 (**2a**)	**4a**	6	87
2	C_6H_5 (**1a**)	4-FC_6H_4 (**2b**)	**4b**	6	86
3	C_6H_5 (**1a**)	4-ClC_6H_4 (**2c**)	**4c**	6	86
4	C_6H_5 (**1a**)	4-BrC_6H_4 (**2d**)	**4d**	6	83
5	C_6H_5 (**1a**)	4-$NO_2C_6H_4$ (**2e**)	**4e**	6	80
6	C_6H_5 (**1a**)	4-$OMeC_6H_4$ (**2f**)	**4f**	6	90
7	C_6H_5 (**1a**)	2-$NO_2C_6H_4$ (**2g**)	**4g**	6	75
8	C_6H_5 (**1a**)	3-$NO_2C_6H_4$ (**2h**)	**4h**	6	76
9	C_6H_5 (**1a**)	2,4-$Cl_2C_6H_3$ (**2i**)	**4i**	6	81
10	C_6H_5 (**1a**)	2,6-$Cl_2C_6H_3$ (**2j**)	**4j**	6	72
11	C_6H_5 (**1a**)	1-Naphthal (**2k**)	**4k**	6	82
12	C_6H_5 (**1a**)	2-Thienyl (**2l**)	**4l**	6	81
13	C_6H_5 (**1a**)	*i*-Butyl (**2m**)	**4m**	6	81
14	C_6H_5 (**1a**)	*n*-Octyl (**2n**)	**4n**	6	77
15	H (**1b**)	4-ClC_6H_4 (**2c**)	**4o**	5	83
16	H (**1b**)	4-Me C_6H_4 (**2o**)	**4p**	5	85
17	H (**1b**)	4-OMe C_6H_4 (**2f**)	**4q**	5	89
18	H (**1b**)	1-Naphthal (**2k**)	**4r**	5	80
19	H (**1b**)	2-Thienyl (**2l**)	**4s**	5	81

[a] Reaction conditions: **1** (1.0 mmol), **2** (1.0 mmol), **3** (1.0 mmol) and C-SO_3H (10 mg) at 80 °C in water. [b] Isolated yields.

To further expand the scope of the substrate, 3-methyl-1*H*-pyrazol-5-amine (**1b**) was employed to react with representative aldehydes (**2**) and thioglycollic acid (**3**). Similar to above multi-component processes, the present reaction was compatible with various aromatic aldehydes including different electronic feature and gave 4-aryl-3-methyl-4,8-dihydro-1*H*-pyrazolo[3,4-*e*][1,4]thiazepin-7(6*H*)-one derivatives with good yields (Table 3, entries 16-19). Subsequently, attempts to replace the methyl-1-phenyl-1*H*-pyrazol-5-amine (**1a**) with 2,6-diaminopyrimidin-4(3*H*)-one (**1c**) resulted in a failure in directional transformation (Scheme 2). Instead, product **5** was obtained with good yield (80%), which probable because of the poor reactivity of -NH_2 group bearing in 2,6-diaminopyrimidin-4(3*H*)-one (**1c**).



Scheme 2. Three-component reaction for unexpected product **5**.

Additionally, in our continued study, it was also found that ethyl 2-(((5-amino-3-methyl-1-phenyl-1*H*-pyrazol-4-yl)(argio)methyl)thio) acetate derivatives **7** were obtained easily in good yields under the similar reactions, when additional substrate ethanol was added to react with 3-methyl-1-phenyl-1*H*-pyrazol-5-amine (**1a**), aldehydes (**2**) and thioglycollic acid (**3**) (Scheme 3). As we anticipated, ethyl-2-mercaptoacetate was formed firstly, which hampered the following cyclization and the four-component product was given successfully. To the best of our knowledge, the ethyl 2-(((5-amino-3-methyl-1-phenyl-1*H*-pyrazol-4-yl)(argio)methyl)thio) acetate derivatives **7**,

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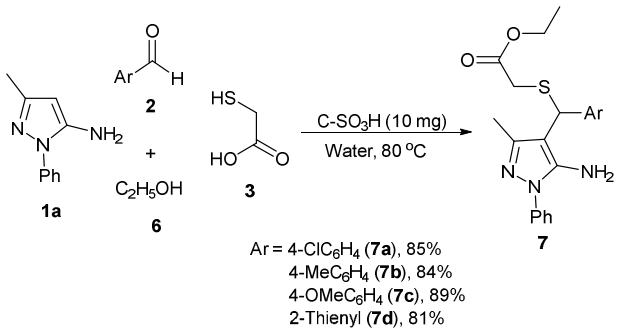
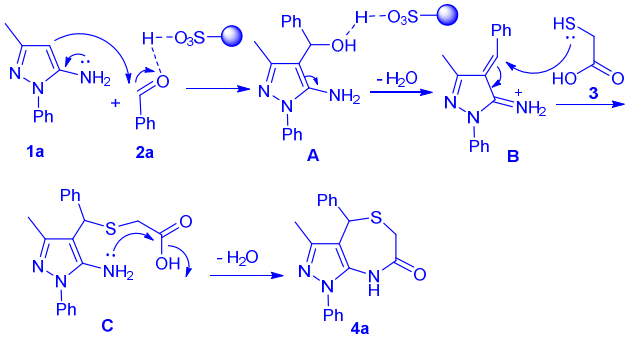
which are not studied and no corresponding compounds were reported in the literature, may be the potential pharmacological molecules with enhanced or unknown bioactivities.



Scheme 3. Four-component reaction for products **7**.

The solid acid catalyst was easily separated by filtered and reused after activation by drying in vacuum oven at 100 °C for 4 h. The catalytic reactivity of the recovered catalyst was verified in the reaction of 3-methyl-1-phenyl-1*H*-pyrazol-5-amine (**1a**), benzaldehyde (**2a**) and thioglycollic acid (**3**). The yield of product **4a** was 87% using fresh solid acid, while the recovery catalyst gave the yield of 86%, 84%, and 83% in the following three cycles respectively. We contributed the slight reduction of catalytic activity to the loss and contamination of the recovered catalyst.



Scheme 4 Proposed mechanism for the formation of product **4a.**

The reaction mechanism of this cyclization is proposed in Scheme 4. Under the effect of solid acid, intermediate **A** was formed by nucleophilic addition of active aldehyde and 3-methyl-1-phenyl-1*H*-pyrazol-5-amine which successively underwent the dehydration to give intermediate **B**. Subsequently, intermediate **C** was formed by nucleophilic function of thioglycollic acid to intermediate **B**, which could be seperated successfully. Finally, the goal product **4a** was obtained by intramolecular dehydration of intermediate **C**.

Conclusions

In conclusion, we have described an efficient synthesis of 3-methyl-4,8-dihydro-1*H*-pyrazolo[3,4-*e*][1,4]thiazepin-7(6*H*)-one derivatives in good to excellent yields employing solid acid (10 mg) as catalyst. The major advantages of this strategy include the mild conditions, high catalytic efficiency and recyclable of catalyst, using clean, cheap, and sustainable water as reaction media, and the structural diversity of products. Thus, the procedure constitutes a straightforward of various biologically active targets without metallic contaminants.

Experimental

General

All commercially available chemicals were used without further purification, unless otherwise stated. Analytical thin layer chromatography (TLC) was performed using Merck silica gel GF254 plates. IR spectra were taken on a FT-IR-Tensor 27 spectrometer in KBr pellets and reported in cm^{-1}. NMR-data were recorded on Bruker Avance 400 Spectrometer. ^{1}H- and ^{13}C-spectra were referenced to the residue solvent signals in the deuterated solvent. ^{1}H NMR spectra were recorded on a 400 MHz instrument. Chemical shifts (δ) are given in ppm relative to TMS as the internal reference, with coupling constants (J) in Hz. ^{13}C NMR spectra were recorded at 100 MHz. Chemical shift were reported in ppm with the internal chloroform signal at 77.0 ppm as a standard. HRMS (ESI) was measured with a Bruker Daltonics APEXII instrument.

General procedure for synthesis of 4,8-dihydro-1*H*-pyrazolo [3,4-*e*][1,4]thiazepin-7(6*H*)-one derivatives (4)

3-Methyl-1*H*-pyrazol-5-amine (**1**, 1.0 mmol) was added to a 10-mL reaction vial in water (3.0 mL), to the resulting solution were sequentially added aldehydes (**2**, 1.0 mmol), thioglycollic acid (**3**, 1.0 mmol), and C-SO_3H (10 mg). The mixture was stirred at the indicated temperature until TLC showed that the conversion of the substrates was complete about 5-6 h. Then, the mixture was cooled to room temperature and the solid was filtered. The result solid was resolved in hot ethanol, filtered, and the mother liquor was concentrated and recrystallized to give goal products (**4**).

General procedure for synthesis of 2-((argio(2,4-diamino-6-oxo-1,6-dihydropyrimidin-5-yl)methyl)thio)acetic acid (5)

2,6-Diaminopyrimidin-4(3*H*)-one (**1c**, 1.0 mmol) was added to a 10-mL reaction vial in water (3.0 mL), to the resulting solution were sequentially added 4-methylbenzaldehyde (**2o**, 1.0 mmol), thioglycollic acid (**3**, 1.0 mmol), and C-SO_3H (10 mg). The mixture was stirred at the indicated temperature until TLC showed that the conversion of the substrates was complete about 6 h. Then, the mixture was cooled to room temperature and the solid was filtered. The result solid was resolved in hot ethanol, filtered, and the mother liquor was concentrated and recrystallized to give goal product (**5**).

General procedure for synthesis of ethyl 2-(((5-amino-3-methyl -1-phenyl-1H-pyrazol-4-yl)(aryl)methyl)thio)acetate (7)

3-Methyl-1-phenyl-1*H*-pyrazol-5-amine (**1a**, 1.0 mmol) was added to a 10-mL reaction vial in water (3.0 mL), to the resulting solution were sequentially added aromatic aldehydes (**2**, 1.0

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mmol), thioglycollic acid (**3**, 1.0 mmol), ethanol (**6**, 3.0 mmol), and C-SO_3H (10 mg). The mixture was stirred at the indicated temperature until TLC showed that the conversion of the substrates was complete about 6 h. Then, the mixture was cooled to room temperature and the solid was filtered. The result solid was resolved in hot ethanol, filtered, and the mother liquor was concentrated. The residue was purified by column chromatography on silica gel using petroleum ether/ethyl acetate as eluent (ethyl acetate/petroleum ether = 1:20~1:4) to provide desired product (**7**).

3-methyl-1,4-diphenyl-4,8-dihydro-1*H*-pyrazolo[3,4-*e*][1,4]thiazepin-7(6*H*)-one (4a)[9c]

Yellow solid, mp: 74-76 °C, ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.58-7.54 (m, 2H, ArH), 7.50-7.47 (m, 3H, ArH), 7.39-7.36 (m, 2H, ArH), 7.33-7.29 (m, 4H, ArH+NH), 5.27 (s, 1H, CH), 3.37 (d, 1H, *J* = 15.2 Hz, CH_2), 3.27 (d, 1H, *J* = 15.6 Hz, CH_2), 1.92 (m, 3H, CH_3).

4-(4-fluorophenyl)-3-methyl-1-phenyl-4,8-dihydro-1*H*-pyrazolo[3,4-*e*][1,4]thiazepi-7(6*H*)-one (4b)[9d]

Yellow crystal, mp: 94-96 °C, ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.57-7.53 (m, 2H, ArH), 7.50-7.45 (m, 3H, ArH), 7.43 (br, s, 1H, NH), 7.29-7.25 (m, 2H, ArH), 7.05 (t, 1H, *J* = 8.4 Hz, ArH), 5.27 (s, 1H, CH), 3.38 (d, 1H, *J* = 15.2 Hz, CH_2), 3.21 (d, 1H, *J* = 15.2 Hz, CH_2), 1.92 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.2, 148.2, 136.9, 134.7, 130.1, 129.8, 129.2, 125.7, 115.8, 115.6, 106.9, 72.8, 42.5, 31.8, 12.8.

4-(4-chlorophenyl)-3-methyl-1-phenyl-4,8-dihydro-1*H*-pyrazolo[3,4-*e*][1,4]thiazepi-7(6*H*)-one (4c)[9b]

Yellow crystal, mp: 99-100 °C, ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.57-7.54 (m, 2H, ArH), 7.50-7.46 (m, 3H, ArH), 7.43 (br, s, 1H, NH), 7.35-7.33 (m, 2H, ArH), 7.23 (d, 2H, *J* = 8.4 Hz, ArH), 5.24 (s, 1H, CH), 3.37 (d, 1H, *J* = 15.2 Hz, CH_2), 3.20 (d, 1H, *J* = 15.2 Hz, CH_2), 1.92 (s, 3H, CH_3).

4-(4-bromophenyl)-3-methyl-1-phenyl-4,8-dihydro-1*H*-pyrazolo[3,4-*e*][1,4]thiazepi-7(6*H*)-one (4d) [9b]

Yellow solid, mp: 101-102 °C, ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.58-7.54 (m, 2H, ArH), 7.50-7.46 (m, 5H, ArH), 7.32 (br, s, 1H, NH), 7.17 (d, 2H, *J* = 8.4 Hz, ArH), 5.22 (s, 1H, CH), 3.37 (d, 1H, *J* = 15.6 Hz, CH_2), 3.20 (d, 1H, *J* = 15.6 Hz, CH_2), 1.93 (s, 3H, CH_3).

3-methyl-4-(4-nitrophenyl)-1-phenyl-4,8-dihydro-1*H*-pyrazolo[3,4-*e*][1,4]thiazepin-7(6*H*)-one (4e)[9b]

Yellow solid, mp: 97-98 °C, ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.24 (d, 2H, *J* = 8.8 Hz, ArH), 7.60-7.55 (m, 2H, ArH), 7.53-7.47 (m, 5H, ArH), 7.33 (br, s, 1H, NH), 5.32 (s, 1H, CH), 3.41 (d, 1H, *J* = 15.2 Hz, CH_2), 3.19 (d, 1H, *J* = 15.2 Hz, CH_2), 1.93 (s, 3H, CH_3).

4-(4-methoxyphenyl)-3-methyl-1-phenyl-4,8-dihydro-1*H*-pyrazolo[3,4-*e*][1,4]thiazepin-7(6*H*)-one (4f) [9b]

Yellow crystal, mp: 103-104 °C, ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.57-7.53 (m, 2H, ArH), 7.50-7.46 (m, 3H, ArH), 7.32 (br, s, 1H, NH), 7.21-7.19 (m, 2H, ArH), 6.90-6.87 (m, 2H, ArH), 5.25 (s, 1H, CH), 3.82 (s, 3H, OMe), 3.36 (d, 1H, *J* = 15.2 Hz, CH_2), 3.25 (d, 1H, *J* = 15.2 Hz, CH_2), 1.93 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.3, 159.1, 148.3, 137.0, 134.6, 132.7, 130.1, 129.3, 129.1, 125.8, 114.0, 107.2, 55.3, 42.6, 31.8, 12.8.

3-methyl-4-(2-nitrophenyl)-1-phenyl-4,8-dihydro-1*H*-pyrazolo[3,4-*e*][1,4]thiazepin-7(6*H*)-one (4g)

Yellow solid, mp: 88-90 °C, IR (KBr, ν, cm^{-1}): 3272, 1691, 1577, 1295, 1144, 1035, 907, 809, 733cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.06 (d, 2H, *J* = 8.0 Hz, ArH), 7.58-7.55 (m, 3H, ArH), 7.52-7.47 (m, 4H, ArH), 7.37 (br, s, 1H, NH), 7.23 (d, 1H, *J* = 7.2 Hz, ArH), 6.25 (s, 1H, CH), 3.30 (d, 1H, *J* = 15.2 Hz, CH_2), 3.17 (d, 1H, *J* = 15.2 Hz, CH_2), 1.94 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.0, 147.9, 134.7, 129.9, 129.7, 128.9, 125.5, 105.7, 67.1, 40.5, 33.5, 12.7; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{19}H_{17}N_4O_3S^+$: 381.1016; found: 381.1019.

3-methyl-4-(3-nitrophenyl)-1-phenyl-4,8-dihydro-1*H*-pyrazolo[3,4-*e*][1,4]thiazepin-7(6*H*)-one (4h) [9b]

Yellow solid, mp: 83-85 °C, ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.20-8.18 (m, 2H, ArH), 7.66 (d, 1H, *J* = 7.6 Hz, ArH), 7.59-7.55 (m, 3H, ArH), 7.52-7.48 (m, 3H, ArH), 7.38 (br, s, 1H, NH), 5.37 (s, 1H, CH), 3.42 (d, 1H, *J* = 15.2 Hz, CH_2), 3.18 (d, 1H, *J* = 15.2 Hz, CH_2), 1.93 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.6, 157.7, 143.4, 135.0, 134.0, 130.2, 129.8, 129.3, 125.7, 123.0, 122.9, 105.8, 42.5, 31.8, 12.9.

4-(2,4-dichlorophenyl)-3-methyl-1-phenyl-4,8-dihydro-1*H*-pyrazolo[3,4-*e*][1,4]thiazepin-7(6*H*)-one (4i)[9b]

Pale yellow crystal, mp: 219-221 °C, ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.58-7.50 (m, 2H, ArH), 7.49-7.46 (m, 4H, ArH), 7.40 (br, s, 1H, NH), 7.24-7.21 (m, 1H, ArH), 7.02 (d, 1H, *J* = 8.4 Hz, ArH), 5.59 (s, 1H, CH), 3.36-3.25 (m, 2H, CH_2), 1.86 (s, 3H, CH_3).

4-(2,6-dichlorophenyl)-3-methyl-1-phenyl-4,8-dihydro-1*H*-pyrazolo[3,4-*e*][1,4]thiazepin-7(6*H*)-one (4j)

Pale yellow crystal, mp: 239-241 °C, IR (KBr, ν, cm^{-1}): 3222, 1684, 1586, 1390, 1252, 1138, 909, 811, 753 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.54-7.50 (m, 2H, ArH), 7.46-7.42 (m, 5H, ArH), 7.29 (br, s, 1H, NH), 7.21 (t, 1H, *J* = 8.0 Hz, ArH), 6.38 (s, 1H, CH), 3.70 (d, 1H, *J* = 14.8 Hz, CH_2), 3.18 (dd, 1H, *J* = 14.8, 2.0 Hz, CH_2), 1.80 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.4, 148.2, 136.0, 135.3, 132.8, 130.2, 129.9, 129.4, 128.9, 126.3, 125.8, 37.7, 31.5, 12.6; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{19}H_{16}Cl_2N_3OS^+$: 404.0386; found: 404.0395.

3-methyl-4-(naphthalen-1-yl)-1-phenyl-4,8-dihydro-1*H*-pyrazolo[3,4-*e*][1,4]thiazepin-7(6*H*)-one (4k)

Yellow solid, mp: 238-240 °C, IR (KBr, ν, cm^{-1}): 3169, 1682, 1588, 1492, 1254, 1138, 905, 738, 723 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.30 (d, 1H, *J* = 8.4 Hz, ArH), 7.95 (d, 1H, *J* = 7.6 Hz, ArH), 7.84 (d, 1H, *J* = 8.4 Hz, ArH), 7.69-7.65 (m, 1H, ArH), 7.61-7.56 (m, 3H, ArH), 7.54-7.50 (m, 3H, ArH), 7.46 (br, s, 1H, NH), 7.41 (t, 1H, *J* = 7.2 Hz, ArH), 7.12 (d, 1H, *J* = 6.4 Hz, ArH), 6.00 (s, 1H, CH), 3.39-3.29 (m, 2H, CH_2), 1.83 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.9, 148.3, 135.4, 134.5, 130.2, 129.3, 129.2, 129.0, 126.7, 126.2, 125.9, 124.9, 124.8, 123.0, 106.7, 39.2, 32.2, 12.6; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{23}H_{20}N_3OS^+$: 386.1322; found: 386.1328.

3-methyl-1-phenyl-4-(thiophen-2-yl)-4,8-dihydro-1*H*-pyrazolo[3,4-*e*][1,4]thiazepin-7(6*H*)-one (4l)

Brown oil, IR (KBr, ν, cm^{-1}): 3175, 1683, 1584, 1492, 1252, 1138, 905, 743, 718 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.57-7.53 (m, 2H, ArH), 7.50-7.45 (m, 3H, ArH), 7.38 (br, s, 1H, NH), 7.31-7.29 (m,

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1H, ArH), 6.95-6.93 (m, 1H, ArH), 6.84 (d, 1H, *J* = 3.2 Hz, ArH), 5.45 (s, 1H, CH), 3.39 (s, 2H, CH_2), 2.09 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.8, 148.1, 146.1, 134.2, 130.1, 129.2, 127.2, 126.7, 126.1, 125.8, 107.4, 38.3, 31.9, 12.6; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{17}H_{16}N_3OS_2^+$: 342.0729; found: 342.0732.

4-isobutyl-3-methyl-1-phenyl-4,8-dihydro-1*H*-pyrazolo[3,4-*e*][1,4]thiazepin-7(6*H*)-one (4m)

Yellow solid, mp: 97-98 °C, IR (KBr, v, cm^{-1}): 3124, 1680, 1591, 1393, 1157, 939, 809, 741, 729 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.52-7.48 (m, 2H, ArH), 7.44-7.40 (m, 3H, ArH), 7.07 (br, s, 1H, NH), 4.09-4.05 (m, 1H, CH), 3.49 (d, 1H, *J* = 14.0 Hz, CH_2), 3.13 (d, 1H, *J* = 13.6 Hz, CH_2), 2.31 (s, 3H, CH_3), 1.87-1.80 (m, 2H, CH_2), 1.76-1.71 (m, 1H, CH), 0.97 (d, *J* = 6.0 Hz, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.8, 147.0, 137.3, 133.6, 129.8, 128.5, 124.7, 112.1, 46.7, 36.2, 31.0, 25.5, 23.1, 21.5, 12.7; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{17}H_{22}N_3OS^+$: 316.1478; found: 316.1483.

3-methyl-4-octyl-1-phenyl-4,8-dihydro-1*H*-pyrazolo[3,4-*e*][1,4]thiazepin-7(6*H*)-one (4n)

Yellow oil, IR (KBr, v, cm^{-1}): 3131, 1681, 1590, 1397, 1155, 939, 806, 740, 725 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.54 (t, 2H, *J* = 7.2 Hz, ArH), 7.49-7.43 (m, 3H, ArH), 4.94 (t, 1H, *J* = 7.2 Hz, CH), 4.44 (br, s, 1H, NH), 3.38-3.25 (m, 2H, CH_2), 2.27-2.23 (m, 2H, CH_2), 2.14-2.09 (m, 5H, CH_3 + CH_2), 1.34-1.26 (m, 10H, CH_2), 0.88 (t, 3H, *J* = 6.4 Hz, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.3, 131.4, 130.1, 129.1, 125.9, 44.3, 31.8, 31.7, 31.0, 29.8, 29.4, 29.2, 29.1, 28.2, 22.7, 14.1, 12.6; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{21}H_{30}N_3OS^+$: 372.2104; found: 372.2108.

4-(4-chlorophenyl)-3-methyl-4,8-dihydro-1*H*-pyrazolo[3,4-*e*][1,4]thiazepin-7(6*H*)-one (4o) [9c]

White solid, mp: 287-288 °C, ^{1}H NMR (400 MHz, $CDCl_3$): δ = 12.32 (br, s, 1H, NH), 9.92 (s, 1H, NH), 7.37-7.33 (m, 2H, ArH), 7.24-7.22 (m, 2H, ArH), 5.47 (s, 1H, CH), 3.25 (dd, 1H, *J* = 14.8, 4.8 Hz, CH_2), 2.98 (dd, 1H, *J* = 14.8, 4.8 Hz, CH_2), 1.80 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.3, 142.3, 132.0, 130.1, 128.8, 106.5, 41.4, 31.9, 10.4.

3-methyl-4-(p-tolyl)-4,8-dihydro-1*H*-pyrazolo[3,4-*e*][1,4]thiazepin-7(6*H*)-one (4p) [9c]

White solid, mp: >300 °C, ^{1}H NMR (400 MHz, $CDCl_3$): δ = 12.30 (br, s, 1H, NH), 9.88 (s, 1H, NH), 7.09 (s, 4H, ArH), 5.40 (s, 1H, CH), 3.25 (d, 1H, *J* = 14.8 Hz, CH_2), 2.98 (d, 1H, *J* = 14.8 Hz, CH_2), 2.25 (s, 3H, CH_3), 1.78 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.4, 140.0, 136.7, 129.4, 128.2, 106.9, 42.0, 32.1, 21.1, 10.4.

4-(4-methoxyphenyl)-3-methyl-4,8-dihydro-1*H*-pyrazolo[3,4-*e*][1,4]thiazepin-7(6*H*)-one (4q) [9c,9d]

Pale yellow solid, mp: 278-280 °C, ^{1}H NMR (400 MHz, $CDCl_3$): δ = 12.31 (br, s, 1H, NH), 9.87 (s, 1H, NH), 7.12 (d, 2H, *J* = 8.4 Hz, ArH), 6.85 (d, 2H, *J* = 8.8 Hz, ArH), 5.40 (s, 1H, CH), 3.71 (s, 3H, OMe), 3.25 (d, 1H, *J* = 14.8 Hz, CH_2), 2.97 (d, 1H, *J* = 14.4 Hz, CH_2), 1.77 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.5, 158.6, 134.8, 129.4, 114.2, 107.1, 66.8, 55.5, 41.9, 32.2, 10.5.

3-methyl-4-(naphthalen-1-yl)-4,8-dihydro-1*H*-pyrazolo[3,4-*e*][1,4]thiazepin-7(6*H*)-one (4r)

White solid, mp: 234-236 °C, IR (KBr, v, cm^{-1}): 3171, 1681, 1589, 1493, 1256, 1137, 905, 737, 721 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 12.30 (br, s, 1H, NH), 10.05 (s, 1H, NH), 8.35 (d, 1H, *J* = 8.0 Hz, ArH), 7.95-7.93 (m, 1H, ArH), 7.82 (d, 1H, *J* = 8.4 Hz, ArH), 7.60-7.52 (m, 2H, ArH), 7.38 (t, 1H, *J* = 7.6 Hz, ArH), 7.04 (d, 1H, *J* = 6.8 Hz, ArH), 6.23 (s, 1H, CH), 3.21 (d, 1H, *J* = 15.2 Hz, CH_2), 3.08 (d, 1H, *J* = 14.8 Hz, CH_2), 1.66 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.1, 137.7, 134.2, 130.4, 129.2, 128.4, 126.6, 126.3, 126.1, 125.5, 124.2, 106.3, 38.7, 32.4, 10.4; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{17}H_{16}N_3OS^+$: 310.1009; found: 310.1015.

3-methyl-4-(thiophen-2-yl)-4,8-dihydro-1*H*-pyrazolo[3,4-*e*][1,4]thiazepin-7(6*H*)-one (4s)

Brown solid, mp: 249-250 °C, IR (KBr, v, cm^{-1}): 3177, 1682, 1585, 1492, 1250, 1137, 905, 746, 720 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 12.32 (br, s, 1H, NH), 9.91 (s, 1H, NH), 7.41-7.38 (m, 1H, ArH), 6.94-6.89 (m, 2H, ArH), 5.71 (s, 1H, CH), 3.28 (d, 1H, *J* = 14.4 Hz, CH_2), 2.97 (d, 1H, *J* = 14.8 Hz, CH_2), 1.94 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.9, 148.1, 127.1, 126.3, 126.2, 107.5, 66.8, 37.3, 32.2, 10.3; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{11}H_{12}N_3OS_2^+$: 266.0416; found: 266.0421.

2-(((2,4-diamino-6-oxo-1,6-dihydropyrimidin-5-yl)(*p*-tolyl)methyl)thio)acetic acid (5)

White solid, mp: 150-152 °C, ^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.07 (br, s, 1H, NH), 7.26 (d, 2H, *J* = 8.0 Hz, ArH), 7.07 (d, 2H, *J* = 8.0 Hz, ArH), 6.21 (s, 2H, NH_2), 5.77 (s, 2H, NH_2), 5.64 (s, 1H, CH), 3.12 (d, 2H, *J* = 2.0 Hz, CH_2), 2.23 (s, 3H, CH_3).

ethyl 2-(((5-amino-3-methyl-1-phenyl-1*H*-pyrazol-4-yl)(4-chlorophenyl)methyl)thio)acetate (6a)

Yellow solid, mp: 146-148 °C, IR (KBr, v, cm^{-1}): 3219, 1688, 1616, 1492, 1250, 1036, 906, 808, 741, 727cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.57 (d, 2H, *J* = 7.2 Hz, ArH), 7.56-7.50 (m, 2H, ArH), 7.47-7.44 (m, 2H, ArH), 7.37 (d, 1H, *J* = 7.6 Hz, ArH), 7.34-7.31 (m, 2H, ArH), 5.44 (s, 1H, CH), 4.41 (s, 2H, NH_2), 4.21-4.13 (m, 2H, CH_2), 3.25-3.15 (m, 2H, CH_2), 2.12 (s, 3H, CH_3), 1.30 (t, 3H, *J* = 7.2 Hz, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.5, 137.6, 133.3, 129.6, 128.8, 127.4, 123.9, 61.6, 44.1, 33.6, 14.2, 12.4; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{21}H_{23}ClN_3O_2S^+$: 416.1194; found: 416.1188.

ethyl 2-(((5-amino-3-methyl-1-phenyl-1*H*-pyrazol-4-yl)(*p*-tolyl)methyl)thio)acetate (6b)

Red brown oil, IR (KBr, v, cm^{-1}): 3179, 1681, 1586, 1492, 1250, 1137, 907, 739, 721 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.63 (d, 2H, *J* = 8.0 Hz, ArH), 7.59-7.53 (m, 2H, ArH), 7.48 (d, 1H, *J* = 8.0 Hz, ArH), 7.37 (d, 2H, *J* = 8.0 Hz, ArH), 7.19 (d, 2H, *J* = 8.0 Hz, ArH), 5.43 (s, 1H, CH), 4.21-4.15 (m, 2H, CH_2), 3.21 (s, 2H, CH_2), 2.36 (s, 3H, CH_3), 2.23 (s, 3H, CH_3), 1.30 (t, 3H, *J* = 7.2 Hz, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.5, 129.8, 129.3, 124.3, 114.1, 61.6, 55.3, 44.0, 33.7, 29.7, 14.2; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{22}H_{26}N_3O_2S^+$: 396.1740; found: 396.1735.

ethyl 2-(((5-amino-3-methyl-1-phenyl-1*H*-pyrazol-4-yl)(4-methoxyphenyl)methyl)thio)acetate (6c)

Red brown oil, IR (KBr, v, cm^{-1}): 3218, 1680, 1608, 1390, 1070, 900, 842, 722 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.61 (d, 2H, *J* = 8.0 Hz, ArH), 7.53 (t, 2H, *J* = 7.6 Hz, ArH), 7.42 (d, 3H, *J* = 8.8 Hz,

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ArH), 6.90 (d, 2H, *J* = 8.8 Hz, ArH), 5.42 (s, 1H, CH), 4.71 (s, 2H, NH_2), 4.22-4.13 (m, 2H, CH_2), 3.82 (s, 3H, OMe), 3.24-3.16 (m, 2H, CH_2), 2.19 (s, 3H, CH_3), 1.30 (t, 3H, *J* = 7.2 Hz, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.5, 130.1, 129.6, 127.9, 124.7, 61.5, 44.3, 33.5, 29.7, 18.9, 14.1; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{22}H_{26}N_3O_3S^+$: 412.1689; found: 412.1694.

ethyl 2-(((5-amino-3-methyl-1-phenyl-1*H*-pyrazol-4-yl)(thiophen-2-yl)methyl)thio)acetate (6d)

Brown oil, IR (KBr, ν, cm^{-1}): 3177, 1680, 1585, 1491, 1259, 1134, 909, 745, 720 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.56 (d, 2H, *J* = 8.0 Hz, ArH), 7.50-7.47 (m, 2H, ArH), 7.37-7.33 (m, 1H, ArH), 7.27-7.24 (m, 1H, ArH), 7.08-7.06 (m, 1H, ArH), 5.65 (s, 1H, CH), 4.30 (s, 2H, NH_2), 4.21-4.13 (m, 2H, CH_2), 3.28-3.20 (m, 2H, CH_2), 2.20 (s, 3H, CH_3), 1.30 (t, 3H, *J* = 7.2 Hz, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.5, 148.3, 143.7, 143.5, 129.6, 127.4, 126.9, 125.9, 125.4, 123.9, 99.2, 61.6, 40.0, 33.6, 14.2, 12.3; HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{19}H_{22}N_3O_2S_2^+$: 388.1148; found: 388.1156.

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Notes and references

1 (a) M. D. Ghooghe, T. Vanlangendonck, K. W. THrnroos and N. De Kimpe, *J. Org. Chem.,* 2006, **71**, 4678-4681; (b) R. Pedrosa, C. AndrIs, P. MendiguchJa and J. Nieto, *J. Org. Chem.,* 2006, **71**, 8854-8863; (c) B. A. Lanman and A. G. Myers, *Org. Lett.,* 2004, **6**, 1045-1047.

2 (a) B. Zaleska, D. Ciez, J. Grochowski, P. Serda and W. Winnik, *Liebigs Ann.,* 1996, **2**, 211-215; (b) P. G. Sammers, *Chem. Rev.,* 1976, **76**, 113-155; (c) S. A. Matlin and L. Chan, *Chem. Commun.,* 1980, 798-799; (d) A. Levai, J. Ott and G. Snatzke, *Monatsh. Chem.,* 1992, **123**, 919-930; (e) J. Bohrisch, H. Faltz, M. Patzel and J. Liebscher, *Tetrahedron,* 1994, **50**, 10701-10708.

3 B. A. Meiners and A. I. Salama, *Eur. J. Pharmacol.,* 1982, **78**, 315-322.

4 F. Manetti, S. Schenone, F. Bondavalli, C. Brullo, O. Bruno, A. Ranise, L. Mosti, G. Menozzi, P. Fossa, M. L. Trincavelli, C. Martini, A. Martinelli, C. Tintori and M. Botta, *J. Med. Chem.,* 2005, **48**, 7172-7185.

5 B. Lynck, M. Khan, H. Teo and F. Pedrotti, *Can. J. Chem.,* 1988, **66**, 420-428.

6 Y. L. Chen, WO9534563 A1, 1995; *Chem. Abstr.,* 1995, **124**, 232447.

7 L. Revesz, E. Blum, F. E. Di Padova, T. Buhl, R. Feifel, H. Gram, P. Hiestand, U. Manning, U. Neumann and G. Rucklin, *Bioorg. Med. Chem. Lett.,* 2006, **16**, 262-266.

8 J. N. Hamblin, T. D. R. Angell, S. P. Ballantine, C. M. Cook, A. W. J. Cooper, J. Dawson, C. J. Delves, P. S. Jones, M. Lindvall, F. S. Lucas, C. J. Mitchell, M. Y. Neu, L. E. Ranshaw, Y. E. Solanke, D. O. Somers and J. O. Wiseman, *Bioorg. Med. Chem. Lett.,* 2008, **18**, 4237-4241.

9 (a) S.-J. Tu, X.-D. Cao, W.-J. Hao, X.-H. Zhang, S. Yan, S.-S. Wu, Z.-G. Han and F. Shi, *Org. Biomol. Chem.,* 2009, **7**, 557-563; (b) F. Shi, X.-N. Zeng, X.-D. Cao, S. Zhang, B. Jiang, W.-F. Zheng and S.-J. Tu, *Bioorg. Med. Chem. Lett.,* 2012, **22**, 743-746; (c) R. Abonia, *Curr. Org. Synth.,* 2014, **11**, 773-786; (d) A. Dandia, R. Singh, J. Joshi and S. Maheshwari, *Res. Chem. Intermed.,* 2015, **41**, 4213-4226.

10 A. F. Lee and K. Wilson, *Catal. Today,* 2015, **242**, 3-18.

11 (a) J. M. Thomas, *Proc. R. Soc. A: Math. Phys. Eng. Sci.,* 2012, **468**, 1884-1903. (b) G. A. Somorjai, H. Frei and J. Y. Park, *J. Am. Chem. Soc.,* 2009, **131**, 16589-16605.

12 (a) K. Narasimharao, D. R. Brown, A. F. Lee, A. D. Newman, P. F. Siril, S. J. Tavener and K. Wilson, *J. Catal.,* 2007, **248**, 226-234; (b) K. Suwannakarn, E. Lotero, K. Ngaosuwan and J. G. Goodwin Jr., *Ind. Eng. Chem. Res.,* 2009, **48**, 2810-2818; (c) M. Kouzu, A. Nakagaito and J.-S. Hidaka, *Appl. Catal. A: Gen.,* 2011, **405**, 36-44; (d) E. Lotero, Y. Liu, D. E. Lopez, K. Suwannakarn, D. A. Bruce and J. G. Goodwin, *Ind. Eng. Chem. Res.,* **2005**, *44*, 5353-5363.

13 (a) R. H. Vekariya, K. D. Patel and H. D. Patel, *RSC Adv.,* 2015, **5**, 90819-90837; (b) S. S. Kauthale, S. U. Tekale, A. B. Rode, S. V. Shinde, K. L. Ameta and R. P. Pawar, *Heterog. Catal.,* 2015, 133-162; (c) G. Mohammadi Ziarani, N. Lashgari and A. Badiei, *J. Mol. Catal. A: Chem.,* 2015, **397**, 166-191; (d) M. B. Gawande, R. Hosseinpour and R. Luque, *Curr. Org. Synth.,* 2014, **11**, 526-544; (e) P. Gholamzadeh, G. Mohammadi Ziarani, N. Lashgari, A. Badiei and P. Asadiatouei, *J. Mol. Catal. A: Chem.,* 2015, **391**, 208-222; (f) M. K. Patil, A. N. Prasad and B. M. Reddy, *Curr. Org. Chem.,* 2011, **15**, 3961-3985.

14 (a) X. Z. Liang, M. F. Zeng and C. Z. Qi, *Carbon,* 2010, **48**, 1844-1848; (b) X. Z. Liang, H. Q. Xiao, Y. M. Shen and C. Z. Qi, *Mater. Lett.,* 2010, **64**, 953-955; (c) X. Z. Liang, *Chem. Eng. J.,* 2015, **264**, 251-257; (d) X. Z. Liang, H. Q. Xiao and C. Z. Qi, *Fuel Process. Technol.,* 2013, **110**, 109-113; (e) X. Z. Liang, *Ind. Eng. Chem. Res.,* 2013, **52**, 6894-6900; (f) X. Z. Liang and J. G. Yang, *Green Chem.,* 2010, **12**, 201-204; (g) X. Z. Liang, S. Gao, J. G. Yang and M. Y. He, *Catal. Lett.,* 2008, **125**, 396-400.

15 (a) C. M. Li, X. Z. Liang, F. R. Zhang and C. Z. Qi, *Catal. Commun.,* 2015, **62**, 6-9; (b) F. R. Zhang, C. M. Li, C. Wang and C. Z. Qi, *Org. Biomol. Chem.,* 2015, **13**, 5022-5027; (c) Z. Chen, Y. X. Shi, Q. Q. Shen, H. X. Xu and F. R. Zhang, *Tetrahedron Lett.,* 2015, **56**, 4749-4752; (d) C. M. L and F. R. Zhang, *RSC Adv.,* 2016, **6**, 75359-75364.

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Synthesis of 4,8-dihydro-1*H*-pyrazolo[3,4-*e*][1,4]thiazepin -7(6*H*)-one derivatives by solid acid-catalyzed multi-component reaction in water