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SYNTHESIS OF 2-(2-(4-PHENYL-2,3-DIHYDROBENZO[B][1,4]THIAZEPIN-2-YL) PHENOXY)-*N*-(*P*-TOLYL)ACETAMIDE

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Abstract: The A new benzothiazepine's derivative names *N*-(*p*-tolyl)-2-(2-(4-phenyl-2,3-dihydrobenzo[*b*][1,4]thiazepin-2-yl)phenoxy)acetamide was synthesized by reaction of *o*-aminothiophenol and *N*-(*p*-tolyl)-2-(2-(3-oxo-3-phenylprop-1-en-1-yl)phenoxy)acetamide, which was prepared from salicylaldehyde and acetophenone through (*E*)-3-(2-hydroxyphenyl)-1-phenylprop-2-en-1-one. The structures of the compounds were determined by IR, ^{1}H-NMR, ^{13}C-NMR and HR-MS spectral data.

***Keywords*:** Acetamide; Benzothiazepine derivatives; Chalcone.

Introduction

Chalcones are important starting materials for the synthesis of biologically important heterocycles such as pyrazolines, isoxazolines, benzodiazepines, benzothiazepines etc. Some of the substituted chalcones and their derivatives have been reported to possess some interesting

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biological properties, which are anti-inflammatory[1] anticancer,[2] antioxidant[3] and anti-diabetic activities.[4]

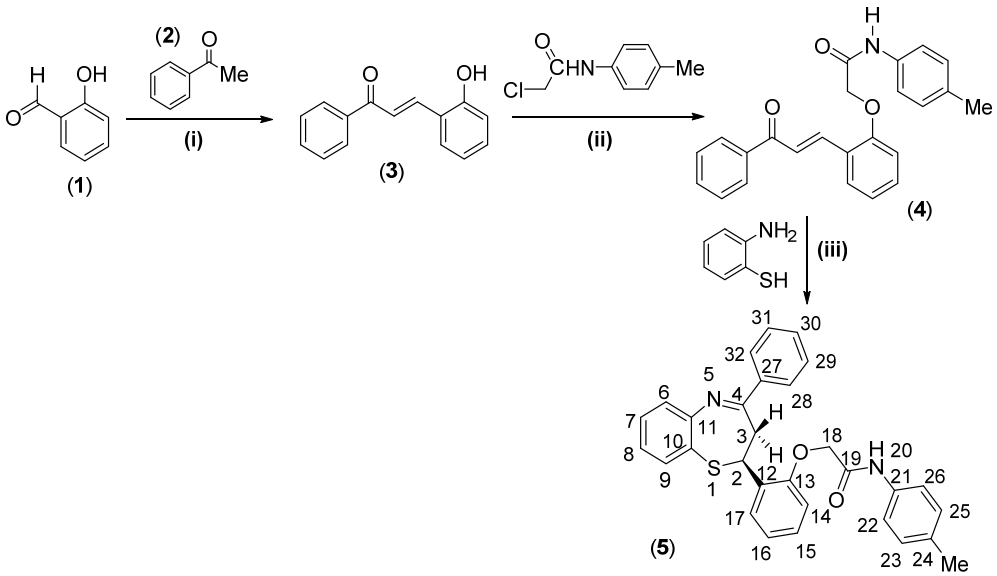
Benzothiazepine derivatives are reported to possess a wide range of biological activities including antimicrobial,[5,6] antioxidant,[7] anticonvulsant[8] and anticancer[9] agents. This study describes the preparation of *N*-(*p*-tolyl)-2-(2-(3-oxo-3-phenylprop-1-en-1-yl)phenoxy)acetamide and transformation of this compound into *N*-(*p*-tolyl)-2-(2-(4-phenyl-2,3-dihydrobenzo[*b*][1,4]thiazepin-2-yl)phenoxy)acetamide .

Results and Discussion

The reaction pathway for synthesis of *N*-(*p*-tolyl)-2-(2-(4-phenyl-2,3-dihydrobenzo[*b*][1,4]thiazepin-2-yl)phenoxy)acetamide (**5**) is illustrated in Scheme 1, with the numeration of formulas given for NMR analysis.

2-Hydroxychalcone (**3**) was prepared by the condensation of salicylaldehyde (**1**) with acetophenone (**2**) in ethyl alcohol under alkaline conditions as described in literatures.[2,10] Physical properties as well as IR and ^{1}H-NMR spectral data of (**3**) were in conformity with referring data in the previous studies.[2,10] In addition, the coupling between α-H (δ = 7.86) and β-H (δ = 8.08) with *spin-spin* coupling constant (*J* = 17,0 Hz) indicated that the chalcone (**3**) existed in the (*E*)-configuration.

Stirring mixture of 2-hydroxychalcone (**3**) and *N*-(4-methylphenyl)-2-chloroacetamide in acetone containing potassium carbonate gave substituted chalcone (**4**). The IR, ^{1}H NMR, ^{13}C-NMR and mass spectra of the product were in agreement with the proposed structure. However, chemical shifts of the α-H and β-H in the ^{1}H NMR spectrum are almost equivalent. Thus, signals of these protons appeared as a singlet with intensity of 2H in the spectrum; coupling was not observed.



Scheme 1. Synthetic route to *N*-(*p*-tolyl)-2-(2-(4-phenyl-2,3-dihydrobenzo[b][1,4]thiazepin-2-yl)phenoxy)acetamide (**5**). Reagents, conditions and yields: **(i)** KOH, EtOH, r.t., 4 h, 69%; **(ii)** K_2CO_3, acetone, reflux, 6 h, 59 %; **(iii)** Ethanol, reflux, 21 h, 44%.

The substituted chalcone (**4**) was converted into benzothiazepine (**5**) upon reaction with 2-aminothiophenol. The structure of the synthesised compound was confirmed by IR, ^{1}H-NMR, ^{13}C-NMR and mass spectra. The formation of the benzothiazepine ring can be easily seen by the presence of three characteristic signals of the protons at the second and the third positions on this ring in the ^{1}H-NMR spectrum. In the ^{1}H NMR spectrum, one of the two diastereotopic protons appeared as a *triplet* at 2.70 ppm, while the other diastereotopic proton and the benzylic proton appeared as two *doublets* of *doublets* at 3.53 and 5.71 ppm, respectively. However, contrary to the expected result, the signal of the methylene protons at 18th position was split instead of *singlet*. The split of this signal can probably be explained by *non–first order splitting* effect. The signals in the ^{1}H-NMR and ^{13}C-NMR of compound (**5**) were assigned by using Heteronuclear

Quantum Coherence (HSQC) spectroscopy and Heteronuclear Multiple Bond Correlation (HMBC) spectroscopy.

Experimental

Materials and measurements

The chemical used e.g., salicylaldehyde **(1)**, acetophenone **(2)** were laboratory grade and supplied by Merck (Singapore). Melting points were determined on a Gallenkamp apparatus and were uncorrected. Infrared (IR) spectra were recorded on a Shimadzu FTIR-8400S spectrophotometer. Nuclear magnetic resonance (NMR) spectra were recorded on a Bruker Avance instrument (500 MHz) using deuterated dimethylsulfoxide solutions containing tetramethylsilane as an internal standard. The *spin-spin* coupling constants (*J*) are given in Hz. HR-MS experiments were performed using a Bruker micrOTOF-Q 10187.

Synthesis and characterization

*General procedure for synthesis of (E)-3-(2-hydroxyphenyl)-1-phenylprop-2-en-1-one (**3**)*

A solution of 0.022 mol acetophenone was slowly added to a potassium hydroxide solution in 10 mL ethanol (3.36 g of potassium hydroxide in 15 mL ethanol) while stirring for 30 minutes. Salicylaldehyde (0.02 mol) was continuously added to this solution for 30 minutes. The obtained mixture was stirred for 3 h at room temperature and kept overnight in a refrigerator. Then, was poured into ice water and acidified with diluted HCl.

The solid obtained was filtered, washed thoroughly with water, and dried. Crystallisation of the crude residue from ethanol afforded 69% of (**3**) as yellow solid; m.p. 147-149 °C (154-155 °C);[2] IR (ν, cm^{-1}, KBr): 3240

(*broad*, OH), 3086 (C-H), 1643 (C=O), 1600 (C=C); ^{1}H NMR (500 MHz, DMSO-d_6): δ 6.96 (1H, *d*, *J* = 7.5, ArH), 6.89 (1H, *dd*, $J_1 = J_2$ = 7.5, ArH), 7.30 (1H, *dd*, $J_1 = J_2$ = 7.5, ArH), 7.57 (2H, *d*, *J* = 7.5, ArH), 7.66 (1H, *dd*, $J_1 = J_2$ = 7.5, ArH), 7.86 (1H, *dd*, J_1 = 7.5, J_2 = 1.5, ArH), 7.86 (1H, *d*, *J* = 17.0, α-H), 8.08 (1H, *d*, *J* = 17.0, β-H), 8.10 (2H, *d*, *J* = 7.5, ArH), 10.29 (1H, *s*, OH); ^{13}C NMR (125 MHz, DMSO-d_6): δ 116.2, 119.4, 121.0, 121.4, 128.3, 128.7, 128.8, 132.1, 132.9, 137.9, 139.6, 157.3, 189.5.

*General procedure for synthesis of (E)-2-(2-(3-oxo-3-phenylprop-1-en-1-yl)phenoxy)-N-(p- tolyl)acetamide (**4**)*

Chalcone (**3**) (0.01 mol) and potassium carbonate (0.012 mol) were stirred in dry acetone (15 mL), and added dropwise to the solution of *N*-(4-methylphenyl) 2-chloroacetamide (0.01 mol) in acetone (10 mL). The reaction mixture was refluxed for 6 h and then cooled to room temperature. After the solid separated was poured in ice cold water, it was filtered and recrystallised from ethanol to give 59% of (**4**) as white needle crystals: m.p. 200-202 °C, IR (ν, cm^{-1}, KBr): ν 3410, 3155 (N-H), 3063 and 2924 (C-H), 1690 (C=O), 1659 and 1597 (C=C); ^{1}H NMR (500 MHz, DMSO-d_6): δ 2.28 (3H, *s*, CH_3), 4.87 (2H, *s*, CH_2), 7.05 (1H, *d*, *J* = 8.0, ArH), 7.08 (1H, *dd*, $J_1 = J_2$ = 7.5, ArH), 7.15 (2H, *d*, *J* = 8.5, ArH), 7.45 (1H, *dd*, $J_1 = J_2$ = 8.5, ArH), 7.53 (2H, *d*, *J* = 8.0, ArH), 7.56 (2H, *dd*, $J_1 = J_2$ = 8.0, ArH), 7.67 (1H, *dd*, $J_1 = J_2$ = 7.5, ArH), 7.98 (1H, *dd*, J_1 = 7.5, J_2 = 1.5, ArH), 8.10 (2H, s, α-H, β-H), 8.17 (2H, *d*, *J* = 8.0, ArH), 10.24 (1H, *s*, NH); ^{13}C NMR (125 MHz, DMSO-d_6): δ 115.8, 118.5, 125.8, 128.3, 128.7, 131.1, 132.8, 138.0, 144.6, 160.0, 189.0; HR-MS calcd for $C_{24}H_{21}NNaO_3$, 394.1419; found, 394.1446 $(M+Na)^+$.

*General procedure for synthesis 2-(2-(4-phenyl-2,3-dihydrobenzo[b] [1,4]thiazepin-2-yl)phenoxy)-N-(p-tolyl)acetamide (**5**)*

Chalcone (**4**) (0.01 mol), and 2-aminothiophenol (0.01 mol) in ethanol (30 mL), along with few drops of glacial acetic acid, were refluxed in a water bath for 21 h, and then cooled to room temperature. The solid separated was filtered and recrystallised from ethanol to give 44% (**5**) as light yellow needle crystals: m.p. 175-176 °C, IR (ν, cm^{-1}, KBr): 3256 (N-H), 3055 and 2924 (C-H), 1674 (C=O), 1605 (C=C); ^{1}H NMR (500 MHz, DMSO-d_6): δ 2.27 (3H, *s*, H-24a), 2.70 (1H, *t, J*= 13.0, H-3), 3.53 (1H, *dd*, J_1=13.0; J_2=4.5, H-3), 4.84 (2H, *q, J*=4.5, H-18), 5.71 (1H, *dd*, J_1=13.0; J_2=4.5, H-2), 7.00 (1H, *dd*, ^3J=7.5, H-16), 7.02 (1H, *d*, ^3J=7.5, H-14), 7.14 (2H, *d*, ^3J= 7.5, H-23,25), 7.21 (1H, *dd*, ^3J=7.5, H-8), 7.27 (1H, *d*, ^3J=7.5, H-6), 7.28 (1H, *dd*, ^3J=7.5, H-15), 7.47 (1H, *dd*, ^3J=7.5, H-29,31), 7.51 (4H, *m*, H-7,22,26,30), 7.58 (1H, *d*, ^3J= 7.5, H-17), 7.71 (1H, *d*, ^3J= 7.5, H-9), 8.22 (2H, *d*, ^3J= 7.5, H-28,32), 10.11 (1H, *s*, H-20); ^{13}C NMR (125 MHz, DMSO-d_6): δ 20.5 (C-24a), 35.7 (C-3), 53.6 (C-2), 67.7 (C-18), 112.0 (C-14), 119.5 (C-22,26), 121.4 (C-16), 121.5 (C-10), 125.1 (C-6), 125.3 (C-8), 126.7 (C-17), 127.4 (C-28,32), 128.7 (C-15), 128.8 (C-29,31), 129.2 (C-23,25), 129.9 (C-7), 131.1 (C-24), 132.2 (C-30), 132.7 (C-12), 134.9 (C-9), 135.9 (C-21), 137.0 (C-27), 152.3 (C-11), 153.4 (C-13), 166.2 (C-19) and 168.8 (C-4); HR-MS calcd for $C_{30}H_{27}N_2O_2S$, 479.1793; found, 479.1777 $(M+H)^+$.

Conclusions

The two new compounds: *N*-(*p*-tolyl)-2-(2-(3-oxo-3-phenylprop-1-en-1-yl)phenoxy)acetamide **(4)** and *N*-(*p*-tolyl)-2-(2-(4-phenyl-2,3-dihydrobenzo[*b*][1,4]thiazepin-2-yl)phenoxy)acetamide **(5)** were synthesized.

Their structures were also determined by IR, ^{1}H-NMR, ^{13}C-NMR and HR-MS spectral data.

References

1. Won, S. J.; Liu, C. T.; Tsao, L. T.; Weng, J. R.; Ko, H. H.; Wang, J. P.; Lin, C. N. Synthetic chalcones as potential anti-inflammatory and cancer chemopreventive agents. *Eur. J. Med. Chem.* **2005**, *40*, 103–112.

2. Syam, S.; Abdelwahab, S. I.; Al-Mamary, M. A.; Mohan, S. Synthesis of chalcones with anticancer activities. *Mol*. **2012**, *17*, 6179–6195.

3. Venkatachalam, H.; Nayak, Y.; Jayashree, B. S. Synthesis, characterization and antioxidant activities of synthetic chalcones and flavones. *APCBEE Proc.* **2012**, *3*, 209–213.

4. Hsieh, C. T.; Hsieh, T. J.; Shazly, E. M.; Chuang, D. W.; Tsai, Y. H.; Yen, C. T.; Wu, S. F.; Wu, Y. C.; Chang, F. R. Synthesis of chalcone derivatives as potential anti-diabetic agents. *Bioorg. Med. Chem. Lett*. **2012**, *22*, 3912–3915.

5. Wang, L.; Zhang, P.; Zhang, X.; Zhang, Y.; Li, Y.; Wang, Y. Synthesis and biological evaluation of a novel series of 1,5-benzothiazepine derivatives as potential antimicrobial agents. *Eur. J. Med. Chem*. **2009**, *44*, 2815–2821.

6. Cherkupally, S. R.; Gurrala, P. R.; Adki, N.; Avula, S. Synthesis and biological study of novel methylene-bis-benzofuranyl-[1,5]-benzothiazepines. *Org. Commun*. **2008**, *4*, 84–94.

7. Renuka, N.; Pavithra, G.; Ajay Kumar, K. Synthesis and their antioxidant activity studies of 1, 4-benzothiazepine analogues. *Der. Pharma. Chem*. **2014**, *6*, 482–485.

8. Garg, N.; Chandra, T.; Jain, A. B.; Kumar, A. Synthesis and evaluation of some new substituted benzothiazepine and benzoxazepine derivatives as anticonvulsant agents. *Eur. J. Med. Chem*. **2010**, *45*, 1529–1553.

9. Ameta, K. L.; Rathore, N. S.; Kumar, B. Synthesis and preliminary evaluation of novel 1, 5-. benzothiazepine derivatives as anti-lung cancer agents. *Int. J. Pharm*. **2013**, *3*, 328–333.

10. Saha, P.; Biswas, A.; Molleti, N.; Singh, V. K. Enantioselective synthesis of highly substituted chromans via the oxa-michael-michael cascade reaction with a bifunctional organocatalyst. *J. Org. Chem*. **2015**, *80*, 11115–11122.