Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron Letters
Tetrahedron Letters 48 (2007) 4461–4465

An efficient synthesis of 4-bromo-N-substituted oxindoles by an intramolecular copper-catalyzed amidation reaction

Adri van den Hoogenband,* Jos H. M. Lange, Jack A. J. den Hartog, Remco Henzen and Jan Willem Terpstra

Solvay Pharmaceuticals, Research Laboratories, C. J. van Houtenlaan 36, 1381 CP Weesp, The Netherlands

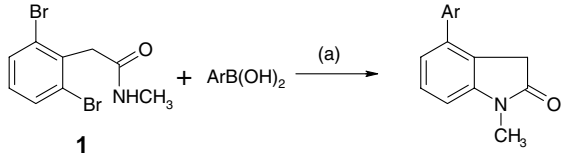
Received 7 February 2007; revised 24 April 2007; accepted 2 May 2007
Available online 10 May 2007

Abstract—A highly efficient synthetic approach to novel 4-bromo-N-substituted oxindoles is described. The method involves a mild intramolecular copper-catalyzed amidation reaction of N-substituted 2,6-dibromophenylacetamides. In contrast to our recently published palladium-catalyzed amidation reaction, no concomitant dimerization on the 3-position of the formed oxindole occurs.

The 1,3-dihydroindol-2-one (oxindole) motif is present in several biologically active compounds like the anti-Parkinson's drug ropinirole[1] and the growth hormone secretagogues.[2] In addition, the oxindole moiety plays an important role in P-glycoprotein-mediated multiple drug resistance inhibitors,[3] anti-inflammatory agents,[4] non-opioid nociceptin receptor ligands[5] and serotonergics.[6,7] Moreover, the oxindole unit is a key element in several natural products[8] and 3-unsubstituted oxindoles are important starting materials for further functionalization.[9] As a consequence, the development of efficient synthetic strategies towards 3-unsubstituted oxindoles is of great importance. Many examples of novel oxindole syntheses have been reported including the intramolecular Heck reaction,[10] the intramolecular palladium-catalyzed α-arylation reaction from 2-halophenylacetamides,[11] from α-chloroacetanilides via an intramolecular palladium-catalyzed C–H functionalization[12] and a palladium-catalyzed domino process.[13] The majority of these methods lead to 3-monosubstituted or 3,3-disubstituted oxindoles whereas straightforward synthetic approaches to the less stable 3-unsubstituted oxindoles are uncommon.

Recently, we disclosed an intramolecular palladium-catalyzed amidation reaction for the preparation of 3-unsubstituted, pharmaceutically interesting *N*-(piperidin-4-yl)-1,3-dihydroindol-2-one as a key intermediate in the synthesis of ORL-1 receptor ligands.[14] The method was based on the work of Buchwald,[15] applying X-Phos.[16] Thereafter, more examples were reported, all based on the same or related methodology.[17] The synthesis of several 4-aryl-1-methyloxindoles involving the intramolecular palladium-catalyzed amidation of *N*-methyl-2,6-dibromophenylacetamide **1**, followed by a Suzuki cross-coupling with arylboronic acids (Scheme 1) in a one-pot reaction, formed an intriguing extension.[18] In the absence of any boronic acid, compound **2** (Fig. 1) was formed instead of 4-bromo oxindole **3**.

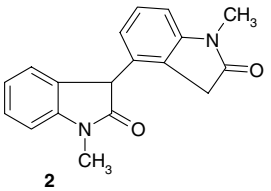
Due to our continued interest in the application of copper chemistry[19] as well as in the preparation of 4-bromo-1-substituted oxindoles, it was decided to investigate the ring closure reaction of *N*-methyl-2,6-dibromophenylacetamide **1** under copper-catalyzed conditions. Copper-catalyzed hetero cross-coupling reactions constitute a fast growing synthetic area.[20] Since Buchwald's pioneering work,[21] significant progress has been made and nowadays copper-catalyzed chemistry has become



Scheme 1. Reagents and conditions: (a) 1.5 mol equiv $ArB(OH)_2$; 3 mol equiv K_2CO_3; 5 mol % $Pd(OAc)_2$; 12.5 mol % X-Phos; *t*-BuOH, 85 °C.

* Corresponding author. Tel.: +31 0 294 479605; fax: +31 0 294 477138; e-mail: adri.vandenhoogenband@solvay.com

0040-4039/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2007.05.009

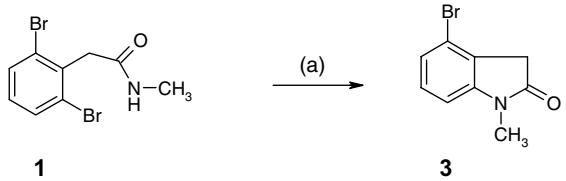


2

Figure 1.

complementary to palladium-catalyzed hetero cross-coupling chemistry. The first attempt to achieve this ring closure reaction of *N*-methyl-2,6-dibromophenylacetamide **1** under copper-catalyzed conditions was inspired by reports from De Vries et al. who disclosed an optimized method for the copper-catalyzed amination of functionalized aryl bromides in which CuCl was applied as a cheap copper catalyst in combination with a commercially available diketone as the ligand.[22] Their results were confirmed by Buchwald.[23] After a brief survey of reaction conditions, the amidation reaction of compound **1** gave 4-bromo-*N*-methyloxindole **3** in a high yield (84%) without a trace of the dimeric compound **2** (Scheme 2). Since a literature survey revealed that 3-unsubstituted 4-bromo-N-substituted oxindoles are very uncommon, it was decided to examine the generality of our copper-based synthetic methodology. The N-substituted 2,6-dibromophenylacetamides **4**–**7** were prepared[18] with only a slight modification in the last step wherein only 1 equiv of the appropriate amine was used and potassium carbonate was applied as an acid scavenger. These amides[24] **4**–**7** were subsequently subjected to the intramolecular copper-catalyzed amidation reactions as described in Table 1 to yield the 4-bromooxindoles **8**–**11**, respectively. It should be noted that all yields refer to isolated pure products.[25,26]

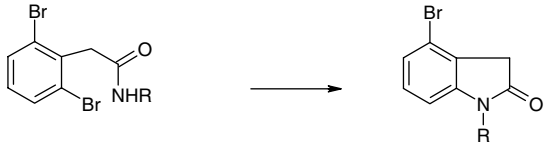
In general, the intramolecular copper-catalyzed amidation reactions proceeded cleanly within a few hours in fair to high yields. Compound **8** is of importance as an attractive synthetic target for further development of ORL-1 receptor ligands. Of special note is the synthesis of **9** and **10** as an alternative method to the direct copper-catalyzed N-arylation of 3-unsubstituted oxindoles recently described by Phillips et al.[27] It is interesting to note that the synthesis of compound **11** required a significantly longer reaction time, probably due to steric hindrance. Decomposition of the 3-unsubstituted oxindole **11**, which turned out to be unstable under the applied basic conditions during the prolonged reaction time, was observed. After 6 h, compound **11** was isolated in a disappointingly low yield of 15%. A prolonged reaction overnight gave a slightly higher yield but resulted in the concomitant formation of intractable material which made purification more difficult. Replacement of the acetylacetonate ligand for 2-acetylcyclohexanone furnished **11** in 20% yield after a reaction time of 22 h accompanied by 50% recovery of the starting material. During the course of our investigations, an article was published concerning the synthesis of 3-substituted N-alkylated oxindoles by a microwave copper-catalyzed amidation[28] wherein steric effects in the ring closure were also reported. In agreement with our results, the formation of their 3-substituted *N*-*t*-butyl oxindoles was found to be very problematical. A competing O-arylation reaction resulting in a 2-(*t*-butylamino)benzo[*b*]furan was not observed during our investigations.



1 **3**

Scheme 2. Reagents and conditions: (a) 1 mol equiv **1**; 5 mol equiv K_2CO_3; 10 mol % CuCl; 25 mol % acetylacetonate (acac); NMP, 85 °C.

Table 1.



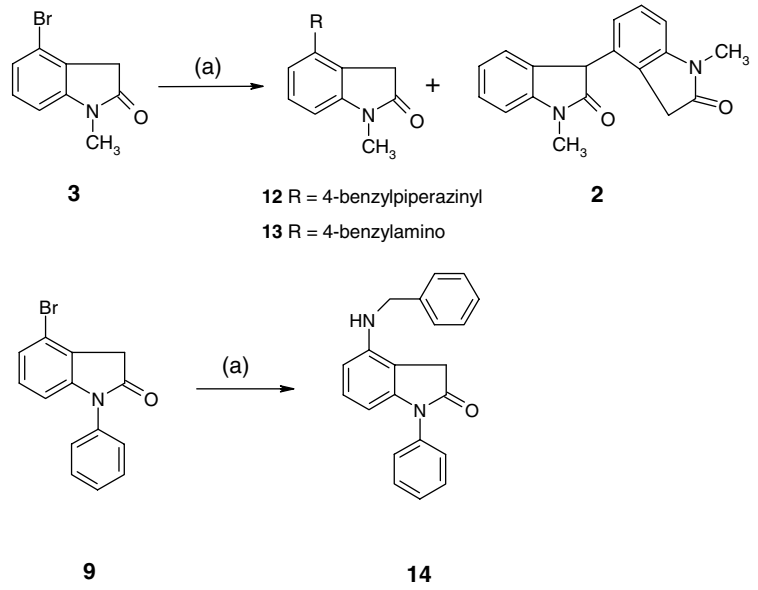
1 and **4-7** **3** and **8-11**

R	Reactant	Product	Time (h)	Yield (%)
Methyl	**1**	**3**	1	84
1-Benzylpiperidin-4-yl	**4**	**8**	3.5	55
Phenyl	**5**	**9**	1	83
4-Pyridyl	**6**	**10**	1	66
t-Butyl	**7**	**11**	22	20[a]

[a] 2-Acetylcyclohexanone as ligand.

Attempts to further optimize the synthesis of 4-bromo-*N*-(*t*-butyl)oxindole **11** from **7** using microwave technology (the same conditions as in the bottom line of Table 1, 100 °C at 250 W over 30 min in an open Milestone Ethos 900 microwave) delivered only starting materials. Raising the temperature to 150 °C over 45 min yielded some starting material and intractable decomposition products, based upon TLC and LC/MS analysis. Applying the ligandless conditions according to the procedure developed for the microwave Goldberg reaction[19a] (10 mol % CuI, 1 equiv K_2CO_3 in degassed NMP at a temperature of 150 °C (250 W) for 30 min) did not furnish any **11**. To obtain further insight on the stability of the 4-bromooxindoles under these reaction conditions, we subjected compound **5** to these ligandless microwave conditions at a temperature of 150 °C. After 3 min we were able to detect compound **9** along with some starting material **5**. After 6 min of microwave heating **5** was still present, but after 9 min we could only detect starting amide **5** together with some debrominated amide. These findings support our earlier observations that 3-unsubstituted (bromo)oxindoles are sensitive under basic condition[29] and as a consequence rapidly decompose at higher reaction temperatures.

Since previous work[18] demonstrated the high propensity of the 4-bromo atom in **3** to be replaced by an aryl



Scheme 3. Reagents and conditions: (a) 1.5 mol equiv amine: 2.5 mol equiv $K_3PO_4 \cdot H_2O$; 5 mol % $Pd(OAc)_2$; 10 mol % DavePhos: toluene 100 °C.

group in the Suzuki reaction, the copper-catalyzed amination of 4-bromo-*N*-methyloxindole **3** was further investigated. Unfortunately, all attempts to replace the bromine with an amine led to decomposition of **3**. As it is known that the palladium-catalyzed replacement of the bromine atom in aryl bromides is more effective than the copper-catalyzed method, we decided to switch to the palladium-catalyzed amination. Indeed, the palladium-catalyzed reaction of **3** with either 1-benzylpiperazine or benzylamine gave more promising results. It was possible to isolate the target 4-aminated *N*-methyloxindoles **12**–**13** in moderate yields (25–30%), when the reaction was conducted in the presence of $Pd(OAc)_2$, 2′-dicyclohexylphosphino-2-(*N*,*N*-dimethylamino)-biphenyl (DavePhos) and $K_3PO_4 \cdot H_2O$ in toluene at 100 °C. The major side reaction was the formation of the dimeric compound **2** accompanied by the formation of intractable material. The analogous reaction from compound **9** produced **14** in 30% yield. It is worth noting that in all cases, the starting material had completely disappeared (Scheme 3).[30]

To summarize, we have developed an efficient and general synthetic method for 3-unsubstituted 4-bromo-N-substituted oxindoles. The key step comprises an intramolecular copper-catalyzed amidation reaction. Steric factors have a negative effect on both the reaction rate and yield. Amination of the 4-bromo substituent in **3** using copper catalysis failed whereas the corresponding palladium-catalyzed aminations were more promising. Further optimization of the palladium-catalyzed amination is in progress.

Acknowledgements

We wish to thank Willem Gorter, Jan Jeronimus, Pieter Spaans and Hugo Morren for the analytical support, Aalt van de Kuilen and Peter Koelman for screening the literature, Jord van Schaik for the preparation of compound **1** and Sjoerd van Schaik for the fruitful discussions.

References and notes

1. Gallagher, G.; Lavanchi, P. G.; Wilson, J. W.; Hieble, J. P.; DeMarinis, R. M. *J. Med. Chem.* **1985**, *28*, 1533–1536.
2. Nagata, R.; Tokunaga, T.; Hume, W.; Umezone, T.; Okazaki, U.; Ueki, Y.; Kumagai, K.; Hourai, S.; Nagamine, J.; Seki, H.; Taiji, M.; Noguchi, H. *J. Med. Chem.* **2001**, *44*, 4641–4649.
3. Smith, C. D.; Zilfou, J. T.; Stratmann, K.; Patterson, G. M. L.; Moore, R. E. *Mol. Pharmacol.* **1995**, *47*, 241–247.
4. (a) Asmawi, M. Z.; Moilanen, E.; Alanko, J.; Vapaatalo, H. *Eicosanoids* **1988**, *1*, 35–39; (b) Alcaraz, M.; Atkinson, S.; Cornwall, P.; Foster, A. C.; Gill, D. M.; Humphries, L. A.; Keegan, P. S.; Kemp, R.; Merifield, E.; Nixon, R. A.; Noble, A. J.; O'Beirne, D.; Patel, Z. M.; Perkins, J.; Rowa, P.; Sadler, P.; Singleton, J. T.; Tornos, J.; Watts, A. J.; Woodland, I. A. *Org. Process Res. Dev.* **2005**, *9*, 555–569.
5. Zaveri, N. T.; Jiang, F.; Olsen, C. M.; Deschamps, J. R.; Parrish, D.; Polgar, W.; Toll, L. *J. Med. Chem.* **2004**, *47*, 2973–2976.
6. Kikuchi, C.; Hiranuma, T.; Koyama, M. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 2549–2552.
7. Mokrosz, M. J.; Duszynska, B.; Misztal, S.; Klodinska, A.; Tatarzynska, E. *Arch. Pharm. Pharm. Med. Chem.* **1998**, *331*, 325–330.
8. (a) Dounay, A. B.; Overman, L. E. *Chem. Rev.* **2003**, *103*, 2945–2963; (b) Marti, C.; Carreira, E. M. *Eur. J. Org. Chem.* **2003**, 2209–2219; (c) Inoue, M.; Sakazaki, H.; Furuyama, H.; Hirama, M. *Angew. Chem., Int. Ed.* **2003**, *42*, 2654–2657; (d) Overman, L. E.; Rosen, M. D. *Angew. Chem., Int. Ed.* **2000**, *39*, 4596–4599; (e) Thiericke, R.; Tang, Y. Q.; Sattler, I.; Grabley, S.; Feng, X. Z. *Eur. J. Org. Chem.* **2001**, 261–267.
9. (a) Adreani, A.; Leoni, A.; Locatelli, A.; Morigi, R.; Rambaldi, M.; Pietra, C.; Villetti, G. *Eur. J. Med. Chem.* **2000**, *35*, 77–82; (b) Adreani, A.; Granaiola, M.; Leoni,

A.; Locatelli, A.; Morigi, R.; Rambaldi, M.; Garaliene, V.; Farraguia, G.; Masotti, L. *Bioorg. Med. Chem. Lett.* **2004**, *12*, 1121–1128; Lin, N.; Xia, P.; Kovar, P.; Park, C.; Chen, Z.; Zhang, H.; Rosenberg, S. H.; Sham, H. L. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 421–426.

10. (a) McDermott, M. C.; Stephenson, G. R.; Hughes, D. L.; Walkington, A. J. *Org. Lett.* **2006**, *8*, 2917–2920; (b) Overman, L. E.; Watson, D. A. *J. Org. Chem.* **2006**, *71*, 2600–2608; (c) Madin, A.; O'Donnell, J.; Oh, T.; Old, D. W.; Overman, L. E.; Sharp, M. J. *J. Am. Chem. Soc.* **2005**, *127*, 18054–18065; (d) Busacca, C. A.; Grossbach, D.; Campbell, S. J.; Dong, D.; Eriksson, M. C.; Harris, R. E.; Jones, P. J.; Kim, J. Y.; Lorentz, J. C.; McKellop, K. B.; O'Brien, E. M.; Qiu, F.; Simpson, R. D.; Smith, L.; So, R. C.; Spinelli, E. M.; Vitous, J.; Zavattaro, C. *J. Org. Chem.* **2004**, *69*, 5187–5195; (e) Harayama, T.; Toko, H.; Nishioka, H.; Abe, H.; Takeuchi, Y. *Heterocycles* **2003**, *59*, 541–546.
11. (a) Arao, T.; Kondo, K.; Aoyama, T. *Tetrahedron Lett.* **2006**, *47*, 1417–1420; (b) Bignan, G. C.; Battista, K.; Connolly, P. J.; Orsini, M. J.; Liu, J.; Middleton, S. A.; Reitz, A. B. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 5022–5026; (c) Trost, M. B.; Frederiksen, M. U. *Angew. Chem., Int. Ed.* **2005**, *44*, 308–310; (d) Zhang, T. Y.; Zhang, H. *Tetrahedron Lett.* **2002**, *43*, 1363–1365; (e) Zhang, T. Y.; Zhang, H. *Tetrahedron Lett.* **2002**, *43*, 193–195; (f) Lee, S.; Hartwig, J. F. *J. Org. Chem.* **2001**, *66*, 3402–3415.
12. Hennessy, E. J.; Buchwald, S. L. *J. Am. Chem. Soc.* **2003**, *124*, 12084–12085.
13. Pinto, A.; Neuville, L.; Retailleau, P.; Zhu, J. *Org. Lett.* **2006**, *8*, 4927–4930.
14. Van den Hoogenband, A.; Den Hartog, J. A. J.; Lange, J. H. M.; Terpstra, J. W. *Tetrahedron Lett.* **2004**, *45*, 8535–8537.
15. Buchwald, S. L.; Yang, B. H. *Org. Lett.* **1999**, *1*, 35–37.
16. Buchwald, S. L.; Nguyen, H. N.; Huang, X. *J. Am. Chem. Soc.* **2003**, *125*, 11818–11819.
17. (a) Kalinski, C.; Umkehrer, M.; Ross, G.; Kolb, J.; Burdack, C.; Hiller, W. *Tetrahedron Lett.* **2006**, *47*, 3423–3426; (b) Kitamura, Y.; Hashimoto, A.; Yoshikawa, S.; Odaira, J.; Furuta, T.; Kan, T.; Tanaka, K. *Synlett* **2006**, 115–117; (c) Turner, N. J.; Poondra, R. R. *Org. Lett.* **2005**, *7*, 863–866.
18. Van den Hoogenband, A.; Lange, J. H. M.; Iwema-Bakker, W. I.; Den Hartog, J. A. J.; Van Schaik, J.; Feenstra, R. W.; Terpstra, J. W. *Tetrahedron Lett.* **2006**, *47*, 4361–4364.
19. (a) Lange, J. H. M.; Hofmeyer, L. J. F.; Hout, F. A. S.; Osnabrug, S. J. M.; Verveer, P. C.; Kruse, C. G.; Feenstra, R. W. *Tetrahedron Lett.* **2002**, *43*, 1101–1104; (b) Van Berkel, S. S.; Van den Hoogenband, A.; Terpstra, J. W.; Tromp, M.; Van Leeuwen, P. W. N. M.; Van Strijdonck, G. P. F. *Tetrahedron Lett.* **2004**, *45*, 7659–7662; (c) Kuil, M.; Bekedam, E. K.; Visser, G. M.; Van den Hoogenband, A.; Terpstra, J. W.; Kamer, P. C. J.; Van Leeuwen, P. W. N. M.; Van Strijdonck, G. P. F. *Tetrahedron Lett.* **2005**, *46*, 2405–2409.
20. Some selected literature references: (a) Corbet, J. P.; Mignani, G. *Chem. Rev.* **2006**, *106*, 2651–2710; (b) Frlan, R.; Kikelj, D. *Synthesis* **2006**, 2271–2285; (c) Beletskaya, I. P.; Cheprakov, A. V. *Coord. Chem. Rev.* **2004**, *248*, 2337–2364; (d) Dehli, J. R.; Legros, J.; Bolm, C. *Chem. Commun.* **2005**, 973–986; (e) Ley, S. V.; Thomas, A. W. *Angew. Chem., Int. Ed.* **2003**, *42*, 5400–5449; (f) Kunz, K.; Scholz, U.; Ganzer, D. *Synlett* **2003**, 2428–2439.
21. Kiyomori, A.; Marcoux, J. F.; Buchwald, S. L. *Tetrahedron Lett.* **1999**, *40*, 2657–2660.
22. (a) Lambers, M. M. H.; De Lange, B.; De Vries, A. H. M.; De Vries, J. G.; Sereinig, N. PCT Int. Appl., to DSM, WO 009431, 2006; *Chem. Abstr.* **2006**, *144*, 170991; (b) De Lange, B.; Lamberts-Verstappen, M. H.; Schieder-van de Vondervoort, L.; Sereinig, N.; De Rijk, R.; De Vries, A. H. M.; De Vries, J. G. *Synlett* **2006**, 3105–3109.
23. Shafir, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2006**, *128*, 8742–8743.
24. Selected analytical data for compounds **4**–**7**: Compound **4**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.32–1.42 (m, 2H), 1.85–1.92 (m, 2H), 2.06–2.14 (m, 2H), 2.69–2.76 (m, 2H), 3.45 (s, 2H), 3.79–3.89 (m, 1H), 3.99 (s, 2H), 5.14 (br d, $J = 8$ Hz, 1H), 7.03 (t, $J = 8$ Hz, 1H), 7.21–7.32 (m, 5H), 7.57 (d, $J = 8$ Hz, 2H). Compound **5**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.20 (s, 2H), 7.05–7.13 (m, 3H), 7.30 (t, $J = 8$ Hz, 2H), 7.46 (d, $J = 8$ Hz, 2H), 7.62 (d, $J = 8$ Hz, 2H). Compound **6**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.23 (s, 2H), 7.07 (t, $J = 8$ Hz, 1H), 7.46 (br d, $J = 7$ Hz, 2H), 7.61 (d, $J = 8$ Hz, 2H), 7.87 (br s, 1H), 8.49 (d, $J = 7$ Hz, 2H). Compound **7**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.32 (s, 9H), 3.94 (s, 2H), 5.15 (br s, 1H), 7.01 (t, $J = 8$ Hz, 1H), 7.57 (d, $J = 8$ Hz, 2H).
25. General procedure for the preparation of compounds **3** and **8**–**11** (Table 1): A dried 50 ml, three-necked reaction vessel was charged with anhydrous and degassed NMP (10 ml), followed by the addition of CuCl (10 mg, 0.1 mmol) and acetylacetonate (25 mg, 0.25 mmol). The mixture was magnetically stirred under a nitrogen atmosphere at room temperature until a clear dark solution was obtained. After adding the N-substituted 2,6-dibromophenylacetamide (1 mmol) and K_2CO_3 (690 mg, 5 mmol), the reaction mixture was heated in a pre-heated oil bath at 85 °C until the starting compound (**1**, **4**–**7**) had disappeared (LCMS, TLC monitoring: CH_2Cl_2/MeOH = 97.5:2.5 (v/v), CH_2Cl_2/MeOH = 99:1 (v/v), CH_2Cl_2/acetone = 9:1 (v/v) or CH_2Cl_2, depending on the starting material). The reaction mixture was allowed to attain room temperature. A solution of NH_4Cl in water and ethyl acetate was added. The organic layer was separated, extracted with water and dried over $MgSO_4$, filtered and concentrated in vacuo. The crude product obtained was further purified by flash chromatography (silica gel 60 (0.040–0.063 mm, Merck)) with the appropriate eluent.
26. Selected analytical data for compounds **3** and **8**–**11**: Compound **3**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.20 (s, 3H), 3.48 (s, 2H), 6.73–6.78 (m, 1H), 7.16–7.19 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$/DMSO = 3:4 (v/v)): δ 26.19, 36.52, 107.19, 118.08, 124.45, 125.17, 129.49, 146.16, 172.83. HRMS (ES+): calcd for C_9H_9BrNO (M+H) 225.9868; found 225.9861. Compound **8**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.66 (br d, $J = 12$ Hz, 2H), 2.13 (br t, $J = 12$ Hz, 2H), 2.36–2.48 (m, 2H), 3.01 (br d, $J = 12$ Hz, 2H), 3.46 (s, 2H), 3.56 (s, 2H), 4.26–4.35 (m, 1H), 7.09–7.16 (m, 3H), 7.25–7.29 (m, 1H), 7.31–7.37 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$/DMSO = 3:4 (v/v)): δ 27.67, 36.84, 50.23, 52.65, 62.18, 108.51, 118.46, 124.03, 125.42, 126.76, 128.01, 128.65, 129.30, 138.36, 144.82, 172.74. HRMS (ES+): calcd for $C_{20}H_{22}BrN_2O$ M+H 385.0915; found 385.0925. Compound **9**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.67 (s, 2H), 6.73 (d, $J = 8$ Hz, 1H), 7.09 (t, $J = 8$ Hz, 1H), 7.21 (d, $J = 8$ Hz, 1H), 7.37–7.45 (m, 3H), 7.54 (br t, $J = 8$ Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$/DMSO = 3:4 (v/v)): δ 36.81, 107.81, 118.53, 124.97, 125.26, 126.58, 128.02, 129.39, 129.45, 134.27, 145.93, 172.31. HRMS (ES+): calcd for $C_{14}H_{11}BrNO$ (M+H) 288.0024; found 288.0023. Compound **10**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.70 (s, 2H), 6.94 (d, $J = 8$ Hz, 1H), 7.16 (t, $J = 8$ Hz, 1H), 7.28 (d, $J = 8$ Hz, 1H), 7.47 (br s, 2H), 8.90 (br s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$/DMSO = 3:4 (v/v)): δ 37.15, 108.42, 119.10, 120.20, 125.57, 126.01, 129.59, 141.92, 144.10,

151.18, 172.07. HRMS (ES+): calcd for $C_{13}H_{10}BrN_2O$ (M+H) 288.9976; found 288.9977. Compound **11**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.71 (s, 9H), 3.42 (s, 2H), 7.05–7.15 (m, 2H), 7.18 (d, $J = 8$ Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$/DMSO = 3:4 (v/v)): δ 28.51, 38.12, 57.42, 111.74, 118.25, 123.75, 128.80, 131.72, 146.10, 173.56. HRMS (ES+): calcd for $C_{12}H_{15}BrNO$ (M+H) 268.0337; found 268.0333.

27. Philipps, D. P.; Hudson, A. R.; Nguyen, B.; Lau, T. L.; McNeill, M. H.; Dalgard, J. E.; Chen, J. H.; Penuliar, R. J.; Miller, T. A.; Zhi, L. *Tetrahedron Lett.* **2006**, *47*, 7137–7138.
28. Feng, G.; Wu, J.; Daí, W. M. *Tetrahedron Lett.* **2007**, *48*, 401–404.
29. Moser, P.; Sallmann, A.; Wiesenberg, I. *J. Med. Chem.* **1990**, *33*, 2358–2368.
30. Selected analytical data for compounds **12**–**14**: Compound **12**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.51–2.56 (m, 4H), 3.00–3.04 (m, 4H), 3.11 (s, 3H), 3.38 (s, 2H), 3.51 (s, 2H), 6.44 (d, $J = 8$ Hz, 1H), 6.59 (d, $J = 8$ Hz, 1H), 7.16 (t, $J = 8$ Hz, 1H), 7.21–7.30 (m, 5H). Compound **13**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.11 (s, 3H), 3.22 (s, 2H), 3.78 (br s, 1H), 4.34 (s, 2H), 6.24 (d, $J = 8$ Hz, 1H), 6.33 (d, $J = 8$ Hz, 1H), 7.07 (t, $J = 8$ Hz, 1H), 7.20–7.25 (m, 1H), 7.26–7.30 (m, 4H). Compound **14**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.48 (s, 2H), 3.89 (br s, 1H), 4.45 (s, 2H), 6.23 (d, $J = 8$ Hz, 1H), 6.43 (d, $J = 8$ Hz, 1H), 7.07 (t, $J = 8$ Hz, 1H), 7.29–7.33 (m, 1H), 7.35–7.55 (m, 9H).