Organic & Biomolecular Chemistry

RSC Publishing

PAPER

View Article Online
View Journal

Multistep divergent synthesis of benzimidazole linked benzoxazole/benzothiazole *via* copper catalyzed domino annulation†

Cite this: DOI: 10.1039/c3ob27177c

Jen-Yu Liao, Manikandan Selvaraju, Chih-Hau Chen and Chung-Ming Sun*

An efficient, facile synthesis of structurally diverse benzimidazole integrated benzoxazole and benzothiazoles has been developed. In a multi-step synthetic sequence, 4-fluoro-3-nitrobenzoic acid was converted into benzimidazole bis-heterocycles, *via* the intermediacy of benzimidazole linked *ortho*-chloro amines. The amphiphilic reactivity of this intermediate was designed to achieve the title compounds by the reaction of various acid chlorides and isothiocyanates in a single step through the *in situ* formation of *ortho*-chloro anilides and thioureas under microwave irradiation. A versatile one pot domino annulation reaction was developed to involve the reaction of benzimidazole linked *ortho*-chloro amines with acid chlorides and isothiocyanates. The initial acylation and urea formation followed by copper catalyzed intramolecular C–O and C–S cross coupling reactions furnished the angularly oriented bis-heterocycles which bear a close resemblance to the *streptomyces* antibiotic UK-1.

Received 8th November 2012,
Accepted 24th January 2013

DOI: 10.1039/c3ob27177c

www.rsc.org/obc

Introduction

Heterocyclic compounds have attracted substantial attention due to their broad biological and therapeutic applications.[1] In particular, privileged heterocycles with two or more heteroatom containing rings have been intensively studied because of their ability to bind to multiple receptors and because they represent the most important class of key structural units in a large number of bioactive molecules.[2] Among these, benzimidazole, benzoxazole and benzothiazole moieties are frequently encountered in many therapeutic agents.[3–5] Construction of these privileged structures in a single molecule leads to the formation of a novel bis-heterocyclic system which is likely to display unique biological properties by a synergistic effect. Synthetic analogues possessing these core structures with direct linkage have considerable medicinal interest and are frequently identified as the most potent heterocyclic motifs for the development of novel therapeutics.[6] The linking of two benzimidazoles at different positions has been employed as a strategy to control the distance between the two azomethine ring nitrogens leading to the synthesis of bis-benzimidazoles for DNA minor groove binding.[7] Benzimidazoles linked with benzoxazoles and benzothiazoles were identified to show significant binding affinity with protein pyruvate kinase.[8] Bis-benzoxazole isolated from *streptomyces* sp. is shown to interact with human topoisomerase II with antitumor activity against various human cell lines.[9,10] Introduction of a piperazine moiety at the C-5 position of the bis-heterocyclic ring revealed its potential role as topoisomerase inhibitor **1**.[11] Carbomethoxylated benzimidazoles **2** as analogues of UK-1 were patented for their selective cytotoxicity against cancer cell lines.[12] Proline bis-amide substituted by benzothiazole **3** serves as an antagonist targeted to orexin receptors and benzothiazole based pyrimidine derivatives **4** are employed as gram positive selective antibacterial agents (Fig. 1).[13,14]

Our primary interest is to focus on the construction of direct-linked bis-heterocyclic derivatives in which benzimidazole is accompanied by another heterocycle in an angular

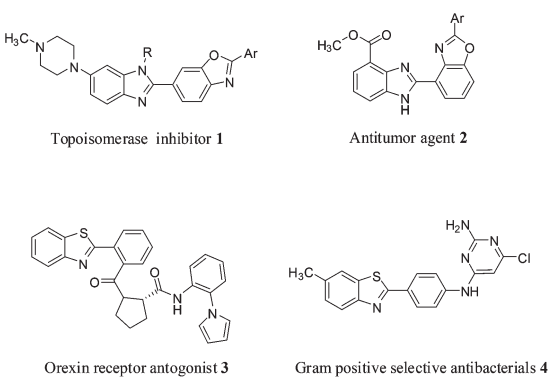


Fig. 1 Structurally related biologically active compounds.

Department of Applied Chemistry, National Chiao Tung University, Hsinchu 300-10, Taiwan. E-mail: cmsun@mail.nctu.edu.tw

†Electronic supplementary information (ESI) available. See DOI: 10.1039/c3ob27177c

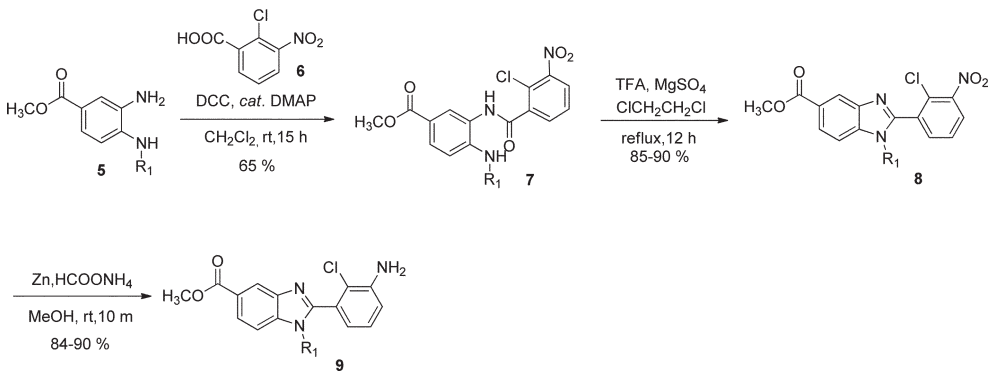
fashion. Even though considerable efforts have been made to obtain derived heterocyclic compounds, there has not been a dedicated effort to explore structurally and functionally modified bis-heterocyclic compounds which linked together directly rather than through a spacer or linker.[15] The conventional method for the formation of benzoxazoles involves the treatment of 2-aminophenol with carboxylic acid derivatives or aldehydes under either strong acid or high temperature conditions.[16] Similarly 2-aminated benzothiazoles are derived from the substitution reaction of 2-halobenzothiazoles or 2-thiobenzothiazoles with nitrogen nucleophiles.[17] These methods require several reaction steps, harsh reaction conditions and it is hard to prepare suitable starting materials. Prompted by the importance of these advantageous structures, it is meritorious to develop a straightforward, atom economical route for the construction of these privileged structures and we have successfully developed synthetic methods for bis-benzimidazoles and benzimidazolyl benzoxazoles on polymer and ionic liquid supports.[18,19] As part of our ongoing efforts devoted to the synthesis of chimeric bis-heterocycles, the present article describes a linear multistep synthetic route which involves copper-catalyzed intramolecular C–O and C–S bond formation by the domino one pot reaction as the key approach for the construction of angularly oriented benzoxazolyl and benzothiazolyl benzimidazoles.

Results and discussion

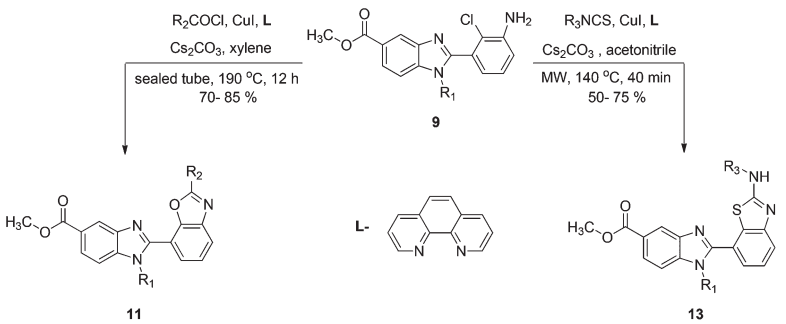
The synthetic sequence commenced with the preparation of the key building block **5** from 4-fluoro-3-nitro benzoic acid which underwent three reaction steps such as esterification, nucleophilic substitution and nitro reduction to furnish the intermediate **5**.[19] The mono-substituted *ortho*-phenylenediamines **5** served as key intermediates in the synthesis and also acted as the first point of structural diversity of various alkyl groups. For the construction of the benzimidazole linked benzoxazoles and benzothiazoles, 2-chloro-3-nitro benzoic acid **6** was employed as a building block through an amide linkage. The chloro and nitro groups were positioned strategically on which the construction of a second angularly oriented heterocycle would be carried out. The regioselective condensation of primary amino functionality of the key intermediate **5** with 2-chloro-3-nitro benzoic acid leads to the aryl amides **7**. The selectivity was achieved due to the presence of the deactivating carbonyl ester group at the *para* position to the secondary amine which results in the decreasing of the nucleophilicity and facilitates the exclusive and selective *N*-acylation with the primary amine. The selectivity was inferred from the ^{1}H NMR spectra which showed an unchanged chemical shift of the methylene group of R_1 (R_1-pentyl). Transformation of the aryl amides **7** into benzimidazoles **8** is conceived to build up five membered rings which require an acid catalyzed intramolecular nucleophilic attack to eliminate water. The formation of benzimidazole linked nitrochlorobenzene was confirmed by the downfield shift of the methylene group (R_1-pentyl) in proton NMR which resulted due to the deshielding effect of the newly formed imidazole ring system. The next step in the construction of a second azole ring was the reduction of the nitro group into amine. Compound **9** was treated as a common building block for the synthesis of benzimidazole linked benzoxazoles as well as benzothiazoles and further steps were focused on exploring the amphiphilic 2-chloroaniline part of the arylated benzimidazoles to obtain the target molecules (Scheme 1). The final endeavor to the present challenging task was the functionalization of the amino group with various isothiocyanates and acid chlorides followed by intramolecular cross coupling in a domino one pot manner (Scheme 2).

Our attempt was initiated by the reaction of intermediate **9** with furan-2-carbonyl chloride in the presence of CuI (5 mol%), 1,10-phenanthroline (10 mol%) and Cs_2CO_3 (2 eq.) in toluene. After 24 h of reflux at 110 °C, a trace level of the benzoxazole product with the anilide intermediate **10** (24%) was formed. However, a great amount of starting material **9** (70%) still remained unreacted (Tables 1 and 2).[20]

Poor conversion of the cross coupling reaction served as a starting point for an optimization study. A survey of various solvents such as xylene, toluene, DMF, THF and DMSO for the same reaction led to the same results with very little conversion to the desired product and left behind the *in situ* generated intermediate **10**. These effects prompted us to conduct

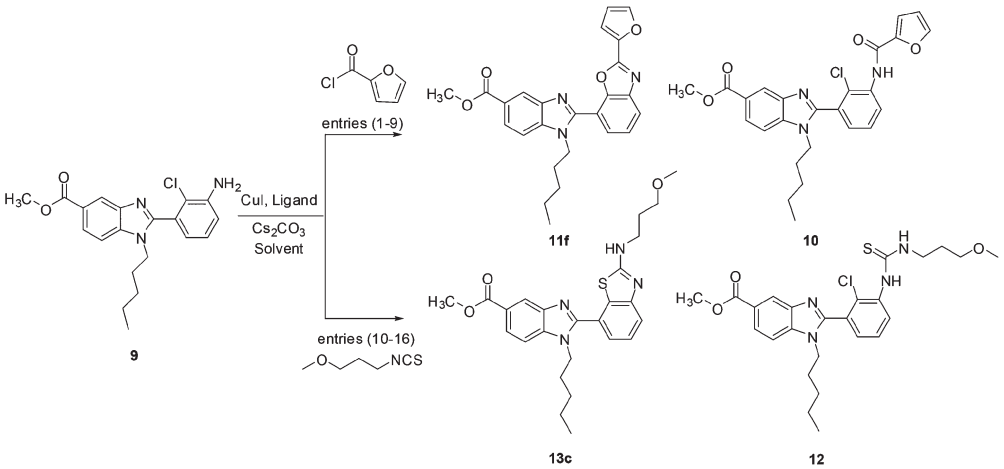


Scheme 1 General strategy for the synthesis of intermediate **9**.



Scheme 2 One pot synthesis of benzimidazole linked benzoxazole and benzothiazole derivatives.

Table 1 Optimization of the reaction conditions

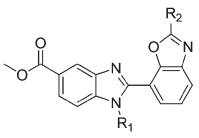


Entry	CuI (mol%)	Ligand (mol%)	Solvent	Condition (temp °C)	Time	Yield[a] (%)
1	5	1,10-Phenanthroline (10)	MeCN	Reflux	24 h	Trace[b]
2	10	1,10-Phenanthroline (10)	Xylene	Reflux	24 h	Trace[b]
3	10	1,10-Phenanthroline (10)	Toluene	Reflux	24 h	Trace[b]
4	10	1,10-Phenanthroline (20)	Toluene	MW (120)	20 m	20
5	10	1,10-Phenanthroline (20)	Xylene	MW (150)	20 m	40
6	10	1,10-Phenanthroline (10)	MeCN	MW (120)	20 m	20
7	10	1,10-Phenanthroline (20)	DMF	MW (150)	20 m	30
8	10	1,10-Phenanthroline (20)	Xylene	Sealed tube (140)	12 h	55
9	10	1,10-Phenanthroline (20)	Xylene	Sealed tube (190)	12 h	80
10	10	1,10-Phenanthroline (20)	Toluene	Reflux	24 h	Trace[b]
11	10	1,10-Phenanthroline (10)	DMF	Reflux	24 h	Trace[b]
12	10	1,10-Phenanthroline (10)	MeCN	MW (120)	20 m	15
13	10	1,10-Phenanthroline (20)	MeCN	MW (140)	30 m	30
14	10	1,10-Phenanthroline (30)	MeCN	MW (140)	40 m	72
15	10	1,10-Phenanthroline (10)	Xylene	MW (160)	20 m	25
16	10	1,10-Phenanthroline (10)	Xylene	Sealed tube (190)	24 h	30

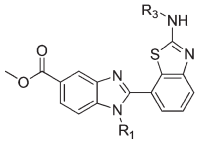
[a] Based on the weight of the purified compounds. [b] By ^{1}H NMR, Cs_2CO_3 (3 eq. relative to **9**).

the reaction with dielectric heating by microwave irradiation. Reaction at various temperatures with different polar and non-polar solvents at various time periods still can not cause the complete conversion of **9** under microwave irradiation. Then we examined the same reaction in xylene at 140 °C under sealed tube conditions to furnish 55% isolated yield and the recovery of 20% intermediate **9**. It is evident that the *in situ* formation of anilides **10** underwent complete cross coupling by the same conditions. Increasing the temperature to 190 °C accelerates the reaction to complete conversion to benzoxazole **12** with 80% isolated yield. No reaction was observed in the absence of the copper catalyst and it was found that employing Cs_2CO_3 as the base showed the best result, while other bases such as TEA, DIPEA, sodium carbonate, and potassium carbonate gave poorer yields under these conditions. Using 2,2′ bipyridyl as a ligand in place of 1,10-phenanthroline did not

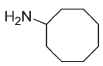
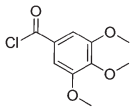
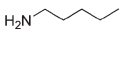
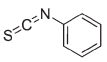
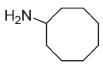
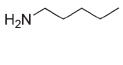
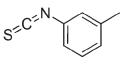
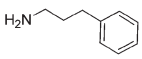
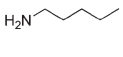
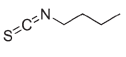
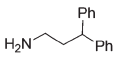
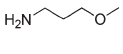
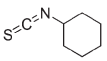
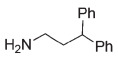
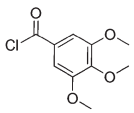
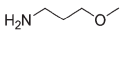
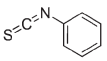
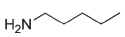
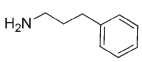
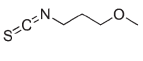
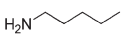
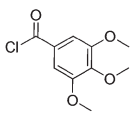
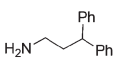
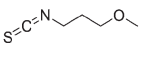
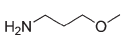
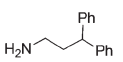
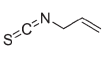
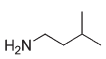
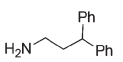
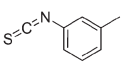
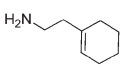
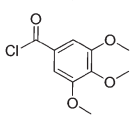
Table 2 Benzimidazole linked benzoxazole **11** and benzothiazole **13**



11



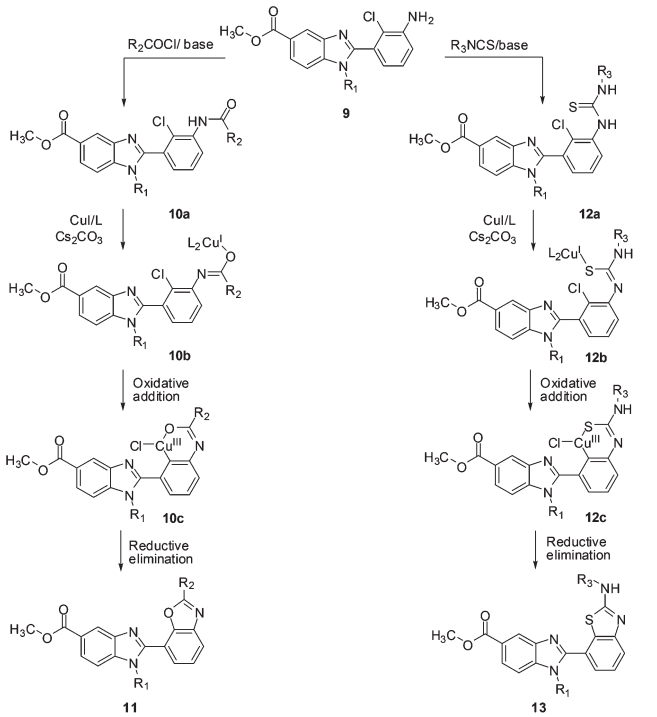
13

Entry[a]	R_1NH_2	R_2COCl	Yield[c] (%)	Entry[b]	R_1NH_2	R_3NCS	Yield[c] (%)
11a			78	**13a**			66
11b			85	**13b**			61
11c			84	**13c**			72
11d			72	**13d**			62
11e			79	**13e**			60
11f			88	**13f**			68
11g			78	**13g**			74
11h			83	**13h**			58
11i			79	**13i**			59
11j			82	**13j**			60

[a] Entries **11a–11j** reaction conditions: CuI (10 mol%), 1,10-phenanthroline (20 mol%), Cs_2CO_3 (3 eq.), in xylene, in a sealed tube 190 °C for 12 h. [b] Entries **13a–13j** reaction conditions: CuI (10 mol%), 1,10-phenanthroline (30 mol%), Cs_2CO_3 (3 eq.), in acetonitrile, MW 140 °C for 40 min. [c] Yields of purified compounds.

accomplish any better conversion to the final product. On the basis of these optimization studies, the most favorable condition employed for the one pot reaction was CuI (10%), 1,10-phenanthroline (20%), and Cs_2CO_3 (3 eq.) in xylene in a sealed tube. The same catalytic system could be applied for the synthesis of benzothiazole derivatives from the intermediate **9** by reacting with various isothiocyanates. The one pot reaction was tried in various solvents under reflux and microwave conditions. All these conditions did not lead to the complete conversion of the starting material **9** and with the yield range from 45–50%. Among these trials, the best condition was chosen as three equivalents of cesium carbonate and 10 mol% of CuI, 30 mol% of 1,10-phenanthroline with the isolated yield of 72% and 12% of the recovered starting material **9** under microwave irradiation. Further increasing the temperature did not improve the yield and led to a complex mixture of products.

It is inferred from the experimental observation that the lower reactivity of isothiocyanates compared to that of acid chloride gave a lower yield of the corresponding intermediate **12** and thus affected the overall yield with slight recovery of the starting material. Reduced yields and harsh conditions are required for the formation of 2-aminobenzothiazoles **13**, because of the strong copper–sulphur bond, which further reduced its nucleophilicity, whereas the weak copper–oxygen bond led to better yields and shorter reaction times for the formation of oxazoles **11**. With the optimized condition in hand we next focused on the exploration of generality and scope of this domino process. The intermediate **9** smoothly reacted with various acid chlorides and isothiocyanates regardless of



Scheme 3 Plausible mechanism for the formation of **11** and **13**.

the electronic and steric properties of the substituents to provide bis-heterocycles in good yields. It is noteworthy to mention that the substituted benzimidazole moiety linked to the benzene ring was well-tolerated under this reaction condition, with the final products obtained in good yields. The noticeable advantage of this protocol is that all the reactions are insensitive to air and moisture, hence, there was no need for an inert atmosphere. The plausible mechanism for the formation of benzimidazole linked benzoxazole **11** and benzothiazole **13** from the common intermediate **9** is shown in Scheme 3.[21] First, the nucleophilic addition of chloroaniline to acid chloride and isothiocyanate furnished anilide (**10a**) and urea (**12a**) conjugates respectively in the presence of base. Second, the obtained intermediates were converted into final products through intramolecular cyclization with the aid of 1,10-phenanthroline and Cs_2CO_3. Initial co-ordination of copper to the intermediates (**10a** and **12a**) leads to the oxidative addition products (**10c** and **12c**). The presence of 1,10-phenanthroline as a ligand was employed to avoid multiple co-ordination of copper with the amide intermediates.[22] Subsequently reductive elimination released the respective products **11** and **13** with the concomitant regeneration of the copper catalyst.

Further the structures of the benzimidazole linked benzoxazole and benzothiazole were unambiguously confirmed by X-ray crystallographic analysis (Fig. 2 and 3). This novel synthetic approach leads to the proficient synthesis of angularly oriented bis-heterocycles in which the hetero-atoms are more favorably oriented for an *in situ* metal chelation or binding with electrophilic sites of the receptors in biomolecules.

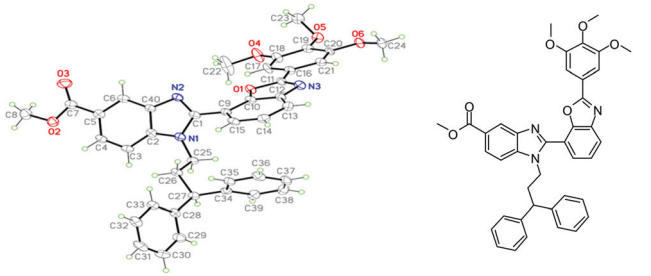


Fig. 2 ORTEP representation of benzimidazole linked benzoxazole.

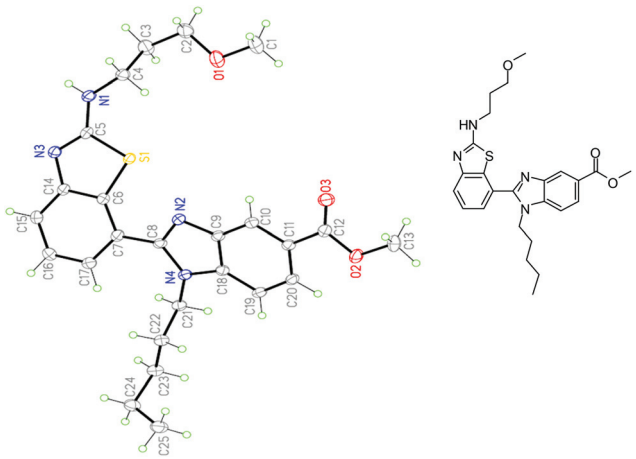


Fig. 3 ORTEP representation of benzimidazole linked benzothiazole.

Conclusion

In summary, the developed synthetic protocol provides concise access to the diverse bis-heterocycles comprising benzimidazoles, benzothiazoles and benzoxazoles. The synthetic sequence involves acid–amine coupling, intramolecular cyclization, and reduction followed by domino, one pot azole formation. The amphiphilic reactivity of 2-chloroaniline has been exploited under Ullmann-like conditions by a catalyst–ligand–base combination for the construction of privileged bis-heterocycles. Activation of the aromatic chloro substituent for such an intramolecular displacement is unique and would provide an impetus for the synthesis of other heterocycles. The intramolecular one pot domino annulation reaction was greatly facilitated by copper iodide/1,10-phenanthroline. The accessibility and generality of this synthetic approach make it highly valuable in view of the medicinal importance of these bis-heterocycles. Assembly of these privileged heterocycles in a single molecule will certainly provide abundant opportunities to discover more interesting compounds with novel biological profiles.

Experimental section

Synthesis of key intermediate 9

Compound **5** (1.0 g, 4.8 mmol), 2-chloro-3-nitrobenzoic acid (1.3 g, 6.7 mmol), DCC (1.4 g, 6.6 mmol), and 4-dimethylaminopyridine (0.006 g, 0.05 mmol) in dry CH_2Cl_2 (25 mL)

were stirred in a round-bottomed flask for 16 h at room temperature. After cooling to 0 °C, the solid dicyclohexylurea (DCU) was filtered off and the solvent was evaporated. The crude product was purified by precipitation and washing with *n*-hexane (20 mL × 3) to afford amide **7** in 60–70% yield. Subsequently, amide **7** (1.0 g, 2.8 mmol) in 1,2-dichloroethane (50 mL) was refluxed for 16 h in 10% trifluoroacetic acid (TFA) (0.43 mL, 5.61 mmol) and $MgSO_4$ (0.5 g, 4.14 mmol). Solvent was removed and the crude product was purified by flash chromatography to give **8** (84–95%). For the next step, zinc dust (15 equiv., 74.6 mmol) and ammonium formate (7 equiv., 34.8 mmol) were added to a solution of **8** (2.0 g, 4.9 mmol) in dry MeOH (100 mL) and the resulting reaction mixture was stirred for 10 min at room temperature. Subsequently, Zn dust was filtered off through a bed of celite, the solvent was evaporated and the product was dissolved in CH_2Cl_2 (100 mL). The precipitated ammonium formate was filtered off and the solvent was evaporated to furnish **9** with 92–96% isolated yields.

General procedure for the synthesis of benzimidazolyl benzoxazole (11)

To a solution of compound **9** (0.5 g, 1.34 mmol) in xylene (20 mL) was added CuI (0.025 g, 0.134 mmol), 1,10-phenanthroline (0.048 g, 0.268 mmol), and Cs_2CO_3 (1.3 g, 4.03 mmol) followed by benzoyl chloride (0.282 g, 2.01 mmol) and the reaction mixture was heated at 190 °C for 12 h in a sealed tube. The reaction mixture was diluted with ethyl acetate (100 mL) and washed with saturated aqueous sodium bicarbonate solution (50 mL) to remove the solid residues. The aqueous layer was extracted with ethyl acetate (50 mL × 2). To the combined organic layers was added $MgSO_4$, filtered and evaporated to obtain the crude product. The crude product was purified by silica-gel column chromatography using EA–hexane (1 : 3) as an eluent to obtain pure product **11i** (78%).

General procedure for the synthesis of benzimidazolyl benzothiazole (13)

To a microwave process vial of compound **9** (0.5 g, 1.34 mmol) in acetonitrile (10 mL) was added CuI (0.025 g, 0.134 mmol), 1,10-phenanthroline (0.048 g, 0.268 mmol), and Cs_2CO_3 (1.3 g, 4.03 mmol) followed by phenylisothiocyanate (0.543 g, 4.02 mmol) and the reaction mixture was heated at 140 °C for 40 min under microwave irradiation. The reaction mixture was cooled to room temperature and was diluted with ethyl acetate (50 mL) and washed with a saturated aqueous sodium bicarbonate solution (50 mL) to remove catalyst and solid residues. The aqueous layer was then extracted with ethyl acetate (50 mL × 2). To the combined organic layers was added $MgSO_4$, filtered and evaporated to obtain the crude product. The obtained crude product was purified by silica-gel column chromatography using EA–hexane (1 : 2) as an eluent to obtain the title compound **13a** (66%).

Spectral data

Methyl-1-cyclooctyl-2-[2-(3,4,5-trimethoxyphenyl)-1,3-benzoxazol-7-yl]-1*H*-benzimidazole-5-carboxylate (11a). ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 8.56 (s, 1H), 8.03 (d, J = 8.5 Hz, 1H), 7.94 (d, J = 7.8 Hz, 1H), 7.64–7.61 (m, 2H), 7.53 (t, J = 7.8 Hz, 1H), 7.43 (s, 2H), 4.48 (m, 1H), 3.96 (s, 3H), 3.91 (s, 9H), 2.43 (m, 2H), 2.10 (m, 2H), 1.76 (m, 2H), 1.39 (m, 6H), 1.10 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 167.5, 163.5, 153.5, 150.5, 148.4, 143.7, 142.5, 141.4, 136.7, 127.2, 125.2, 124.4, 124.0, 122.7, 121.8, 121.3, 114.2, 112.1, 104.9, 61.0, 58.0, 56.3, 52.1, 33.4, 26.1, 25.7, 25.2; MS (EI): m/z 569.25 (M^+); HRMS (EI): calcd for $C_{33}H_{35}N_3O_6$ 569.2526, found 569.2523; IR (neat) 3417, 2927, 1716 cm^{-1}.

Methyl-1-cyclooctyl-2-[2-(furan-2-yl)-1,3-benzoxazol-7-yl]-1*H*-benzimidazole-5-carboxylate (11b). ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 8.56 (d, J = 1.2 Hz, 1H), 8.02 (dd, J = 8.6, 1.2 Hz, 1H), 7.93 (dd, J = 7.8, 1.1 Hz, 1H), 7.66–7.61 (m, 3H), 7.54 (t, J = 7.8 Hz, 1H), 7.24 (dd, J = 3.5, 0.5 Hz, 1H), 6.59 (dd, J = 3.5, 1.7 Hz, 1H), 4.46 (m, 1H), 3.96 (s, 3H), 2.45–2.41 (m, 2H), 2.14–2.07 (m, 2H), 1.80–1.75 (m, 2H), 1.45–1.40 (m, 6H), 1.15–1.10 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 167.5, 155.8, 150.4, 147.8, 146.2, 143.0, 142.3, 141.9, 138.6, 127.1, 125.4, 124.7, 124.5, 122.6, 122.1, 115.2, 114.3, 112.4, 110.0, 52.1, 45.1, 29.2, 28.7, 21.9, 13.7; MS (EI): m/z 469 (M^+); HRMS (EI): calcd for $C_{28}H_{27}N_3O_4$ 469.2002, found 469.1995; IR (neat): 3397, 2927, 1716 cm^{-1}.

Methyl-2-[2-(furan-2-yl)-1,3-benzoxazol-7-yl]-1-(3-phenylpropyl)-1*H*-benzimidazole-5-carboxylate (11c). ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 8.57 (s, 1H), 8.05 (d, J = 8.5 Hz, 1H), 7.87 (d, J = 7.8 Hz, 1H), 7.60 (t, J = 7.8 Hz, 1H), 7.57 (s, 1H), 7.46 (t, J = 7.8 Hz, 1H), 7.39 (d, J = 8.5 Hz, 1H), 7.20 (m, 1H), 7.09–7.07 (m, 3H), 6.89–6.87 (m, 2H), 6.55–6.53 (m, 1H), 4.21 (t, J = 7.6 Hz, 2H), 3.93 (s, 3H), 2.48 (t, J = 7.2 Hz, 2H), 2.17–2.10 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 167.3, 155.5, 150.2, 147.4, 146.0, 142.9, 142.1, 141.7, 139.7, 138.5, 128.3, 127.8, 127.0, 126.1, 125.3, 124.6, 124.5, 122.5, 122.0, 115.1, 114.0, 112.2, 109.8, 52.0, 44.2, 32.4, 30.5; MS (EI): m/z 477 (M^+); HRMS (EI): calcd for $C_{29}H_{23}N_3O_4$ 477.1689, found 477.1691; IR (neat) 3405, 2944, 1714 cm^{-1}.

Methyl-1-(3,3-diphenylpropyl)-2-(2-propyl-1,3-benzoxazol-7-yl)-1*H*-benzimidazole-5-carboxylate (11d). ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 8.58 (s, 1H), 8.06 (d, J = 8.6, Hz, 1H), 7.85 (d, J = 7.8 Hz, 1H), 7.6 (d, J = 7.8 Hz, 1H), 7.44 (t, J = 7.8 Hz, 1H), 7.32–7.25 (m, 2H), 7.18–7.12 (m, 5H), 6.99–6.97 (m, 4H), 4.21 (t, J = 7.9 Hz, 2H), 3.96 (s, 3H), 3.77 (t, J = 7.9 Hz, 1H), 2.77 (t, J = 7.5 Hz, 2H), 2.47–2.39 (m, 2H), 1.84–1.73 (m, 2H), 0.97 (t, J = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 167.5, 167.4, 150.5, 148.1, 142.9, 142.0, 138.4, 128.6, 127.6, 127.1, 126.6, 126.3, 124.7, 124.6, 124.6, 122.5, 121.7, 113.5, 109.7, 52.1, 48.4, 43.5, 35.3, 30.2, 20.0, 13.6; MS (EI): m/z 529 (M^+); HRMS (EI): calcd for $C_{34}H_{31}N_3O_3$ 529.2365, found 529.2355; IR (neat) 3409, 2940, 1716 cm^{-1}.

Methyl-1-(3,3-diphenylpropyl)-2-[2-(3,4,5-trimethoxyphenyl)-1,3-benzoxazol-7-yl]-1*H*-benzimidazole-5-carboxylate (11e). ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 8.59 (d, J = 0.8 Hz, 1H), 8.09 (dd, J = 8.6, 0.8 Hz, 1H), 7.92 (d, J = 7.7 Hz, 1H), 7.58 (d, J = 7.7Hz, 1H), 7.47 (t, J = 7.7 Hz, 1H), 7.38 (s, 2H), 7.36 (d, J = 8.6 Hz, 1H), 7.14–7.07 (m, 6H), 6.97–6.95 (m, 4H), 4.21 (t, J = 7.8 Hz, 2H), 3.97 (s, 3H), 3.93 (s, 3H), 3.89 (s, 6H), 3.78 (t, J = 7.8 Hz, 2H),

2.55–2.47 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$: δ_C 167.4, 163.4, 153.5, 150.4, 148.1, 143.0, 142.7, 142.7, 141.4, 138.5, 128.6, 127.1, 126.9, 126.7, 125.2, 124.8, 124.6, 122.6, 121.9, 121.4, 113.7, 109.8, 104.9, 61.0, 56.4, 52.2, 48.6, 43.7, 35.3; MS (EI): *m*/*z* 653 (M^+); HRMS (EI): calcd for $C_{40}H_{35}N_3O_6$ 653.2526, found 653.2523; IR (neat) 3382, 2888, 1712 cm^{-1}.

Methyl-2-[2-(furan-2-yl)-1,3-benzoxazol-7-yl]-1-pentyl-1*H*-benzimidazole-5-carboxylate (11f). ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 8.57 (d, *J* = 0.9 Hz, 1H), 8.08 (dd, *J* = 8.5, 0.9 Hz, 1H), 7.91 (dd, *J* = 7.9, 0.9 Hz, 1H), 7.68–7.65 (m, 2H), 7.55–7.49 (m, 2H), 7.26 (d, *J* = 3.5 Hz, 1H), 6.59 (dd, *J* = 3.5, 1.7 Hz, 1H), 4.22 (t, *J* = 7.5 Hz, 2H), 3.96 (s, 3H), 1.85–1.76 (m, 2H), 1.11–1.07 (m, 4H), 0.71 (t, *J* = 6.7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 167.5, 155.8, 150.3, 147.8, 146.2, 143.0, 142.3, 141.9, 138.6, 127.1, 125.4, 124.7, 124.5, 122.6, 122.1, 115.2, 114.3, 112.4, 110.0, 52.1, 45.1, 29.2, 28.6, 21.9, 13.7; MS (EI): *m*/*z* 429 (M^+); HRMS (EI): calcd for $C_{25}H_{23}N_3O_4$ 429.1689, found 429.1691; IR (neat) 3444, 2951, 1716 cm^{-1}.

Methyl-1-pentyl-2-[2-(3,4,5-trimethoxyphenyl)-1,3-benzoxazol-7-yl]-1*H*-benzimidazole-5-carboxylate (11g). ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 8.56 (s, 1H), 8.07 (d, *J* = 8.6 Hz, 1H), 7.9 (d, *J* = 7.0 Hz, 1H), 7.6 (d, *J* = 7.0 Hz, 1H), 7.56–7.51 (m, 2H), 7.41 (s, 2H), 4.21 (t, *J* = 7.5 Hz, 2H), 3.93 (s, 3H), 3.89 (s, 6H), 3.88 (s, 3H), 1.78 (t, *J* = 7.5 Hz, 2H), 1.08–1.04 (m, 4H), 0.67 (t, *J* = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 167.4, 163.5, 153.4, 150.5, 148.4, 142.9, 142.7, 141.4, 138.5, 126.8, 125.0, 124.6, 124.4, 122.5, 121.7, 121.4, 114.0, 109.9, 105.0, 60.9, 56.3, 52.0, 44.9, 29.1, 28.5, 21.8, 13.6; MS (EI): *m*/*z* 529 (M^+); HRMS (EI): calcd for $C_{30}H_{31}N_3O_6$ 529.2213, found 529.2227; IR (neat) 3394, 2944, 1712 cm^{-1}.

Methyl-2-[2-(furan-2-yl)-1,3-benzoxazol-7-yl]-1-(3-methoxypropyl)-1*H*-benzimidazole-5-carboxylate (11h). ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 8.35 (s, 1H), 7.85 (d, *J* = 8.6 Hz, 1H), 7.68 (d, *J* = 7.9 Hz, 1H), 7.47 (d, *J* = 7.9 Hz, 1H), 7.41 (m, 1H), 7.33–7.29 (m, 2H), 7.04 (t, *J* = 3.5 Hz, 1H), 6.35 (dd, *J* = 3.5, 1.7 Hz, 1H), 4.17 (t, *J* = 6.9 Hz, 2H), 3.72 (s, 3H), 2.89 (t, *J* = 5.6 Hz, 2H), 2.79 (s, 3H), 1.81–1.73 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 167.4, 155.6, 150.3, 147.6, 146.1, 142.7, 142.2, 141.7, 138.6, 127.0, 125.3, 124.7, 124.5, 122.3, 122.0, 115.1, 114.0, 112.3, 110.0, 68.3, 58.3, 52.0, 41.8, 29.6; MS (EI): *m*/*z* 439 (M^+); HRMS (EI): calcd for $C_{24}H_{21}N_3O_5$ 431.1482, found 431.1479; IR (neat) 3453, 2894, 1718 cm^{-1}.

Methyl-1-(3-methylbutyl)-2-(2-phenyl-1,3-benzoxazol-7-yl)-1*H*-benzimidazole-5-carboxylate (11i). ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 8.61 (d, *J* = 1.0 Hz, 1H), 8.22 (dd, *J* = 7.9, 1.7 Hz, 2H), 8.11 (dd, *J* = 8.5, 1.0 Hz, 1H), 7.96 (dd, *J* = 7.9, 0.9 Hz, 1H), 7.68 (dd, *J* = 7.9, 0.9 Hz, 1H), 7.56–7.50 (m, 5H), 4.27 (t, *J* = 7.8 Hz, 2H), 3.98 (s, 3H), 1.74–1.67 (m, 2H), 1.48–1.35 (m, 1H), 0.72 (s, 3H), 0.70 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 167.6, 163.7, 150.5, 148.4, 143.0, 142.7, 138.5, 132.0, 129.0, 127.8, 127.0, 126.4, 125.2, 124.8, 124.6, 122.6, 122.1, 114.1, 110.0, 52.2, 43.5, 38.2, 25.7, 22.0; MS (EI): *m*/*z* 439 (M^+); HRMS (EI) calcd for $C_{27}H_{25}N_3O_3$ 439.1896, found 439.1902; IR (neat) 3450, 2950, 1716 cm^{-1}.

Methyl-1-[2-(cyclohex-1-en-1-yl)ethyl]-2-[2-(3,4,5-trimethoxyphenyl)-1,3-benzoxazol-7-yl]-1*H*-benzimidazole-5-carboxylate (11j). ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 8.58 (d, *J* = 1.1 Hz, 1H), 8.10 (dd, *J* = 8.6, 1.1 Hz, 1H), 7.92 (dd, *J* = 7.7, 1.1 Hz, 1H), 7.64 (dd, *J* = 7.7, 1.1 Hz, 1H), 7.52 (t, *J* = 7.7 Hz, 1H), 7.51 (d, *J* = 8.6 Hz, 1H), 7.43 (s, 2H), 5.06 (s, 1H), 4.33 (t, *J* = 7.0 Hz, 2H), 3.96 (s, 3H), 3.92 (s, 3H), 3.91 (s, 9H), 2.36 (t, *J* = 7.0 Hz, 2H), 1.70 (m, 2H), 1.57–1.56 (m, 2H), 1.30–1.29 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 167.5, 163.6, 153.5, 150.7, 148.3, 143.0, 142.8, 141.5, 138.6, 132.7, 126.9, 125.1, 124.9, 124.7, 124.4, 122.5, 121.8, 121.5, 114.2, 110.8, 105.0, 61.0, 56.4, 52.1, 43.5, 37.6, 27.9, 24.9, 22.3, 21.7; MS (EI): *m*/*z* 567 (M^+); HRMS (EI): calcd for $C_{33}H_{33}N_3O_6$ 567.2369, found 567.2365; IR (neat) 3417, 2935, 1716 cm^{-1}.

Methyl-1-pentyl-2-[2-(phenylamino)-1,3-benzothiazol-7-yl]-1*H*-benzimidazole-5-carboxylate (13a). ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 8.56 (s, 1H), 8.06 (d, *J* = 8.5, Hz, 1H), 7.66 (d, *J* = 7.6 Hz, 1H), 7.52 (d, *J* = 7.7 Hz, 2H), 7.47–7.34 (m, 5H), 7.15 (t, *J* = 7.4 Hz, 1H), 4.29 (t, *J* = 7.6 Hz, 2H), 3.96 (s, 3H), 1.86–1.79 (m, 2H), 1.22–1.20 (m, 4H), 0.80 (t, *J* = 6.7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 167.6, 166.9, 153.6, 152.2, 142.3, 139.5, 138.8, 131.4, 129.5, 126.0, 124.7, 124.6, 124.6, 123.4, 122.4, 121.7, 120.6, 120.5, 109.9, 52.1, 45.1, 29.4, 28.6, 22.0, 13.8; MS (EI): *m*/*z* 470 (M^+); HRMS (EI): calcd for $C_{27}H_{26}N_4O_2S$ 470.1776, found 470.1772; IR (neat) 3261, 2954, 1716 cm^{-1}.

Methyl-2-{2-[(3-methylphenyl)amino]-1,3-benzothiazol-7-yl}-1-pentyl-1*H*-benzimidazole-5-carboxylate (13b). ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 8.59 (d, *J* = 0.9 Hz, 1H), 8.08 (dd, *J* = 8.5, 0.9 Hz, 1H), 7.66 (d, *J* = 7.2 Hz, 1H), 7.48–7.43 (m, 2H), 7.37–7.35 (m, 2H), 7.31–7.26 (m, 2H), 7.00 (d, *J* = 7.3 Hz, 1H), 4.31 (t, *J* = 7.6 Hz, 2H), 3.98 (s, 3H), 2.37 (s, 3H), 1.87–1.80 (m, 2H), 1.28–1.22 (m, 4H), 0.82 (t, *J* = 6.7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 167.6, 167.2, 153.7, 152.6, 142.4, 139.5, 138.8, 131.6, 129.4, 125.9, 125.5, 124.6, 124.5, 124.5, 123.4, 122.4, 121.6, 121.5, 120.4, 117.8, 109.8, 52.1, 45.5, 29.4, 28.6, 22.0, 21.5, 13.8; MS (EI): *m*/*z* 484 (M^+); HRMS (EI): calcd for $C_{28}H_{28}N_4O_2S$ 484.1933, found 484.1931; IR (neat) 2952, 2858, 1716 cm^{-1}.

Methyl-2-[2-(butylamino)-1,3-benzothiazol-7-yl]-1-pentyl-1*H*-benzimidazole-5-carboxylate (13c). ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 8.58 (s, 1H), 8.07 (d, *J* = 8.5 Hz, 1H), 7.64 (d, *J* = 7.9 Hz, 1H), 7.45 (d, *J* = 8.5 Hz, 1H), 7.44 (t, *J* = 7.3 Hz, 1H), 7.30 (d, *J* = 7.6 Hz, 1H), 4.32 (t, *J* = 7.6 Hz, 2H), 3.96 (s, 3H), 3.42 (t, *J* = 7.0 Hz, 2H), 1.88–1.81 (m, 2H), 1.68 (t, *J* = 7.3 Hz, 2H), 1.49–1.37 (m, 2H), 1.24–1.23 (m, 4H), 0.95 (t, *J* = 7.3 Hz, 3H), 0.82 (t, *J* = 6.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 169.7, 167.6, 153.8, 152.9, 142.4, 138.9, 126.0, 124.7, 124.7, 124.6, 123.3, 122.4, 120.8, 119.8, 109.8, 52.1, 45.5, 45.2, 31.5, 29.5, 28.7, 22.0, 20.0, 13.8, 13.7; MS (EI): *m*/*z* 450 (M^+); HRMS (EI): calcd for $C_{25}H_{30}N_4O_2S$ 450.2089, found 450.2088; IR (neat) 3424, 2956, 1712 cm^{-1}.

Methyl-2-[2-(cyclohexylamino)-1,3-benzothiazol-7-yl]-1-(3-methoxypropyl)-1*H*-benzimidazole-5-carboxylate (13d). ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 8.59 (d, *J* = 1.2 Hz, 1H), 8.07 (dd, *J* = 8.6, 1.2 Hz, 1H), 7.61 (dd, *J* = 7.9, 1.1 Hz, 1H), 7.51 (d, *J* = 8.6 Hz, 1H), 7.43 (t, *J* = 7.8 Hz, 1H), 7.34 (dd, *J* = 7.6, 1.1 Hz, 1H), 4.48 (t, *J* = 7.1 Hz, 2H), 3.97 (s, 3H), 3.54 (m, 1H), 3.22 (t, *J* = 5.6 Hz, 2H), 3.16 (s, 3H), 2.17–2.09 (m, 2H), 2.04–2.01 (m, 2H), 1.78–1.74 (m, 4H), 1.43–1.25 (m, 6H); ^{13}C NMR (75 MHz,

$CDCl_3$) δ_C 168.7, 167.6, 153.9, 153.6, 142.4, 139.1, 132.0, 125.9, 124.7, 124.6, 123.2, 122.4, 120.6, 120.0, 109.9, 68.6, 58.6, 54.7, 52.2, 42.0, 33.3, 30.1, 25.4, 24.7; MS (EI): *m*/*z* 478 (M^+); HRMS (EI): calcd for $C_{26}H_{30}N_4O_3S$ 478.2039, found 478.2044; IR (neat) 3228, 2929, 1712 cm^{-1}.

Methyl-1-(3-methoxypropyl)-2-[2-(phenylamino)-1,3-benzothiazol-7-yl]-1*H*-benzimidazole-5-carboxylate (13e). ^1H NMR (300 MHz, $CDCl_3$) δ_H 8.57 (d, *J* = 1.1 Hz, 1H), 8.07 (dd, *J* = 8.5, 1.1 Hz, 1H), 7.64 (dd, *J* = 6.1, 2.9 Hz, 1H), 7.54 (d, *J* = 7.6 Hz, 2H), 7.49 (d, *J* = 8.5 Hz, 1H), 7.42–7.34 (m, 4H), 7.14 (d, *J* = 7.3 Hz, 1H), 4.46 (t, *J* = 6.9 Hz, 2H), 3.96 (s, 3H), 3.20 (t, *J* = 5.5 Hz, 2H), 3.14 (s, 3H), 2.00 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 167.5, 166.8, 153.6, 152.6, 142.1, 139.7, 138.9, 131.4, 129.4, 129.2, 125.9, 124.6, 124.5, 124.2, 123.1, 122.2, 121.6, 120.4, 109.9, 68.4, 58.4, 52.1, 41.9, 29.9; MS (EI): *m*/*z* 472 (M^+); HRMS (EI): calcd for $C_{26}H_{24}N_4O_3S$ 472.1569, found 472.1573; IR (neat) 3263, 2948, 1714 cm^{-1}.

Methyl-2-{2-[(3-methoxypropyl)amino]-1,3-benzothiazol-7-yl}-1-(3-phenylpropyl)-1*H*-benzimidazole-5-carboxylate (13f). ^1H NMR (300 MHz, $CDCl_3$) δ_H 8.57 (d, *J* = 1.1 Hz, 1H), 8.03 (dd, *J* = 8.5, 1.1 Hz, 1H), 7.60 (dd, *J* = 8.0, 0.8 Hz, 1H), 7.33–7.31 (m, 1H), 7.30–7.29 (m, 1H), 7.27–7.20 (m, 3H), 7.13 (dd, *J* = 7.6, 0.8 Hz, 1H), 7.06–7.04 (m, 2H), 6.30 (s, 1H), 4.30 (t, *J* = 7.7 Hz, 2H), 3.95 (s, 3H), 3.52 (m, 4H), 3.33 (s, 3H), 2.58 (t, *J* = 7.2 Hz, 2H), 2.16 (m, 2H), 1.94 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 169.4, 167.5, 153.8, 153.6, 142.3, 139.9, 138.7, 132.0, 128.6, 128.2, 126.4, 125.8, 124.6, 124.5, 123.0, 122.3, 120.5, 119.9, 109.7, 71.3, 58.2, 52.1, 44.3, 43.9, 32.6, 30.9, 28.9; MS (EI): *m*/*z* 514 (M^+); HRMS (EI): calcd for $C_{29}H_{30}N_4O_3S$ 514.2039, found 514.2040; IR (neat) 3226, 2925, 1714 cm^{-1}.

Methyl-1-(3,3-diphenylpropyl)-2-{2-[(3-methoxypropyl)amino]-1,3-benzothiazol-7-yl}-1*H*-benzimidazole-5-carboxylate (13g). ^1H NMR (300 MHz, $CDCl_3$) δ_H 8.57 (s, 1H), 8.02 (d, *J* = 8.4 Hz, 1H), 7.61 (d, *J* = 7.4 Hz, 1H), 7.28–7.19 (m, 7H), 7.14–7.08 (m, 7H), 4.30 (t, *J* = 7.6 Hz, 2H), 3.96 (s, 3H), 3.88 (t, *J* = 7.9 Hz, 1H), 3.57–3.53 (m, 4H), 3.36 (s, 3H), 2.62–2.54 (m, 2H), 1.99–1.95 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 169.3, 167.5, 153.7, 143.1, 142.4, 138.7, 131.9, 128.7, 127.5, 127.3, 126.7, 125.8, 124.7, 124.5, 122.9, 122.3, 120.4, 120.0, 109.6, 71.4, 58.9, 52.1, 48.5, 44.0, 43.9, 35.4, 28.9; MS (EI): *m*/*z* 590 (M^+); HRMS (EI): calcd for $C_{35}H_{34}N_4O_3S$ 590.2352, found 590.2355; IR (neat) 3226, 2925, 1714 cm^{-1}.

Methyl-1-(3,3-diphenylpropyl)-2-[2-(prop-2-en-1-ylamino)-1,3-benzothiazol-7-yl]-1*H*-benzimidazole-5-carboxylate (13h). ^1H NMR (300 MHz, $CDCl_3$) δ_H 8.54 (d, *J* = 1.1 Hz, 1H), 8.03 (dd, *J* = 8.5, 1.1 Hz, 1H), 7.28–7.14 (m, 9H), 7.13–7.08 (m, 3H), 6.94 (dd, *J* = 8.1, 1.5 Hz, 1H), 6.82 (dd, *J* = 7.4, 1.5 Hz, 1H), 5.89–5.76 (m, 2H), 5.46 (t, *J* = 5.4 Hz, 2H), 5.18 (q, *J* = 1.9 Hz, 1H), 5.13 (q, *J* = 1.8 Hz, 1H), 5.08 (q, *J* = 1.5 Hz, 1H), 5.04 (q, *J* = 1.5 Hz, 1H), 4.36 (s, 1H), 4.02 (t, *J* = 8.0 Hz, 1H), 3.96 (s, *3*H), 3.78–3.75 (m, 3H), 2.42 (q, *J* = 7.9 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 167.6, 153.0, 143.8, 143.1, 142.4, 137.7, 129.9, 128.7, 128.6, 127.6, 127.5, 127.4, 126.8, 126.6, 124.4, 124.3, 122.4, 120.8, 118.4, 117.3, 109.5, 52.0, 48.4, 43.10, 35.2, 30.9; MS (EI): *m*/*z* 558 (M^+); HRMS (EI) calcd for $C_{34}H_{30}N_4O_2S$ 558.2089, found 558.2092; IR (neat) 3311, 2939, 1714 cm^{-1}.

Methyl-1-(3,3-diphenylpropyl)-2-{2-[(3-methylphenyl)amino]-1,3-benzothiazol-7-yl}-1*H*-benzimidazole-5-carboxylate (13i). ^1H NMR (300 MHz, $CDCl_3$) δ_H 8.56 (s, 1H), 8.02 (d, *J* = 8.5 Hz, 1H), 7.63 (d, *J* = 7.4 Hz, 1H), 7.35–7.11 (m, 16H), 6.98 (d, *J* = 8.0 Hz, 1H), 4.27 (t, *J* = 7.9 Hz, 2H), 3.96 (s, 3H), 3.86 (t, *J* = 7.8 Hz, 1H), 2.59–2.51 (m, 2H), 2.36 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 167.5, 167.1, 153.4, 152.5, 143.0, 142.4, 139.6, 139.5, 138.7, 131.4, 129.4, 128.7, 127.5, 126.7, 126.0, 125.5, 124.7, 124.6, 123.0, 122.4, 121.4, 121.4, 120.5, 117.6, 109.7, 63.6, 52.1, 48.5, 43.9, 35.4, 21.5; MS (EI): *m*/*z* 608 (M^+); HRMS (EI): calcd for $C_{38}H_{32}N_4O_2S$ 608.2246, found 608.2248; IR (neat) 3058, 2925, 1714 cm^{-1}.

Methyl-2-[2-(cyclohexylamino)-1,3-benzothiazol-7-yl]-1-(3,3-diphenylpropyl)-1*H*-benzimidazole-5-carboxylate (13j). ^1H NMR (300 MHz, $CDCl_3$) δ_H 8.60 (s, 1H), 8.03 (d, *J* = 8.5 Hz, 1H), 7.60 (d, *J* = 8.0 Hz, 1H), 7.30–7.20 (m, 9H), 7.16–7.13 (m, 4H), 4.31 (t, *J* = 7.9 Hz, 2H), 3.98 (s, 3H), 3.89 (t, *J* = 7.7 Hz, 1H), 3.56–3.49 (m, 1H), 2.62–2.53 (m, 2H), 2.15–2.12 (m, 2H), 1.80–1.76 (m, 2H), 1.44–1.33 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 169.2, 168.0, 154.1, 154.0, 143.5, 142.9, 139.2, 132.3, 129.2, 127.9, 127.2, 126.3, 125.1, 125.0, 123.4, 122.8, 120.9, 120.3, 110.1, 55.2, 52.6, 49.0, 44.4, 35.9, 33.7, 25.8, 25.1; MS (EI): *m*/*z* 600 (M^+); HRMS (EI): calcd for $C_{37}H_{36}N_4O_2S$ 600.2559, found 600.2555; IR (neat) 2927, 2854, 1714 cm^{-1}.

Acknowledgements

The authors thank the National Science Council of Taiwan for financial support and the authorities of the National Chiao Tung University for providing the laboratory facilities. This study was particularly supported by the "Centre for bioinformatics research of aiming for the Top University Plan" of the National Chiao Tung University and Ministry of Education, Taiwan.

References

1 (*a*) N. T. Patil and Y. Yamamoto, *Chem. Rev.*, 2008, **108**, 3395–3442; (*b*) S. Fustero, M. Sánchez-Roselló, P. Barrio and A. Simón-Fuentes, *Chem. Rev.*, 2011, **111**, 6984–7034.

2 (*a*) Y. Hu and J. J. Bajorath, *Chem. Inf. Model.*, 2010, **50**, 500–510; (*b*) R. W. Desimone, K. S. Currie, S. A. Mitchell, J. W. Darrow and D. A. Pippin, *Comb. Chem. High Throughput Screening*, 2004, **7**, 473–494.

3 (*a*) S. Ozden, D. Atabey and H. Goker, *Bioorg. Med. Chem.*, 2005, **13**, 1587–1597; (*b*) H. Goker, C. Kus and D. W. Boykin, *Eur. J. Med. Chem.*, 2005, **40**, 1062–1069; (*c*) S. Jain, A. K. Shah, J. Bariwal, S. M. Shelke, A. P. Kale, J. R. Jagtap and A. V. Bhosale, *Bioorg. Med. Chem.*, 2007, **15**, 1181–1205.

4 S. Yoshida, S. Shiokawa, K. Kawano, T. Ito, H. Murakami, H. Suzuki and Y. Sato, *J. Med. Chem.*, 2005, **48**, 7075–7079.

5 (*a*) I. Caleta, M. Kralj, M. Marjanovic, B. Bertosa, S. Tomic, G. Pavlovic, K. Pavelic and G. K. Zamola, *J. Med. Chem.*,

2009, **52**, 1744–1756; (*b*) S. Bondock, W. Fadaly and M. Metwally, *Eur. J. Med. Chem.*, 2010, **45**, 3692–3701.

6 (*a*) R. E. Dolle, *J. Comb. Chem.*, 2005, **6**, 623–679; (*b*) R. E. Dolle, *J. Comb. Chem.*, 2006, **7**, 739–798; (*c*) R. E. Dolle, B. Le Bourdonnec, A. J. Goodman, G. A. Morales, J. M. Salvino and W. Zhang, *J. Comb. Chem.*, 2007, **9**, 855; (*d*) R. E. Dolle, B. Le Bourdonnec, A. J. Goodman, G. A. Morales, C. J. Thomas and W. Zhang, *J. Comb. Chem.*, 2008, **10**, 753.

7 J. Mann, A. Baron, Y. Opoku-Boahen, E. Johansson, G. Parkinson, L. R. Kelland and S. Neidle, *J. Med. Chem.*, 2001, **44**, 138–144.

8 N. Angelopoulos, A. Hadjiprocopis and M. D. Walkinshaw, *J. Chem. Inf. Model.*, 2009, **49**, 1547–1557.

9 S. Sato, T. Kajiura, M. Noguchi, K. Takehana, T. Kobayashi and T. Tsuji, *J. Antibiot.*, 2001, **54**, 102–104.

10 P. S. M. Sommer, R. C. Almedia, K. Schneider, W. Beil, R. D. Sussmuth and H. P. Fiedler, *J. Antibiot.*, 2008, **61**, 683–686.

11 T. A. Beerman, M. M. McHugh, R. Sigmund, J. W. Lown, K. E. Rao and Y. Bathini, *Biochim. Biophys. Acta*, 1992, **1131**, 53–61.

12 S. M. Kerwin, *U.S Patent* 7, 294, 643, 2007.

13 J. M. Bergman, P. J. Coleman, C. Cox, H. G. D. C. Lindsley, S. P. Mercer, A. J. Roecker and D. B. Whitman, *PCT Int. Appl.*, WO2006127550, 2006.

14 A. Ali, G. E. Taylor and D. W. Graham, *PCT Int. Appl.*, WO2001028561, 2001.

15 (*a*) M. Soural, I. Bouillon and V. Krchňák, *J. Comb. Chem.*, 2008, **10**, 923–933; (*b*) J. Cao and X. Huang, *J. Comb. Chem.*, 2008, **10**, 923–933.

16 G. V. Boyd, in *Science of Synthesis: Houben-Weyl Methods of Molecular Transformations*, ed. E. Schaumann, Thieme, Stuttgart, 2001, vol. 11, pp. 481–492.

17 G. W. Stewart, C. A. Baxter, E. Cleator and F. J. Sheen, *J. Org. Chem.*, 2009, **74**, 3229–3231.

18 K. Chanda, B. Maiti, C. C. Tseng and C. M. Sun, *ACS Comb. Sci.*, 2012, **14**, 115–123.

19 C. H. Chen, M. H. Chien, M. L. Kuo, C. T. Chou, J. J. Lai, S. F. Lin, S. Thummanagoti and C. M. Sun, *J. Comb. Chem.*, 2009, **11**, 1038–1046.

20 (*a*) R. D. Viirre, G. Evindar and R. A. Batey, *J. Org. Chem.*, 2008, **73**, 3452–3459; (*b*) Q. Ding, X. He and J. Wu, *J. Comb. Chem.*, 2009, **11**, 587–591; (*c*) E. A. D. Jaseer, J. C. Prasad, A. Dandapat and G. Sekar, *Tetrahedron Lett.*, 2010, **51**, 5009–5012.

21 A. Salcedo, L. Neuville and J. Zhu, *J. Org. Chem.*, 2008, **73**, 3600–3603.

22 (*a*) D. Ma, S. Xie, P. Xue, X. Zhang, J. Dong and Y. Jiang, *Angew. Chem., Int. Ed.*, 2009, **48**, 4222–4225; (*b*) G. Shen, X. Lv and W. Bao, *Eur. J. Org. Chem.*, 2009, **34**, 5897–5901; (*c*) G. Evindar and R. A. Batey, *J. Org. Chem.*, 2006, **71**, 1802–1808.