Alternative conditions for the synthesis of novel spiro[1,3-*N*,*N*-heterocyclic-adamantanes]

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Abstract

A series of new spiro[*N*-heterocyclic-adamantanes] was synthesized through the reaction of 2-adamantanone with *β*-amino carboxamides. Depending on the chemical and physical characteristics of the starting compounds, the cyclocondensations proceeded under simple and mild (aqueous, solvent-free, ball-milling or/and microwave-assisted) conditions with no necessity for chromatographic purification of the products. The reaction was extended to leucinamide and salicylamide.

Keywords: Environmentally friendly methods, aqueous, solvent-free, mechanochemical, ball-milling reactions, microwave-assisted

Introduction

The adamantane cage has been successfully utilized as a stable lipophilic scaffold[1] in the development of numerous lead compounds that demonstrate activity in the central nervous system.[2] The 1-adamantyl group is crucial for the antiparasitic activity of 1,2,4-trioxane derivatives,[3] and replacement of the 2-(adamantan-1-yl)acetyl group with other hydrophobic moieties abolished the anti-EboV activity of a new class of antiviral dipeptides.[4] The incorporation of a spiroadamantane unit into 1,2,4-trioxanes[5] and 1,2,4,5-tetraoxanes[6] enhanced the antimalarial activity, together with low toxicity and high stability profiles both *in vitro* and *in vivo*.

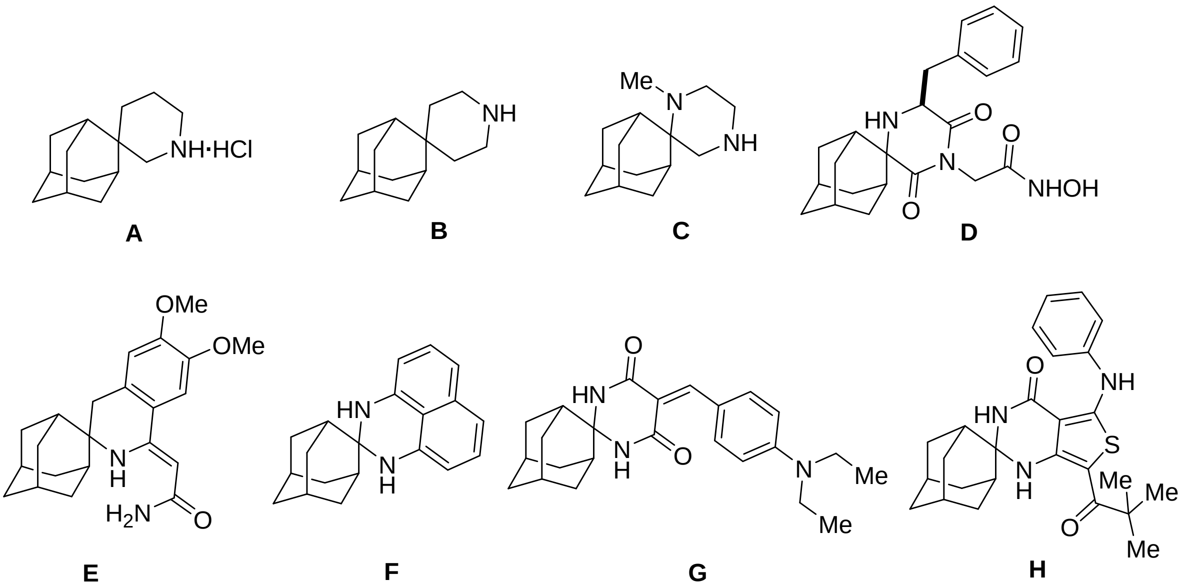


Figure 1. Selected spiro[*N*-heterocyclic-2'-adamantane] derivatives.

In the search for new analogues of adamantine and rimantadine, a number of six-membered spiroadamantane rings bearing one or two nitrogens, has been prepared. The *in vivo* antiviral activity of 3-piperidine derivative **A** against Japanese influenza A_2 was found to be approximately the same as that of 1-adamantanamine.[7] 4-Piperidine derivative **B** proved to display significant anti-influenza A (H3N2) and trypanocidal activity,[8] while piperazine **C** likewise inhibited H3N2 influenza A virus replication.[9] The (*S*)-enantiomer of acethydroxamic acid **D** was the most effective in a study of the trypanidical activities of hydroxamic acid-based derivatives.[10] In a series of spiro[isoquinoline-3,2'-adamantanes], compound **E** emerged as a promising neurotropic candidate, and at the same time was not toxic towards normal cells.[11]

To the best of our knowledge, only the spiro[1,3-*N*,*N*-heterocyclic-adamantanes] **F**,[12] **G**[13] and **H**[14] have been synthetized previously; moreover pharmacological investigations have not been performed on such spiro ring systems.

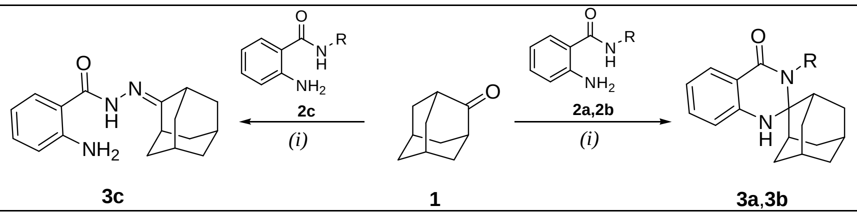
In the series of spirocyclic adamantanes, we have focused mainly on the synthesis of spiro[quinazoline-2,2'-adamantanes] through green chemistry methodology and alternative forms of energy input. All of the products were prepared from commercially available adamantan-2-one (**1**);[15] the spirocyclizations were carried out with *α*- and *β*-amino acid derivatives in the presence of a catalytic amount of I_2.[16]

Results and Discussion

We have previously described ecofriendly methods for the preparation of quinazolin-4(1*H*)-ones in aqueous[17] or solvent-free medium from a 2-aminobenzamide (**2a**)[18] or 2-aminobenzhydrazides (**2b** and **2c**)[19] and a number of aldehydes[20] or ketones.[21] Inspired by the excellent results of the mechanochemical synthesis (*e.g.*, **3a**, Table 1, conversion ~ 99%), we decided to extend the ring closure of **1** with the reactions of a number of amides and hydrazides under either aqueous or ball-milling conditions.

The idea for our initial mechanochemical experiment stemmed from the study by Oliveira *et al.*,[22] in which a series of hydrazones was synthetized by the ball-milling of aldehydes with hydrazines in the solid state at rt. Conversions of 85–99% were obtained, depending on the aldehyde/hydrazide used. These observations on the mechanical solvent-free and solid-state procedures led us to investigate the solid–solid reactions of equimolar amounts of hydrazides **2b** and **2c** with **1**, catalyzed by I_2 (5 mol%) in a vibrational ball-mill. The progress of the reactions was monitored by TLC, and the conversions of the mechanochemical reactions were determined by ^{1}H NMR.

Table 1. Syntheses of spiroadamantane-2,2'-quinazolinones (**3a,3b**) and 2-(adamantan-2-ylidene)hydrazide (**3c**) through the application of mechanical forces



Entry	R	Amide/Hydrazide equiv.		Temp. [°C]	Time [h]	Product	Yield [%][a]	Mp [°C][b]
1	H	**2a**	1	25	2	**3a**	99 (90)[c]	270–274 (281–283)[21]
2	NHPh	**2b**[23]	1	25	4	**3b**	95 (91)[c]	220–225 (228–230)[d]
3	NH_2	**2c**[23]	1	25	1	**3c**	98 (93)[c]	231–235 (244–246)[e]

(*i*) 2 mmol of each reactant, 25 mg (5 mol%) of I_2, in a stainless-steel jar (25 mL) with two ZrO_2 balls (15 mm) at 25 Hz; [a] on the basis of ^{1}H NMR; [b] from aqueous suspension; [c] isolated yields from aqueous work-up (3 mL of 2% $Na_2S_2O_5$ and 5 mL of water, 25 Hz for 5 min, filtration, and washing with 5 mL of water); [d] from EtOH; [e] from MeOH–Et_2O.

After grinding for 4 h, the ^{1}H NMR spectrum revealed that the conversion of **1** and **2b** to quinazoline **3b** was almost complete (95%). The use of ZrO_2 balls insteated of stainless-steel balls was essential in order to avoid the paramagnetic impurity effects in the NMR determination of the conversions of the crude products in our further mechanochemical studies.[21,24] When it was necessary to eliminate I_2 from the crude products **3a**–**3i**, a simple aqueous work-up technique was applied (Tables 1 and 2[c]). Analytically pure samples of ball-milled **3a–3i** were prepared by crystallization from a suitable solvent.

For a comparison of the reactivities of **2b** and **2c**, the mixture of **1** and **2c** were mixed in the presence of iodine at 25 Hz for 1 h. NMR analysis demonstrated the presence of hydrazone **3c** in a conversion of 98%. The rearrangement of **3c** to the thermodynamically favored quinazolinone[17] was not observed on heating at reflux hydrazone **3c** in EtOH or in water, or on the application of microwave (MW) irradiation in the same solvents at 160 °C either without a catalyst or in the presence of I_2 or *p*-TSA as catalyst. It is presumed that rearrangement through the transimination of **3c** did not occur because of the steric hindrance of the adamantane moiety. On the other hand, the presence of the phenyl substituent on the benzhydrazide component led to regioselective ring closure of **1** with **2b**.[25]

Since (cyclo)aliphatic amines are usually good nucleophiles, we extended the ball-milling methodology to the spirocyclizations of β-aminoamides **2d–2h** with **1**. First, a mixture of **1** and **2d** was milled at 25 Hz for 1 h in the absence of the I_2 catalyst. The ^{1}H NMR spectrum of the reaction mixture showed that product **3d** was obtained in a yield of 8–10% [Figure 2 (I)]. When 5 mol% of solid I_2 was added to the mixture and the mechanical treatment was continued for an additional 1 h under the same conditions, crude **3d** was formed with a conversion of 85% (Figure 2 II). The results shown in Figure 2 can be explained by the fact that I_2 promotes activation of the imine (Schiff base) in the intramolecular cyclization.[26]

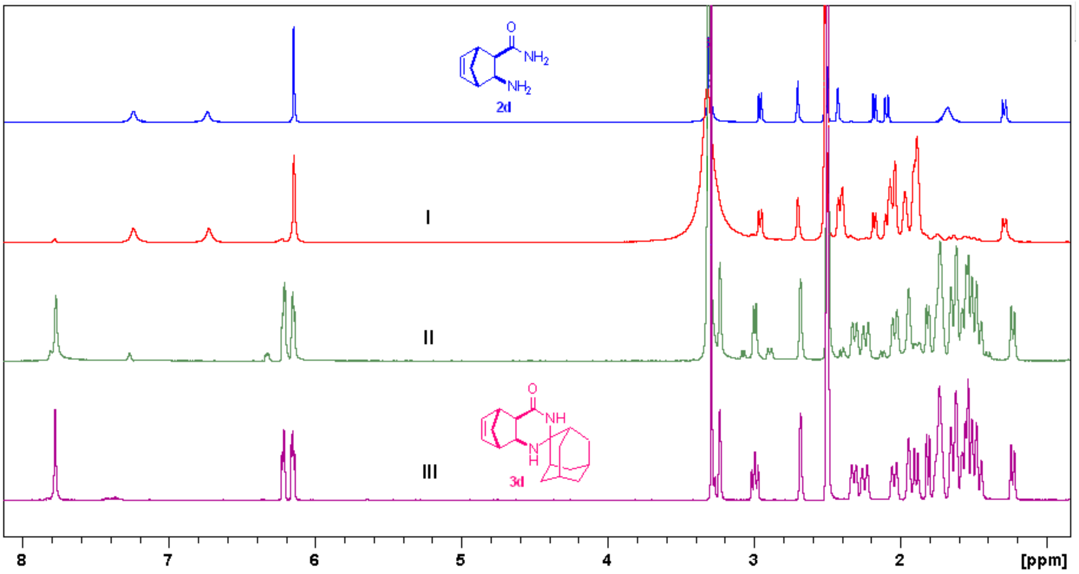
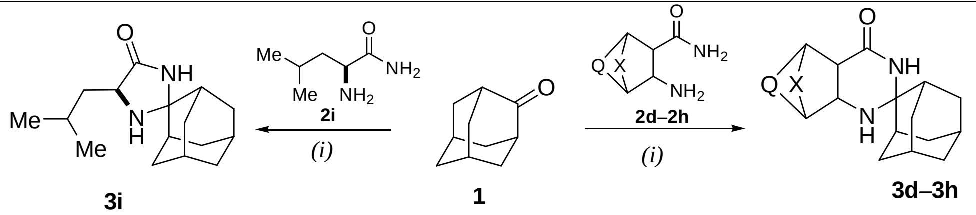
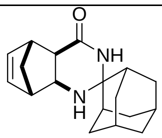
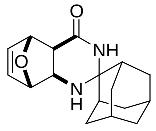
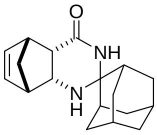
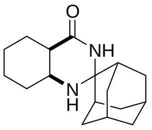
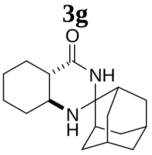
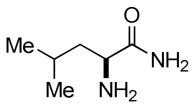
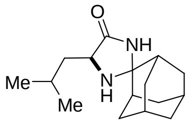


Figure 2. ^{1}H NMR spectra of (I) a catalyst-free reaction mixture of **2d** and **1** after ball-milling for 1 h, (II) the reaction mixture after the addition of 5 mol% I_2 followed by mechanochemical treatment for 1 h, and (III) the mixture of I_2, **1** and **2d** after milling for 2 h.

Table 2. Syntheses of 2-spiroquinazolinones (**3d–3h**) and 2-spiroimidazolidine (**3i**) in a vibrational ball-mill



Entry	Config.	X	Q	Amide	equiv.	Temp. [°C]	Time [h]	Product	Yield [%][a]	Mp [°C][b]
1	*diexo*	CH$_2$	–CH=CH–	**2d**[28]	1	25	2	 **3d**	99 (95)[c]	210–213 (221–222)[d]
2	*diexo*	O	–CH=CH–	**2e**[29]	1	25	3	 **3e**	97 (93)[c]	185–190 (190–192)[d]
3	*diendo*	CH$_2$	–CH=CH–	**2f**[28]	1	25	3	 **3f**	98 (94)[c]	207–210 (211–212)[d]
4	*cis*	—	–CH$_2$CH$_2$–	**2g**[30]	1	25	2	 **3g**	99 (91)[c]	204–208 (208–210)[d]
5	*trans*	—	–CH$_2$CH$_2$–	**2h**[30]	1	25	6	 **3h**	87 (65)	243–246 (252–254)[e]
6				**2i**[31]	1	25	4	 **3i**	99 (88)[c]	206–210 (215–216)[f]

(*i*) 2 mmol of reactants, 25 mg (5 mol%) of I$_2$, stainless-steel jar (25 mL) with two ZrO$_2$ balls (15 mm) at 25 Hz; [a] on the basis of ^{1}H NMR; [b] from aqueous suspension; [c] isolated yields from aqueous work-up (2 mL of 2% Na$_2$S$_2$O$_5$ and 3 mL of water, 25 Hz for 5 min, filtration, and washing with 3 mL of water); [d] from EtOAc; [e] from EtOH; [f] from *i*-Pr$_2$O.

Encouraged by this result, we investigated the reactions of **1** with alicyclic amides **2e**−**2h** and α-amino acid derivative **2i** under the application of mechanical forces (entries 2−5). The reactions were complete in 2−4 h at 25 Hz, leading to powdery products; a liquid phase[27] was not observed. Surprisingly, under such reaction conditions the *N*-methylamide derivatives **2a**, **2d** and **2e** did not give spirocyclic products. During the ball-milling procedure, melt mixtures were seen; perhaps because of the steric effects of the methyl group, mainly imine formation occurred.

In the light of our work on spirocyclization in/on water[17–19] and reported aqueous protocols for the synthesis of nitrogen heterocycles by several research groups,[32–34] we were motivated to attempt the preparation of **3a–3h** in aqueous medium. For the condensation reactions followed by intramolecular cyclizations, an I_2/KI catalyst was used.[21,26]

We first re-examined the reaction of **1** with **2a**, after the addition of 1 mol% (0.5 mL of 1% aqueous solution) of I_2/KI[35] to a stirred suspension of stoichiometric amounts (2 mmol) of **1** and **2a** in water (10 mL). After stirring for 24 h at rt, **3a** was filtered off in a yield of 86%. The spectroscopic data and the mp of **3a** corresponded well with the literature values.[21]

Table 3. Synthesis of adamantane derivatives **3a–3i** in aqueous media (*ii*)

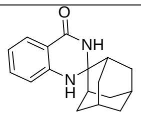
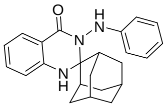
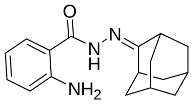
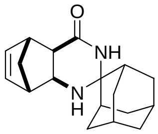
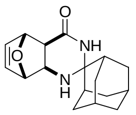
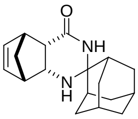
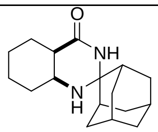
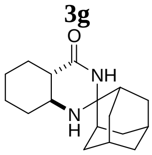
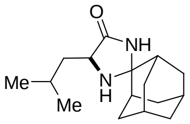
Entry	Amide/Hydrazide	equiv.	Temp. [°C]	Time [h]	Product	Yield [%][a]	Mp [°C][b]
1	**2a**	1	25	24	 **3a**	86	271–273
2	**2b**	1	25	24	 **3b**	79	222–225
3	**2c**	1	25	24	 **3c**	82	231–233
4	**2d**	1	25	24	 **3d**	76	218–220
5	**2e**	1	25	24	 **3e**	73	187–190
6	**2f**	1	25	24	 **3f**	68	207–209

Table 3 (continued)

Entry	Amide/Hydrazide	equiv.	Temp. [°C]	Time [h]	Product	Yield [%][a]	Mp [°C][b]
7	**2g**	1	25	24	 **3g**	80	206–208
8	**2h**	1	25	24	 **3h**	in traces	–
8	**2i**	1	25	72	 **3i**	51	212–213

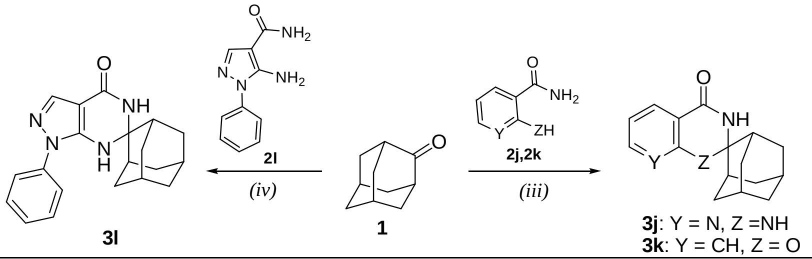
(ii) A mixture of 2 mmol of each of the reactants and 0.5 mL of 1% I_2/KI solution was stirred in 10 mL (**3a–3c**) or in 3 mL (**3d–3i**) of water for 24 h at rt. The precipitates were filtered off, washed with 3 mL of water, and dried; [a] isolated yields from aqueous suspension; [b] melting points of filtered and dried products.

We further employed this ecofriendly protocol for the preparation of **3b** and **3c** (Table 3, entries 1–3). It is important to note that condensations of **1** with the more water-soluble (cyclo)alkyl amides **2d–2h** were carried out in 3 mL of water (Entries 4–8). The moderate yield and longer reaction time of **3i** can be explained by the higher solubilities of **2i** and **3i** in water. The ^{1}H NMR data on the crude products isolated from aqueous media corresponded well with those on the analytically pure samples of **3a–3i**.

To examine the mechanochemical and in/on water reaction limitations and the scope of the cyclizations of **1** with different amides, we applied 2-aminonicotinamide (**2j**),[36] salicylamide (**2k**) and 5-amino-1-phenylpyrazole-4-carboxamide (**2l**)[37] to attempt to produce spiroadamantane-heterocycles. We found that ball-milling or treatment in water did not lead to I_2-catalyzed ring closure: no desired compound was isolated. In a series of further experiments, pyrido[2,3-*d*]pyrimidine **3j** and pyrazolo[3,4-*d*]pyrimidine **3l** were prepared under MW irradiation, while benz[1,3]oxazine **3k** separated out from a refluxed solution in EtOH (Table 4).

Heterocycle **3j** was synthesized in an analogous manner to spiro[cyclohexane-1,2'-pyrido[2,3-*d*]pyrimidine][38] through the use of MW irradiation. When a mixture of **1** and **2j** with 1 mol% of I_2 was irradiated (100 W) in a sealed vial, **3j** was obtained in good yield with excellent purity (Entry 1). Melzig reported the synthesis of photochromic **3k** when a reaction mixture of **1**, **2k** and polyphosphate ethyl ester was refluxed in $CHCl_3$. The pale-yellow crystalline product melted at 220–225 °C,[39] but its IR and NMR data were not published. In view of the lack of a spectroscopic analysis, we decided to attempt to prepare **3k** by a greener procedure. An equimolar ratio of **1** and **2k** with 1 mol% of I_2 was refluxed in EtOH under conventional heating for 8 h. Water was added to the cooled solution, and **3k** separated out as a colourless precipitate in a yield of 71%.

Table 4. Synthesis of adamantane derivatives **3j–3l** in EtOH (*iii*) or in DCM (*iv*)



Entry	Solvent	Catalyst	Amide/ equiv.		Temp. [°C]	Time [h]	Product	Yield [%][a]	Mp [°C]
1	EtOH	I_2	**2j**	1	160 (MW)	6	**3j**	67	(299–302)[b] 303–304[c]
2	EtOH	I_2	**2k**	1	78 (reflux)	8	**3k**	71	(279–282)[b] 281–283[d]
3	DCM	$AlCl_3$	**2l**	1.3	110 (MW)	2	**3l**	81	221–223[c]

(iii) A mixture of 2 mmol of each of the reactants, and 5 mg (1 mol%) of I_2 was irradiated or refluxed in EtOH; (*iv*) a mixture of 1.5 mmol of **1**, **2l** and $AlCl_3$ (2 mmol), MW in DCM; [a] isolated yield of crude products; [b] mp-s from EtOH–H_2O; [c] from EtOAc; [d] from EtOH.

For a route to the preparation of biologically and pharmaceutically important pyrazolo[3,4-*d*]pyrimidines[40] with avoidance of the formation of a pyrazolopyridine, we used **2l** rather than *o*-aminopyrazolcarbonitrile.[41] Methods (*i*) and (*ii*) led to insufficient yields, and we catalyzed the MW-induced reaction of **1** with **2l** with various Lewis acids and solvents. We found that 1.3 equiv. of $AlCl_3$ in DCM was the best of the traditional Lewis acids. When the reaction was carried out at 110 °C (60 W) for 2 h, crude **3l** was isolated in a yield of 81%.

In conclusion, various conditions have been examined for the condensation of 2-adamantanone with hydrazides or amides **2a–2l**, including solvent-free ball-milling, in/on water or in EtOH solution, and MW irradiation in EtOH solution or in DCM. The relative reactivities, solubilities in water and melting points of the nucleophiles all influenced the above protocols. These methods have a number of advantages over other methods: the reaction techniques are very simple, and the syntheses proceed under mild reaction conditions without the need for costly catalysts and chromatographic purification.

Experimental Section

General. The reaction courses and the purities of products were monitored by TLC. ^{1}H NMR spectra of the dried crude mixtures were recorded in DMSO-d_6 or $CDCl_3$ to confirm the conversion to **3a**–**3i**. Analytically pure samples of **3a**–**3l** were prepared by crystallization and their ^{1}H NMR (400 Hz) and ^{13}C NMR (100 MHz) spectra were recorded on a Bruker Avance DRX 400 spectrometer with TMS as internal reference. Melting points were determined on a Kofler apparatus. FT-IR spectra were recorded in KBr pellets on a Perkin-Elmer 100 FT-IR spectrometer. Elemental analyses were carried out on a Perkin-Elmer 2400 elemental analyzer. The MW-promoted reactions were performed in sealed reaction vials (10 mL) through use of the MW reactor (CEM, Discover) cavity. The ball-milling experiments were carried out in a Retsch MM400 mixer mill with two ZrO_2 balls 15 mm in diameter in a stainless-steel jar (25 mL) at 25 Hz at rt.

Preparation of spiroadamantanes (3a,3b and 3d–3l) and hydrazone (3c)

A. 2b–**2i** (2.0 mmol), **1** (0.30 g, 2.0 mmol), 25 mg (5 mol%) of I_2 and two ZrO_2 balls 15 mm in diameter were placed in a stainless-steel jar. The vessel was vibrated at 25 Hz for the appropriate length of time. The reaction progress was monitored by TLC. The products were recovered as solids (directly from the jar) and dried. The conversions to **3b–3i** were determined by ^{1}H NMR.

In the aqueous work-up procedure, 2 or 3 mL of 2% $Na_2S_2O_5$ solution and 3 or 5 mL of water were added to the reaction mixture in the jar. The aqueous suspension was mixed at 25 Hz for 5 min, filtered off, washed with water (3 or 5 mL) and dried. The isolated yields and melting points of crude **3b–3i** were determined. Analytically pure samples of compounds **3b–3i** were recrystallized from a suitable solvent.

B. To a stirred mixture of **1** (0.30 g, 2.0 mmol) in 0.5 mL of 1% I_2/KI (1 g of I_2 and 1.6 g of KI in 100 mL of water) and 3–10 mL of water in a round-bottomed flask (25 mL), **2a–2c** (2 mmol) was added in portions. The flask was sealed with a Teflon cap. After vigorous stirring at rt for 24 h, **3a–3i** precipitated. The product was filtered off, washed with water (3 mL) and dried. The purities of **3a–3i** were established by ^{1}H NMR measurements.

C. A stirred mixture of 5 mg (1 mol%) of I_2, **2k** (0.27 g, 2 mmol) and **1** (0.30 g, 2 mmol) in EtOH (5 mL) was refluxed for 8 h. To the cooled mixture, 5 mL of water was added. The solid product was separated by filtration and dried. For **3j**, I_2 (5 mg, 1 mol%), **2j** (0.28 g, 2 mmol) and **1** (0.30 g, 2 mmol) were placed in a MW test-tube (10 mL) (which was subsequently sealed with a Teflon cap) which contained a magnetic stirrer and EtOH (2 mL). The test-tube was placed in the CEM Discover MW reactor. The solution was irradiated for 6 h at 160 °C (100 W). To the cooled solution, water (4 mL) was added, and the precipitated product was filtered off and dried. The melting points of both the crude and the recrystallized **3j** and **3k** were determined.

D. 0.30 g (1.5 mmol) of **2l**, 0.23 g (1.5 mmol) of **1** and 0.26 g (2 mmol) of $AlCl_3$ were placed in a MW test-tube (10 mL) (sealed with a Teflon cap) containing a magnetic stirrer and 2 mL of DCM. The test-tube was placed in the MW reactor (CEM, Discover) cavity, microwaved at

110 °C (60 W) for 2 h and then cooled to room temperature. The reaction mixture was poured onto water (50 mL) and extracted with DCM (3 × 10 mL), and the extract was evaporated *in vacuo*. The residue was recrystallized from EtOAc.

Analytical and spectroscopic data on **3b–3l** are given below.

3'-(Phenylamino)-1'*H*-spiro[tricyclo[3.3.1.1^{3,7}]decane-2,2′(1′*H*)-quinazolin]-4′(3′*H*)-one (3b). Beige crystals, mp 228–230 °C (EtOH); IR (cm^{-1}): 3428, 3357, 3266, 3034, 2915, 2855, 1623, 1615, 1496, 1481, 761, 750. ^{1}H NMR δ (DMSO-d_6, ppm): 1.35−2.18 (m, 12H, adamantyl), 2.28 (s, 1H, adamantyl), 3.09 (d, *J* 12.7 Hz, 1H, adamantyl), 6.65 (t, *J* 7.3 Hz, 1H, ArH), 6.73–6.81 (m, 3H, ArH), 6.86 (br s, 1H, NH), 7.08 (t, 1H, ArH), 7.20 (d, *J* 8.0 Hz, 1H, ArH), 7.35 (m, 1H, ArH), 7.59 (d, *J* 7.6 Hz, 1H, ArH), 8.31 (br s, 1H, NH); ^{13}C NMR δ (DMSO-d_6, ppm): δ 26.9 27.3, 32.1, 34.1, 34.5 (2×C), 34.8, 36.0, 38.7, 78.3, 113.0 (2×C), 116.8, 118.4, 118.5, 119.2, 128.1, 129.6 (2×C), 134.1, 146.2, 150.7, 164.0; Anal. calcd. for $C_{23}H_{25}N_3O$ (359.46) (%): C, 76.85; H, 7.01; N, 11.69. Found: C, 76.65; H, 7.11; N, 11.55.

2-Amino-*N′*-tricyclo[3.3.1.1^{3,7}]decanylidenebenzohydrazide (3c). Colourless crystals, mp 244–246 °C (MeOH–Et$_2$O); IR (cm^{-1}): 3484, 3358, 3210, 2910, 2899, 2849, 1646, 1636, 1584, 1530, 1489, 1447, 751. ^{1}H NMR δ (DMSO-d_6, ppm): 1.74−2.08 (m, 12H, adamantyl), 2.60 (s, 1H, adamantyl), 3.21 (s, 1H, adamantyl), 6.17 (br s, 2H, NH$_2$), 6.52 (t, *J* 7.5 Hz, 1H, ArH), 6.70 (d, *J* 8.1 Hz, 1H, ArH), 7.14 (m, 1H, ArH), 7.43 (d, *J* 8.0 Hz, 1H, ArH), 10.34 (br s, 1H, CONH); ^{13}C NMR δ (DMSO-d_6, ppm): δ 28.1 (2×C), 32.6, 36.8, 38.1 (2×C), 39.4 (2×C), 40.0, 115.5 (2×C), 117.0 (2×C), 129.6, 132.4, 150.2, 168.2 (HMQC, HMBC); Anal. calcd. for $C_{17}H_{21}N_3O$ (283.37) (%): C, 72.06; H, 7.47; N, 14.83. Found: C, 72.15; H, 7.29; N, 14.59.

***diexo*-5',8'-Methano-4a',5',8',8a'-tetrahydro-1'*H*-spiro[tricyclo[3.3.1.1^{3,7}]decane-2,2'-quinazolin]-4'(3'*H*)-one (3d).** Colourless crystals, mp 221–222 °C (EtOAc); IR (cm^{-1}): 3291, 3056, 2899, 2844, 1635, 711 (*diexo*).[42] ^{1}H NMR δ (DMSO-d_6, ppm): 1.24 (d, *J* 9.0 Hz, 1H, 9'-H), 1.43−1.80 (m, 11H, adamantyl and 9'-H), 1.82 (d, *J* 7.3 Hz, 1H, 4a'-H), 1.86–2.38 (m, 5H, adamantyl and 1'-NH), 2.69 (s, 1H, 8'-H), 3.00 (t, *J* 8.0 Hz, 1H, 8a'-H), 3.25 (s, 1H, 5'-H), 6.16 (dd, *J* 3.1 Hz, *J* 5.5 Hz, 1H, 7'-H), 6.23 (dd, *J* 2.9 Hz, *J* 5.5 Hz, 1H, 6'-H), 7.79 (s, 1H, CONH); ^{13}C NMR (DMSO-d_6, 100 MHz, ppm): δ 27.3 27.4, 32.7, 33.4, 33.7, 33.9, 35.7, 37.4, 38.6, 42.8, 44.7, 45.4, 48.0, 52.8, 72.5, 136.7, 138.6, 172.3; Anal. calcd. for $C_{18}H_{24}N_2O$ (284.40) (%): C, 76.02; H, 8.51; N, 9.85. Found: C, 76.15; H, 8.39; N, 9.59.

***diexo*-5',8'-Epoxy-4a',5',8',8a'-tetrahydro-1'*H*-spiro[tricyclo[3.3.1.1^{3,7}]decane-2,2'-quinazolin]-4'(3'*H*)-one (3e).** Colourless crystals, mp 190–192 °C (EtOAc); IR (cm^{-1}): 3268, 3221, 3044, 3025, 2990, 2943, 2909, 2866, 1642, 872, 707 (*diexo*). ^{1}H NMR δ (DMSO-d_6, ppm): 1.40−2.43 (m, 16H, adamantyl, 4a'-H and 1'-NH), 3.18 (dd, *J* 6,8 Hz, *J* 11,2 Hz, 1H, 8a'-H), 4.72 (s, 1 H, 8'-H), 5.20 (s, 1H, 5'-H), 6.42 (d, *J* 5,6 Hz, 1H, 7'-H), 6.54 (d, *J* 5,6 Hz, 1H, 6'-H), 8.02 (s, 1H, CONH); ^{13}C NMR (DMSO-d_6, ppm): δ 27.3, 27.4, 32.6, 33.2, 33.7, 33.9, 36.0, 37.7, 38.5, 42.3, 52.2, 72.7, 81.8, 83.3, 135.1, 138.1, 170.8; Anal. calcd. for $C_{17}H_{22}N_2O_2$ (286.37) (%): C, 71.30; H, 7.74; N, 9.78. Found: C, 71.15; H, 7.95; N, 9.58.

***diendo*-5',8'-Methano-4a',5',8',8a'-tetrahydro-1'*H*-spiro[tricyclo[3.3.1.1^{3,7}]decane-2,2'-quinazolin]-4'(3'*H*)-one (3f).** Colourless crystals, mp 207–210 °C (EtOAc); IR (cm^{-1}): 3291, 3056, 2916, 2903, 2866, 1640, 872, 754 (*diendo*). ^{1}H NMR δ (DMSO-d_6, ppm): 0.56 (d, *J* 11.8 Hz, 1H, 1'-NH), 1.31−2.40 (m, 17H, adamantyl, 4a'-H and 9'-H), 2.97 (s, 1H, 8'-H), 3.17 (s, 1H, 5'-H), 3.74 (m, 1H, 8a'-H), 6.14 (dd, *J* 2.8 Hz, *J* 5.6 Hz, 1H, 7'-H), 6.22 (dd, *J* 2.8 Hz, *J* 5.5 Hz, 1H, 6'-H), 7.67 (s, 1H, CONH); ^{13}C NMR (DMSO-d_6, ppm): δ 27.3 27.4, 32.6, 33.2, 33.7, 34.0, 36.8, 37.9, 38.5, 43.2, 46.3, 46.7, 47.4, 54.1, 73.4, 134.0, 140.0, 172.2; Anal. calcd. for $C_{18}H_{24}N_2O$ (284.40) (%): C, 76.02; H, 8.51; N, 9.85. Found: C, 75.85; H, 8.58; N, 9.69.

cis-Hexahydro-1'_H_-spiro[tricyclo[3.3.1.1^{3,7}]decane-2,2'-quinazolin]-4'(3'_H_)-one (3g). Colourless crystals, mp 208–210 °C (EtOAc); IR (cm^{-1}): 3213, 2906, 1642, 1457, 1101, 807, 775. ^{1}H NMR δ (DMSO-d_6, ppm): 1.08−2.37 (m, 25H, adamantyl, cyclohexyl and 1'-NH), 7.43(s, 1H, CONH); ^{13}C NMR (DMSO-d_6, 100 MHz, ppm): δ 20.5, 25.5, 25.8, 27.3, 27.7, 30.7, 32.5, 32.7, 34.1, 34.5, 36.8, 38.8, 39.8, 42.9, 44.4, 72.4, 174.2;Anal. calcd. for $C_{17}H_{26}N_2O$ (274.40) (%): C, 74.41; H, 9.55; N, 10.21. Found: C, 74.65; H, 9.58; N, 9.99.

trans-Hexahydro-1'_H_-spiro[tricyclo[3.3.1.1^{3,7}]decane-2,2'-quinazolin]-4'(3'_H_)-one (3h). Colourless crystals, mp 252–254 °C (EtOAc); IR (cm^{-1}): 3224, 2931, 2906, 2847, 1637, 1435, 814. ^{1}H NMR δ (CDCl$_3$, ppm): 0.85−2.41 (m, 24H, adamantyl, cyclohexyl and 1'-NH), 2.63 (m, 1H, cyclohexyl) 6.55(s, 1H, CONH); ^{13}C NMR (CDCl$_3$, ppm): δ 26.0 (2×C), 26.3, 27.2, 27.5, 33.2, 33.6, 33.7, 34.1, 34.2, 37.2, 38.4, 40.8, 49.1, 51.4, 72.7, 173.2; Anal. calcd. for $C_{17}H_{26}N_2O$ (274.40) (%): C, 74.41; H, 9.55; N, 10.21. Found: C, 74.45; H, 9.75; N, 10.19.

(5'_S_)-5'-Isobutylspiro[tricyclo[3.3.1.1^{3,7}]decane-2,2'-imidazolidin]-4'-one (3i). $[\alpha]_D^{25}$ –10.8 ° (EtOH, c 0.535). Colourless crystals, mp 215–216 °C (*i*-Pr$_2$O); IR (cm^{-1}): 3197, 3074, 2910, 2867, 1693, 1460, 880, 825, 778. ^{1}H NMR δ (DMSO-d_6, ppm) 0.82–0.96 (m, 6H, 2×CH$_3$), 1.22 (m, 1H, isobutyl), 1.43−2.16 (m, 17H, adamantyl, isobutyl, 1'-NH), 2.57, (m, 1H, 5'-H), 8.68 (s, 1H, CONH); ^{13}C NMR (DMSO-d_6, ppm): δ 22.6, 24.2, 25.7, 26.9, 27.2, 33.9 (2×C), 34.1, 34.5, 38.1, 38.7, 40.8, 43.2, 57.0, 77.9, 178.1; Anal. calcd. for $C_{16}H_{26}N_2O$ (262.39) (%): C, 73.24; H, 9.99; N, 10.68. Found: C, 73.45; H, 9.74; N, 10.49.

1'_H_-Spiro[tricyclo[3.3.1.1^{3,7}]decane-2,2'-pyrido[2,3-_d_]pyrimidin]-4'(3'_H_)-one (3j). Colourless crystals, mp 303–304 °C (EtOAc); IR (cm^{-1}): 3402, 3233, 2925, 2894, 1660, 1600, 1446, 1257, 769. ^{1}H NMR δ (DMSO-d_6, ppm): δ 1.49−2.30 (m, 14H, adamantyl), 6.74 (m, 1H, ArH), 7.30 (br s, 1H, ArNH), 7.91 (m, 1H, ArH), 8.07 (br s, 1H, NHCO), 8.20 (m, 1H, ArH); ^{13}C NMR (DMSO-d_6, ppm): δ 26.7 26.9, 32.6 (2×C), 33.1 (2×C), 37.3 (2×C), 38.5, 72.1, 110.6, 114.7, 136.4 (2×C), 153.6, 157.5; Anal. calcd. for $C_{16}H_{19}N_3O$ (269.34) (%): C, 71.35; H, 7.11; N, 15.60. Found: C, 71.45; H, 7.24; N, 15.49.

Spiro[tricyclo[3.3.1.1^{3,7}]decane-2,2'-pyrido[3,2-_e_][1,3]oxazin]-4'(3'_H_)-one (3k). Colourless crystals, mp 281–283 °C (EtOH); IR (cm^{-1}): 3221, 3086, 2931, 2920, 2888, 1669, 1468, 1383, 999, 756. ^{1}H NMR δ (DMSO-d_6, ppm): 1.47−2.18 (m, 14H, adamantyl), 6.96–7.13 (m, 2H, ArH), 7.52 (m, 1H, ArH), 7.74 (m, 1H, ArH), 8.66 (s, 1H, NHCO); ^{13}C NMR (DMSO-d_6, ppm): δ 26.7 26.9, 33.0 (2×C), 33.5 (2×C), 36.3 (2×C), 37.8, 91.4, 117.9, 119.5, 122.6, 127.9, 135.2, 155.5, 162.2; Anal. calcd. for $C_{17}H_{19}NO_2$ (269.34) (%): C, 75.81; H, 7.11; N, 5.20. Found: C, 75.65; H, 7.23; N, 5.09.

1'-Phenyl-5',7'-dihydrospiro[tricyclo[3.3.1.1^{3,7}]decane-2,6'-pyrazolo[3,4-d]pyrimidin]-4'(1'H)-one (3l). Colourless crystals, mp 221–223 °C (EtOAc); IR (cm^{-1}): 3238, 3079, 2923, 2901, 2887, 1663, 1596, 1560, 1508, 871, 777, 756. ^{1}H NMR δ (DMSO-d_6, ppm): 1.50−2.23 (m, 14H, adamantyl), 6.42 (s, 1H, NH), 7.30–7.33 (m, 2H, ArH and NHCO), 7.55 (m, 2H, ArH), 7.77–7.89 (m, 3H, ArH and pyrazolyl), ^{13}C NMR (DMSO-d_6, ppm): δ 27.1 (2×C), 32.8 (2×C), 34.1 (2×C), 35.8 (2×C), 38.4, 74.5, 104.9, 121.6 (2×C),127.4, 130.2 (2×C), 138.6, 139.5, 148.5, 161.9; Anal. calcd. for $C_{20}H_{22}N_4O$ (334.41) (%): C, 71.83; H, 6.63; N, 16.75. Found: C, 71.85; H, 6.83; N, 16.89.

References

1. Wanka, J.; Iqbal, K.; Schreiner, P. R. *Chem. Rev.* **2013**, *113*, 3516–3604. http://dx.doi.org/10.1021/cr100264t
2. Joubert, J.; Geldenhuys, W. J.; Van der Schyf, C. J.; Oliver, D. W.; Kruger, H. G.; Govender, T.; Malan, S. F. *ChemMedChem*, **2012**, *7*, 375–384. http://dx.doi.org/10.1002/cmdc.201100559
3. Griesbeck, A. G.; Schlundt, V. *Synlett*, **2011**, 2430–2432. http://dx.doi.org/10.1055/s-0030-1261225
4. Lee, K.; Ren, T.; Côté, M.; Gholamreza, B.; Misasi, J.; Bruchez, A.; Cunningham, J. *ACS Med. Chem. Lett.* **2013**, *4*, 239–243. http://dx.doi.org/10.1021/ml300370k
5. Zhao, Q.; Vargas, M.; Dong, Y.; Zhou, L.; Wang, X.; Sriraghavan, K.; Keiser, J.; Vennestrom, J. L. *J. Med. Chem.* **2010**, *53*, 4223–4233. http://dx.doi.org/10.1021/jm100226t
6. Ellis, G. L.; Amewu, R.; Sabbani, S.; Stocks, P. A.; Shone, A.; Stanford, D.; Gibbons, P.; Davies, J.; Vivas, L.; Charnaud, S.; Bongard, E.; Hall, C.; Rimmer, K.; Lozanom, S.; Jesús, M.; Gargallo, D.; Ward, S. A.; O'Neill, P. M. *J. Med. Chem.* **2008**, *51*, 2170–2177. http://dx.doi.org/10.1021/jm701435h
7. van Hes, R.; Smit, A.; Kralt, T.; Peters, A. *J. Med. Chem.* **1972**, *15*, 132–136. http://dx.doi.org/10.1021/jm00272a004
8. Kolocouris, N.; Zoidis, G.; Foscolos, G. B.; Fytas, G.; Prathalingham, S. R.; Kelly, J. M.; Naesens, L.; De Clercq, E. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 4358–4362. http://dx.doi.org/10.1016/j.bmcl.2007.04.108
9. Fytas, C.; Kolocouris, A.; Fytas, G.; Zoidis, G.; Valmas, C.; Basler, C. F. *Bioorg. Chem.* **2010**, *38*, 247–251. http://dx.doi.org/10.1016/j.bioorg.2010.09.001
10. Fytas, C.; Zoidis, G.; Tzoutzas, N.; Taylor, M. C.; Fytas, G.; Kelly, J. M. *J. Med. Chem.* **2011**, *54*, 5250–5254. http://dx.doi.org/10.1021/jm200217m

11. Anikina, L. V.; Vikharev, Yu. B.; Rozhkova, Yu. S.; Shklyaev, Yu. V. *Pharm. Chem. J.* **2013**, *46*, 707–710.
http://dx.doi.org/10.1007/s11094-013-0874-9
12. Kim, S.-H.; Kim, J.-H.; Cui, J.-Z.; Gal, Y.-S.; Jin, S.-H.; Koh, K. *Dyes Pigments* **2002**, *55*, 1–7.
http://dx.doi.org/10.1016/S0143-7208(02)00051-7
13. Chung, S.-C.; Li, Y.-T.; Fan, C.-H.; Li, M.-C.; Chu, C.-S. US 20130324722, 2013; *Chem Abstr*. **2013**, *160*, 49231.
14. Vovk, M. V.; Sukach, V. A.; Pyrozhenko, V. V.; Bol'but, A. V. *Heteroatom Chem.* **2006**, *17*, 104–111.
http://dx.doi.org/10.1002/hc.20181
15. Kon'kov, S. A.; Moiseev, I. K.; Zemtsova, M. N.; Bormasheva, K. M. *Russ. Chem. Rev.* **2014**, *83*, 377–390.
http://dx.doi.org/10.1070/RC2014v083n05ABEH004374
16. Alizadeh, A.; Mokhtari, J. *Tetrahedron* **2013**, *69*, 6313–6316.
http://dx.doi.org/10.1016/j.tet.2013.03.102
17. Miklós, F.; Fülöp, F. *J. Heterocycl. Chem.* **2014** *in press*
http://onlinelibrary.wiley.com/doi/10.1002/jhet.1844/pdf
18. Miklós, F.; Fülöp, F. *Eur. J. Org. Chem.* **2010**, 959–965.
http://dx.doi.org/10.1002/ejoc.200901052
19. Miklós, F.; Fülöp, F. *Acta Chim. Slov.* **2009**, *56*, 674–679.
20. Magyar, T.; Miklós, F.; Lázár, L.; Fülöp, F. *Chem. Heterocycl. Compd.* **2015**, *50*, 1463–1469.
http://dx.doi.org/10.1007/s10593-014-1611-3
21. Miklós, F.; Hum, V.; Fülöp, F. *Arkivoc* **2014**, *6*, 25–37.
http://dx.doi.org/10.3998/ark.5550190.p008.717
22. Oliveira, P. F. M.; Baron, M.; Shamayou, A.; André-Barrès, C.; Guidetti, B.; Baltas, M. *RSC Adv*. **2014**, *4*, 56736–56742.
http://dx.doi.org/10.1039/C4RA10489G
23. Liu, K. C.; Hu, M. K. *Arch. Pharm. (Weinheim, Ger.)* **1987**, *166*, 166–171.
http://dx.doi.org/10.1002/ardp.19873200213
24. Ranu, B.; Stolle, A. *Ball Milling Towards Green Synthesis*, The Royal Society of Chemistry, Cambridge, **2015**, Chapter 10, p. 241–276.
25. Patil, N. T.; Lakshmi, P. G. V. V.; Sridhar, B.; Patra, S.; Bhadra, M. P.; Patra, C. R. *Eur. J. Org. Chem.* **2012**, 1790–1799.
http://dx.doi.org/10.1002/ejoc.201101822
26. Rai, P.; Srivastava, M.; Singh, J.; Sing, J. *RSC Adv.* **2014**, *4*, 779–783.
http://dx.doi.org/10.1039/C3RA44315A

27. Paveglio, G. C.; Longhi, K.; Moreira, D. N.; München, T. S.; Tier, A. Z.; Gindri, I. M.; Bender, C. R.; Frizzo, C. P.; Zanatta, N.; Bonacorso, H. G., Martins, M. A. P. *ACS Sustainable Chem. Eng.* **2014**, *2*, 1895–1901.
http://dx.doi.org/10.1021/sc5002353
28. Stájer, G.; Szabó, A. E.; Fülöp, F.; Bernáth, G.; Sohár, P. *Chem. Ber.* **1987**, *120*, 259–265.
http://dx.doi.org/10.1002/cber.19871200302
29. Stájer, G.; Szabó, A. E.; Sohár, P.; Csámpai, A.; Sillanpää, R. *J. Mol. Struct.* **2006**, *784*, 239–243.
http://dx.doi.org/10.1016/j.molstruc.2005.09.011
30. Pihlaja, K.; Fülöp, F.; Mattinen, J.; Bernáth, G. *Acta Chem. Scand.* **1987**, *41B*, 228–231.
http://dx.doi.org/10.3891/acta.chem.scand.41b-0228
31. Shin, J.; Nho, Y. C.; Howard, A. S.; *Bull. Korean Chem. Soc.* **2008**, *29*, 1998–2004.
http://dx.doi.org/10.5012/bkcs.2008.29.10.1998
32. Rai, P.; Srivastava, M.; Singh, J.; Singh, J. *RSC Adv.* **2013**, *3*, 18775–17782.
http://dx.doi.org/10.1039/c3ra43023e
33. Verma, A. K.; Saunthwal, R. K.; Patel, M.; Tiwari, R. K.; Parang, K. *Green Chem.* **2015**, *17*, 1434–1441.
http://dx.doi.org/10.1039/C4GC02154A
34. Marković, V.; Joksović, M. D. *Green Chem.* **2015**, *17*, 842–847.
http://dx.doi.org/10.1039/C4GC02028F
35. Bakavoli, M.; Shiri, A.; Ebrahimpour, Z.; Rahimizadeh, M.; *Chin. Chem. Lett.* **2008**, *19*, 1403–1406.
http://dx.doi.org/10.1016/j.cclet.2008.07.016
36. Parish, H. A.; Gillom, R. D. *J. Med. Chem.* **1982**, *25*, 98–102.
http://dx.doi.org/10.1021/jm00343a022
37. Schmiedeberg, N.; Furet, P.; Imbach, P.; Holzer, P. WO2006050946, 2006; *Chem Abstr.* **2006**, *144*, 488.
38. Yang, L.; Shi, D.; Chen, S.; Chai, H.; Huang, D.; Zhang, Q.; Li, J. *Green. Chem.* **2012**, *14*, 945-951.
http://dx.doi.org/10.1039/c2gc16469h
39. Melzig, M., WO 9003379, 1990; *Chem Abstr.* **1991**, *114*, 42796.
40. Abdelazeem, A. H.; Abdelatef, S. A.; El-Saadi, M. T.; Omar, H. A.; Khan, S.i.; McCurdy, C. R.; El-Moghazy, S. M. *Eur. J. Pharm. Sci.* **2014**, *62*, 197–211.
http://dx.doi.org/10.1016/j.ejps.2014.05.025
41. Zhang, L.-J.; Shi, D.-X.; Li, J.-R. *Synth. Commun.* **2009**, *39*, 4010–4018.
http://dx.doi.org/10.1080/00397910902883629
42. Kas'yan, I. L.; Karpenko, V. D.; Kas'yan, O. A.; Isaev, K. A. *Russ. J. Org. Chem.* **2005**, *41*, 678-688.
http://dx.doi.org/10.1007/s11178-005-0226-7