Green Chemistry

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"All water chemistry" for a concise total synthesis of the novel class anti-anginal drug (*RS*), (*R*), and (*S*)-ranolazine†

Cite this: *Green Chem.*, 2013, **15**, 756

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A novel strategy of 'all water chemistry' is reported for a concise total synthesis of the novel class anti-anginal drug ranolazine in its racemic (*RS*) and enantiopure [(*R*) and (*S*)] forms. The reactions at the crucial stages of the synthesis are promoted by water and led to the development of new water-assisted chemistries for (i) catalyst/base-free *N*-acylation of amine with acyl anhydride, (ii) base-free *N*-acylation of amine with acyl chloride, (iii) catalyst/base-free one-pot tandem *N*-alkylation and *N*-Boc deprotection, and (iv) base-free selective mono-alkylation of diamine (*e.g.*, piperazine). The distinct advantages in performing the reactions in water have been demonstrated by performing the respective reactions in organic solvents that led to inferior results and the beneficial effect of water is attributed to the synergistic electrophile and nucleophile dual activation role of water. The new 'all water' strategy offers two green processes for the total synthesis of ranolazine in two and three steps with 77 and 69% overall yields, respectively, and which are devoid of the formation of the impurities that are generally associated with the preparation of ranolazine following the reported processes.

Received 10th December 2012,
Accepted 17th January 2013

DOI: 10.1039/c3gc36997h

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Introduction

Cardiovascular diseases (CVDs) are the leading cause of death worldwide, accounting for one-third (16.6 million) of global deaths in 2001[1] and 1 million deaths every year in the western world. According to the Lancet report of 2005, hypertension (high blood pressure) is one of the five major CVDs affecting more than 330 million adults in Europe and North America and Vision gain predicted more than 1.5 billion people to suffer from this disease worldwide by 2025. Globally, the hypertension therapeutics market is one of the largest and most profitable with total sales of $36 600 million in 2006. Stable angina pectoris affects more than 9 million US individuals as part of the morbidity related to coronary artery disease. The pharmacotherapy of angina involves the corrective measure of imbalance of the myocardial oxygen demand and supply.[2] β-Adrenergic blocking agents are effective life-saving medicines in the management of cardiovascular disorders,[3] including hypertension,[4] angina pectoris, cardiac arrhythmias and other disorders[5] related to the sympathetic nervous system and have had widespread and generally safe use for more than 25 years. These drugs reduce the oxygen demand by reducing the heart rate and lowering the blood pressure (BP) and the calcium channel blockers. They are also commonly used therapeutics for angina as they dilate the blood vessels and lower the BP.[6] However, due to intolerability on BP or heart rate and adverse hemodynamic side effects such as hypotension, bradycardia, and sexual dysfunction, often it is not possible to increase the doses of these drugs to the desired level. Moreover, at least 25% of the patients on medically optimized regimens still have the clinically relevant angina at 5-year follow-up.[7] Hence for full control of chronic stable angina, drugs with an alternative mode of action are needed.[8]

Ranolazine, *N*-(2,6-dimethylphenyl)-2-[4-{2-hydroxy-3-(2-methoxyphenoxy)propyl}piperazin-1-yl]acetamide (**1**) (Fig. 1), offers a new approach to treating chronic angina pectoris. It was approved by the US FDA in January 2006[9] and launched in the US in March 2006 for patients who do not show adequate response to other anti-anginals and is the first drug of a novel class to be approved in the US in more than 20 years for treatment of this disease condition.

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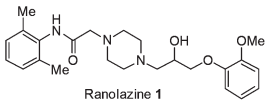
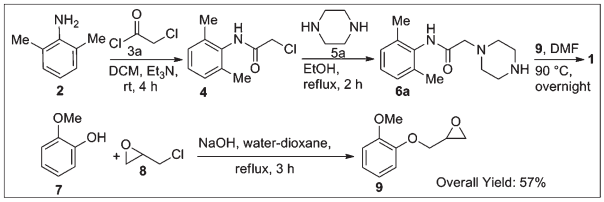
†Electronic supplementary information (ESI) available: List of impurities for reported procedure of synthesis, optimisation study and scanned spectra. See DOI: 10.1039/c3gc36997h

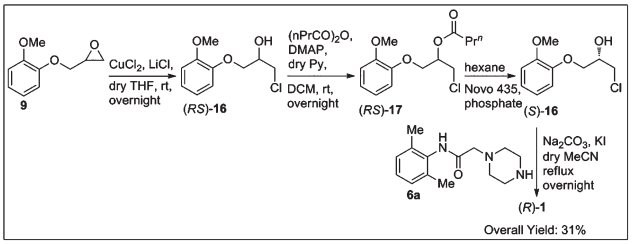


Ranolazine **1**

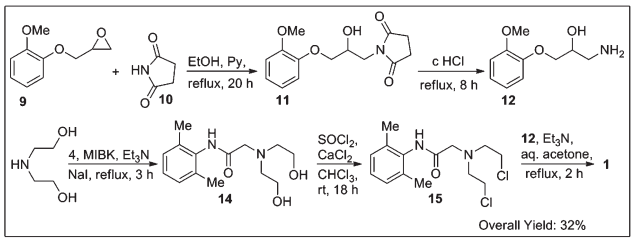
Fig. 1 The anti-anginal drug ranolazine (**1**).



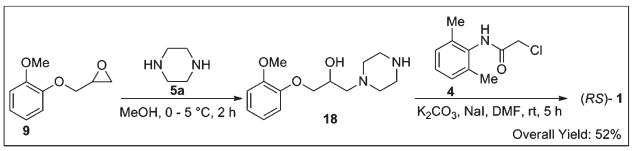
Scheme 1 Route A for the synthesis of ranolazine (**1**).



Scheme 3 Route C for the synthesis of ranolazine (**1**).



Scheme 2 Route B for the synthesis of ranolazine (**1**).



Scheme 4 Route D for the synthesis of ranolazine (**1**).

Various processes have been reported for the synthesis of ranolazine.[10] Route A (Scheme 1) involves the reaction of 2,6-dimethylaniline (**2**) with chloroacetyl chloride (**3a**) in the presence of Et_3N using DCM as solvent, to form the 2-chloro-*N*-(2,6-dimethylphenyl)acetamide (**4**) which is subsequently treated with piperizine (**5a**) to obtain the *N*-(2,6-dimethylphenyl)-2-(piperazin-1-yl)acetamide (**6a**). The treatment of 2-((2-methoxyphenoxy)methyl)oxirane (**9**) with **6a** in DMF at 90 °C for a prolonged period results in the formation of (*RS*)-**1**. The intermediate **9** is synthesized by the reaction 2-methoxyphenol (**7**) with epichlorohydrine (**8**) in the presence of NaOH using water–dioxane as the reaction medium under reflux.

Route B (Scheme 2) involves the condensation of 1-amino-3-(2-methoxyphenoxy)propan-2-ol (**12**), prepared from **9** by opening of the epoxide ring with succinimide in the presence of pyridine in EtOH under reflux for 20 h followed by hydrolysis of the intermediate **11**, with 2-[bis(2-chloroethylamino)-*N*-(2,6-dimethylphenyl)]acetamide (**15**) in the presence of Et_3N using aq. acetone as solvent. The preparation of the intermediate **15** requires *N*-alkylation of diethanolamine with **4** in methyl isobutyl ketone (MIBK) in the presence of Et_3N and NaI under reflux to form **14** followed by treatment with $SOCl_2$ in chloroform in the presence of $CaCl_2$.

In Route C (Scheme 3), (*R*)-**1** is prepared by *N*-alkylation of **6a** with (*S*)-1-chloro-3-(2-methoxyphenoxy)propan-2-ol (**16**) in the presence of Na_2CO_3 and KI in dry MeCN under reflux overnight. The intermediate (*S*)-**16** is obtained by enzymatic hydrolysis of (*RS*)-**17**, prepared by DMAP-catalysed acylation of (*RS*)-**16** with isobutyric anhydride in DCM overnight. (*RS*)-**16** is obtained by copper-catalysed opening of the epoxide ring in **9** by LiCl in THF overnight.

Route D involves *N*-alkylation of 1-(2-methoxyphenoxy)-3-(piperazin-1-yl)propan-2-ol (**18**) with **4** in the presence of K_2CO_3 and NaI in DMF (Scheme 4). The intermediate **18** is prepared by the reaction of **9** with **5a** in MeOH.

These reported processes for the synthesis of **1** (Schemes 1–4)[10] have several drawbacks such as the use of Et_3N, pyridine, $SOCl_2$ (harmful, carcinogenic), volatile organic solvents (DCM, $CHCl_3$, THF, dioxane, MeCN, DMF, *etc.*), auxiliary agents, long reaction times and the involvement of a multiple (4–7) step sequence. The other noticeable and most critical disadvantage is that various impurities are generated.† The removal/separation of these impurities is a difficult task and requires elaborative purification procedures. Identification, estimation, and minimisation of these impurities have been the major focus of pharmaceutical industries.[11] These drawbacks press the need for a concise and more effective process for the synthesis of **1**.

Analysis of the reported processes (Schemes 1–4) reveals that these are based on the common synthetic strategy to use **9** as the key intermediate and most of the impurities are generated during the preparation of **9** by reaction of **8** with **7** and non-selective reaction of **9** with other reactants such as **6a** and **5a**.† In some cases, the use of the intermediate **6a** also adds up to the list of impurities as the preparation of **6a** is associated with the formation of the corresponding *N*,*N*-dialkylated by-product **6c** during the reaction of **4** with **5a**. The use of excess **5a** also becomes a cause for generating further impurities in the subsequent stages of the synthesis.†

It was realised that (i) as **8** is ambidently electrophilic and (ii) the reaction is performed under basic conditions (to generate the phenolate anion due to the poor nucleophilicity of the phenolic oxygen in **7**), the formation of these by-products is inevitable. Thus, a new synthetic strategy that would avoid the preparation and use of **9** is in dire necessity.

To avoid the generation of the impurities associated with the formation and use of the intermediate **9**, it was realized that incorporation of the 2-hydroxypropane moiety, derived from **8**, by reaction of the amine component (as amine is a better nucleophile than phenol and might not require base)

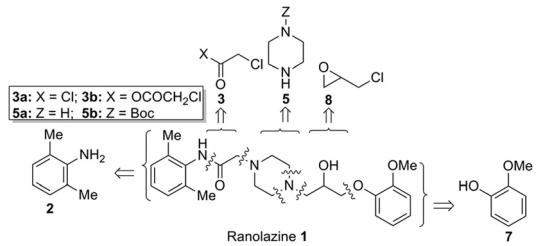
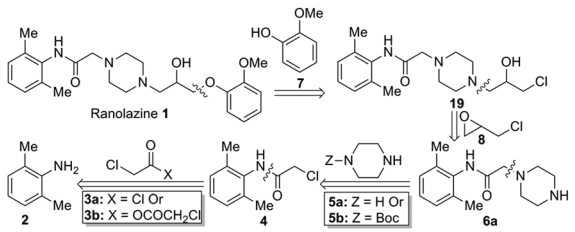


Fig. 2 New disconnection approaches for **1**.



Scheme 5 New alternate strategy for synthesis of **1**.

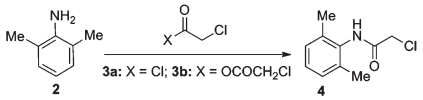
and insertion of the 2-methoxyphenol moiety in the final step would be advantageous (Fig. 2) and a new and alternate synthetic strategy (Scheme 5) was devised.

Results and discussion

The reported procedures for the synthesis of **4** involve acylation of **2** with chloroacetyl chloride (**3a**) in the presence of stoichiometric amounts of bases in halogenated solvents that do not comply with the demand for eco-friendly/green approaches (sustainable chemistry development).[12] The major drive for sustainable development in the pharmaceutical industry is the replacement of volatile organic solvents (VOSs) by green reaction media.[13] In this regard, water is considered as the most preferred solvent.[12,14] It was realised that the preparation of the essential starting material **4** by acylation of **2** requires catalytic assistance to avoid the use of stoichiometric quantities of bases as the auxiliary substances. Although a green initiative is in practice in the use of Lewis/Brönstead acid catalysts[15] for acylation, a metal-free procedure is desirable. Thus attention was directed towards the 'electrophile nucleophile dual activation' role of water in promoting *N*-Boc formation and other organic reactions.[16] However, with the apprehension of the potential of hydrolytic decomposition of **3a** in aqueous medium, the less water-sensitive acylating agent, chloroacetic anhydride (**3b**), was chosen and reacted with **2** in water as well as in a few common organic solvents (Table 1).

Excellent yields (93–94%) were obtained in water (entries 1–3, col 4, Table 1). After addition of the reactants, the reaction mixture took a cloudy appearance during the progress of the reaction which was followed by the formation of a white solid upon completion of the reaction. The comparable results obtained in tap, pure, and ultra-pure water suggest that the

Table 1 Water-assisted *N*-acylation of **2** with **3a** and **3b** to form **4** under metal/base-free conditions[a]

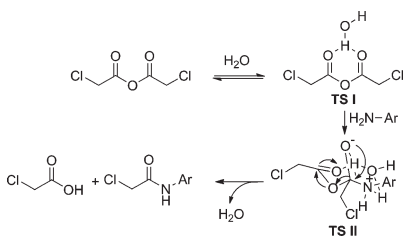


Entry	Solvent	Yield[b] (%) With **3a**	With **3b**
1	Tap water	45[c]	94
2	Pure water[d]	—	93
3	Ultra-pure water[e]	—	94
4	MeOH	41[f]	21[g]
5	EtOH	—	20
6	^{i}PrOH	—	17
7	^{t}BuOH	—	15
8	1,4-Dioxane	65	Trace
9	THF	58	Trace
10	MeCN	60	Trace
11	DMF	63	Trace
12	Hexane	36	Trace
13	DCE	55	Trace
14	TFE	70	94[h]
15	HFIP	73	94[i]
16	None	38	Trace

[a] **2** (1 mmol) was treated with **3a** (1.5 mmol, 1.5 equiv.) or **3b** (1 mmol, 1 equiv.) in the indicated solvent (1 mL) at rt (~35 °C) for 2 h. [b] Isolated yield of **4**. [c] 59% yield was obtained at 20 °C. [d] The pure water was obtained by purification of normal/tap water through reverse osmosis and ionic/organic removal and has a resistivity of 15 MΩ cm at 25 °C. [e] The ultrapure water was obtained by further subjecting pure water to UV treatment (185/254 nm), deionization and ultra membrane filtration (0.01 μm) under pressure upto 145 psi (10 bar) and has resistivity of 18.2 MΩ cm at 25 °C. [f] The remaining product was methyl chloroacetate. [g] **4** was formed in 90% yield after 4 h. [h] The reaction was completed in 30 min. [i] The reaction was completed in 20 min.

outcome is not influenced by any dissolved metallic or organic impurities in the water. The limited reports on acylation of amines or amine hydrochlorides with anhydrides in aqueous medium require catalytic assistance or stoichiometric amounts of base.[17] Thus, the catalyst/base-free protocol developed under this study offers a novel water-assisted *N*-acylation chemistry. The inefficiency of organic solvents (entries 4–13, Table 1) or neat conditions (entry 16, Table 1) clearly indicates specific rate acceleration by water. The role of water in promoting the acylation may be depicted in Scheme 6.

The excellent yield in water is attributed to its hydrogen bond donor (HBD) ability (to activate the electrophile) in promoting the acylation. To support this proposal we used



Scheme 6 Plausible role of water in promoting *N*-acylation of amine.

trifluoroethanol (TFE) and hexafluoroisopropanol (HFIP) that have better HBD values[18] and were pleased to obtain comparable yields (entries 14 and 15, Table 1). As a matter of fact, the reaction took place in shorter time periods (30 and 20 min, respectively) in TFE and HFIP compared to that in water (2 h). The poor results in alcohols could be rationalised due to their inferior HBD values. The optimal amount of water required for acylation with **3b** was found to be 0.5 mL $mmol^{-1}$ of **2** whereas a 3 molar equiv. of TFE and 2 molar equiv. of HFIP afforded[19] comparable yields (~95%) after 30 and 20 min, respectively.† However, water offered advantages in the isolation/purification stage as the product (**4**) precipitated out in aqueous medium and was isolated by filtration. Therefore, further execution of the synthetic planning (Scheme 5) **4** was prepared following the water-assisted *N*-acylation chemistry.

The feasibility of using **3a** was considered for the water-assisted *N*-acylation of **2** to synthesise **4** but poor yield was obtained in water due to the competitive hydrolytic decomposition (entry 1, col 3, Table 1). The use of alcohol (*e.g.*, MeOH) gave poor yield due to the competitive ester formation. However, TFE and HFIP afforded 70 and 73% yields, respectively, as the competitive interaction of TFE/HFIP with **3a** is significantly decreased due to the poor nucleophilicity of TFE and HFIP. To suppress the hydrolysis and facilitate the *N*-acylation, it was planned to take advantage of the surfactants as catalytic aids.[20] Out of the various neutral, cationic, and anionic surfactants used (Table 2), sodium dodecyl sulfate (SDS) gave 80% yield during the treatment of **2** with **3a** in water (1 mL per mmol of **2**) at 20 °C (entry 10, Table 2). The reaction mixture became milky white when all of the reactants were added in water and remained as such until completion.

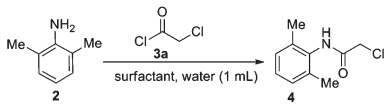
Further studies on the optimisation of the reaction conditions to minimize the competitive hydrolytic decomposition of **3a** revealed that the reaction temperature and the amount of water is crucial (Table 3). Use of 5 molar equiv. of water at 20 °C provided the best result (90% yield, entry 3, Table 3). A decrease in the yield of **4** was observed either in decreasing or increasing the amount of water and increasing the reaction temperature above 20 °C.

To assess any advantage of using water over organic solvents, the SDS-promoted acylation of **2** with **3a** was performed in a few commonly used organic solvents (Table 4) that afforded inferior yields of **4** and demonstrated the distinct advantage of the use of an aqueous medium.

The classical Schotten–Baumann procedure involves acylation of aromatic amines with acyl halides in large excess aqueous alkali.[21] The reported procedure for acylation of aniline (a representative aromatic amine) with **3a** in aqueous medium used 3 equiv. of NaOH and afforded the corresponding *N*-acylated compound in poor (58%) yield after prolonged period (overnight).[22] Hence, the base-free protocol developed under the present study provides a novel water-assisted *N*-acylation chemistry. The poor yields obtained in using organic solvents (entries 2–7, Table 4) clearly suggest the beneficial effect of water and may be rationalized due to the synergistic electrophile nucleophile dual activation ability of water akin to that depicted for the water-assisted *N*-acylation using acyl anhydride (Scheme 6).

Therefore, two new water-assisted *N*-acylation procedures have been developed for the preparation of **4**, the essential starting material for the synthesis of **1**: (i) the catalyst-free reaction of **2** with **3b** in water (0.5 mL per mmol of **2**) at room temperature (25–30 °C) and (ii) the base-free reaction of **2** with

Table 2 Water-assisted *N*-acylation of **2** with **3a** to form **4** under base-free conditions[a]



Entry	Surfactant	Yield[b] (%)
1	Span 80	65
2	Tween 80	68
3	Triton X-100	71
4	β-Cyclodextrin hydrate	62
5	Benzalkonium chloride	52
6	Tetrabutylammonium bromide	45
7	Tetrabutylammonium iodide	48
8	Cetyltrimethylammonium bromide	55
9	Hexadecyl pyridinium chloride	52
10	SDS	80
11	Sodium deoxy cholate	65
12	Sodium dioctyl sulfosuccinate	78

[a] Reaction of **2** (1 mmol) with **3a** (1.5 mmol, 1.5 equiv.) in the presence of surfactant (5 mol%) in water (1 mL) at 20 °C for 30 min. [b] Isolated yield of **4**.

Table 3 The influence of the amount of water during the water-assisted *N*-acylation of **2** with **3a** to form **4** under base-free conditions[a]

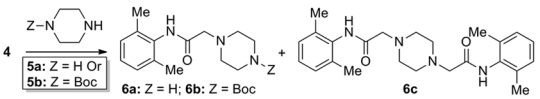
Entry	Amount of water	Yield[b] (%)
1	1 mmol	52
2	3 mmol	85
3	5 mmol	90
4	10 mmol	86
5	1 mL	80

[a] Reaction of **2** (1 mmol) with **3a** (1.5 mmol, 1.5 equiv.) in the presenceof surfactant (5 mol%) in different amounts of water at 20 °C for 30 min. [b] Isolated yield of **4**.

Table 4 The SDS-catalysed reaction of **2** with **3a** in organic solvents[a]

Entry	Solvent	Yield[b] (%)
1	Water	90[c]
2	MeOH	52[c]
3	1,4-Dioxane	42[d]
4	Hexane	25[d]
5	Toluene	35[d]
6	DCE	36[d]
7	TFE	55[d]

[a] **2** (1 mmol) was treated with **3a** (1.5 mmol, 1.5 equiv.) in the presence of SDS (5 mol%) in different solvents at 20 °C for 30 min. [b] The isolated yield of **4**. [c] The reaction was performed using 5 mmol of the solvent. [d] The reaction was performed using 1 mL of the solvent.



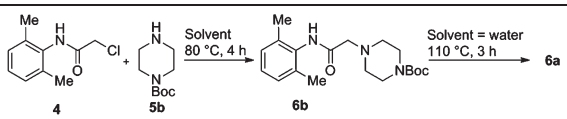
Scheme 7 Formation of **6** by the reaction of **4** with **5**.

3a in water (5 molar equiv. of **2**) in the presence of SDS (5 mol%) at 20 °C. The water-assisted acylation of **2** with **3a** or **3b** under the respective optimized reaction conditions afforded comparable yields (~90%) up to 30 mmol scale reaction. However, for larger scale (*e.g.*, 50 mmol) operation, the use of **3b** proved to be advantageous as a decrease in the product yield was observed using **3a** (80% yield) perhaps due to the ineffectiveness in suppressing the hydrolytic cleavage and accuracy in maintaining the reaction temperature at 20 °C (due to local heating) in the presence of a larger volume of water. Although the use of **3a** would have the projected advantage in terms of cost and atom efficiency, the use of 1 equiv. of **3b** as compared to the requirement of the use of 1.5 equiv. of **3a** would to some extent compensate for these aspects.

The preparation of **6a** by the reaction of **4** with **5a** has the potential problem to form the corresponding *N*,*N*-dialkylated derivative **6c** as a side product (Scheme 7).

Thus, **4** was treated with the *N*-Boc piperazine (**5b**) in water at 80 °C for 4 h to afford the *N*-(2,6-dimethylphenyl)-2-[(4-*tert*-butoxycarbonyl)piperazin-1-yl]acetamide (**6b**) in 95% yield (entry 1, Table 5). After addition of all of the reactants in water the reaction mixture took a cloudy appearance and a white solid precipitated after completion of the reaction. No significant amount of **6b** was formed in performing the reaction at rt and 39% yield was obtained when carrying out the reaction at 60 °C (footnotes c and d, respectively; entry 1, Table 5).

Table 5 The influence of the solvent on *N*-monoalkylation of 2-chloro-*N*-(2,6-dimethylphenyl)acetamide (**4**) with *N*-Boc-piperazine (**5b**)[a]



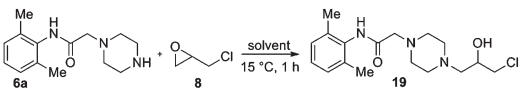
Entry	Solvent	Yield of **6b**[b] (%)
1	Water	95 (Trace,[c] 36[d])
2	Pure water	94
3	Ultrapure water	95
4	MeOH	94
5	EtOH	95
6	1,4-Dioxane	92
7	CH_3CN	90
8	DMF	92
9	Toluene	88
10	DCE	89
11	TFE	92
12	None	0

[a] Reaction of **4** (1 mmol) with *N*-Boc-piperazine (**5b**) (1 mmol, 1 equiv.) in solvent (5 mL) at 80 °C (oil bath) for 4 h. [b] Isolated yield of **6b**. [c] Yield of **6b** at rt. [d] Yield of **6b** at 60 °C (oil bath).

Comparable results were obtained in organic solvents. However, it was observed that when the *N*-alkylation of **4** with **5b** was carried out in water, an *in situ* *N*-*t*-Boc deprotection[23] can be achieved by further treatment of the reaction mixture at 110 °C (oil bath) for 3 h to afford **6a** in 94% yield. Treatment of **4** with **5b** in EtOH under reflux for 4 h afforded **6b** in 95% yield, which remained unchanged on further treatment in EtOH under reflux for 3 h and **6a** could be obtained in poor (12%) yield after a prolonged period (~8 h).† This further highlighted the advantage of using water. Although *N*-alkylation of an aromatic amine has been performed in water under microwave heating at 150 °C,[24] *N*-alkylation of **5b** has been reported in DMF containing Et_3N and the *N*-Boc deprotection involved treatment with aq. HCl to form the resultant *N*-mono-alkylated piperazine.[25] Thus, the water-assisted one-pot tandem *N*-alkylation-*N*-Boc-deprotection method represents a novel synthetic process for the preparation of **6a** from **4**.

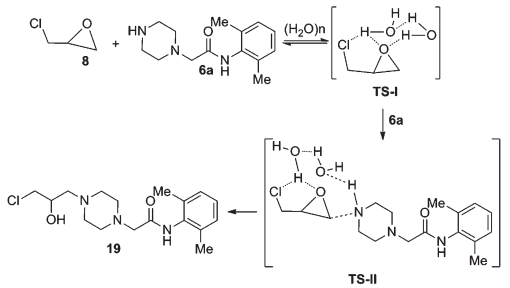
The synthesis of the final intermediate 2-[4-(3-chloro-2-hydroxypropyl)piperazin-1-yl]-*N*-(2,6-dimethylphenyl)acetamide (**19**) would involve opening of the epoxide ring of **8** with **6a**. The aminolysis of epoxide remains the mainstay of the synthesis of β-adrenergic blocking agents and various Lewis/Brönstead acid catalysts have been developed to promote the reaction.[26] A metal/catalyst-free condition was adopted for the reaction of **6a** with (*RS*)-**8** in different solvents (Table 6). Excellent yield (97%) of **19** was obtained in water (entry 1, Table 6).[27] The reaction mixture became cloudy after mixing all of the reactants in water and remained as such until

Table 6 Influence of solvent on epoxide aminolysis during the reaction of **8** with **6a** to form **19**[a]

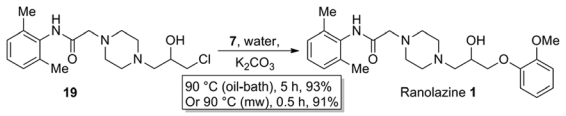


Entry	Solvent	Yield[b] (%)
1	Water	97
2	Pure water[c]	96
3	Ultra-pure water[d]	96
4	MeOH	20
5	EtOH	18
6	^{i}PrOH	19
7	^{t}BuOH	15
8	1,4-Dioxane	Trace
9	THF	Trace
10	CH_3CN	Trace
11	DMF	Trace
12	Toluene	Trace
13	$MeNO_2$	Trace
14	TFE	25
13	HFIP	31

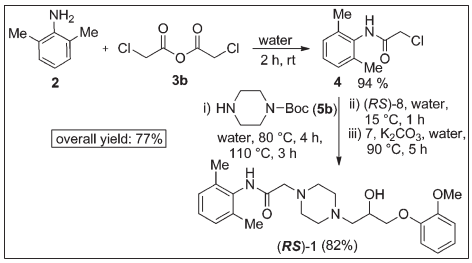
[a] **8** (1 mmol) was treated with **6a** (1 mmol, 1 equiv.) in different solvents (1 mL) at 15 °C for 1 h. [b] The isolated yield of **19**. [c] Pure water was obtained by purification of normal/tap water through reverse osmosis and ionic/organic removal and has a resistivity of 15 MΩ cm at 25 °C. [d] Ultra-pure water was obtained by further subjecting pure water to UV treatment (185/254 nm), deionization and ultra membrane filtration (0.01 μm under pressure upto 145 psi (10 bar) and has a resistivity of 18.2 MΩ cm at 25 °C.



Scheme 8 The role of water in epoxide aminolysis.



Scheme 9 The *O*-alkylation of **7** with **19** to form **1**.



Scheme 10 Two step 'all water' process for the synthesis of (*RS*)-**1**.

completion. The use of organic solvents afforded poor yields and highlighted the importance of using an aqueous medium. Surprisingly, TFE and HFIP were ineffective.[28]

The comparison of the results of entries 1–3 with those of entries 4–13 (Table 6) clearly indicates the specific assistance by water in promoting the epoxide aminolysis. The comparable yields obtained in using the different types of water (entries 1–3, Table 6) rule out any possible catalytic assistance by trace amounts of inorganic/organic impurities in the water. Although the rate acceleration during epoxide aminolysis in water has been marked,[27a] there has been no specific mechanistic proposal to rationalise the water-assisted epoxide aminolysis. To account for the water-assisted aminolysis of **8** with **6a** we envisaged a synergistic electrophile nucleophile dual activation role by water (Scheme 8).

An initial activation of the epoxide ring of **8** takes place through bifurcated HB formation involving the epoxide oxygen and the water dimer to form the **TS-I**. This is followed by nucleophilic attack by the secondary nitrogen (NH) of the piperidine moiety of **6a** at the terminal carbon of the epoxide ring to form **TS-II** in which the NH hydrogen forms HB (nucleophilic activation) with the oxygen atom of the second water molecule of the water dimer. Thus, in **TS-II**, a synergistic electrophile nucleophile dual activation occurs through a relay of HB formation *via* the water dimer.[29] The inability of the organic solvents such as dioxane, THF, MeCN, DMF, and $MeNO_2$ to form the relay of HB akin to **TS-II** justify the inefficiency of these solvents to promote the epoxide aminolysis. The poor results with the alcoholic solvents may be due to their inferior HBD values compared to that of water.[18] On the other hand the lack of hydrogen bond acceptor (HBA) properties of TFE and HFIP (the HBA values, β, of TFE, HFIP and water are 0.00. 0.00, and 0.18, respectively) might be the reason for the poor results obtained in these solvents.

In the final step, the *O*-alkylation of **19** with **7** was tried under various conditions to form (*RS*)-**1** (Scheme 9).† The best result was obtained in the presence of K_2CO_3 (1.3 equiv.) in water affording 93% yield at 90 °C after 5 h. The reaction mixture took a dull white appearance and remained as such until completion of the reaction. In order to reduce the reaction time, the reaction was performed under microwave irradiation to obtain a comparable yield in 30 min.[30]

Having the chemistry at each step standardised, (*RS*)-**1** could be obtained in 82% yield from **4** by sequential treatment with **5b**, (*RS*)-**8**, and **7** in one-pot without isolation of the intermediately formed products **6b**, **6a**, and **19**. The reaction mixture took a dull white appearance and remained as such until completion. The overall synthesis of **1** from **2** was executed by a two step sequence (Scheme 10) involving the tandem water-assisted *N*-alkylation and *N*-Boc deprotection chemistry (to form **6a** from **4** and **5b**) to afford (*RS*)-1 in 77% overall yield (starting from **2**). This represents a new and shorter (two step) synthesis of **1** from **2**.

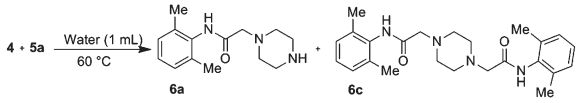
For a protecting group free synthesis,[31] it was planned to exploit the dual activation ability of water for the reaction of **4** with **5a**. However, no significant amount of product formation was observed either at rt or at 60 °C. The use of a phase transfer catalyst (PTC) proved to be beneficial and **6a** was obtained in 85, 88, and 81% yields in the presence (10 mol%) of TBAB, TBAI, and CTAB, respectively (entries 11, 12, and 13; Table 7). The use of other PTCs afforded lesser yields of **6a** along with the formation of increasing amounts of **6c**.

The use of water proved to be beneficial as the TBAI-catalysed reaction of **4** with **5a** in various organic solvents (protic/aprotic polar, ethereal, and hydrocarbon) afforded inferior yields (35–68% as compared to 88% yield obtained in water) of **6a** with concomitant formation of **6c** in higher amounts (10–18%) compared to that (6%) obtained in water (Table 8).

Next, the tandem epoxide ring opening of (*RS*)-**8** with **6a** to form (*RS*)-**19** followed by *O*-alkylation with **7** was performed *via* a one-pot reaction to form (*RS*)-**1** in 85% yield (Scheme 11). The reaction mixture took a dull white appearance and remained as such until completion. The overall sequence provides a new three step synthesis of **1** from **2**.

Ranolazine contains one stereocentre and exhibits chirality. There has been a growing concensus against the marketing of racemates, and as per FDA guidelines,[32] it is necessary to evaluate the physicochemical differences of the racemic and single enantiomer in terms of solubility, stability *etc.* in

Table 7 Influence of surfactant on *N*-alkylation of **4** with **5a** to form **6a**[a]



Entry	Surfactant	Yield[b] (%) 6a	6c
1	None	Trace	0
2	Span 80	10	Trace
3	Tween 80	14	Trace
4	Triton X-100	52	13
5	Triton X-114	55	15
6	Triton X-135	50	15
7	β-Cyclodextrin hydrate	30	12
8	Benzalkonium chloride	31	10
9	Tetrabutylammonium fluoride	35	10
10	Tetrabutylammonium chloride	48	8
11	Tetrabutyl ammonium bromide	85	5
12	Tetrabutylammonium iodide (TBAI)	88	6
13	Cetyltrimethylammonium bromide	81	12
14	Hexadecyl pyridinium chloride	40	10
15	Sodium dodecyl sulphate (SDS)	42	13
16	Sodium deoxycholate	38	12
17	Sodium dioctyl sulfosuccinate	59	20
18	Cetrimide	35	15

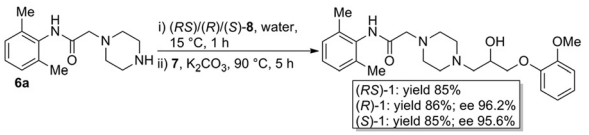
[a] Reaction of **4** (1 mmol) with **5a** (1 mmol, 1.5 equiv.) in the presence of catalyst (10 mol%) in water (1 mL) at 60 °C (oil bath) for 3 h. [b] Isolated yield.

Table 8 The TBAI-catalysed reaction of **4** with **5a** in organic solvents[a]

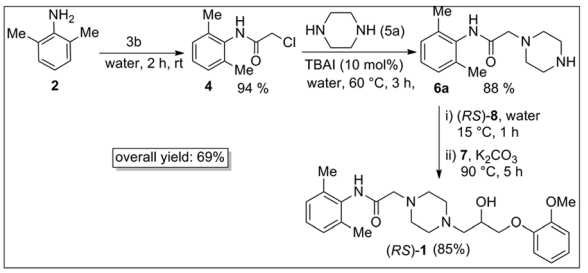
Entry	Solvent	Yield[b] (%) 6a	6c
1	Water	88	6
2	MeOH	65	12[c,d]
3	EtOH	68	15
4	^{i}PrOH	66	13
5	^{t}BuOH	62	15
6	1,4-Dioxane	45	10
7	THF	38	13
8	CH_3CN	40	15
9	DMF	35	10
10	Toluene	42	12
11	$MeNO_2$	46	18
12	TFE	62	16
13	HFIP	60	18
14	None	0	0

[a] Reaction of **4** (1 mmol) with **5a** (1 mmol, 1.5 equiv.) in the presence of TBAI (10 mol%) in the respective solvent (1 mL, except for entry) at 60 °C (bath temp.) for 3 h. [b] Isolated yield. [c] **6a** and **6c** were formed in 70 and 25% yields, respectively, when performing the reaction under reflux (bath temp 80 °C) for 4 h. [d] **6a** and **6c** were formed in 65 and 20% yields, respectively, when performing the reaction under reflux (bath temp 80 °C) for 2 h.

addition to the data on pharmacology. Thus, efforts were made to prepare **1** in enantio form.[10c] However, the activities of the racemic and single enantiomer of **1** have been tested for clinical efficacy and showed only a slight difference in the efficacy of (*R*)-**1** and (*S*)-**1**. Therefore **1** is prescribed as a racemic mixture.[10c]



Scheme 11 One-pot synthesis of (*RS*)-**1**.



Scheme 12 Three step 'all water' process for the synthesis of (*RS*)-**1**.

To prepare **1** in optically pure forms, the water-assisted aminolysis of (*R*)-**8** and (*S*)-**8** was performed with **6a** to afford (*R*)-**19** and (*S*)-**19** in 97 and 96% yields with 98.7 and 98.5% *ee*, respectively. The one-pot tandem epoxide ring opening of (*R*)-**8** and (*S*)-**8** with **6a** followed by *O*-alkylation of the *in situ* formed (*R*)-**19** and (*S*)-**19** with **7** afforded (*R*)-**1** and (*S*)-**1** in 86 and 85% yields with 96.2 and 95.6% *ee*, respectively (Scheme 11).

The overall synthesis of **1** in (*RS*), (*R*), and (*S*) forms in the second process was executed *via* a three step sequence (Scheme 12) involving a protecting group-free strategy for the preparation of **6a** from **4** and **5b** to obtain (*RS*)-1 in 69% overall yield (starting from **2**).

Conclusions

A new strategy of 'all water chemistry' has been demonstrated for concise (two and three steps) total synthesis of the novel class anti-anginal drug ranolazine in racemic (*RS*) and enantiopure [(*R*) and (*S*)] forms in higher overall yields (69–77%). The new synthetic designs avoided the generation of the side products normally associated with the reported processes for the preparation of ranolazine. In the critical stages of the synthesis, the reactions have been promoted by water and generated novel chemistries through the development of new water-assisted synthetic methodologies such as, (i) catalyst/base-free *N*-acylation of amine with acid anhydride, (ii) base-free *N*-acylation of amine with acid chloride, (iii) catalyst/base-free tandem *N*-alkylation and *N*-Boc deprotection, and (iv) base-free selective mono *N*-alkylation of diamine (*e.g.*, piperazine). In each stage, the advantage of using water has been demonstrated by performing the respective reactions in organic solvents that afforded inferior yields. The beneficial effect of water has been depicted according to its role for 'synergistic dual activation of the electrophile and the nucleophile.' In view of the ongoing

concern over the environmental impact of chemical processes, the present work provides cleaner and greener reaction conditions. The use of water as the reaction medium, shorter reaction times, excellent chemoselectivity, high overall yields, prevention/minimisation of waste/by-products, avoidance of auxiliary substances (*e.g.*, organic solvents, additional reagents, metal catalysts *etc.*), and ease of product isolation/purification comply with the 'triple bottom-line philosophy of green chemistry'[33] and make the present process environmentally benign.

Experimental

Chemicals and all solvents were commercially available and used without further purification. The ^{1}H and ^{13}C NMR spectra were recorded on a 400 MHz NMR spectrometer in $CDCl_3$ with residual undeuterated solvent ($CHCl_3$: 7.26/77.0) using TMS as an internal standard. Chemical shifts (δ) are given in ppm and J values are given in Hz. The ^{13}C NMR spectra were fully decoupled and were referenced to the middle peak of the solvent $CHCl_3$ at 77.00 ppm. Splitting patterns were designated as s, singlet; bs, broad singlet; d, doublet; dd, doublet of doublet; t, triplet; m, multiplet. Mass spectra were recorded under APCI mode of ionisation. Infrared (IR) spectra were recorded in the range 4000–600 cm^{-1} either as neat for liquid or KBr pellets for solid samples. Purity compounds were checked on the silica gel GF-254 under UV at 254 nm. Melting points were measured using melting point apparatus and were uncorrected. Evaporation of solvents was performed at reduced pressure, using a rotary vacuum evaporator.

Typical experimental procedure for *N*-acylation of 2,6-dimethylaniline (2) with chloroacetic anhydride (3b) in water (entry 1, Table 1)

To the magnetically stirred mixture of 2,6-dimethylaniline (**2**) (6.05 g, 50 mmol) in water (50 mL) at rt was added chloroacetic anhydride (**3b**) (8.45 g, 50 mmol, 1 equiv.) and stirring was continued at the same temperature. After completion of the reaction (2 h, TLC), the white precipitate was filtered off, washed with cold water (3 × 5 mL) and dried to get pure 2-chloro-*N*-(2,6-dimethylphenyl)acetamide (**4**) (9.26 g, 94%); White solid; mp = 147–148 °C; IR (Neat) ν: 3219, 3031, 2947, 1640, 1600, 1590, 1468, 1451, 1255, 1160 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.84 (brs, 1H), 7.16–7.08 (m, 3H), 4.25 (s, 2H), 2.24 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 164.3, 135.3, 132.7, 128.4, 127.9, 42.8, 18.3; MS (APCI) m/z 198.1 $(M + H)^{+}$.[11a]

Typical experimental procedure for *N*-acylation of 2,6-dimethylaniline (2) with chloroacetic anhydride (3b) in TFE (entry 14, Table 1)

To the magnetically stirred mixture of 2,6-dimethylaniline (**2**) (6.05 g, 50 mmol) in TFE (150 mmol) at rt was added chloroacetic anhydride (**3b**) (8.45 g, 50 mmol, 1 equiv.) and stirring was continued at the same temperature. After completion of reaction (30 min, TLC), the solvent was evaporated under rotary vacuum evaporation. To the above crude reaction mixture, water (100 mL) was added and stirred for 0.5 h at rt. The white precipitate was filtered off, washed with cold water (3 × 5 mL) and dried to get pure 2-chloro-*N*-(2,6-dimethylphenyl)acetamide (**4**) (9.26 g, 94%).[11a]

Typical experimental procedure for *N*-acylation of 2,6-dimethylaniline (2) with chloroacetic anhydride (3b) in HFIP (entry 15, Table 1)

To the magnetically stirred mixture of 2,6-dimethylaniline (**2**) (6.05 g, 50 mmol) in HFIP (20 mmol) at rt was added chloroacetic anhydride (**3b**) (8.45 g, 50 mmol, 1 equiv.) and stirring was continued at the same temperature. After completion of reaction (20 min, monitored by TLC), the solvent was evaporated under rotary vacuum evaporation. To the above crude reaction mixture, water (25 mL) was added and stirred for 0.5 h at rt. The white precipitate was filtered off, wash with cold water (3 × 2 mL) and dried to get pure 2-chloro-*N*-(2,6-dimethylphenyl)acetamide (**4**) (0.92 g, 94%).[11a]

Representative experimental procedure for small scale synthesis of 2-chloro-*N*-(2,6-dimethylphenyl)acetamide by the reaction of 2,6-dimethylaniline (2) with chloroacetyl chloride (3a) (entry 1, Table 3)

To the magnetically stirred mixture of 2,6-dimethylaniline (**2**) (0.60 g, 5 mmol) and SDS (5 mol%) in water (25 mmol) at 20 °C was added chloroacetyl chloride (**3a**) (0.84 g, 7.5 mmol, 1.5 equiv.) and stirring was continued at the same temperature for 30 min (TLC). The reaction mixture was neutralized with $NaHCO_3$ (until the effervescence ceases), precipitate was filtered off, washed with cold water (3 × 1 mL) and dried. The crude product was recrystallized in toluene to get pure 2-chloro-*N*-(2,6-dimethylphenyl)acetamide (**4**) (0.88 g, 90%).

Representative experimental procedure for large scale synthesis of 2-chloro-*N*-(2,6-dimethylphenyl)acetamide by the reaction of 2,6-dimethylaniline (2) with chloroacetyl chloride (3a) (entry 1, Table 3)

To the magnetically stirred mixture of 2,6-dimethylaniline (**2**) (6.05 g, 50 mmol), and SDS (5 mol%) in water (250 mmol) at 20 °C was added chloroacetyl chloride (**3a**) (8.39 g, 75 mmol, 1.5 equiv.) and stirring was continued at the same temperature for 30 min (TLC). The reaction mixture was neutralized with $NaHCO_3$ (until the effervescence ceases), precipitate was filtered off, washed with cold water (3 × 5 mL) and dried. The crude product was recrystallized in toluene to get pure 2-chloro-*N*-(2,6-dimethylphenyl)acetamide (**4**) (7.68 g, 78%).[11a]

Typical experimental procedure for the synthesis of *tert*-butyl 4-(2-((2,6-dimethylphenyl)amino)-2-oxoethyl)piperazine-1-carboxylate (6b) using *tert*-butyl piperazine-1-carboxylate (entry 1, Table 5)

To the magnetically stirred mixture of 2-chloro-*N*-(2,6-dimethylphenyl)acetamide (**4**) (1.97 g, 10 mmol) in water

(50 mL) at 80 °C was added *tert*-butyl piperazine-1-carboxylate (**5b**) (1.86 g, 10 mmol, 1 equiv.) and stirring was continued for 4 h (TLC). The reaction mixture was cooled to rt, the precipitate was filtered off, washed with cold water (3 × 2 mL) and dried to get analytically pure *tert*-butyl 4-(2-((2,6-dimethylphenyl)amino)-2-oxoethyl)piperazine-1-carboxylate (**6b**) (3.29 g, 95%); white solid; mp: 117–119 °C; IR (Neat) ν: 3326, 3015, 2985, 2866, 1746, 1679, 1595, 1470, 1255, 1158; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 8.58 (brs, 1H), 7.11–7.08 (m, 3H), 3.51 (t, J = 4.72 Hz, 4H), 3.22 (s, 2H), 2.64 (t, J = 4.64 Hz, 4H), 2.23 (s, 6H), 1.47 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 168.1, 154.6, 134.9, 133.5, 128.3, 127.3, 80.1, 61.9, 53.6, 28.4, 18.6; HRMS (ESI) m/z calcd for $C_{19}H_{30}N_3O_3$ [M + H$^+$], 348.2282; Found 348.2280.[11a]

Typical experimental procedure for the synthesis of *N*-(2,6-dimethylphenyl)-2-(piperazin-1-yl)acetamide (6a) using *tert*-butyl piperazine-1-carboxylate (5b)

To the magnetically stirred mixture of 2-chloro-*N*-(2,6-dimethylphenyl)acetamide (**4**) (3.94 g, 20 mmol) in water (100 mL) at 80 °C was added *tert*-butyl piperazine-1-carboxylate (**5b**) (3.72 g, 20 mmol, 1 equiv.) and stirring was continued for 4 h. Thereafter the reaction temperature was increased to 110 °C and the stirring continued for further 3 h (TLC). The reaction mixture was cooled to rt and neutralized with sodium bicarbonate (until the effervescence ceases). The precipitate was filtered off, washed with cold water (3 × 4 mL) and dried to get analytically pure *N*-(2,6-dimethylphenyl)-2-(piperazin-1-yl)acetamide (**6a**) (4.69 g, 95%); white solid; mp = 115–117 °C; IR (Neat) ν: 3324, 3285, 3010, 2931, 1679, 1590, 1476, 1252, 1152 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 8.69 (brs, 1H), 7.10–7.06 (m, 3H), 3.18 (s, 2H), 2.96 (d, J = 9.64 Hz, 4H), 2.67–2.66 (m, 2H), 2.23 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 168.5, 134.9, 133.6, 128.3, 127.2, 62.4, 55.1, 46.3, 18.6; MS (APCI) m/z 248.1 (M + H)$^+$.[11a]

Typical experimental procedure for the synthesis of (*RS*)-2-(4-(3-chloro-2-hydroxypropyl)piperazin-1-yl)-*N*-(2,6-dimethylphenyl)acetamide (19) (entry 1, Table 6)

To the magnetically stirred mixture of *N*-(2,6-dimethylphenyl)-2-(piperazin-1-yl)acetamide (**6a**) (4.94 g, 20 mmol) in water (20 mL) at 15 °C was added epichlorohydrine (**8**) (1.84 g, 20 mmol, 1 equiv.) and stirring was continued for 1 h (TLC). The reaction mixture was extracted with EtOAc (3 × 10 mL) and concentrated under rotary vacuum evaporation to get analytically pure (*RS*)-2-(4-(3-chloro-2-hydroxypropyl)piperazin-1-yl)-*N*-(2,6-dimethylphenyl)acetamide (**19**) (6.57 g, 97%); colourless viscous liquid; IR (Neat) ν: 3345, 3018, 2978, 1671, 1592, 1466, 1245, 1139 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.17 (brs, 3H), 4.85–4.75 (m, 1H), 4.62–4.58 (m, 2H), 4.26–4.15 (m, 2H), 3.75 (brs, 2H), 3.67 (brs, 2H), 2.95–2.71 (m, 4H), 2.26 (brs, 1H), 2.22 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 170.9, 136.8, 135.0, 129.2, 128.6, 73.1, 62.6, 61.1, 60.8, 59.8, 54.8, 18.6; HRMS (ESI) m/z calcd for $C_{17}H_{27}ClN_3O_2$ [M + H$^+$], 34.1786; Found 340.1784.

Typical experimental procedure for the synthesis of (*R*)-2-(4-(3-chloro-2-hydroxypropyl)piperazin-1-yl)-*N*-(2,6-dimethylphenyl)acetamide (*R*-19)

To the magnetically stirred mixture of *N*-(2,6-dimethylphenyl)-2-(piperazin-1-yl)acetamide (**6a**) (0.494 g, 2 mmol) in water (1 mL) at 15 °C was added (*R*)-epichlorohydrine (*R*-8) (0.184 g, 2 mmol, 1 equiv.) and stirring was continued for 1 h (TLC). The reaction mixture was extracted with EtOAc (3 × 2 mL) and concentrated under rotary vacuum evaporation to get analytically pure (*R*)-2-(4-(3-chloro-2-hydroxypropyl)piperazin-1-yl)-*N*-(2,6-dimethylphenyl)acetamide (*R*-19) (0.66 g, 97%). The product was subjected to chiral HPLC analysis using a chiral AD-H column and the two enantiomers were eluted at t_S = 34.4 min and t_R = 38.9 min (80 : 20 : 0.1, hexane : 2-propanol : diethylamine) and the optical purity was found to be 98.7% *ee*.

Typical experimental procedure for the synthesis of (*S*)-2-(4-(3-chloro-2-hydroxypropyl)piperazin-1-yl)-*N*-(2,6-dimethylphenyl)acetamide (*S*-19)

To the magnetically stirred mixture of *N*-(2,6-dimethylphenyl)-2-(piperazin-1-yl)acetamide (**6a**) (0.494 g, 2 mmol) in water (1 mL) at 15 °C was added (*S*)-epichlorohydrine (*S*-9) (0.184 g, 2 mmol, 1 equiv.) and stirring was continued for 1 h (TLC). The reaction mixture was extracted with EtOAc (3 × 2 mL) and concentrated under rotary vacuum evaporation to get analytically pure (*R*)-2-(4-(3-chloro-2-hydroxypropyl)piperazin-1-yl)-*N*-(2,6-dimethylphenyl)acetamide (*S*-**19**) (0.65 g, 96%). The product was subjected to chiral HPLC analysis using a chiral AD-H column and the two enantiomers were eluted at t_S = 34.3 min and t_R = 39.1 min (80 : 20 : 0.1, hexane : 2-propanol : diethylamine) and the optical purity was found to be 98.5% *ee*.

Typical experimental procedure for the synthesis of (*RS*)-ranolazine (1) (Scheme 9)

To the magnetically stirred mixture of 2-methoxyphenol (**7**) (0.124 g, 1 mmol, 1 equiv.) and K_2CO_3 (0.18 g) in water (1 mL) at 90 °C was added (*RS*)-2-(4-(3-chloro-2-hydroxypropyl)piperazin-1-yl)-*N*-(2,6-dimethylphenyl)acetamide (**19**) (0.339 g, 1 mmol) and stirring was continued for 5 h (TLC). The reaction mixture was cooled to rt and neutralized with $NaHCO_3$ (until the effervescence ceases). The reaction mixture was cooled to 0–5 °C and diluted with 1 : 1 methanol and acetone (5 mL). The solid that precipitated out (2–3 h) was filtered off, washed with chilled methanol (2 mL), and dried to get analytically pure ranolazine (**1**) (0.4 g, 93%).[11a]

Typical experimental procedure for a protecting group free synthesis of *N*-(2,6-dimethylphenyl)-2-(piperazin-1-yl)-acetamide (6a) using piperizine (5a) (entry 12, Table 7)

To the magnetically stirred mixture of 2-chloro-*N*-(2,6-dimethylphenyl)acetamide (**4**) (9.85 g, 50 mmol) and piperazine (**5a**) (6.45 g, 75 mmol, 1.5 equiv.) in water (50 mL) at rt was added tetrabutylammoniumiodide (10 mol%) and the reaction temperature raised to 60 °C and stirring was continued for 3 h. The reaction mixture was cooled to 5–10 °C and

sodium bicarbonate was added (till the effervescence ceases). The mixture was evaporated to dryness under rotary vacuum evaporation and the solid residue was triturated with methanol (3 × 10 mL). The combined methanolic extracts are concentrated under vacuum rotary evaporation and the solid residue washed with cold water (2 × 5 mL) and dried to get analytically pure *N*-(2,6-dimethylphenyl)-2-(piperazin-1-yl)acetamide (**6a**) (10.5 g, 85%).[11a]

Typical experimental procedure for the synthesis of (*RS*)-ranolazine (*RS*-1) under microwave condition (Scheme 9)

The mixture of (*RS*)-2-(4-(3-chloro-2-hydroxypropyl)piperazin-1-yl)-*N*-(2,6-dimethylphenyl)acetamide (**19**) (0.339 g, 1 mmol) and 2-methoxyphenol (**7**) (0.124 g, 1 mmol, 1 equiv.) and K_2CO_3 (0.18 g) in water (1 mL) was stirred magnetically at 100 °C under microwave for 30 min (TLC). The reaction mixture was cooled to rt and neutralized with $NaHCO_3$ (till the effervescence ceases). The mixture was cooled to 0–5 °C and diluted with 1 : 1 methanol and acetone (5 mL). The precipitated solid (2–3 h) was filtered, washed with chilled methanol (2 mL), and dried to get analytically pure ranolazine (**1**) (0.38 g, 91%).[11a]

Typical experimental procedure for tandem *N*-alkylation and deprotection and *O*-alkylation for the synthesis of (*RS*)-ranolazine (*RS*-1) (Scheme 10)

To the magnetically stirred mixture of 2-chloro-*N*-(2,6-dimethylphenyl)acetamide (**4**) (3.94 g, 20 mmol) in water (100 mL) at 80 °C was added *tert*-butyl piperazine-1-carboxylate (**5b**) (3.72 g, 20 mmol, 1 equiv.) and stirring was continued for 4 h. Thereafter, the reaction temperature was increased to 110 °C and the stirring was continued for a further 3 h (TLC). The reaction mixture was cooled to rt and neutralized with sodium bicarbonate (until the effervescence ceases). The reaction mixture was further cooled to 10 to 15 °C, to which epichlorohydrine (**8**) (1.84 g, 20 mmol, 1 equiv.) was added and stirring continued for 1 h (TLC) followed by addition of 2-methoxyphenol (**7**) (2.48 g, 20 mmol, 1 equiv.) and K_2CO_3 (3.61 g, 26 mmol, 1.3 equiv.). The reaction temperature was raised to 90 °C and the stirring continued for a further 5 h (TLC). The reaction mixture was cooled to rt and neutralized with $NaHCO_3$ (until the effervescence ceases). The mixture was cooled to 0–5 °C and diluted with 1 : 1 methanol and acetone (20 mL). The precipitated solid (~2–3 h) was filtered, washed with chilled methanol (3 × 5 mL), and dried to get analytically pure ranolazine (**1**) (3.5 g, 82%); white solid; mp = 121–122 °C; IR (Neat) ν: 3329, 3012, 2975, 2935, 1676, 1586, 1505, 1475, 1259, 1149 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ: 6.98–6.96 (m, 3H), 6.86–6.77 (m, 4H), 4.06–4.02 (m, 1H), 3.89–3.86 (m, 1H), 3.82–3.78 (m, 1H), 3.71 (s, 3H), 2.58 (brs, 8H), 2.55–2.43 (m, 2H) 2.08 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 170.2, 149.4, 148.3, 135.3, 133.7, 127.7, 127.0, 121.4, 120.9, 113.7, 112.0, 71.9, 67.0, 60.9, 60.5, 55.1, 53.1, 52.9, 17.3; MS (APCI) *m*/*z* 428.2 $(M + H)^+$.[11a]

Typical experimental procedure for tandem ring opening of epichlorohydrine (7) with 6a and *O*-alkylation of 2-methoxyphenol (8) for the synthesis of (*RS*)-ranolazine (*RS*-1) (Scheme 11)

To the magnetically stirred mixture of *N*-(2,6-dimethylphenyl)-2-(piperazin-1-yl)acetamide (**6a**) (4.94 g, 20 mmol) in water (20 mL) at 15 °C was epichlorohydrine (**8**) (1.84 g, 20 mmol, 1 equiv.) and stirring was continued for 1 h (TLC) followed by addition of 2-methoxyphenol (**7**) (2.48 g, 20 mmol, 1 equiv.) and the stirring continued at 90 °C for further 5 h (TLC). The reaction mixture was cooled to rt and neutralized with $NaHCO_3$ (until the effervescence ceases). The mixture was cooled to 0–5 °C and diluted with 1 : 1 methanol and acetone (20 mL). The solid that precipitated out (2–3 h) was filtered, washed with chilled methanol (5 mL), and dried to get analytically pure ranolazine (**1**) (7.25 g, 85%).[11a]

Typical experimental procedure for tandem ring opening of epichlorohydrine (7) with 6a and *O*-alkylation of 2-methoxyphenol (8) for the synthesis of (*R*)-ranolazine (*R*-1) (Scheme 11)

To the magnetically stirred mixture of *N*-(2,6-dimethylphenyl)-2-(piperazin-1-yl)acetamide (**6a**) (0.497 g, 2 mmol) in water (2 mL) at 15 °C was added (*R*)-epichlorohydrine (*R*-8) (0.18 g, 2 mmol, 1 equiv.) and stirring was continued for 1 h (TLC) followed by addition of 2-methoxyphenol (**7**) (0.25 g, 2 mmol, 1 equiv.) and the stirring continued at 90 °C for further 5 h (TLC). The reaction mixture was cooled to rt and neutralized with $NaHCO_3$ (until the effervescence ceases). The reaction mixture was cooled to 0–5 °C and diluted with 1 : 1 methanol and acetone (5 mL). The solid that precipitated out (2–3 h) was filtered, washed with chilled methanol (2 mL), and dried to get analytically pure ranolazine (*R*-1) (0.73 g, 86%). The product was subjected to chiral HPLC analysis using a chiral AD-H column and the two enantiomers were eluted at t_R = 27.1 min and t_S = 46.2 min (70 : 30 : 0.1, hexane : 2-propanol : diethylamine) and the optical purity was found to be 96.2% *ee*.

Typical experimental procedure for tandem ring opening of epichlorohydrine and *O*-alkylation of 2-methoxyphenol for the synthesis of (*S*)-ranolazine (*S*-1) (Scheme 11)

To the magnetically stirred mixture of *N*-(2,6-dimethylphenyl)-2-(piperazin-1-yl)acetamide (**6a**) (0.497 g, 2 mmol) in 1 mL water at 15 °C was added (*S*)-epichlorohydrine (*S*-8) (0.18 g, 2 mmol, 1 equiv.) and stirring was continued for 1 h (TLC) followed by addition of 2-methoxyphenol (**7**) (0.25 g, 2 mmol, 1 equiv.) and the stirring continued at 90 °C for a further 5 h (TLC). The reaction mixture was cooled to rt and neutralized with $NaHCO_3$ (until the effervescence ceases). The reaction mixture was then cooled to 0–5 °C and diluted with 1 : 1 methanol and acetone (5 mL). The solid that precipitated out (2–3 h) was filtered, washed with chilled methanol (2 mL), and dried to get analytically pure ranolazine (*S*-1) (0.72 g, 85%). The product was then subjected to chiral HPLC analysis using a chiral AD-H column and the two enantiomers were

eluted at t_R = 27.9 min and t_S = 46.5 min (70 : 30 : 0.1, hexane : 2-propanol : diethylamine) and the optical purity was found to be 95.6% *ee*.

Acknowledgements

DNK and DK thank CSIR, New Delhi, India for a Senior Research fellowship and Research Associateship, respectively.

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