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Dual basic ionic liquid as a catalyst for synthesis of (2-amino-3-cyano-4*H*-chromen-4-yl) phosphonic acid diethyl ester and its molecular docking study

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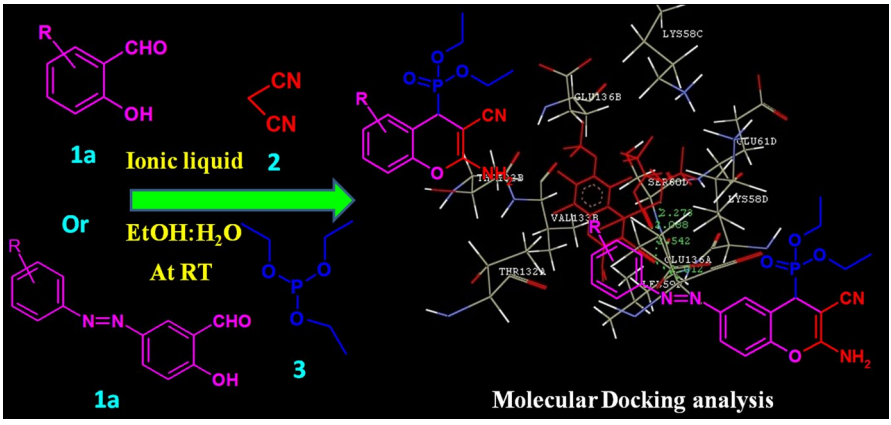
Abstract

A series of (2-amino-3-cyano-4*H*-chromen-4-yl) phosphonic acid diethyl ester derivatives were synthesized from salicylaldehyde, malononitrile and triethylphosphite in ethanol/water (1:1) system using a new dual basic ionic liquid, i.e., 1-[3-(dimethylamino)propyl]-1,4-diazabicyclo[2.2.2]octan-1-ium hydroxide at ambient temperature. The attractive features of this protocol are higher yields (more than 95%), low cost, reduced environmental impact, shorter reaction time, reusability of IL (up to 7 times) and convenience of procedure. The possible bioactivity study was also carried out by using molecular docking study for all the synthesized compounds and molecules can be act as anticancer agent.

Graphic abstract

Synthesis of some new (2-amino-3-cyano-4*H*-chromen-4-yl) phosphonic acid diethyl ester derivatives by using new dual basic ionic liquid.



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Extended author information available on the last page of the article

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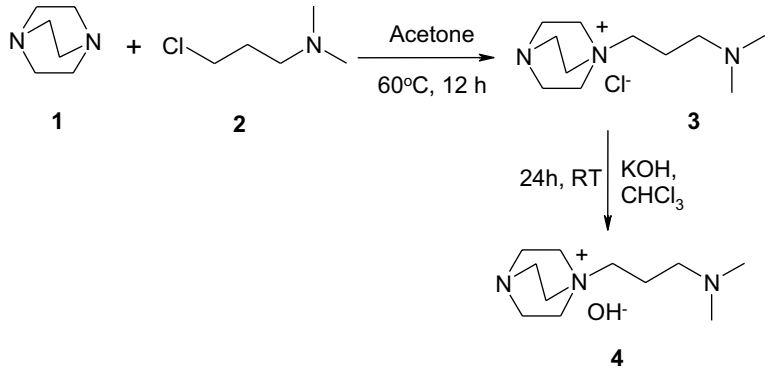
Keywords Task-specific ionic liquid · Phosphonate · Green chemistry · Azo salicylaldehydes

Introduction

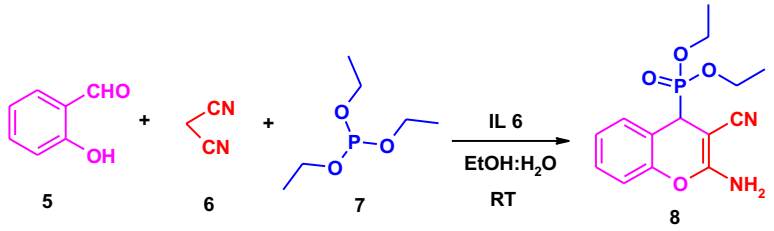
Ionic liquids (ILs), usually considered as greener organic compounds due to their thermal stability, low vapor pressures, non-flammable, have good recovery and reusability, alternatives to hazardous, harmful organic solvents and catalyst, solvation of organic molecules, etc. [1–6] Hence, due to these, they are also known as 'green solvents.' ILs have endless properties and applications. There are many scientific communities who consider use of ILs is the highest level of green chemistry, but some of the researchers are in contrast stating that their preparation procedures are not green. Some of the group of scientist considers water as a greener solvent even though sometimes it is not safe when it is contaminated or used from awful source. In the perspective of green chemistry principles, solvent is green if it is recovered back after reaction or any other work [7, 8]. So, in this context, IL fits well and has showed promising results. They have been studied as solvents, catalysts and reagents [9–11]. Looking toward the versatility of ILs nowadays, many industries attracted their attention to synthesize list of ionic liquids [12]. In the year 2002, the German chemical manufacturer BASF synthesized first 1-alkylimidazole for scavenging acid by-products generated in organic processes [13, 14].

In the current decade, scientific society is tackling with synthesis and application of functionalized ILs, where both the cation and anion were tethered with specific functional group. They are specifically called as task-specific ionic liquids (TSILs) [15, 16]. ILs with dual functionality are emerging into the new period of research. Both cation and anion of ILs consist of definite functionality which may act as a catalyst or regent and can accelerate the reaction forward [17, 18]. This is because of capacity of ILs to generate internal pressure and to endorse the association of reactants in solvent cavities and to make them excellent media for formation of multiple bonds. Their wide solvating capacity and liquid range also clearly render them suitable solvents for organic reactions. Here, is reported a new method for the preparation of TSILs containing Brønsted–Lewis basic groups for the synthesis of (2-amino-4*H*-chromen-4-yl) phosphonates.

The compounds containing strong bond between carbon and phosphorus are termed as organophosphorus compounds among these phosphonates and their derivatives are prepared in large quantity because of their applications in multifarious area [19, 20]. Some of the functionalized phosphonates interacts with various metal ions and forms a stable complex with them, and these complexes show biological, biomedical, industrial and nano-technological applications [21–23]. Along with this, phosphonates act as anthropogenic complexing agents or chelating agents containing one or more C–$PO(OH)_2$ groups [24]. In the field of biomedical, they have extended their role as anticancer, antibiotic and antimicrobial agent [25–27]. Till date, so many methods have been proposed to synthesize these types of phosphonates and they are formed through Knoevenagel, Pinner-cyclisation and phospha-Michael reactions in a one-pot method [20, 28]. The versatility of Knoevenagel and



Scheme 1 Synthesis of dual basic IL



Scheme 2 A model reaction

Michael addition reactions has reflected into numerous applications in the elegant synthesis of fine chemicals, number of heterocyclic compounds and many bioactive molecules. In continuation with our earlier work in the heterocycle synthesis [29, 30], we decided to synthesize the (2-amino-4*H*-chromen-4-yl)phosphonates by using newly synthesized IL 1-[3-(dimethylamino)propyl]-1,4-diazabicyclo[2.2.2] octan-1-ium hydroxide as a catalyst.

Result and discussion

The synthesis of TSIL 1-[3-(dimethylamino)propyl]-1,4-diazabicyclo[2.2.2]octan-1-ium hydroxide (Scheme 1) was achieved by carrying out reactions in the sequence as shown in Scheme 1. Detailed procedure is in the experimental section. The structure of which was confirmed with ^{1}H and ^{13}CNMR spectroscopy. The synthesized IL is used as a catalyst for (2-amino-4*H*-chromen-4-yl) phosphonates.

In the standardization of organic reactions, solvent plays an important role, and using appropriate solvent is of essential significance for making a successful organic synthesis. In light of this, reaction between salicylaldehyde (**5**), malononitrile (**6**) and triethylphosphite (**7**) was examined in toluene, 1,4-dioxane, DCM, acetonitrile, DMF, DMSO, methanol and ethanol used as solvents at room temperature (Scheme 2). All the results are summarized in Table 1.

Table 1 Screening of solvent for synthesis of (2-amino-3-cyano-4*H*-chromen-4-yl) phosphonic acid diethyl ester

Entry	Solvent	Time	Yield[a]
1	Toluene	8	–
2	1,4-dioxane	9	–
3	DCM	8	20
4	Acetonitrile	10	32
5	DMF	6	Trace
6	DMSO	12	40
7	Methanol	2.5	80
8	Ethanol	1	97
9	Water	6	40
10	Ethanol/water (1:1)	1	97
11	Ethanol/water (1:2)	3	55

Reaction condition: salicylaldehyde (1 mmol), malononitrile (1 mmol), triethylphosphite (1 mmol), IL 6 (20 mol %), solvent (10 mL), at room temperature

[a]Isolated yield

From the results obtained during optimization of reaction, it can be stated that reaction in protic solvent such as methanol and ethanol gave superior yields in shorter reaction times (Table 1, Entries 7, 8). Using water as a protic reaction media is the highest level of green chemistry procedure, but when it was observed that reaction became sluggish giving only 40% of desired product (Table 1, Entry 9).This might be because of low solubility of organic molecules in the aqueous media. Aprotic solvents toluene, 1,4-dioxane, DCM, acetonitrile, DMF, DMSO (Table 1, Entries 1–6) resulted in inferior yield. Hence, it can be concluded that reaction gives excellent output in protic media and ethanol could be the best choice of solvent giving 97% of yield. In addition to this, using ethanol/water (1:1)system reaction furnished into an excellent yield of 97%. But increase in water in ethanol did not much improve the yield of the reaction (Table 1, Entry 11). For all the above detailed study, IL 6 is used as a catalyst (Fig. 1).

Achieving the ethanol/water (1:1) solvent system next focused to investigate the effect of IL as a catalyst. Different functionalized TSIL was chosen for the present study.

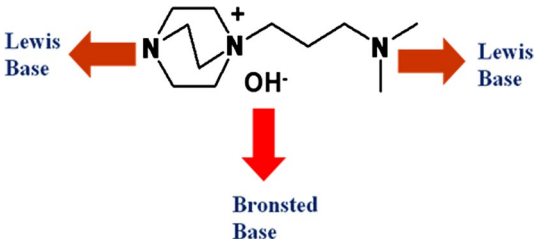


Fig. 1 Characteristic of dual basic ionic liquid

ILs with diverse functionality may affect the reaction rate and yield of the product. Hence, in this circumstance, investigating the effect of IL on the synthesis of phosphonic acid diethyl ester with different TSILs is examined on the model reaction (Fig. 2). Poorer results were obtained in the presence of IL 1, IL 2, IL 3 and IL 4 (Table 2, entries 2–5), whereas moderate yield of product was found when IL 5 was employed as a catalyst (Table 2, entry 6). Pleasingly, in the presence of catalytic amount of IL 6, 1-[3-(dimethylamino)propyl]-1,4-diazabicyclo[2.2.2]octan-1-ium hydroxide, the reaction proceeded smoothly furnished desired product in 97% yield within 1 h (Table 2, entry 7). To examine the impact of catalyst loading on model reaction, amount of IL 6 was varied from 10 to 30 mol% (Table 2, entries 8, 9). From Table 2, it can be concluded that 20 mol% of IL 6 was sufficient to catalyze present transformation, yielded desired product in 97%. No significant progress in the yield was observed even though 30 mol% of it was employed, whereas 10 mol% catalyst loading resulted into comparatively lower yield of product. The product formed precipitated from the reaction mixture, the work-up procedure involves simple filtration, followed by washing with cold ethanol for its purification. The structure of isolated products was confirmed by spectral techniques viz. ^{1}H and ^{13}C NMR, analysis. Thus, IL 6 was found to be the catalyst of choice for present transformation with respect to yield and reaction time.

To study the scope and limitations of the protocol next extended to check the effect of differently substituted aromatic salicylaldehydes either with electron-withdrawing groups (such as nitro or halide groups) or with electron-donating groups (such as alkoxyl or methyl groups) under same conditions (Scheme 3)

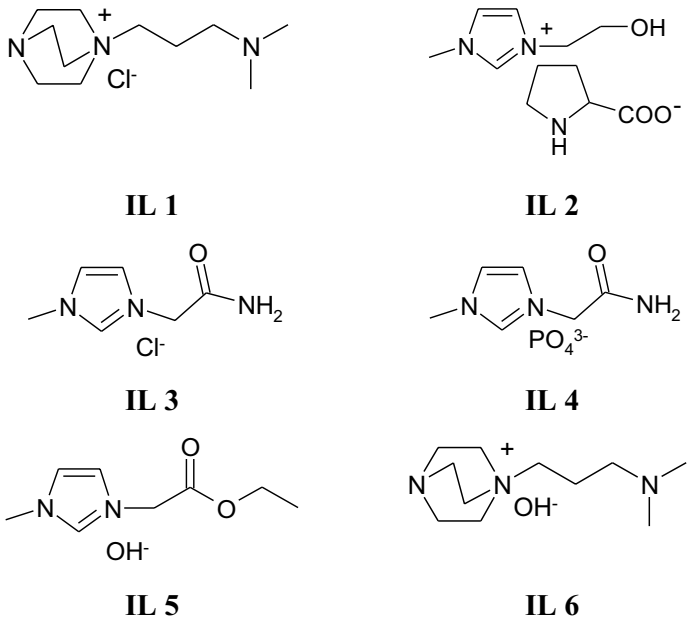


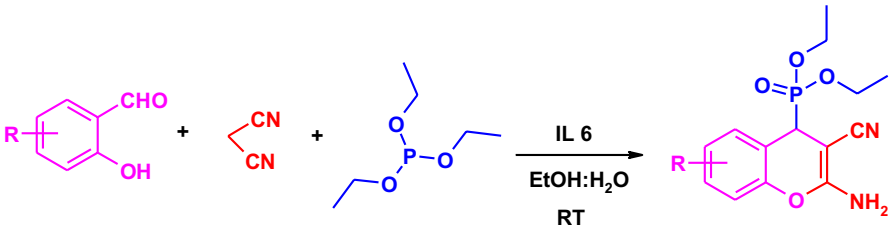
Fig. 2 Different ionic liquids (ILs) studied

Table 2 Screening of catalyst for synthesis of (2-amino-3-cyano-4*H*-chromen-4-yl) phosphonic acid diethyl ester

Entry	Catalyst (mol%)	Time in h	Yield[a]
1	–	12	Trace
2	IL 1 (20)	5	50
3	IL 2 (20)	5	40
4	IL 3 (20)	5	25
5	IL 4 (20)	5	60
6	IL 5 (20)	3	80
7	IL 6 (20)	1	97
8	IL 6 (10)	3	79
9	IL 6 (30)	1	97
10	NH_4OH	12	45
11	NH_4Cl	12	30
13	NH_4OAc	5	65

Reaction condition: salicylaldehyde (1 mmol), Malononitrile (1 mmol), Triethylphosphite (1 mmol), ethanol/water (1:1) (10 mL), at room temperature

[a]Isolated yield



Scheme 3 General reaction

(Table 3). It can be concluded that the electronic nature of the substituents has no significant effect on this reaction giving excellent results. Surprising results obtained when some newly substituted azo salicylaldehydes used (Scheme 4) for the synthesis of novel phosphonic acid diethyl ester derivatives. Under the present reaction conditions, outstanding results were obtained with all kinds of azo salicylaldehydes. All the results are summarized in Table 3.

We envisioned that IL 6 could be a suitable catalyst for the present transformation, initially the basic ionic liquid abstract a proton from malononitrile to form carbanion. This carbanion attacks the aldehyde to form cyano olefin (9) followed by ring closure via nucleophilic attack of the OH group on the cyano group to furnish imino coumarin (10). The subsequent phospha-Michael addition of triethylphosphite (7) affords the target compound (8). A plausible mechanism for the formation of (2-amino-3-cyano-4*H*-chromen-4-yl) phosphonic acid diethyl ester is depicted in Scheme 5.

Table 3 Synthesis of (2-amino-3-cyano-4*H*-chromen-4-yl) phosphonic acid diethyl ester

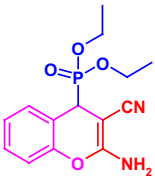
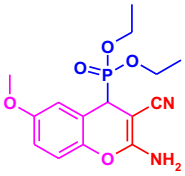
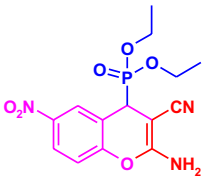
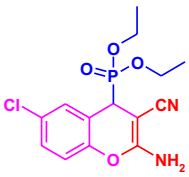
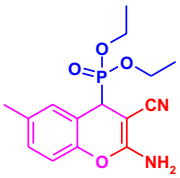
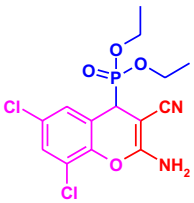
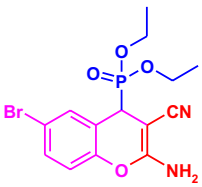
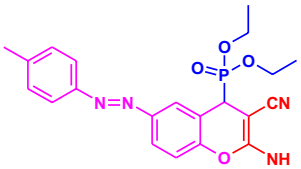
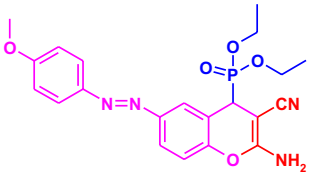
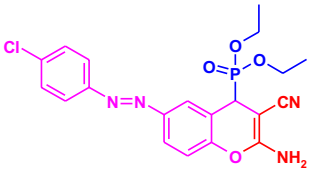
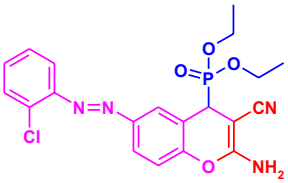
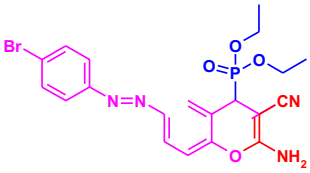
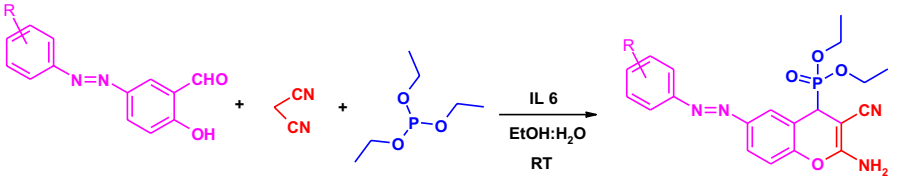
Sr. No.	Substituent (R)	Time in h	Yield (%)[a]	M.P. °C[ref.]
1		1	97	153–155 [26]
2		1	97	180–182 [31]
3		2.5	90	218–220 [31]
4		1.5	95	150–152 [31]
5		1	95	160–162 [32]
6		1.5	92	172–176 [31]
7		1.5	92	180–184 [31]

Table 3 (continued)

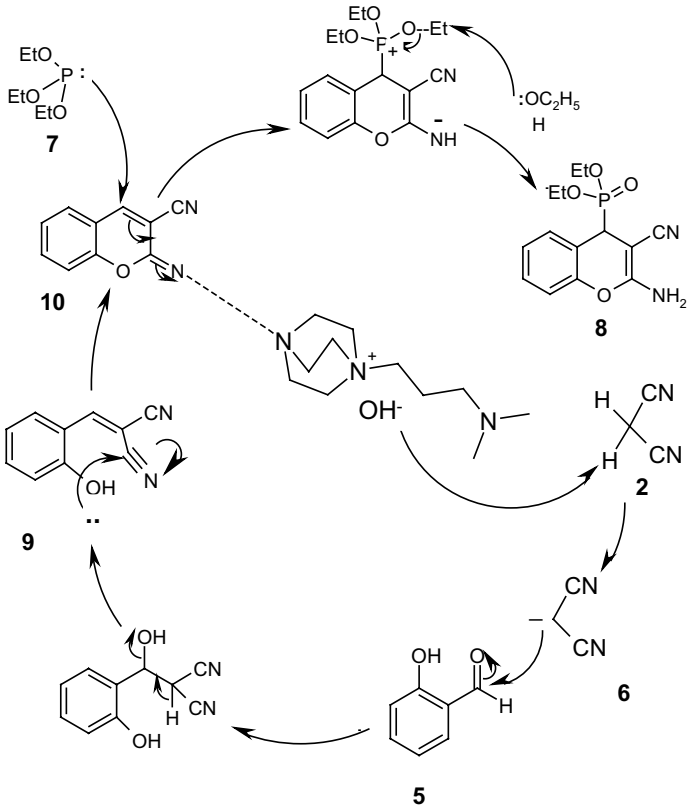
Sr. No.	Substituent (R)	Time in h	Yield (%)[a]	M.P. °C[ref.]
8		2	91	190–192
9		2	90	220–224
10		2	91	230–232
11		1.5	90	236–238
12		2	90	240–242

Reaction condition: salicylaldehyde (1 mmol), malononitrile (1 mmol), triethylphosphite (1 mmol), IL (20 mol %), ethanol/water (1:1) (10 mL), at room temperature

[a]Isolated yield



Scheme 4 Reaction with azo salicylaldehydes



Scheme 5 Proposed mechanism for the synthesis of (2-amino-3-cyano-4*H*-chromen-4-yl) phosphonic acid diethyl ester

Reusability of ionic liquid

One of the principals of green chemistry is to reuse the catalyst used for the reaction. Hence, we carried out the reusability study of the IL used during the reaction. After completion of reaction, we isolated the product by just filtration and evaporated the filtrate to recover the IL. Then, it was purified by giving washings with ethyl acetate and diethyl ether followed by drying in oven at 60 °C for 12 h and used as it is for reaction. The reaction resulted in the formation of the expected product without considerable loss in catalytic activity even after seven runs (Fig. 3).

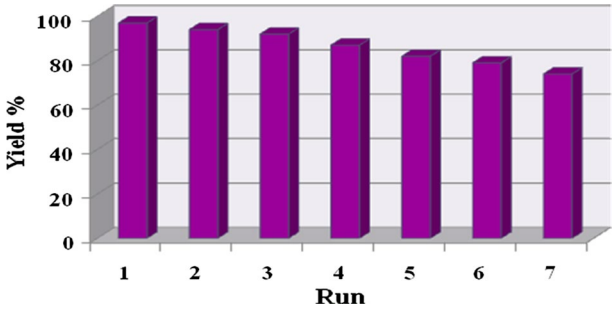


Fig. 3 Reusability study

Molecular docking analysis

Molecular docking analysis was performed for possible bioactivity prediction of synthesized derivatives. Phosphonic acid derivatives are known for anticancer potential with possible binding on the number of protein target like BCL 2. BCL-2 is group of proteins, which are highly expressed over 60% in all types of cancer. Efficiency of the BCL-2 protein to act as anticancer target is proved via development of geneses. Molecular docking reveled all developed 12 molecules are binding with similar binding site. Binding energy of all molecules ranged from − 31.40 to − 0.216 kcal/Mol. Binding interactions of all molecules are given in the following Table 4, and their images are from Figs. 4, 5, 6, 7, 8 and 9.

Conclusion

In conclusion, we have introduced a efficient, ecobenign and atom-economical method for the preparation of (2-amino-3-cyano-4*H*-chromen-4-yl) phosphonic acid diethyl esters from readily available starting materials salicylaldehydes, malononitrile and triethyl phosphite/diethyl phosphite. The reaction follows Knoevenagel–phospha-Michael reaction mechanism to furnish the desired product in just one step. The DABCO-based IL 1-[3-(dimethylamino)propyl]-1,4-diazabicyclo[2.2.2]octan-1-ium hydroxide acts as a catalyst, which can be recycled seven times without considerable loss in yields. The molecular docking analysis was also carried out for all the synthesized products. Phosphonic acid derivatives are known for anticancer potential with possible binding on the number of protein target like BCL 2. BCL-2 is a group of proteins, which are highly expressed over 60% in all types of cancer. The analysis shows that molecules can act as promising anticancer agents.

Table 4 Binding Interactions for all molecules

Molecule No.	Molecular interactions		
	Hydrogen bond	Hydrophobic	Vdw
1.		THR132, VAL133, GLU136, LYS58, SER60, GLU61	THR132, GLU136, VAL133, LYS58, LEU59, SER60, GLU61
2.	LEU59, SER60	THR132, VAL133, GLU136, LYS58, SER60, GLU61	THR132, GLU136, VAL133, LYS58, LEU59, SER60, GLU61
3.	SER60	THR132, VAL133, GLU136, LYS58, LEU59, SER60, GLU61	THR132, VAL133, GLU136, LYS58, LEU59, SER60, GLU61
4.	LEU59, SER60	LYS58, LEU59, SER60, GLU61,THR132, VAL133, GLU136,	THR132,GLU136,VAL133LYS58, LEU59, SER60, GLU61
5.	LEU59	THR132, GLU136, LYS58, SER60	GLN118, THR132, VAL133, GLU136, LYS57, LYS58, SER60
6.		THR132, GLU136, LYS58, SER60	GLN118, THR132, VAL133, GLU136, LYS57, LYS58, SER60
7.	THR132, SER60	LYS58, LEU59, SER60, GLU61, THR132, VAL133, GLU136	THR132, GLU136, VAL133 LYS58, LEU59, SER60, GLU61
8.		LYS58, LEU59, SER60, GLU61, THR132, VAL133, GLU136	THR132, GLU136, VAL133 LYS58, LEU59, SER60, GLU61
9.		LYS58, LEU59, SER60, GLU61, THR132, VAL133, GLU136	THR132, GLU136, VAL133 LYS58, LEU59, SER60, GLU61
10.		THR132, GLU136, LYS58, SER60	GLN118, THR132, VAL133, GLU136, LYS57, LYS58, SER60
11.		THR132, VAL133, GLU136, LYS58, SER60, GLU61	THR132, GLU136, VAL133, LYS58, LEU59, SER60, GLU61
12.	SER60	THR132, GLU136, LYS58, SER60	GLN118, THR132, VAL133, GLU136, ARG139, LYS57, LYS58, LEU59, SER60

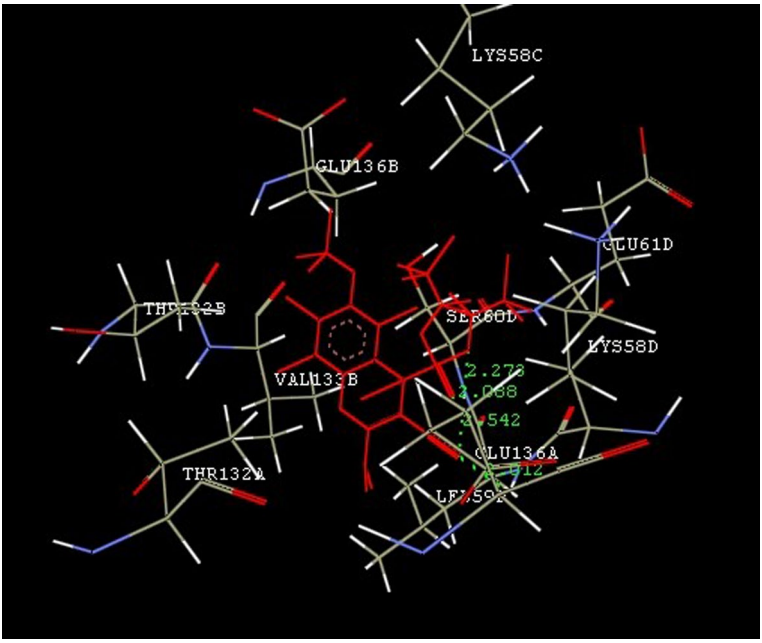


Fig. 4 Binding interaction of molecule no 2 (Table 2, Entry 2)

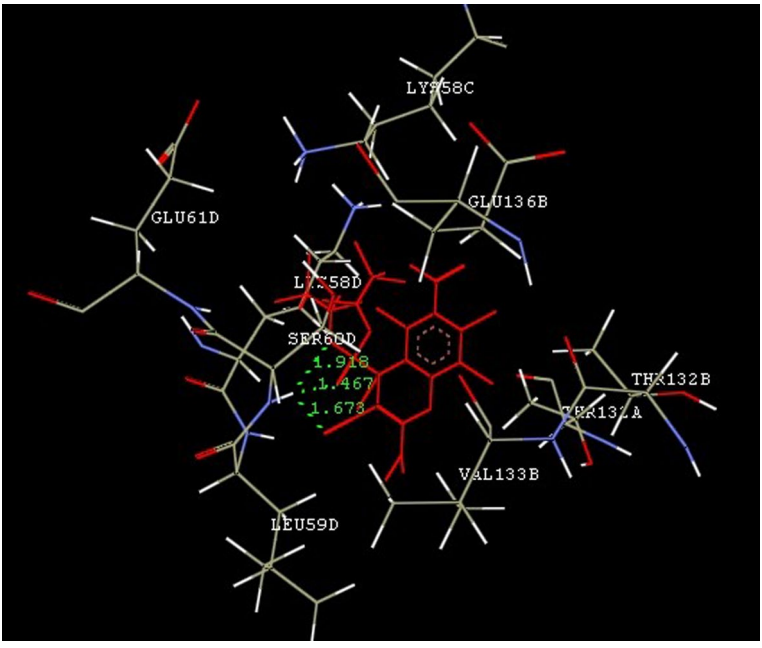


Fig. 5 Binding interaction of molecule no 3 (Table 2, Entry 3)

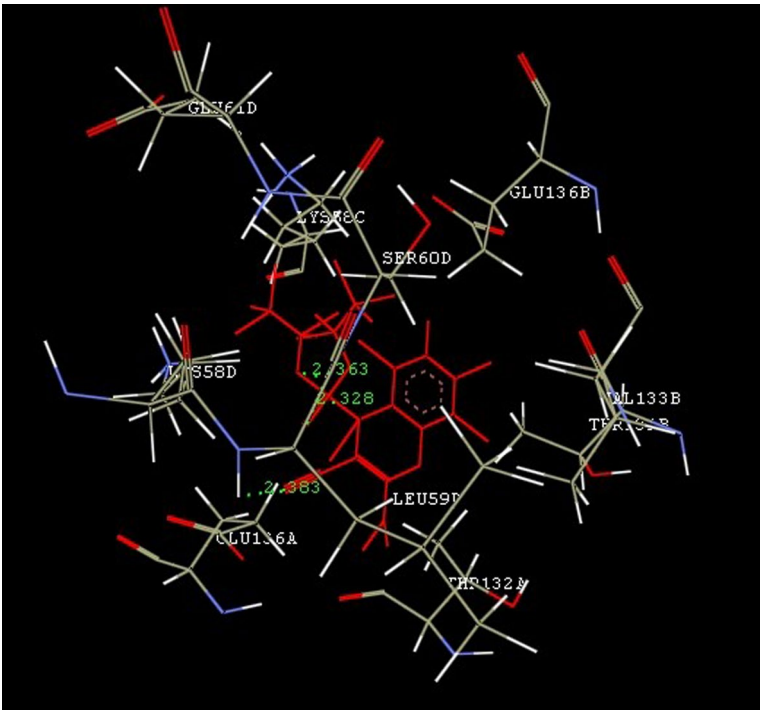


Fig. 6 Binding interaction of molecule no 4 (Table 2, Entry 4)

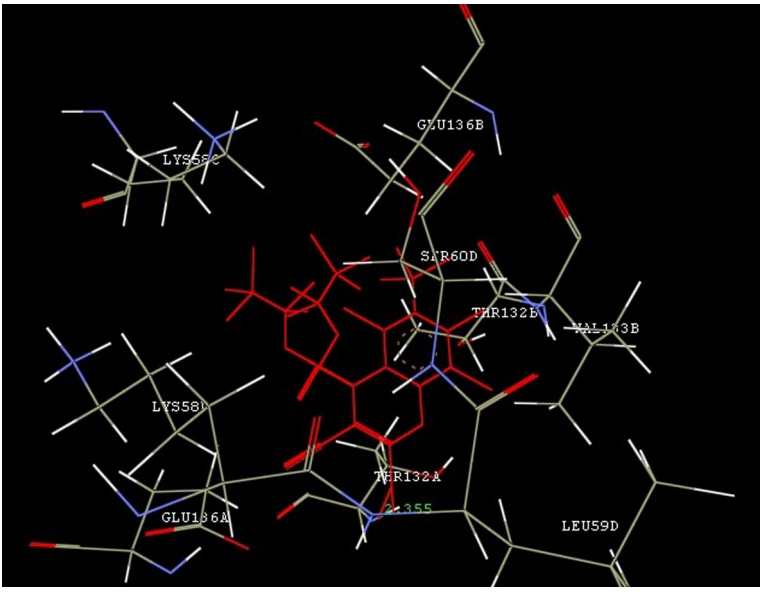


Fig. 7 Binding interaction of molecule no 5 (Table 2, Entry 5)

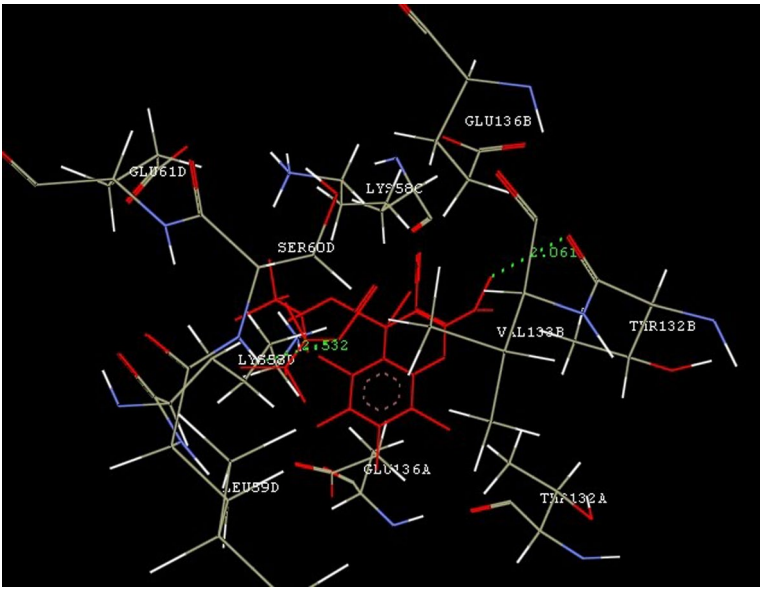


Fig. 8 Binding interaction of molecule no 7 (Table 2, Entry 7)

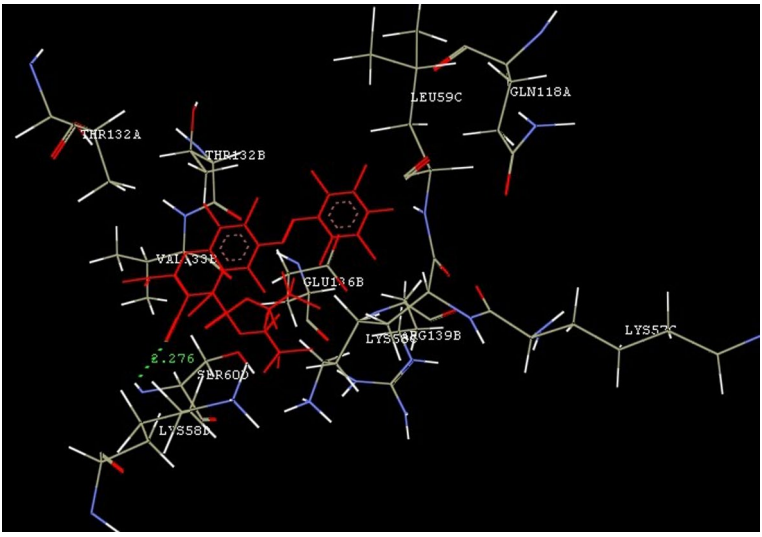


Fig. 9 Binding interaction of molecule no 12 (Table 2, Entry 12)

Experimental

Chemicals and apparatus

The chemicals used in this work were obtained from Spectrochem, Aldrich and were used without purification. Melting points were measured by open capillary method and were uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a BRUKER DRX-400 AVANCE spectrometer at 400.13 and 100 MHz. ^{1}H and ^{13}C NMR spectra were obtained in solutions in DMSO-d^6 using TMS.

Procedure for synthesis of IL 1-[3-(dimethylamino)propyl]-1,4-diazabicyclo[2.2.2]octan-1-ium hydroxide

To a vigorously stirred solution of bicyclo[2.2.2]octane, i.e., DABCO (10 mmol) in toluene (25 mL), 3-chloro-*N*,*N*-dimethylpropan-1-amine (11 mmol) was slowly added at room temperature and quaternization was carried out at 80 °C for 24 h, after which it was cooled at room temperature for 1 h. Toluene was decanted, and the remaining viscous oil was repeatedly washed with diethyl ether to yield white viscous ionic liquid, which was dried in vacuum furnished 1-[3-(dimethylamino) propyl]-1,4-diazabicyclo[2.2.2]octan-1-ium chloride.

1-[3-(dimethylamino)propyl]-1,4-diazabicyclo[2.2.2]octan-1-ium chloride (10 mmol) was then dissolved in chloroform and cooled at 0 °C followed by addition of potassium hydroxide (11 mmol) and stirred it for 24 h at room temperature. The suspension was filtered to remove the precipitated potassium chloride salt, and the solvent was evaporated under reduced pressure furnished 1-[3-(dimethylamino) propyl]-1,4-diazabicyclo[2.2.2]octan-1-ium hydroxide.

Procedure for synthesis of (2-amino-3-cyano-4*H*-chromen-4-yl) phosphonic acid diethyl esters

A mixture of salicylaldehyde (1 mmol), malononitrile (1 mmol), triethylphosphite (1 mmol) and IL (20% mol) in EtOH/H_2O (10 mL) was stirred at room temperature for time mentioned in Table 3. After completion of the reaction, the reaction mixture was filtered and the precipitate washed with cold ethanol (2×5 mL) to afford the pure product.

Procedure for reusability study

After completion of reaction on TLC, the solid product formed was filtered on Whatmann filter paper No.1 and collect the filtrate in a beaker. The filtrate was then evaporated in oven at 60 °C and purified by giving washings with ethyl acetate and diethyl ether solvent. After washing, the remaining IL was then dried in oven at 60 °C for 12 h and then used as it is for further reaction with salicylaldehyde, malononitrile and triethyl phosphate. The IL can be reused very effectively for seven times with any significant loss.

Molecular docking

Molecular docking simulations were performed for predicting activity potential of the synthesized derivatives on *BCL2 protein.* Docking analysis was accrued out using crystal structure of *BCL2* (PDB ID/ 2xa0) downloaded from free protein database www.rcsb.org. Biopredicta module of V life MDS 4.3 was utilized to perform docking simulation.

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