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Reagent-Controlled Divergent Synthesis of 2-Amino-1,3-Benzoxazines and 2-Amino-1,3-Benzothiazines

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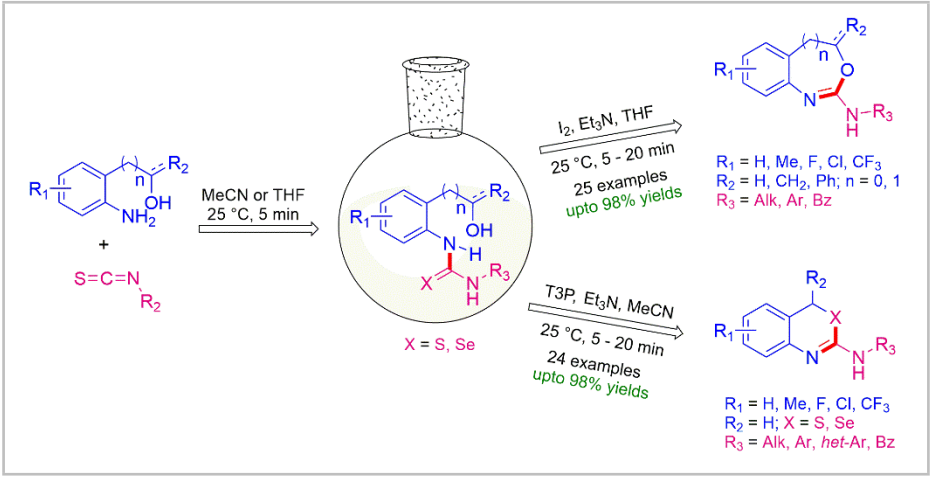
ABSTRACT: A reagent-controlled chemoselective process has been devised for the synthesis of 4*H*-1,3-benzoxazines and related biologically important heterocycles in high yields under mild conditions. These scaffolds could be efficiently constructed using two different chemoselective reactions rely on the choice of reagents and reaction conditions. The treatment of various 2-amino-arylalkyl alcohols with isothiocyanates afforded thiourea intermediates, which were reacted *in-situ* with molecular iodine in the presence of triethylamine to give the 2-amino-4*H*-1,3-benzoxazines, whereas the corresponding 2-amino-4*H*-1,3-benzothiazines were obtained by the reaction of thiourea intermediates in the presence of T3P (a mild cyclodehydrating agent) and triethylamine as base. The described protocol represents as the first example for the synthesis of 4*H*-1,3-benzoxazines *via* dehydrosulfurization method using molecular iodine as reagent.



INTRODUCTION:

The N,O- and N,S-containing six membered heterocycles constitute a diverse range of drug molecules and herbicides.[1] These scaffolds are extensively engaged as the immense building blocks for bioactive molecules. Benzoxazine derivatives evident interesting biological and pharmaceutical properties such as

progesterone receptor (PR) modulation, antianxiety (Etifoxine is an anxiolytic and anticonvulsant drug), anti-HIV, agonist, and antagonist activities (Figure 1, **A**, **B**).[1] Whereas, benzothiazine skeletons are ubiquitous bioactive molecules[2] and are well studied and extensively appealed in biochemical fields (Figure 1, **C**-**G**).[2g,3] Favourably, several related molecules such as 2-amino-4*H*-1,3-benzothiazine scaffolds also allure unique biological properties[4] and have secured increasing attention in the medicinal chemistry. For example, it was investigated that 2-(4-piperidinamino)-4*H*-1,3- benzothiazines (Figure 1, **D**) displays appreciable cytoprotective properties towards the heart or neurons.[4b] Recent findings witnessed that the guanidine, amidine and thiourea embedded scaffolds of 2-amino-1,3-benzothiazine (Figure 1, **E**, **F**, **G**) were identified as the suitable medicinal compounds for the purpose of neurodegenerative disorders which are instigated by Alzheimer's disease and cranial trauma.[4d] Hence, there have been a noticeable attention gratified towards the potential applications of 2-amino-4*H*-1,3-benzothiazine and 2-amino-4*H*-1,3-benzoxazine scaffolds.[5]

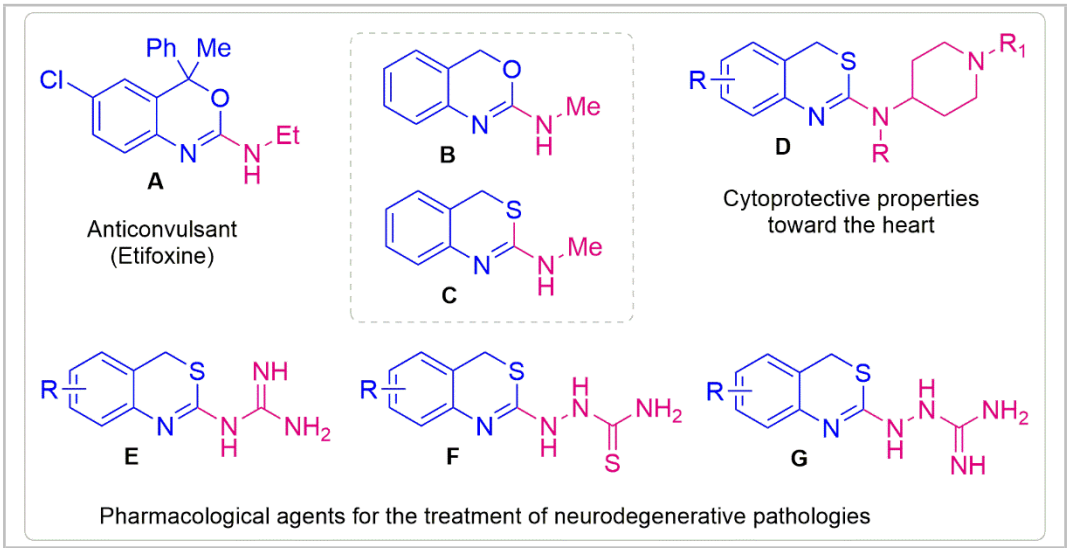
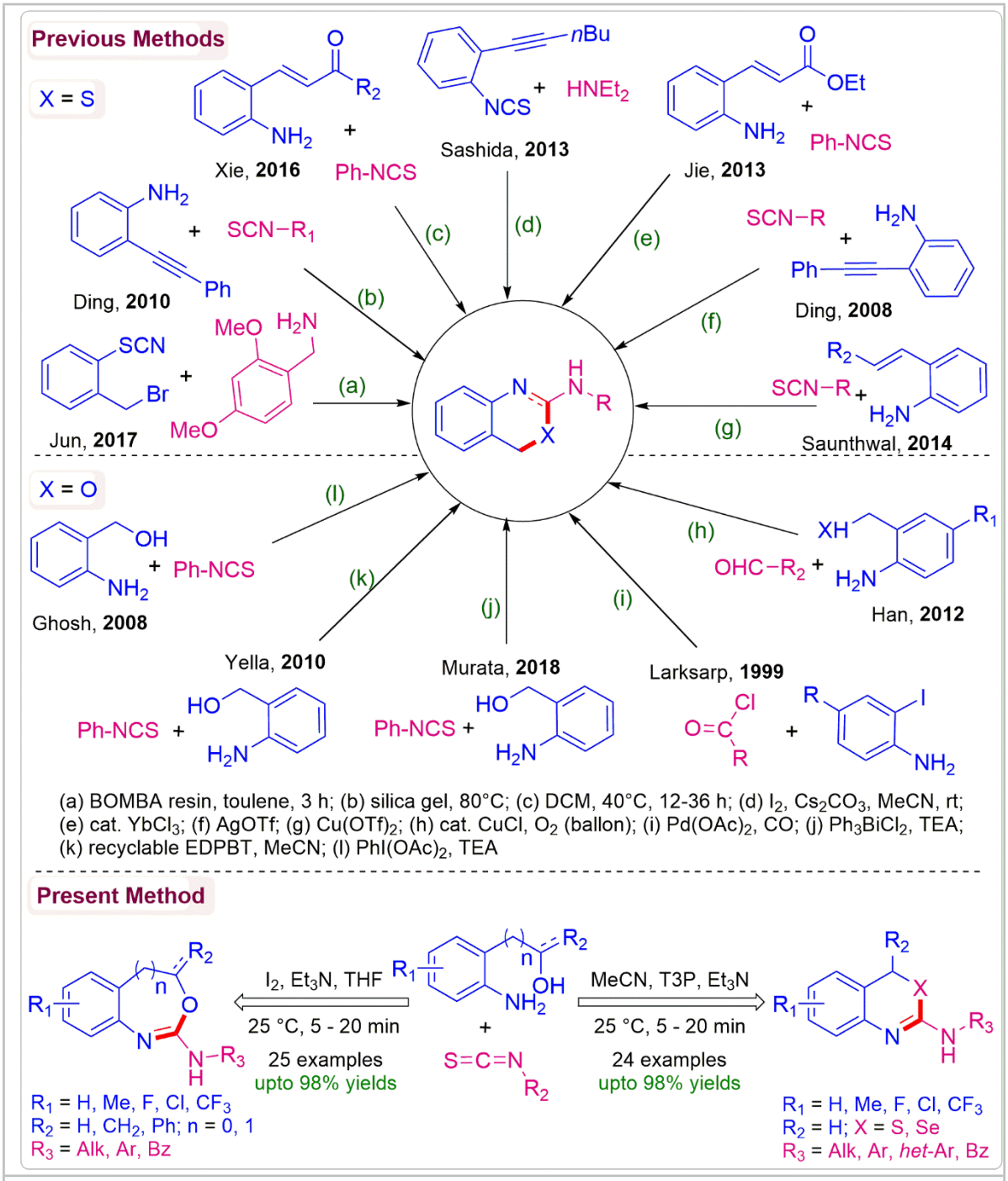


Figure 1. Potential pharmacological agents containing a 2-amino-1,3-benzoxazine and 2-amino-1,3-benzothiazine structural units.

Due to their immense importance in medicinal chemistry, consequently a spectrum of methods have been described for their synthesis. Among these approaches, the traditionally and the most extensively attempted protocols are (i) metal-catalyzed tandem addition-cyclization reactions and oxidative synthesis,[3e,6] (ii) non-metal catalyzed/dehydrosulfurization methods,[7] and (iii) non-catalytic approaches.[8] A summary of the known procedures towards the synthesis of 1,3-benzoxazines and 1,3-benzothiazines are presented in Scheme 1. Jie and co-workers have achieved an easy synthesis of 2-amino-4*H*-1,3-benzothiazines *via* the reaction between *o*-aminocinnamate and isothiocyanates using $YbCl_3$ as catalyst (Scheme 1e).[3e] The similar transformation has also been achieved by Ding et al under the silver-catalyzed reactions of 2-alkynylbenzenamines with isothiocyanates (Scheme 1f).[6c] Saunthwal et al described the synthesis of these scaffolds by the reaction of 2-aminoaryl acrylates with isothiocyanates *via in-situ* thioamidation reaction and concomitant chemoselective intramolecular thia-michael addition (Scheme 1g).[6g] Han and co-workers have reported an efficient method towards 1,3-benzoxazines by the reaction between aldehydes and 2-aminobenzylamines or 2-aminobenzyl alcohols *via* an aerobic oxidative synthesis in the presence of Cu-catalyst (Scheme 1h).[6e] A cyclocarbonylation reaction of *o*-iodoanilines with acid chlorides was demonstrated by Larksarp and co-workers to afford the synthesis of 1,3-benzoxazines (Scheme 1i).[6a]

Various non-catalytic conditions were also reported for the synthesis of these molecules, those include the reaction between 2-alkynylbenzeneamines and isothiocyanates promoted by silicagel mediated tandem addition-cyclization (Scheme 1b).[8d] The reaction of 2-amino chalcones with isothiocyanates could also deliver these molecules (Scheme 1c),[8g] and recently, Jun and co-workers have described a microwave-assisted solid-phase synthesis of 1,3-benzothiazines using BOMBA Resin as support (Scheme 1a).[8h]



Scheme 1. Approaches towards the synthesis of 1,3-benzoxazine and 1,3-benzothiazines

In addition, the metal-free approaches for the synthesis of 1,3-benzothiazines have been also achieved by the reaction between *o*-ethynylphenyl isothiocyanates and primary or secondary amines.[8e] The reaction was catalyzed by molecular iodine to accomplish the transformation (Scheme 1d). Moreover, these scaffolds were constructed by dehydrosulfurization method by the reaction of 2-amino benzylalcohols with isothiocyanates using $PhI(OAc)_2$ and EDPBT as the reagents (Scheme 1k-l).[7b,7a]

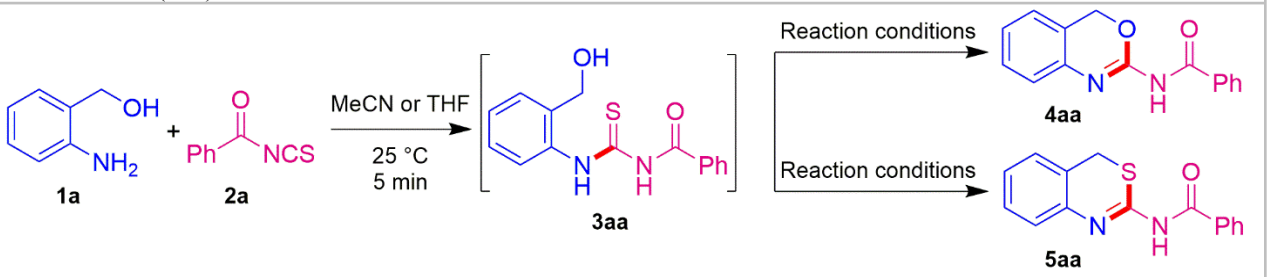
Recently, the dehydrosulfurization technique towards the preparation of 1,3-benzoxazines gained noteworthy attention and remained as one of the most attractive routes.[7a-b,f] Murata and co-workers have reported the preparation of the same scaffolds using Ph_3BiCl_2 as dehydrosulfurizing agent (Scheme 1j).[7f] Several known desulfurization reagents include transition metal salts such as $CuCl_2$,[9] NiO,[10] HgO,[7b,11] $FeCl_3$[12] and bronsted acids such as CF_3CO_2H[13] and TfOH,[14] and other reagents like TsCl/NaOH,[15] $LiOH/H_2O_2$,[16] polymer supported carbodiimides,[17] hypervalent iodine(III),[7a] 1,10-(ethane-1,2-diyl)dipyridinium bistribromide (EDPBT)[7b] and Ar_3BiCl_2.[7f] These reagents were extensively served for the synthesis of 1,3-benzoxazines and 1,3-benzothiazines.[1-7] Moreover, these reported conditions suffer from the disadvantages such as substrate scope, scalability and the long reaction times. Therefore, the development of an efficient and easy to access approach towards the preparation of 2-amino-1,3-benzoxazines and 2-amino-1,3-benzothiazines could be an useful tool in organic synthesis. On the other hand, T3P (2,4,6-tripropyl-1,3,5,2,4,6-trioxatriphosphorinane-2,4,6-trioxide solution) has been widely employed in both academia and industry as a mild coupling reagent for the synthesis wide variety of biologically important molecules.[18] It is well documented in literature that T3P is a choice of reagent in acid-amine coupling reactions, because of its ease of handing and robustness. In this regards, our attention was drawn to the concept of molecular iodine assisted dehydrosulfurization for the synthesis of 1,3-benzoxazines and T3P mediated cyclodehydration for the synthesis of 1,3-1,3-benzothiazines. To the best of our knowledge, these strategies are not much explored in literature till date. Here, we report two different reagent specific routes for the convenient preparation of 2-amino-1,3-benzoxazines and 2-amino-1,3-benzothiazines under mild reaction conditions and short reaction time.

RESULTS AND DISCUSSION

To identify suitable experimental conditions for the dehydrosulfurization of thiourea intermediate (**3aa**), several reagents were investigated. The intermediate (**3aa**) was obtained from the reaction between 2-amino benzylalcohol (**1a**) and benzoyl isothiocyanate (**2a**) at room temperature, which was reacted with molecular iodine in the presence of mild organic bases like DMAP (4-Dimethylaminopyridine), pyridine, Et_3N, DIPEA (*N*,*N*-Diisopropylethylamine), DBU (1,8-Diazabicyclo[5.4.0]undec-7-ene) and DABCO (1,8-Diazabicyclo[5.4.0]undec-7-ene) (Table 1, Entries 1-6). Interestingly, it was observed that the reactions using a combination of organic base and molecular iodine as oxidant afforded excellent yields of the product 1,3-benzoxazine (**4aa**) ranging from 81-98% (Entries 1-6). However, the bases such as DMAP, pyridine, Et_3N, DIPEA were more efficient to deliver 1,3-benzoxazine (**4aa**) in slightly better yields (Entries 1 - 4) than DBU and DABCO (Entries 5-6). In addition, the efficacies of the inorganic bases were also examined. A varity of inorganic bases such as KOH, LiOH, NH_3 and K_2CO_3 were employed for this transformation (Entries 7-10). Among the inorganic bases tested, NH_3 as base was found to be effective for this transformation with the formation of the 1,3-benzoxazine (**4aa**) in 43% yield (Entry 9). However, when the reactions were carried out only in the presence of iodine, bromine or triethylamine, the formation of 1,3-benzoxazine (**4aa**) was not observed (Entries 11-13). It was also noticed that NBS (*N*-Bromosuccinimide) and NIS (*N*-Iodosuccinimide) as oxidant were inefficient for the transformation to yield 1,3-benzoxazine

(**4aa**) (Entries 14-15). However, the attempted activating reagents were found to be inactive for the formation of 1,3-benzoxazine (**4aa**). Then, varieties of solvents were employed for the described transformation (Entries 16-21). Among the tested solvents, acetonitrile, 1,4-dioxane, toluene and dichloromethane were efficient to accomplish the transformation in good yields ranging from 49-68% (Entries 16-19) and polar-protic solvents such as *iso*-propanol and water were found to be ineligible to yield the product **4aa** (Entries 20-21). Additionally, better outcomes have not been observed by varying the amounts of base and oxidizing agent (Entries 22-23). During the survey of the reaction conditions, surprisingly it was observed that when the reactions were carried out in presence of T3P (2,4,6-Tripropyl-1,3,5,2,4,6-trioxatriphosphorinane-2,4,6-trioxide) as mild cyclodehydrating agent and Et_3N as base, the corresponding 1,3-benzoxazine (**4aa**) was not formed, rather it gave the 1,3-benzthiazine (**5aa**) as the exclusive product (Entries 24-27). These conditions lead us to develop the reagent specific protocols for the synthesis of both 1,3-benzoxazine (**4aa**) and 1,3-benzothiazine (**5aa**). Next, we introduced various activating agents like DCC (*N,N'*-Dicyclohexylcarbodiimide), BOP ((Benzotriazol-1-yloxy)tris(dimethylamino)phosphonium hexafluorophosphate), EDC·HCl (1-Ethyl-3-(3'-dimethylaminopropyl)carbodiimide·hydrochloride), PyBOP ((Benzotriazole-1-yl-oxy-tris-pyrrolidino-phosphonium hexafluorophosphate) and HATU ((1-[Bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxid-hexafluorophosphate) as reagents for accelerating this transformation (Entries 28-32). Nevertheless, no satisfactory results were obtained towards the betterment of the desired transformation, rather the intermediate **3aa** was recovered in all the cases. A Detailed optimization study (Table 1) showed that the highest yield of the product 1,3-benzoxazine (**4aa**) was obtained when the conversion of the intermediate **3aa** was performed in the presence of 1.1 equiv. molecular iodine and 2.0 equiv. of Et_3N in THF as solvent at room temparature (25 °C) for 5-20 minutes (Table 1, Entry 3). Consequently, the corresponding product 1,3-benzothiazine (**5aa**) was obtained in maximum yield when the reaction was performed using 1.1 equiv. of T3P as cyclodehydrating agent and 2.2 equiv. of Et_3N at room temperature (25 °C) for 5-20 minutes (Table 1, Entry 24). The developed conditions were considered as the standard reaction conditions to inspect the further scope of the developed methods towards the synthesis of 1,3-benzoxazines and 1,3-benzothiazines.

Table 1. Screening of the reaction conditions towards the selective synthesis of 1,3-benzoxazine (**4aa**) and 1,3-benzothiazine (**5aa**).[a]

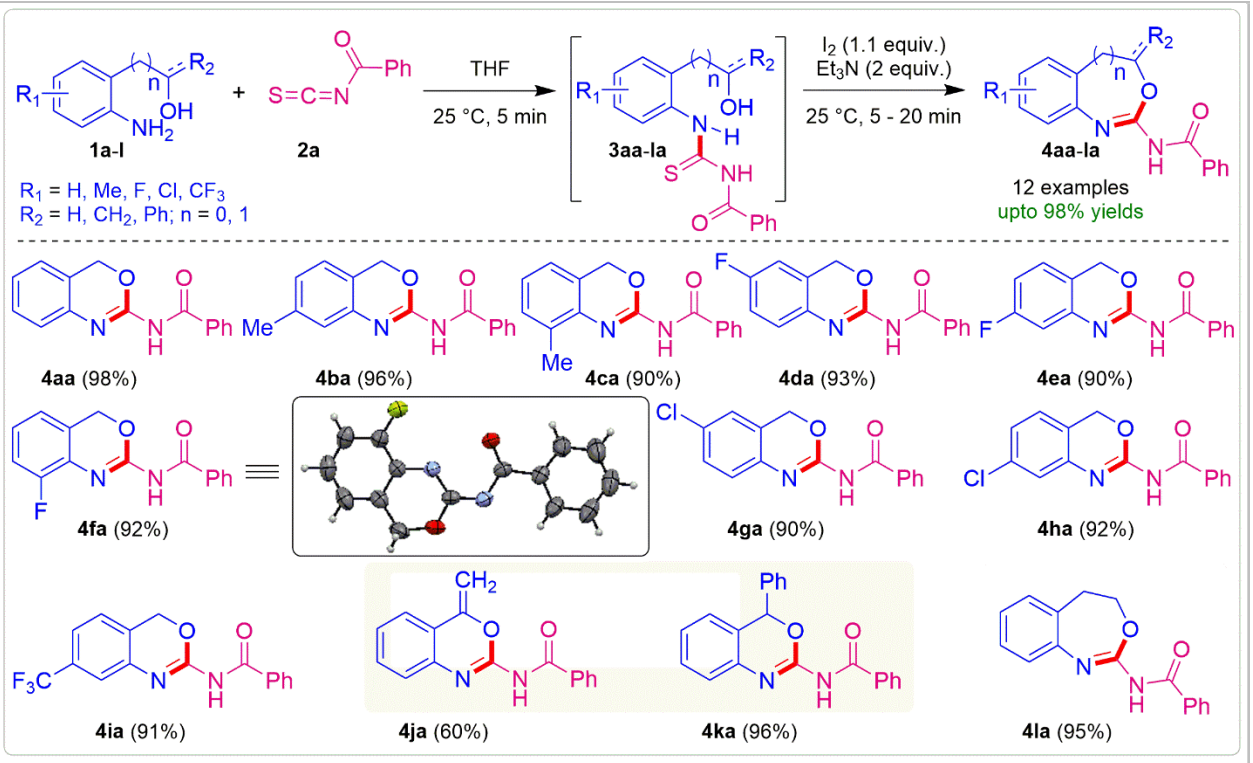


Entry	Reaction Conditions	**4aa**, % Yield[b] (% Conversion)[c]	**5aa**, % Yield[b] (% Conversion)[c]
1	I_2 (1.1 equiv.), DMAP (2 equiv.)	97 (100)	0
2	I_2 (1.1 equiv.), Pyridine (2 equiv.)	95 (100)	0
3	**I_2 (1.1 equiv.), Et_3N (2 equiv.)**	**98 (100)**	**0**
4	I_2 (1.1 equiv.), DIPEA (2 equiv.)	93 (100)	0

5	I_2 (1.1 equiv.), DBU (2 equiv.)	87 (100)	0
6	I_2 (1.1 equiv.), DABCO (2 equiv.)	81 (100)	0
7	I_2 (1.1 equiv.), KOH (2 equiv.)	< 10 (60)	0
8	I_2 (1.1 equiv.), LiOH (2 equiv.)	< 10 (50)	0
9	I_2 (1.1 equiv.), NH_3 (2 equiv.)	43 (100)	0
10	I_2 (1.1 equiv.), K_2CO_3 (2 equiv.)	21 (100)	0
11	I_2 (1.1 equiv.)	0 (100)	0
12	Br_2 (1.1 equiv.)	0 (100)	0
13	Et_3N (2 equiv.)	0 (100)	0
14	NIS (1.1 equiv.), Et_3N (2 equiv.)	32 (50)	0
15	NBS (1.1 equiv.), Et_3N (2 equiv.)	18 (70)	0
16	I_2 (1.1 equiv.), Et_3N (2 equiv.), MeCN	57 (100)	0
17	I_2 (1.1 equiv.), Et_3N (2 equiv.), 1,4-dioxane	55 (100)	0
18	I_2 (1.1 equiv.), Et_3N (2 equiv.), PhMe	49 (60)	0
19	I_2 (1.1 equiv.), Et_3N (2 equiv.), DCM	68 (100)	0
20	I_2 (1.1 equiv.), Et_3N (2 equiv.), *i*PrOH	0 (0)	0
21	I_2 (1.1 equiv.), Et_3N (2 equiv.), H_2O	0 (0)	0
22	I_2 (0.5 equiv.), Et_3N (2 equiv.)	38 (50)	0
23	I_2 (1.5 equiv.), Et_3N (2.5 equiv.)	97 (100)	0
24[d]	**T3P (1.1 equiv.), Et_3N (2.2 equiv.), MeCN**	**trace**	**95 (100)**
25	T3P (1.1 equiv.), Et_3N (2.2 equiv.), THF	< 5	78 (100)
26	T3P (1.1 equiv.), Et_3N (2.2 equiv.), DCM	< 5	81 (100)
27[e]	T3P (1.1 equiv.), Et_3N (2.2 equiv.)	< 5	69 (100)
28[f]	EDC□HCl (1.1 equiv.), Et_3N (2.2 equiv.), MeCN	< 5 (< 20)	0
29[f]	DCC (1.1 equiv.), Et_3N (2.2 equiv.), MeCN	< 5 (< 20)	0
30[f]	BOP (1.1 equiv.), Et_3N (2.2 equiv.), MeCN	< 5 (< 20)	0
31[f]	PyBOP (1.1 equiv.), Et_3N (2.2 equiv.), MeCN	< 5 (< 20)	0
32[f]	HATU (1.1 equiv.), Et_3N (2.2 equiv.), MeCN	< 5 (< 20)	0

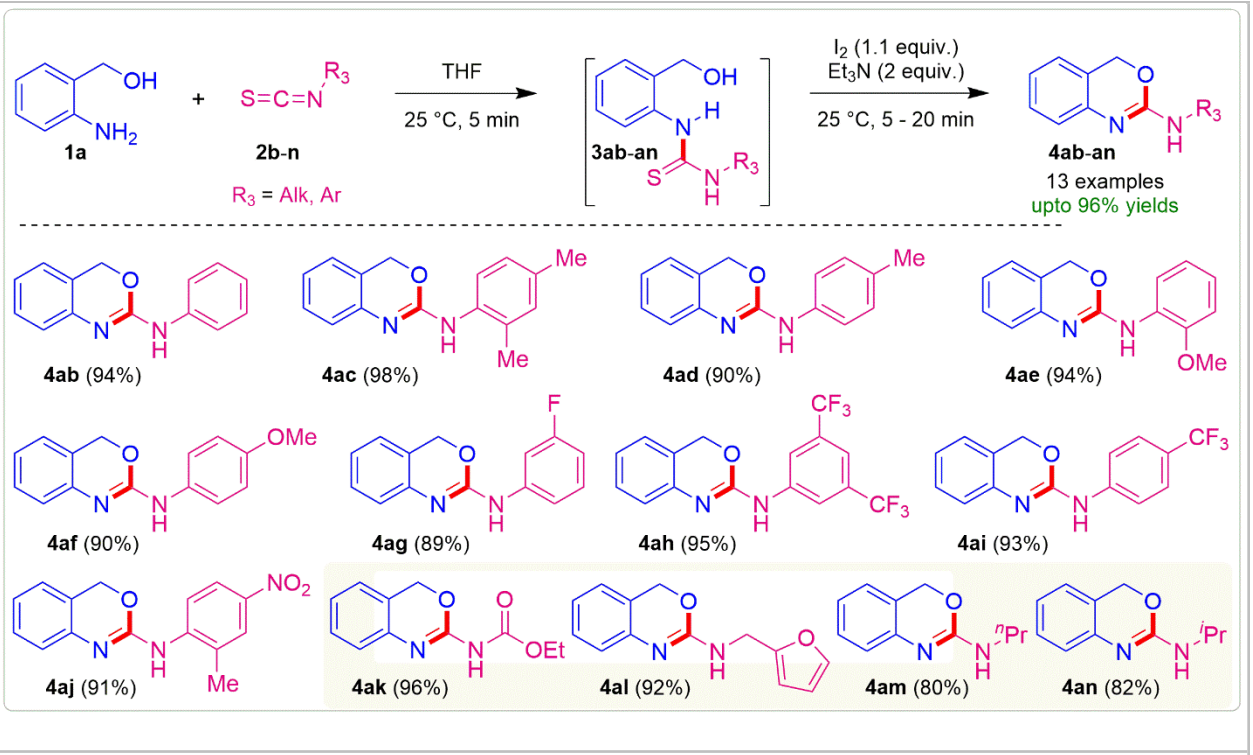
[a] Reactions were carried out using 1.0 mmol **1a**, 1.0 mmol **2a** in 2 mL THF (Entries 1-15, 22-23) and in 2 mL of MeCN (Entries 24-32) at 25 °C for 5-20 minutes. [b] Isolated yields. [c] Conversion was monitored by LC-MS. [d] T3P anhydride solution ≥50 wt. % in ethyl acetate was used. [e] Reaction was carried out without solvent. [f] Intermediate **3aa** was recovered .

Having these optimal results, initially we explored the scope of the reaction by employing various 2-amino-arylalkyl alcohols (**1a-l**) with benzoyl isothiocyanate (**2a**) to obtain the desired products 2-amino-1,3-benzoxazines (**4aa-la**). In general, 2-amino-arylalkyl alcohols with different substitution pattern including electron-withdrawing as well as electron-donating groups could be successfully reacted in this transformation. The novel transformations proceeded smoothly, and all the reactions were completed within 20 minutes giving the 2-amino-1,3-benzoxazines (**4aa-la**) in excellent yields (Scheme 2). To evaluate the efficiency and generality of the reaction, we drawn our attention in exploring other substituents on the benzylic position of the **1a**. These substituents were also well tolerated and delivered the products (**4ja-ka**) with moderate to excellent yields. Further, 2-(2-aminophenyl)ethan-1-ol (**1l**) could be efficiently employed in the reaction to provide the desired benzo[1,3]oxazepine (**4la**) in 95% yield (Scheme 2). The structure of the compound **4fa** was further confirmed by X-ray crystallographic data (Provided in SI).



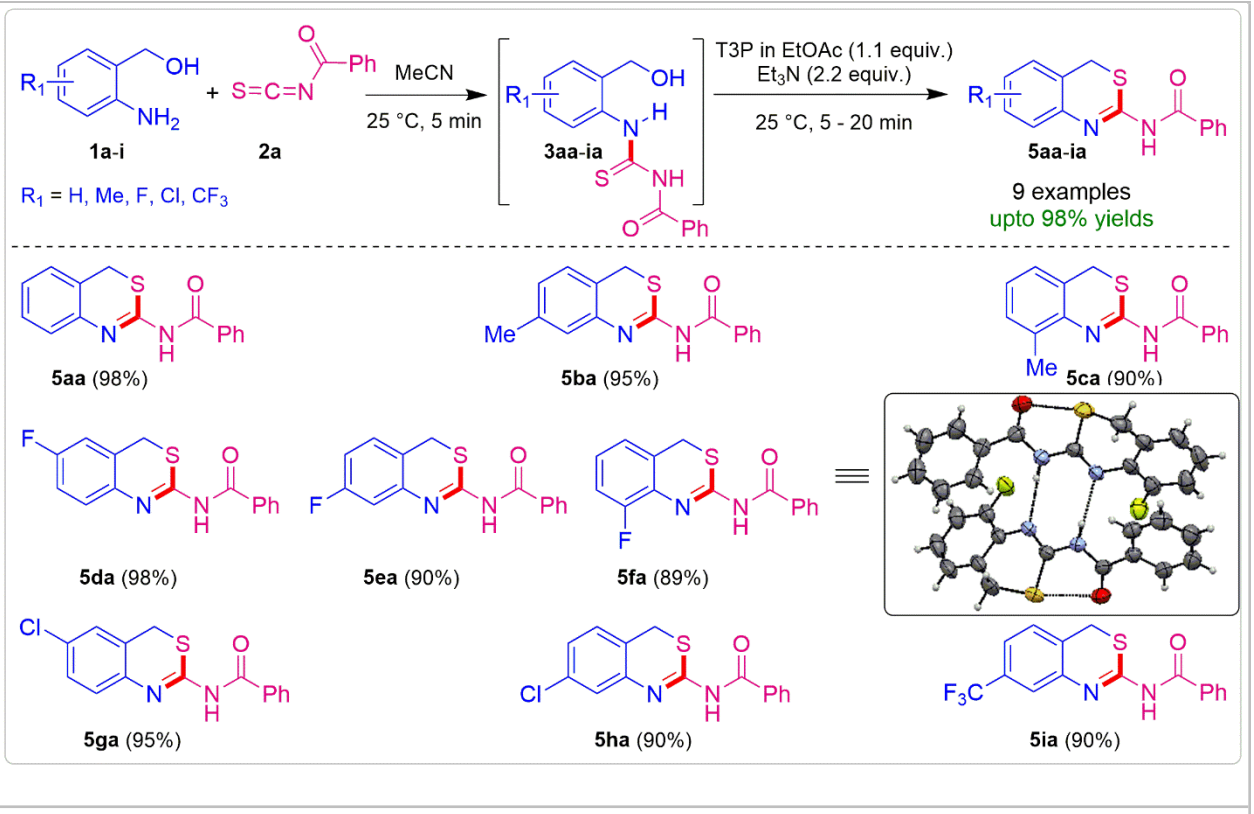
Scheme 2. Synthesis of 1,3-benzoxazine derivatives using various 2-amino-aralkyl alcohols and ORTEP diagram of **4fa**.

Later, the scope of the reaction was also extended by taking various isothiocyanates (**2b-n**) with 2-aminobenzylalcohol (**1a**) to obtain the desired 1,3-benzoxazine derivatives (**4ab-an**). The aryl and alkyl isothiocyanates were effectively surveyed for the transformation to afford the desired 1,3-benzoxazine derivatives (**4ab-an**) (Scheme 3). It has been realized that the electron-donating groups such as methyl, methoxy and the electron-withdrawing substituents such as F, CF_3, and NO_2 groups were well tolerated on the aromatic moieties of the isothiocyanates. The substrate scope revealed that the nature of functional groups have no considerable impact towards the outcome of the reactions. Hence, the yield of the desired products (**4ab-an**) found to be general (ranging from 89-96%) apart from the electronic nature of the substituents. Further, scope of the described approach has been verified with isothiocyanates containing alkyl (**2k**, **2m-n**) and alkyl moiety embedded with *hetero*-aromatic group (**2l**) to afford the corresponding products **4ak**, **4am-an** and **4al** respectively in good yields (Scheme 3).



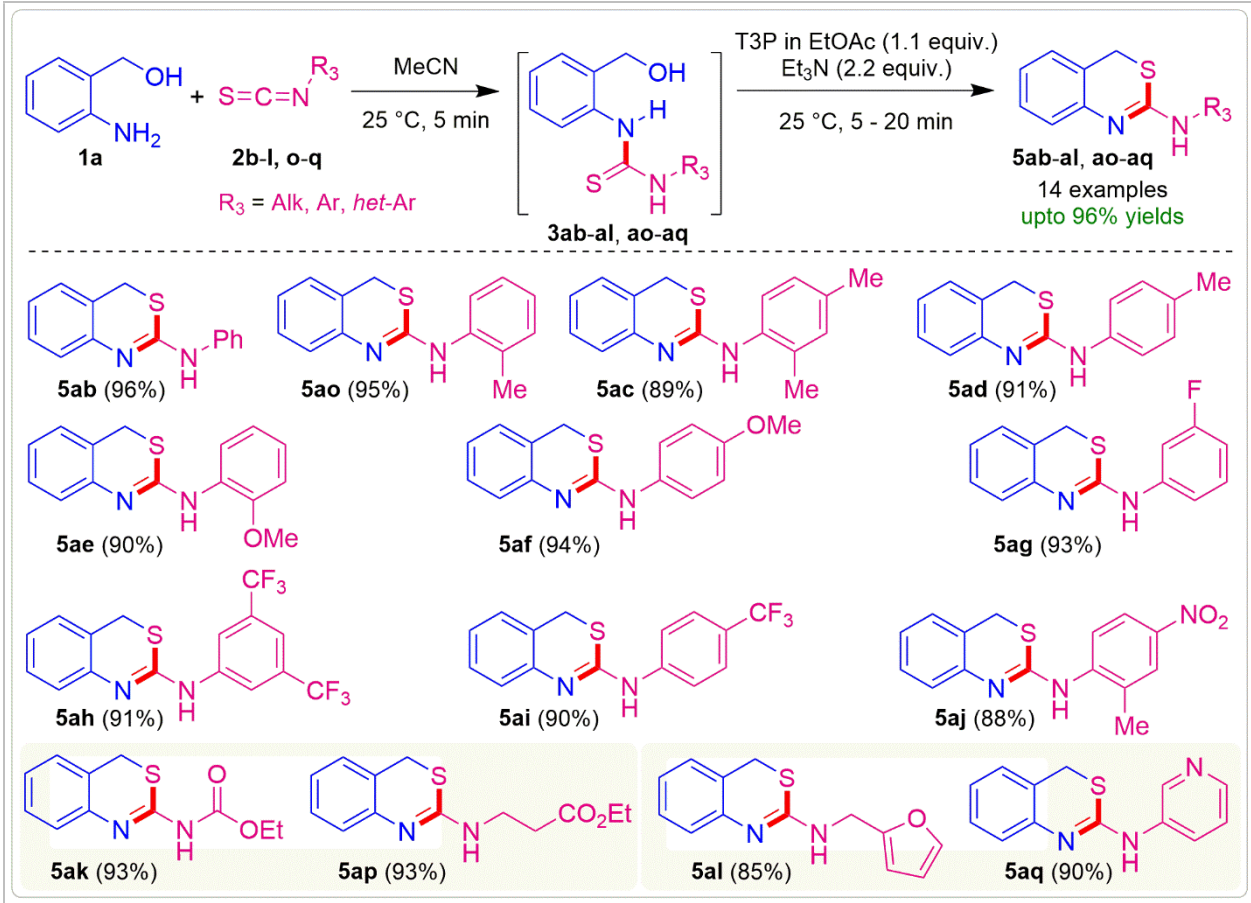
Scheme 3. Substrate scope for the synthesis of 1,3-benzoxazine derivatives using various isothiocyanates.

On the other hand, the T3P mediated reaction conditions were investigated for the synthesis of 1,3-benzothiazine derivatives. It was observed that the developed method was successfully employed on variety of 2-aminobenzyl alcohols (**1a-i**) and benzoyl isothiocyanate (**2a**) to obtain the desired 1,3-benzothiazine derivatives (**5aa-ia**) (Scheme 4). The reactions proceeded smoothly in the presence of both electron-donating group such as methyl and the electron-withdrawing substituents such as F, Cl, CF_3 and NO_2 on the aromatic moieties of the isothiocyanates to furnish the expected product 1,3-benzothiazines (**5aa-ia**) in yields ranging from 89-98%. The structure of the compound **5fa** was further affirmed by X-ray crystallographic data (Provided in SI).



Scheme 4. Substrate scope of 2-*N*-substituted-1,3-benzothiazine derivatives and ORTEP diagram of **5fa**.

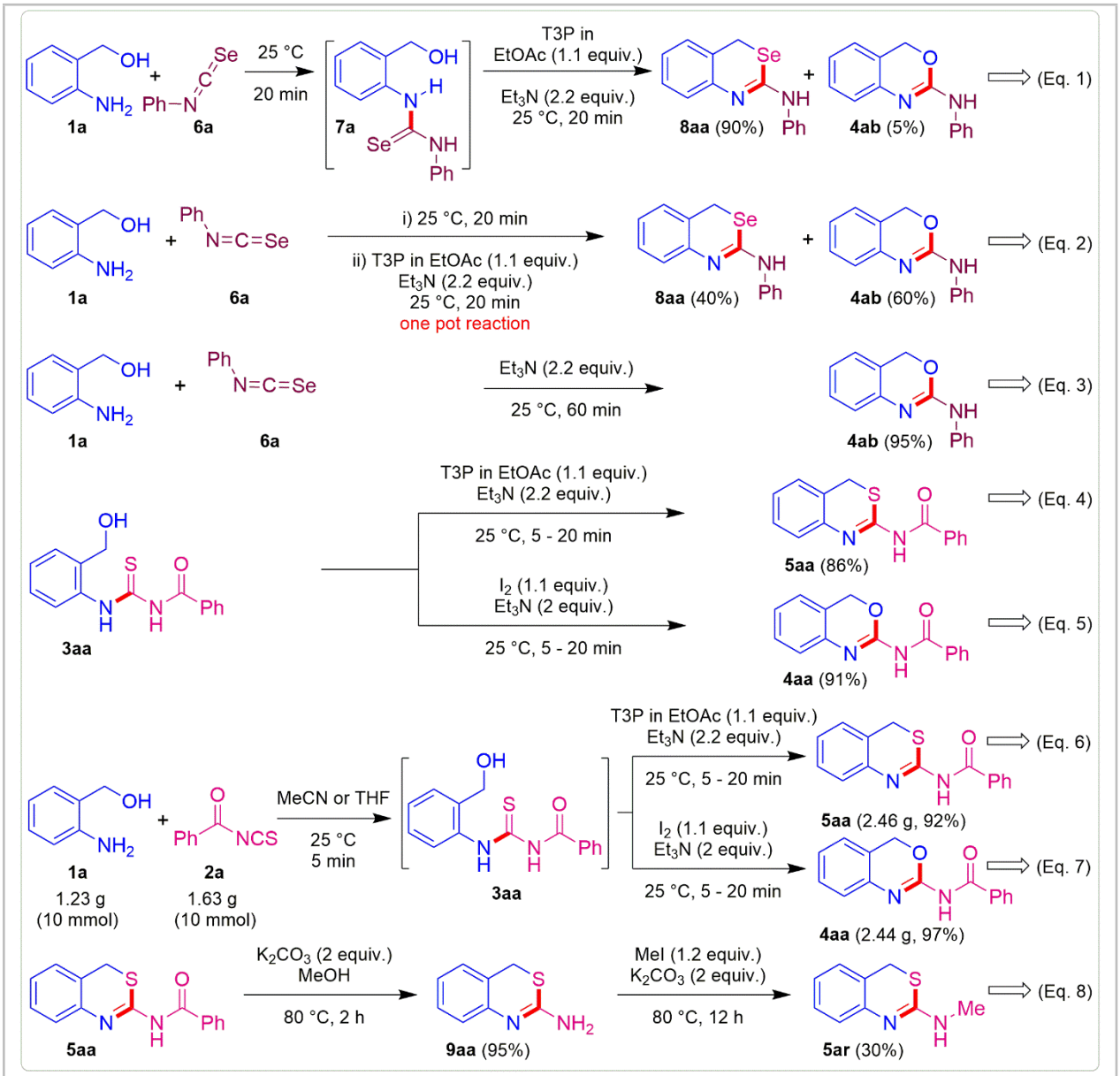
Further, the reactivity of a broad range of isothiocyanates (**2b-l**, **o-q**) was examined by reacting with 2-aminobenzyl alcohol (**1a**). It was evident that the isothiocyanates substrates with varieties of functional groups were permitted a spectrum of 1,3-benzothiazines (**5ab-al**, **ao-aq**) in excellent yields (85-96%) under optimized reaction conditions. Subsequently, the isothiocyanates with ester group and alkyl moiety embedded furan, and pyridine were also allowed to afford the corresponding products **5ak**, **5al** and **5aq** in high yields (Scheme 5) under the developed conditions.



Scheme 5. Substrate Scope of 2-*N* substituted-1,3-benzothiazine derivatives using isothiocyanates.

To identify the further scope of the developed transformation, the reactivity of 2-aminobenzylalcohol (**1a**) with phenyl isoselenocyanate (**6a**) was investigated under the optimized conditions (Scheme 6). It was found that the developed conditions can effectively induce the reaction of **1a** with **6a** which resulted the desired 1,3-selenazine derivative (**8aa**) in 90% yield, along with the formation of 1,3-benzoxazine (**4ab**) in 5% yield as minor product (Scheme 6, Eq. 1). It was also noteworthy that the formation of corresponding 1,3-selenazine (**8aa**) was reduced remarkably, in case of one-pot manner (Scheme 6, Eq. 2). However, the formation of 1,3-benzoxazine (**4ab**) was increased up to 95%, when the reaction was performed in absence of T3P as cyclodehydrating agent (Scheme 6, Eq. 3). Next, to know the insight into the reaction mechanism, we have carried out the reactions of the isolated intermediate **3aa** as substrate under the standard reaction conditions. It was found that under the described conditions both the desired products 1,3-benzoxazines (**4aa**) and 1,3-benzothiazines (**5aa**) were obtained in 91% and 86% isolated yields respectively (Scheme 6, Eq. 5 and 4). To evaluate the practical and synthetic utility of the present protocol, gram scale synthesis of 1,3-benzoxazine (**4aa**) (Scheme 6, Eq. 7) and 1,3-benzothiazine (**5aa**) (Scheme 6, Eq. 6) were carried out. To our delight, the reaction conditions were efficient to bring about the conversion affording 1,3-benzoxazine in 97% and 1,3-benzothiazine in 92% yields. Also, we have performed the derivatization of the 1,3-benzothiazine (**5aa**) by the removal of *N*-benzoyl group *via* base mediated

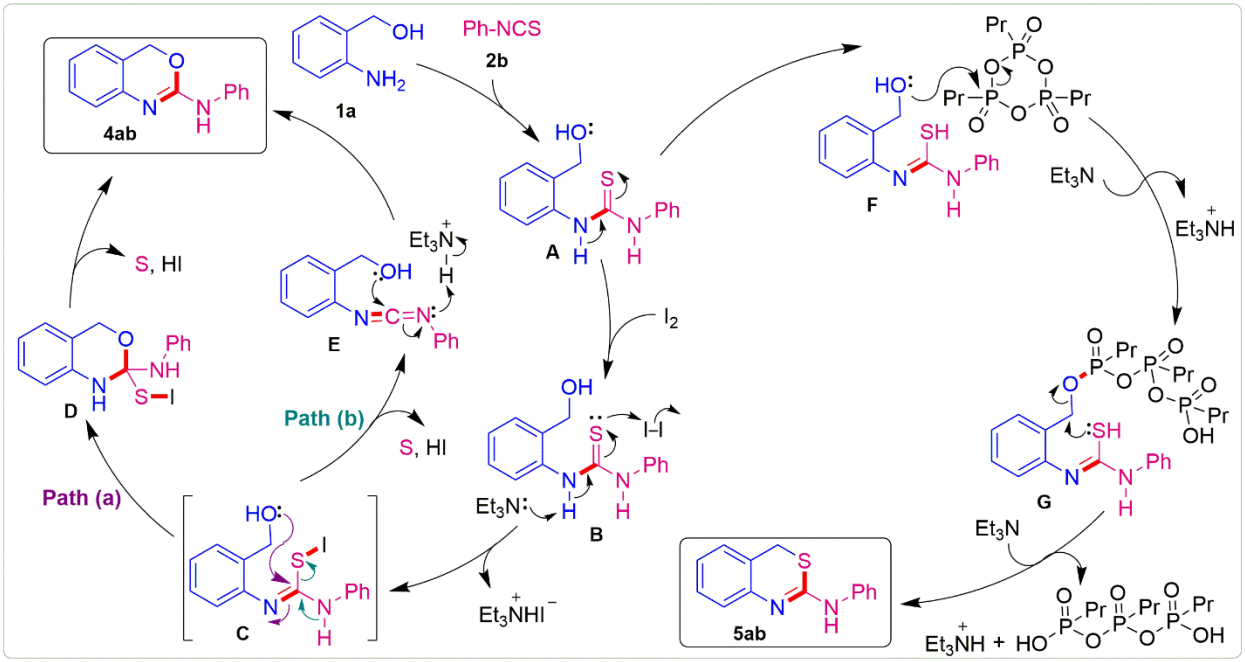
hydrolysis followed by *N*-methylation of the product **9aa** using methyl iodide to afford the *N*-methylated product **5ar** in 30% yield (Scheme 6, Eq. 8).



Scheme 6. Synthesis of 1,3-benzoselenazines, mechanistic insights, practical and synthetic utility of the developed reaction conditions.

Having surveyed the experimental results and literature evidences,[7a-b,7f,18-20] the plausible mechanism has been presented for the synthesis of 1,3-benzoxazines and 1,3-benzothiazines (Scheme 7). The proposed mechanism for the formation of carbodiimide intermediate **E** *via* dehydrosulfurization of intermediate **C** is well established in literature.[19-20] The mechanism is supported by the isolation of precipitated elemental sulfur.[19c] In the described method the role of 2.0 equiv. of triethylamine as base seems to be essential. We considered that the mechanism would be similar to the synthesis of heterocyclic compounds using dehydrosulfurization reagents such as triphenylbismuth dichloride and hypervalent iodine compounds.

Hence, we propose that the initial step of the reaction would follow the generation of intermediate **B** from the reaction of 2-aminobenzyl alcohol (**1a**) with phenyl isothiocyanate (**2a**) followed by nucleophilic attack of the sulfur atom of **B** on to the molecular iodine leading to the formation of intermediate **C**. The Intermediate **C** then delivers the desired products **4ab** *via* two different reaction pathways. In path (a), the intermediate **C** undergoes intramolecular cyclization to give 1,3-benzoxazine (**4ab**). Another potential route could be the formation of carbodiimide intermediate **E**, which delivers the corresponding 1,3-benzoxozine (**4ab**) (path b). On the other hand, the plausible pathway for the formation of 1,3-benzothiazine can be suggested (Scheme 7) based on the literature evidences.[18] The reaction involves the activation of thiourea moiety **A** by T3P, leading to the formation of intermediate **G**. The next step in the suggested mechanism involves the intramolecular nucleophilic attack of thiol group on to the T3P bound carbon to furnish the corresponding 1,3-benzothiazines (**5ab**). The reason for this controlled selectivity of reagents can be attributed as follows, it is evident from literature that the tendency of T3P towards the water molecule is greater than the tendency of T3P towards sulfur atom. It is well known that T3P is an excellent coupling reagent and water scavenger. Moreover, Iodine is recognized as desulfurizing agent, hence it tends to take up sulfur rather than an oxygen atom to bring about the required chemical transformations.



Scheme 7. Plausible reaction pathways towards the synthesis of 1,3-benzoxazine and 1,3-benzothiazine.

CONCLUSIONS

In summary, two different reagent-selective methods for the synthesis of 1,3-benzoxazines and 1,3-benzothiazines have been described. The 2-*N*-substituted-1,3-benzoxazines were synthesized in moderate to excellent yields *via* a simple one-pot two-step reaction involving the reaction between 2-aminobenzyl alcohols and isothiocyanates in the presence of molecular iodine and base under mild reaction conditions. Whereas the 2-*N* substituted-1,3-benzothiazines were obtained in the presence of T3P reagent and base as reagents. In case of 1,3-benzoxazines, the molecular iodine promoted the successful dehydrosulfurization

of thiourea which leading to the formation of elemental sulphur. This protocol represents as the first example for the synthesis of 2-amino 4*H*-1,3-Benzoxazines *via* iodine promoted dehydrosulfurization method.

EXPERIMENTAL SECTION

General Methods

All starting materials were purchased from commercial suppliers (Sigma-Aldrich, Alfa-Aesar, SD fine chemicals, Merck, HI Media) and were used without further purification unless otherwise indicated. All reactions were performed in a 10 mL round bottom flask with magnetic stirring. Solvents used in extraction and purification were distilled prior to use. Thin-layer chromatography (TLC) was performed on TLC plates purchase from Merck. Compounds were visualized with UV light ($\lambda = 254$ nm) and/or by immersion in $KMnO_4$ staining solution followed by heating. Products were purified by CombiFlash MPLC. ^1H (^{13}C) NMR spectra were recorded at 400 (100) MHz on a Brucker spectrometer using $CDCl_3$ and DMSO-d_6 as a solvent. The ^1H and $^{13}C\{^1H\}$ chemical shifts were referenced to residual solvent signals at $\delta_{H/C}$ 7.26 /77.28 ($CDCl_3$) and $\delta_{H/C}$ 2.51 /39.50 (DMSO-d_6) relative to TMS as internal standards. Coupling constants J [Hz] were directly taken from the spectra and are not averaged. Splitting patterns are designated as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), overlapped and br (broad).

General experimental procedure for the synthesis of 2-amino-1,3-benzoxazines (4aa-la, 4ab-an)

A 10 mL round bottom flask was charged with 2-amino-aralkyl alcohols **1a-l** (1.0 mmol), aryl or alkyl isothiocyanates **2a-n** (1.0 mmol) in THF (2 mL) and the reaction mixture was stirred at room temperature (25 °C) for 5 mins. The reaction progress was monitored by TLC (SiO_2, Hexane/EtOAc = 8:2) and LC-MS. The TLC and LCMS analysis showed the absence of both the starting materials and the formation of thiourea intermeiate. The reaction was then cooled to 0 °C, followed by the simultaneous addition of Et_3N (2 mmol), I_2 (1.1 mmol) and the reaction mixture was stirred at room temperature (25 °C) for 5-20 mins. After completion of the reaction (progress was monitored by TLC; SiO_2, Hexane/EtOAc = 8:2 and LC-MS), the recation mixture was extracted with ethyl acetate (3 × 15 mL), water (20 mL). The combined organic layer was washed with sodium thiosulphate solution (3 × 10 mL) and dried over anhydrous Na_2SO_4. Solvent was removed under reduced pressure and the remaining residue was purified over CombiFlash MPLC using DCM/EtOAc = 92:8 as an eluent to obtain the desired 2-amino-1,3-benzoxazines (**4aa-la**, **4ab-an**) in high yields.

General experimental procedure for the synthesis of 2-amino-1,3-benzothiazines (5aa-ia, **5ab-al**, **5ao-aq)**

A 10 mL round bottom flask was charged with 2-amino-aralkyl alcohols **1a-i** (1.0 mmol), aryl or alkyl isothiocyanates **2a-l**, **2o-q** (1.0 mmol) in MeCN (2 mL) and the reaction mixture was stirred at room temperature (25 °C) for 5 mins. The reaction progress was monitored by TLC (SiO_2, Hexane/EtOAc = 8:2) and LC-MS. The TLC and LCMS analysis showed the absence of both the starting materials and the formation of thiourea intermeiate. The reaction was then cooled to 0 °C, followed by the simultaneous addition of Et_3N (2.2 mmol), T3P anhydride solution ≥50 wt. % in ethyl acetate (1.1 mmol) and the reaction mixture was stirred at room temperature (25 °C) for 5-20 mins. After completion of the reaction (progress was monitored by TLC; SiO_2, Hexane/EtOAc = 8:2 and LC-MS), the recation mixture was extracted with ethyl acetate (3 × 15 mL), water (20 mL). The combined organic layer was washed with sodium thiosulphate solution (3 × 10 mL) and dried over anhydrous Na_2SO_4. Solvent was removed under reduced pressure and the remaining residue was purified over CombiFlash MPLC using Hexane/EtOAc = 70:30 as an eluent to obtain the desired 2-amino-1,3-benzothiazines (**5aa-ia**, **5ab-al**, **5ao-aq**) in high yields.

Experimental procedures and analytical data of synthesized *N*-((2-(hydroxymethyl)phenyl)carbamothioyl) benzamide (3aa) and 2-amino-1,3-benzoxazines (4aa-la, 4ab-an)

Synthesis of *N*-((2-(hydroxymethyl)phenyl)carbamothioyl)benzamide (3aa)

The reactions between 2-aminobenzyl alcohol (**1a**) (1.0 mmol, 123 mg), benzoyl isothiocyanate (**2a**) (1.0 mmol, 163 mg) in 2 mL THF or 2 mL of MeCN were performed to obtain the desired *N*-((2-(hydroxymethyl)phenyl) carbamothioyl)benzamide (**3aa**) in 99% (283 mg) yield as off-white solid.

***N*-((2-(hydroxymethyl)phenyl)carbamothioyl)benzamide (3aa)**[21] (Table 1, Scheme 6): **Off-white solid**; $\mathbf{R_f}$ = 0.30 (SiO_2, Hexane/EtOAc = 7:3); **Purification system**: Not required; **Yield**: 283 mg (99%); **^{1}H NMR** (400 MHz, DMSO-d_6) δ = 12.32 (br, 1H), 11.54 (br, 1H), 7.98 (d, *J* = 7.6 Hz, 2H), 7.64 (t, *J* = 7.2 Hz, 2H), 7.54-7.45 (m, 3H), 7.29 (m, 2H), 5.42 (s, 1H), 4.49 (s, 2H) ppm; **^{13}C{^{1}H} NMR** (100 MHz, DMSO-d_6) δ = 180.6, 168.5, 137.6, 136.5, 133.55, 132.6, 129.15, 128.9, 128.3, 127.5, 127.33, 127.3, 60.5 ppm; **HRMS** (**ESI-QTOF,** $[M + H]^+$): calculated for $C_{15}H_{15}N_2O_2S$: 287.0854; found: 287.0850.

Synthesis of *N*-(4*H*-benzo[*d*][1,3]oxazin-2-yl)benzamide (4aa)

According to the general procedure, reactions between 2-aminobenzyl alcohol (**1a**) (1.0 mmol, 123 mg), benzoyl isothiocyanate (**2a**) (1.0 mmol, 163 mg), Et_3N (2.0 mmol, 202 mg), I_2 (1.1 mmol, 140 mg) in 2 mL THF were performed to obtain the desired *N*-(4*H*-benzo[*d*][1,3]oxazin-2-yl)benzamide (**4aa**) in 98% (247 mg) yield as white solid.

***N*-(4*H*-benzo[*d*][1,3]oxazin-2-yl)benzamide (4aa)** (Table 1, Scheme 2): **White solid**; $\mathbf{R_f}$ = 0.40 (SiO_2, Hexane/EtOAc = 8:2); **Purification system**: CombiFlash MPLC (DCM/EtOAc = 97:3); **Yield**: 247 mg (98%); **m.p** = 126 - 127 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 12.78 (br, 1H), 8.26 (d, *J* = 7.6 Hz, 2H), 7.52 (t, *J* = 7.2 Hz, 1H), 7.43 (t, *J* = 7.6 Hz, 2H), 7.34 (t, *J* = 8.0 Hz, 1H), 7.19 - 7.12 (m, 2H), 6.99 (d, *J* = 8.0 Hz, 1H), 5.42 (s, 2H) ppm; **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ = 179.8, 161.2, 136.6, 132.3, 129.6, 129.4, 128.1, 125.1, 124.5, 119.0, 115.7, 67.6 ppm; **MS** (APCI): $[M + 1]^+$ = 253.1 (95.83%); **HRMS** (**ESI-QTOF,** $[M + H]^+$): calculated for $C_{15}H_{13}N_2O_2$: 253.0977; found: 253.0974.

Synthesis of *N*-(7-methyl-4*H*-benzo[*d*][1,3]oxazin-2-yl)benzamide (4ba)

According to the general procedure, reactions between 2-amino-4-methylbenzyl alcohol (**1b**) (1.0 mmol, 137 mg), benzoyl isothiocyanate (**2a**) (1.0 mmol, 163 mg), Et_3N (2.0 mmol, 202 mg), I_2 (1.1 mmol, 140 mg) in 2 mL THF were performed to obtain the desired *N*-(7-methyl-4*H*-benzo[*d*][1,3]oxazin-2-yl)benzamide (**4ba**) in 96% (255 mg) yield as off-white solid.

***N*-(7-methyl-4*H*-benzo[*d*][1,3]oxazin-2-yl)benzamide (4ba)** (Scheme 2): **Off-white solid**; $\mathbf{R_f}$ = 0.40 (SiO_2, Hexane/EtOAc = 8:2); **Purification system**: CombiFlash MPLC (DCM/EtOAc = 95:5); **Yield**: 255 mg (96%); **m.p** = 136 - 137 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 12.78 (br, 1H), 8.25 (d, *J* = 7.2 Hz, 2H), 7.50 (d, *J* = 5.6 Hz, 1H), 7.43 (t, *J* = 7.2 Hz, 2H), 6.99 (q, *J* = 7.2 Hz, 2H), 6.82 (s, 1H), 5.38 (s, 2H), 2.36 (s, 3H) ppm; **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ = 179.7, 161.0, 139.9, 136.7, 132.2, 129.4, 128.0, 125.7, 124.3, 116.2, 116.0, 67.6, 21.2 ppm; **MS** (APCI): $[M + 1]^+$ = 267.1 (100%); **HRMS** (**ESI-QTOF,** $[M + H]^+$): calculated for $C_{16}H_{15}N_2O_2$: 267.1133; found: 267.1129.

Synthesis of *N*-(8-methyl-4*H*-benzo[*d*][1,3]oxazin-2-yl)benzamide (4ca)

According to the general procedure, reactions between 2-amino-3-methylbenzyl alcohol (**1c**) (1.0 mmol, 137 mg), benzoyl isothiocyanate (**2a**) (1.0 mmol, 163 mg), Et_3N (2.0 mmol, 202 mg), I_2 (1.1 mmol, 140 mg) in 2 mL THF were performed to obtain the desired *N*-(8-methyl-4*H*-benzo[*d*][1,3]oxazin-2-yl)benzamide (**4ca**) in 90% (240 mg) yield as off-white solid.

***N*-(8-methyl-4*H*-benzo[*d*][1,3]oxazin-2-yl)benzamide (4ca)** (Scheme 2): **Off-white solid**; $\mathbf{R_f}$ = 0.40 (SiO_2, Hexane/EtOAc = 8:2); **Purification system**: CombiFlash MPLC (DCM/EtOAc = 95:5); **Yield**: 240 mg (90%); **m.p** = 124 - 125 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 13.0 (br, 1H), 8.27 (d, *J* = 7.6 Hz, 2H), 7.51 (t, *J* = 7.6 Hz, 1H), 7.43 (t, *J* = 7.2 Hz, 2H), 7.19 (d, *J* = 7.6 Hz, 1H), 7.07 (t, *J* = 7.6 Hz, 1H), 6.98 (d, *J* = 7.2 Hz, 1H), 5.39 (s, 2H), 2.41 (s, 3H) ppm; **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ = 180.1, 161.2, 136.7, 132.2, 131.5, 129.6, 129.4, 128.2, 124.6, 123.7, 122.0, 118.6, 67.7, 16.21 ppm; **MS** (APCI): $[M + 1]^+$ = 267.1 (97.6%); **HRMS** (**ESI-QTOF,** $[M + H]^+$): calculated for $C_{16}H_{15}N_2O_2$: 267.1133; found: 267.1130.

Synthesis of *N*-(6-fluoro-4*H*-benzo[*d*][1,3]oxazin-2-yl)benzamide (4da)

According to the general procedure, reactions between 2-amino-5-fluorobenzyl alcohol (**1d**) (1.0 mmol, 141 mg), benzoyl isothiocyanate (**2a)** (1.0 mmol, 163 mg), Et_3N (2.0 mmol, 202 mg), I_2 (1.1 mmol, 140 mg) in 2 mL THF were

performed to obtain the desired *N*-(6-fluoro-4*H*-benzo[*d*][1,3]oxazin-2-yl)benzamide (**4da**) in 93% (251 mg) yield as off-white solid.

***N*-(6-fluoro-4*H*-benzo[*d*][1,3]oxazin-2-yl)benzamide (4da)** (Scheme 2): **Off-white solid**; $\mathbf{R_f}$ = 0.50 (SiO_2, Hexane/EtOAc = 8:2); **Purification system**: CombiFlash MPLC (DCM/EtOAc = 95:5); **Yield**: 251 mg (93%); **m.p** = 108 - 109 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 12.80 (br, 1H), 8.24 (d, *J* = 6.8 Hz, 2H), 7.54 - 7.50 (m, 1H), 7.45 - 7.41 (m, 2H), 7.05 (dt, *J* = 7.2, 2.8 Hz, 1H), 6.99 - 6.94 (m, 1H), 6.88 (dd, *J* = 7.6, 2.8 Hz, 1H), 5.38 (s, 2H) ppm; **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ = 179.9, 161.0, 160.8, 159.7 (d, *J* = 244.7 Hz), 136.4, 132.4, 131.9, 129.4, 128.5, 128.1, 127.3, 120.7, 120.6, 117.2, 117.1, 116.4, 116.2, 112.0, 111.7, 67.1 ppm; **MS** (APCI): $[M + 1]^+$ = 271.1 (96.7%); **HRMS** (**ESI-QTOF,** $[M + H]^+$): calculated for $C_{15}H_{12}FN_2O_2$: 271.0882; found: 271.0880.

Synthesis of *N*-(7-fluoro-4*H*-benzo[*d*][1,3]oxazin-2-yl)benzamide (4ea)

According to the general procedure, reactions between 2-amino-4-fluorobenzyl alcohol (**1e**) (1.0 mmol, 141 mg), benzoyl isothiocyanate (**2a**) (1.0 mmol, 163 mg), Et_3N (2.0 mmol, 202 mg), I_2 (1.1 mmol, 140 mg) in 2 mL THF were performed to obtain the desired *N*-(7-fluoro-4*H*-benzo[*d*][1,3]oxazin-2-yl)benzamide (**4ea**) in 90% (243 mg) yield as off-white solid.

***N*-(7-fluoro-4*H*-benzo[*d*][1,3]oxazin-2-yl)benzamide (4ea)** (Scheme 2): **Off-white solid**; $\mathbf{R_f}$ = 0.40 (SiO_2, Hexane/EtOAc = 8:2); **Purification system**: CombiFlash MPLC (DCM/EtOAc = 95:5); **Yield**: 243 mg (90%); **m.p** = 132 - 133 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 12.89 (br, 1H), 8.25 (d, *J* = 8.0 Hz, 2H), 7.55 - 7.51(m, 1H), 7.46 – 7.42 (m, 2H), 7.11 (t, *J* = 7.6 Hz, 1H), 6.89 - 6.85 (m, 1H), 6.74 (d, *J* = 7.6 Hz, 1H), 5.37 (s, 2H) ppm; **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ = 179.9, 163.1 (d, *J* = 246.3 Hz), 160.4, 136.3, 134.0, 133.9, 132.5, 131.9, 129.5, 128.5, 128.1, 127.3, 126.1, 126.0, 114.8, 114.7, 111.8, 111.6, 103.7, 103.4, 67.2 ppm; **MS** (APCI): $[M + 1]^+$ = 271.1 (88.6%); **HRMS** (**ESI-QTOF,** $[M + H]^+$): calculated for $C_{15}H_{12}FN_2O_2$: 271.0882; found: 271.0879.

Synthesis of *N*-(8-fluoro-4*H*-benzo[*d*][1,3]oxazin-2-yl)benzamide (4fa)

According to the general procedure, reactions between 2-amino-3-fluorobenzyl alcohol (**1f**) (1.0 mmol, 141 mg), benzoyl isothiocyanate (**2a**) (1.0 mmol, 163 mg), Et_3N (2.0 mmol, 202 mg), I_2 (1.1 mmol, 140 mg) in 2 mL THF were performed to obtain the desired *N*-(8-fluoro-4*H*-benzo[*d*][1,3]oxazin-2-yl)benzamide (**4fa**) in 92% (249 mg) yield as off-white solid.

***N*-(8-fluoro-4*H*-benzo[*d*][1,3]oxazin-2-yl)benzamide (4fa)** (Scheme 2): **Off-white solid**; $\mathbf{R_f}$ = 0.40 (SiO_2, Hexane/EtOAc = 8:2); **Purification system**: CombiFlash MPLC (DCM/EtOAc = 95:5); **Yield**: 249 mg (92%); **m.p** = 122 - 124 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 12.95 (br, 1H), 8.26 (d, *J* = 7.2 Hz, 2H), 7.51 (d, *J* = 7.2 Hz, 1H), 7.44 (t, *J* = 7.2 Hz, 2H), 7.13 (d, *J* = 6.4 Hz, 2H), 6.94 (s, 1H), 5.43 (s, 2H) ppm; **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ = 179.7, 160.0 (d, *J* = 248.8 Hz), 136.4, 132.4, 129.5, 128.5, 128.3, 128.1, 127.6, 127.3, 125.29, 125.23, 121.0, 119.84, 119.81, 116.0, 115.8, 115.5, 67.2 ppm; **MS** (APCI): $[M + 1]^+$ = 271.3 (97.84%); **HRMS** (**ESI-QTOF,** $[M + H]^+$): calculated for $C_{15}H_{12}FN_2O_2$: 271.0882; found: 271.0881.

Synthesis of *N*-(6-chloro-4*H*-benzo[*d*][1,3]oxazin-2-yl)benzamide (4ga)

According to the general procedure, reactions between 2-amino-5-chlorobenzyl alcohol (**1g**) (1.0 mmol, 157.6 mg), benzoyl isothiocyanate (**2a**) (1.0 mmol, 163 mg), Et_3N (2.0 mmol, 202 mg), I_2 (1.1 mmol, 140 mg) in 2 mL THF were performed to obtain the desired *N*-(6-chloro-4*H*-benzo[*d*][1,3]oxazin-2-yl)benzamide (**4ga**) in 90% (258 mg) yield as off-white solid.

***N*-(6-chloro-4*H*-benzo[*d*][1,3]oxazin-2-yl)benzamide (4ga)** (Scheme 2): **Off-white solid**; $\mathbf{R_f}$ = 0.30 (SiO_2, Hexane/EtOAc = 8:2); **Purification system**: CombiFlash MPLC (DCM/EtOAc = 95:5); **Yield**: 258 mg (90%); **m.p** = 166 - 167 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 12.79 (br, 1H), 8.24 (d, *J* = 6.8 Hz, 2H), 7.54 (d, *J* = 5.6 Hz, 1H), 7.43 (t, *J* = 7.6 Hz, 2H), 7.12 (d, *J* = 8.0 Hz, 1H), 7.06 (d, *J* = 8.0 Hz, 1H), 6.87 (s, 1H), 5.37 (s, 2H) ppm; **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ = 179.6, 160.3, 136.3, 132.4, 130.2, 129.6, 129.4, 128.5, 124.7, 120.6, 117.0, 115.2, 67.0 ppm; **HRMS** (**ESI-QTOF,** $[M + H]^+$): calculated for $C_{15}H_{12}ClN_2O_2$: 287.0587; found: 287.0580.

Synthesis of *N*-(7-chloro-4*H*-benzo[*d*][1,3]oxazin-2-yl)benzamide (4ha)

According to the general procedure, reactions between 2-amino-4-chlorobenzyl alcohol (**1h)** (1.0 mmol, 157.6 mg), benzoyl isothiocyanate (**2a**) (1.0 mmol, 163 mg), Et_3N (2.0 mmol, 202 mg), I_2 (1.1 mmol, 140 mg) in 2 mL THF were performed to obtain the desired *N*-(7-chloro-4*H*-benzo[*d*][1,3]oxazin-2-yl)benzamide (**4ha**) in 92% (264 mg) yield as off-white solid.

***N*-(7-chloro-4*H*-benzo[*d*][1,3]oxazin-2-yl)benzamide (4ha)** (Scheme 2): **Off-white solid**; $\mathbf{R_f}$ = 0.50 (SiO_2, Hexane/EtOAc = 8:2); **Purification system**: CombiFlash MPLC (DCM/EtOAc = 95:5); **Yield**: 264 mg (92%); **m.p** = 146 - 147 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 12.79 (br, 1H), 8.24 (d, *J* = 6.8 Hz, 2H), 7.54 (d, *J* = 5.6 Hz, 1H), 7.43 (t, *J* = 7.6 Hz, 2H), 7.12 (d, *J* = 8.0 Hz, 1H), 7.06 (d, *J* = 8.0 Hz, 1H), 6.87 (s, 1H), 5.37 (s, 2H) ppm; **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ = 179.8, 160.4, 136.3, 135.3, 131.9, 129.5, 128.5, 128.1, 125.6, 125.4, 117.4, 116.0, 67.2 ppm; **MS** (APCI): $[M + 1]^+$ = 287.0 (92.72%); **HRMS** (**ESI-QTOF,** $[M + H]^+$): calculated for $C_{15}H_{12}ClN_2O_2$: 287.0587; found: 287.0584.

Synthesis of *N*-(7-(trifluoromethyl)-4*H*-benzo[*d*][1,3]oxazin-2-yl)benzamide (4ia)

According to the general procedure, reactions between 2-amino-4-(trifluoromethyl)benzyl alcohol (**1i**) (1.0 mmol, 191 mg), benzoyl isothiocyanate (**2a**) (1.0 mmol, 163 mg), Et_3N (2.0 mmol, 202 mg), I_2 (1.1 mmol, 140 mg) in 2 mL THF were performed to obtain the desired *N*-(7-(trifluoromethyl)-4*H*-benzo[*d*][1,3]oxazin-2-yl)benzamide (**4ia**) in 91% (291 mg) yield as off-white solid.

***N*-(7-(trifluoromethyl)-4*H*-benzo[*d*][1,3]oxazin-2-yl)benzamide (4ia)** (Scheme 2): **Off-white solid**; $\mathbf{R_f}$ = 0.40 (SiO_2, Hexane/EtOAc = 8:2); **Purification system**: CombiFlash MPLC (DCM/EtOAc = 95:5); **Yield**: 291 mg (91%); **m.p** = 107 - 108 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 12.89 (br, 1H), 8.25 (d, *J* = 7.6 Hz, 2H), 7.52 (t, *J* = 7.6 Hz, 1H), 7.44 (t, *J* = 8.0 Hz, 3H), 7.25 (s, 2H), 5.45 (s, 2H) ppm; **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ = 180.7, 163.6, 136.2, 132.6 (q, *J* = 247.6 Hz), 129.5, 128.6, 128.1, 127.3, 125.2, 124.9, 124.6, 122.7, 121.9, 121.6, 121.0, 112.8, 111.0, 67.1 ppm; **MS** (APCI): $[M]^+$ = 320.0 (89.0%); **HRMS** (**ESI-QTOF,** $[M + H]^+$): calculated for $C_{16}H_{12}F_3N_2O_2$: 321.0850; found: 321.0845.

Synthesis of *N*-(4-methylene-4*H*-benzo[*d*][1,3]oxazin-2-yl)benzamide (4ja)

According to the general procedure, reactions between 1-(2-aminophenyl)ethen-1-ol (**1j**) (1.0 mmol, 135 mg), benzoyl isothiocyanate (**2a**) (1.0 mmol, 163 mg), Et_3N (2.0 mmol, 202 mg), I_2 (1.1 mmol, 140 mg) in 2 mL THF were performed to obtain the desired *N*-(4-methylene-4*H*-benzo[*d*][1,3]oxazin-2-yl)benzamide (**4ja**) in 60% (159 mg) yield as white solid.

***N*-(4-methylene-4*H*-benzo[*d*][1,3]oxazin-2-yl)benzamide (4ja)** (Scheme 2): **White solid**; $\mathbf{R_f}$ = 0.60 (SiO_2, Hexane/EtOAc = 8:2); **Purification system**: CombiFlash MPLC (DCM/EtOAc = 97:3); **Yield**: 159 mg (60%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 12.91 (br, 1H), 8.26 (d, *J* = 7.4 Hz, 2H), 7.55 - 7.49 (m, 3H), 7.44 (t, *J* = 7.6 Hz, 1H), 7.36 (t, *J* = 7.6 Hz, 1H), 7.16 (t, *J* = 8.0 Hz, 1H), 6.96 (d, *J* = 7.6 Hz, 1H), 5.03 (d, *J* = 13.6 Hz, 2H) ppm; **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ = 179.8, 157.3. 150.0, 136.4, 132.7, 132.4, 132.1, 131.2, 129.4, 128.1, 125.6, 123.8, 116.6, 116.3, 91.2 ppm; **MS** (APCI): $[M]^+$ = 265.1 (100.0%); **HRMS** (**ESI-QTOF,** $[M + H]^+$): calculated for $C_{16}H_{13}N_2O_2$: 265.0977; found: 265.0970.

Synthesis of *N*-(4-phenyl-4*H*-benzo[*d*][1,3]oxazin-2-yl)benzamide (4ka)

According to the general procedure, reactions between 2-aminobenzhydrol (**1k**) (1.0 mmol, 199 mg), benzoyl isothiocyanate (**2a**) (1.0 mmol, 163 mg), Et_3N (2.0 mmol, 202 mg), I_2 (1.1 mmol, 140 mg) in 2 mL THF were performed to obtain the desired *N*-(4-phenyl-4*H*-benzo[*d*][1,3]oxazin-2-yl)benzamide (**4ka**) in 96% (315 mg) yield as white solid.

***N*-(4-phenyl-4*H*-benzo[*d*][1,3]oxazin-2-yl)benzamide (4ka)** (Scheme 2): **White solid**; $\mathbf{R_f}$ = 0.50 (SiO_2, Hexane/EtOAc = 8:2); **Purification system**: CombiFlash MPLC (DCM/EtOAc = 95:5); **Yield**: 315 mg (96%); **m.p** = 178 - 179 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 12.87 (br, 1H), 8.25 (d, *J* = 7.6 Hz, 2H), 7.50 (t, *J* = 7.6 Hz, 1H), 7.43 - 7.39 (m, 7H), 7.38 (t, *J* = 8 Hz, 1H), 7.12 (d, *J* = 7.2 Hz, 1H), 7.05 (d, *J* = 7.6 Hz, 1H), 6.87 (d, *J* = 7.2 Hz, 1H), 6.45 (s, 1H) ppm; **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ = 179.9, 160.2, 136.8, 136.7, 137.27, 137.22, 129.7, 129.5,

128.8, 128.1, 128.0, 126.1, 125.0, 122.3, 115.7, 80.5 ppm; **MS** (APCI): $[M]^+$ = 329.1 (93.79%); **HRMS** (**ESI-QTOF,** $[M + H]^+$): calculated for $C_{21}H_{17}N_2O_2$: 329.1290; found: 329.1286.

Synthesis of *N*-(4,5-dihydrobenzo[*d*][1,3]oxazepin-2-yl)benzamide (4la)

According to the general procedure, reactions between 2-aminophenethyl alcohol (**1l**) (1.0 mmol, 137 mg), benzoyl isothiocyanate (**2a**) (1.0 mmol, 163 mg), Et_3N (2.0 mmol, 202 mg), I_2 (1.1 mmol, 140 mg) in 2 mL THF were performed to obtain the desired *N*-(4,5-dihydrobenzo[*d*][1,3]oxazepin-2-yl)benzamide (**4la**) in 95% (253 mg) yield as off-white solid.

***N*-(4,5-dihydrobenzo[*d*][1,3]oxazepin-2-yl)benzamide (4la)** (Scheme 2): **Off-white solid**; $\mathbf{R_f}$ = 0.50 (SiO_2, Hexane/EtOAc = 8:2); **Purification system**: CombiFlash MPLC (DCM/EtOAc = 96:4); **Yield**: 253 mg (95%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 13.90 (br, 1H), 8.25 (d, *J* = 7.2 Hz, 2H), 7.50 (d, *J* = 7.6 Hz, 1H), 7.43 (t, *J* = 6.8 Hz, 2H), 7.30 (s, 1H), 7.17 - 6.99 (m, 3H), 4.67 (s, 2H), 3.29 (s, 2H) ppm; **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ = 178.8, 162.2, 136.8, 135.4, 132.0, 130.2, 129.3, 129.2,128.2,127.7, 124.7, 121.6, 70.0, 35.0 ppm; **HRMS** (**ESI-QTOF,** $[M + H]^+$): calculated for $C_{16}H_{15}N_2O_2$: 267.1133; found: 267.1130.

Synthesis of *N*-phenyl-4*H*-benzo[*d*][1,3]oxazin-2-amine (4ab)

According to the general procedure, reactions between 2-aminobenzyl alcohol (**1a)** (1.0 mmol, 123 mg), phenyl isothiocyanate (**2b**) (1.0 mmol, 135 mg), Et_3N (2.0 mmol, 202 mg), I_2 (1.1 mmol, 140 mg) in 2 mL THF were performed to obtain the desired *N*-phenyl-4*H*-benzo[*d*][1,3]oxazin-2-amine (**4ab**) in 94% (211 mg) yield as off-white solid.

***N*-phenyl-4*H*-benzo[*d*][1,3]oxazin-2-amine (4ab)**[7f] (Scheme 3, 6 and 7): **Off-white solid**; $\mathbf{R_f}$ = 0.50 (SiO_2, Hexane/EtOAc = 8:2); **Purification system**: CombiFlash MPLC (DCM/EtOAc = 95:5); **Yield**: 211 mg (94%); **m.p** = 143 - 144 °C (Lit[7f] 144 - 147 °C); **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.47 (d, *J* = 7.2 Hz, 2H), 7.31 (t, *J* = 8 Hz, 3H), 7.05 - 6.99 (m, 4H), 5.24 (s, 2H) ppm; **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ = 151.9, 141.0, 139.6, 129.0, 128.9, 123.7, 123.0, 122.9, 121.0, 120.8, 120.5, 67.7 ppm; **MS** (APCI): $[M]^+$ = 225.1 (99.85%); **HRMS** (**ESI-QTOF,** $[M + H]^+$): calculated for $C_{14}H_{13}N_2O$: 225.1027; found: 225.1024.

Synthesis of *N*-(2,4-dimethylphenyl)-4*H*-benzo[*d*][1,3]oxazin-2-amine (4ac)

According to the general procedure, reactions between 2-aminobenzyl alcohol (**1a)** (1.0 mmol, 123 mg), 2,4-dimethylphenyl isothiocyanate (**2c**) (1.0 mmol, 163 mg), Et_3N (2.0 mmol, 202 mg), I_2 (1.1 mmol, 140 mg) in 2 mL THF were performed to obtain the desired *N*-(2,4-dimethylphenyl)-4*H*-benzo[*d*][1,3]oxazin-2-amine (**4ac**) in 98% (247 mg) yield as off-white solid.

***N*-(2,4-dimethylphenyl)-4*H*-benzo[*d*][1,3]oxazin-2-amine (4ac)**[7b] (Scheme 3): **Off-white solid**; $\mathbf{R_f}$ = 0.30 (SiO_2, Hexane/EtOAc = 8:2); **Purification system**: CombiFlash MPLC (DCM/EtOAc = 95:5); **Yield**: 247 mg (98%); **m.p** = 163 - 165 °C (Lit[7b] 163 - 166 °C); **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.69 (s, 1H), 7.25 - 7.20 (m, 1H), 7.06 (d, *J* = 7.6 Hz, 1H), 7.01 - 6.98 (m, 3H), 6.85 (d, *J* = 7.6 Hz, 1H), 5.20 (s, 2H), 2.34 (s, 3H), 2.33 (s, 3H) ppm; **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ = 147.0, 136.3, 133.0, 131.4, 125.4, 124.2, 121.9, 120.1, 118.96, 118.90, 117.8, 115.8, 115.6, 62.9, 16.39, 12.77 ppm; **MS** (APCI): $[M]^+$ = 253.1 (99.81%); **HRMS** (**ESI-QTOF,** $[M + H]^+$): calculated for $C_{16}H_{17}N_2O$: 253.1340; found: 253.1337.

Synthesis of *N*-(*p*-tolyl)-4*H*-benzo[*d*][1,3]oxazin-2-amine (4ad)

According to the general procedure, reactions between 2-aminobenzyl alcohol (**1a)** (1.0 mmol, 123 mg), *p*-tolyl isothiocyanate (**2d**) (1.0 mmol, 149 mg), Et_3N (2.0 mmol, 202 mg), I_2 (1.1 mmol, 140 mg) in 2 mL THF were performed to obtain the desired *N*-(*p*-tolyl)-4*H*-benzo[*d*][1,3]oxazin-2-amine (**4ad**) in 90% (214 mg) yield as off-white solid.

***N*-(*p*-tolyl)-4*H*-benzo[*d*][1,3]oxazin-2-amine (4ad)**[22] (Scheme 3): **Off-white solid**; $\mathbf{R_f}$ = 0.50 (SiO_2, Hexane/EtOAc = 8:2); **Purification system**: CombiFlash MPLC (DCM/EtOAc = 95:5); **Yield**: 214 mg (90%); **m.p** = 115 - 117 °C (Lit[22] 116 - 118°C); **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.33 (d, *J* = 8.0 Hz, 2H), 7.27 - 7.23 (m, 1H), 7.12 (d, *J* = 8.0

Hz, 2H), 7.08 - 7.04 (m, 1H), 7.03 - 6.98 (m, 2H), 5.25 (s, 2H), 2.32 (s, 3H) ppm; **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ = 151.9, 141.3, 136.5, 132.7, 129.4, 129.0, 123.6, 122.8, 121.3, 120.8, 120.5, 67.7, 20.7 ppm; **MS** (APCI): $[M]^+$ = 239.1 (100%); **HRMS** (**ESI-QTOF,** $[M + H]^+$): calculated for $C_{15}H_{15}N_2O$: 239.1184; found: 239.1180.

Synthesis of *N*-(2-methoxyphenyl)-4*H*-benzo[*d*][1,3]oxazin-2-amine (4ae)

According to the general procedure, reactions between 2-aminobenzyl alcohol (**1a)** (1.0 mmol, 123 mg), 2-methoxyphenyl isothiocyanate (**2e**) (1.0 mmol, 165 mg), Et_3N (2.0 mmol, 202 mg), I_2 (1.1 mmol, 140 mg) in 2 mL THF were performed to obtain the desired *N*-(2-methoxyphenyl)-4*H*-benzo[*d*][1,3]oxazin-2-amine (**4ae**) in 94% (239 mg) yield as off-white solid.

***N*-(2-methoxyphenyl)-4*H*-benzo[*d*][1,3]oxazin-2-amine (4ae)**[7b] (Scheme 3): **Off-white solid**; $\mathbf{R_f}$ = 0.40 (SiO_2, Hexane/EtOAc = 8:2); **Purification system**: CombiFlash MPLC (DCM/EtOAc = 97:3); **Yield**: 239 mg (94%); **m.p** = 110 - 111 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 8.41 - 8.39 (m, 1H), 7.25 (t, *J* = 7.6 Hz, 1H), 7.12 (d, *J* = 8.0 Hz, 1H), 7.03 - 696 (m, 4H), 6.87 - 6.85 (m, 1H), 5.24 (s, 2H), 3.88 (s, 3H) ppm; **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ = 151.3, 147.8, 141.8, 128.9, 128.2, 123.5, 123.2, 122.5, 122.2, 121.2, 121.0, 119.0, 109.9, 67.5, 55.6 ppm; **MS** (APCI): $[M]^+$ = 255.1 (100%); **HRMS** (**ESI-QTOF,** $[M + H]^+$): calculated for $C_{15}H_{15}N_2O_2$: 255.1133; found: 255.1129.

Synthesis of *N*-(4-methoxyphenyl)-4*H*-benzo[*d*][1,3]oxazin-2-amine (4af)

According to the general procedure, reactions between 2-aminobenzyl alcohol (**1a)** (1.0 mmol, 123 mg), 4-methoxyphenyl isothiocyanate (**2f**) (1.0 mmol, 165 mg), Et_3N (2.0 mmol, 202 mg), I_2 (1.1 mmol, 140 mg) in 2 mL THF were performed to obtain the desired *N*-(4-methoxyphenyl)-4*H*-benzo[*d*][1,3]oxazin-2-amine (**4af**) in 90% (229 mg) yield as off-white solid.

***N*-(4-methoxyphenyl)-4*H*-benzo[*d*][1,3]oxazin-2-amine (4af)**[22] (Scheme 3): **Off-white solid**; $\mathbf{R_f}$ = 0.30 (SiO_2, Hexane/EtOAc = 8:2); **Purification system**: CombiFlash MPLC (DCM/EtOAc = 95:5); **Yield**: 229 mg (90%); **m.p** = 132 - 133 °C (Lit[22] 133 - 135 °C); **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.35 (d, *J* = 8.0 Hz, 2H), 7.22 (d, *J* = 7.6 Hz, 1H), 7.02 - 6.98 (m, 3H), 6.87 (d, *J* = 7.2 Hz, 2H), 5.21 (s, 2H), 3.79 (s, 3H) ppm; **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ = 155.8, 152.3, 141.3, 132.4, 129.0, 123.6, 122.6, 122.5, 120.9, 120.7, 114.1, 67.7, 55.5 ppm; **MS** (APCI): $[M]^+$ = 255.1 (98.06%); **HRMS** (**ESI-QTOF,** $[M + H]^+$): calculated for $C_{15}H_{15}N_2O_2$: 255.1133; found: 255.1131.

Synthesis of *N*-(3-fluorophenyl)-4*H*-benzo[*d*][1,3]oxazin-2-amine (4ag)

According to the general procedure, reactions between 2-aminobenzyl alcohol (**1a**) (1.0 mmol, 123 mg), 3-fluorophenyl isothiocyanate (**2g**) (1.0 mmol, 153 mg), Et_3N (2.0 mmol, 202 mg), I_2 (1.1 mmol, 140 mg) in 2 mL THF were performed to obtain the desired *N*-(3-fluorophenyl)-4*H*-benzo[*d*][1,3]oxazin-2-amine (**4ag**) in 89% (216 mg) yield as off-white solid.

***N*-(3-fluorophenyl)-4*H*-benzo[*d*][1,3]oxazin-2-amine (4ag)** (Scheme 3): **Off-white solid**; $\mathbf{R_f}$ = 0.40 (SiO_2, Hexane/EtOAc = 8:2); **Purification system**: CombiFlash MPLC (DCM/EtOAc = 95:5); **Yield**: 216 mg (89%); **m.p** = 120 - 121 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.45 (d, *J* = 7.2 Hz, 1H), 7.28 - 7.19 (m, 2H), 7.05 - 6.99 (m, 4H), 6.73 (t, *J* = 7.6 Hz, 1H), 5.25 (s, 2H) ppm; **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ = 163.1 (d, *J* = 243.3 Hz), 151.2, 141.6 (d, *J* = 10.7 Hz), 140.4, 129.8 (d, *J* = 9.8 Hz), 129.1, 123.7, 123.2, 120.9, 120.6, 115.6, 109.6 (d, *J* = 21.3 Hz), 107.7 (d, *J* = 80 Hz), 67.8 ppm; **MS** (APCI): $[M]^+$ = 243.1 (98.81%); **HRMS** (**ESI-QTOF,** $[M + H]^+$): calculated for $C_{14}H_{12}FN_2O$: 243.0933; found: 243.0930.

Synthesis of *N*-(3,5-bis(trifluoromethyl)phenyl)-4*H*-benzo[*d*][1,3]oxazin-2-amine (4ah)

According to the general procedure, reactions between 2-aminobenzyl alcohol (**1a**) (1.0 mmol, 123 mg), 3,5-bis(trifluoromethyl)phenyl isothiocyanate (**2h**) (1.0 mmol, 271 mg), Et_3N (2.0 mmol, 202 mg), I_2 (1.1 mmol, 140 mg) in 2 mL THF were performed to obtain the desired *N*-(3,5-bis(trifluoromethyl)phenyl)-4*H*-benzo[*d*][1,3]oxazin-2-amine (**4ah**) in 95% (342 mg) yield as off-white solid.

***N*-(3,5-bis(trifluoromethyl)phenyl)-4*H*-benzo[*d*][1,3]oxazin-2-amine (4ah)** (Scheme 3): **Off-white solid**; $\mathbf{R_f}$ = 0.30 (SiO_2, Hexane/EtOAc = 8:2); **Purification system**: CombiFlash MPLC (DCM/EtOAc = 95:5); **Yield**: 342 mg (95%);

m.p = 150 - 151 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.83 (s, 2H), 7.51 (s, 1H), 7.28 - 7.24 (m, 1H), 6.05 (d, *J* = 8.0 Hz, 2H), 6.95 (d, *J* = 8.0 Hz, 1H), 5.26 (s, 2H) ppm; **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ = 150.7, 143.6, 138.2, 132.5 (q, *J* = 33.27 Hz), 129.3, 124.0, 123.4, 123.2 (q, *J* = 270.2 Hz), 121.4, 119.8, 119.2, 118.5, 116.0, 68.1 ppm; **MS** (APCI): $[M]^+$ = 361.0 (100%); **HRMS** (**ESI-QTOF,** $[M + H]^+$): calculated for $C_{16}H_{11}F_6N_2O$: 361.0775; found: 361.0772.

Synthesis of *N*-(4-(trifluoromethyl)phenyl)-4*H*-benzo[*d*][1,3]oxazin-2-amine (4ai)

According to the general procedure, reactions between 2-aminobenzyl alcohol (**1a**) (1.0 mmol, 123 mg), 4-(trifluoromethyl)phenyl isothiocyanate (**2i**) (1.0 mmol, 203 mg), Et_3N (2.0 mmol, 202 mg), I_2 (1.1 mmol, 140 mg) in 2 mL THF were performed to obtain the desired *N*-(4-(trifluoromethyl)phenyl)-4*H*-benzo[*d*][1,3]oxazin-2-amine (**4ai**) in 93% (272 mg) yield as yellow solid.

***N*-(4-(trifluoromethyl)phenyl)-4*H*-benzo[*d*][1,3]oxazin-2-amine (4ai)** (Scheme 3): **Yellow solid**; $\mathbf{R_f}$ = 0.30 (SiO_2, Hexane/EtOAc = 8:2); **Purification system**: CombiFlash MPLC (DCM/EtOAc = 95:5); **Yield**: 272 mg (93%); **m.p** = 168 - 169 °C; **^{1}H NMR** (400 MHz, DMSO-d_6) δ = 9.74 (br, 1H), 7.92 (br, 2H), 7.61 (d, *J* = 8.0 Hz, 2H), 7.22 (t, *J* = 7.6 Hz, 1H), 7.08 (d, *J* = 6.8 Hz, 1H), 7.02 - 6.97 (m, 2H), 5.28 (s, 2H) ppm; **^{13}C{^{1}H} NMR** (100 MHz, DMSO-d_6) δ = 151.2, 144.2, 141.2, 129.1, 126.2, 125.5 (q, *J* = 246.27 Hz), 124.5, 123.5, 122.7, 122.3 (d, *J* = 34.0 Hz), 119.3, 67.2 ppm; **MS** (APCI): $[M]^+$ = 293.1 (99.78%); **HRMS** (**ESI-QTOF,** $[M + H]^+$): calculated for $C_{15}H_{12}F_3N_2O$: 293.0901; found: 293.0898

Synthesis of *N*-(2-methyl-4-nitrophenyl)-4*H*-benzo[*d*][1,3]oxazin-2-amine (4aj)

According to the general procedure, reactions between 2-aminobenzyl alcohol (**1a**) (1.0 mmol, 123 mg), 2-methyl-4-nitrophenyl isothiocyanate (**2j**) (1.0 mmol, 194 mg), Et_3N (2.0 mmol, 202 mg), I_2 (1.1 mmol, 140 mg) in 2 mL THF were performed to obtain the desired *N*-(2-methyl-4-nitrophenyl)-4*H*-benzo[*d*][1,3]oxazin-2-amine (**4aj**) in 91% (258 mg) yield as yellow solid.

***N*-(2-methyl-4-nitrophenyl)-4*H*-benzo[*d*][1,3]oxazin-2-amine (4aj)** (Scheme 3): **Yellow solid**; $\mathbf{R_f}$ = 0.20 (SiO_2, Hexane/EtOAc = 8:2); **Purification system**: CombiFlash MPLC (DCM/EtOAc = 92:8); **Yield**: 258 mg (91%); **m.p** = 186 - 188 °C; **^{1}H NMR** (400 MHz, DMSO-d_6) δ = 10.15 (br, 1H), 8.04 (s, 1H), 7.95 (d, *J* = 7.6 Hz, 1H), 7.24 (t, *J* = 8.0 Hz, 1H), 7.15 (d, *J* = 7.2 Hz, 1H), 7.09 (br, 1H), 6.96 (d, *J* = 8.0 Hz, 2H), 5.19 (s, 2H), 2.22 (s, 3H) ppm; **^{13}C{^{1}H} NMR** (100 MHz, DMSO-d_6) δ = 148.5, 142.0, 137.5, 131.9, 129.3, 125.4, 124.8, 123.4, 122.3, 119.9, 115.2, 67.6, 18.41 ppm; **MS** (APCI): $[M]^+$ = 284.1 (99.78%); **HRMS** (**ESI-QTOF,** $[M + H]^+$): calculated for $C_{15}H_{14}N_3O_3$: 284.1035; found: 284.1031.

Synthesis of ethyl (4*H*-benzo[*d*][1,3]oxazin-2-yl)carbamate (4ak)

According to the general procedure, reactions between 2-aminobenzyl alcohol (**1a**) (1.0 mmol, 123 mg), ethoxycarbonyl isothiocyanate (**2k**) (1.0 mmol, 131 mg), Et_3N (2.0 mmol, 202 mg), I_2 (1.1 mmol, 140 mg) in 2 mL THF were performed to obtain the desired ethyl (4*H*-benzo[*d*][1,3]oxazin-2-yl)carbamate (**4ak**) in 96% (211 mg) yield as white solid.

ethyl (4*H*-benzo[*d*][1,3]oxazin-2-yl)carbamate (4ak) (Scheme 3): **White solid**; $\mathbf{R_f}$ = 0.30 (SiO_2, Hexane/EtOAc = 8:2); **Purification system**: CombiFlash MPLC (DCM/EtOAc = 95:5); **Yield**: 211 mg (96%); **m.p** = 91 - 92 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 11.0 (br, 1H), 7.30 (t, *J* = 8.0 Hz, 1H), 7.14 - 7.09 (m, 2H), 6.92 (d, *J* = 7.6 Hz, 1H), 5.31 (s, 2H), 4.19 (q, *J* = 7.2 Hz, 2H), 1.31 (t, *J* = 7.6 Hz, 3H) ppm; **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ = 132.8, 129.5, 124.6, 124.4, 118.8, 115.4, 67.6, 61.7, 14.3 ppm; **MS** (APCI): $[M]^+$ = 221.1 (99.74%); **HRMS** (**ESI-QTOF,** $[M + H]^+$): calculated for $C_{11}H_{13}N_2O_3$: 221.0926; found: 221.0920.

Synthesis of *N*-(furan-2-ylmethyl)-4*H*-benzo[*d*][1,3]oxazin-2-amine (4al)

According to the general procedure, reactions between 2-aminobenzyl alcohol (**1a**) (1.0 mmol, 123 mg), 2-(isothiocyanatomethyl)furan (**2l**) (1.0 mmol, 139 mg), Et_3N (2.0 mmol, 202 mg), I_2 (1.1 mmol, 140 mg) in 2 mL THF were performed to obtain the desired *N*-(furan-2-ylmethyl)-4*H*-benzo[*d*][1,3]oxazin-2-amine (**4al**) in 92% (210 mg) yield as off-white solid.

***N*-(furan-2-ylmethyl)-4*H*-benzo[*d*][1,3]oxazin-2-amine (4al)** (Scheme 3): **Off-white solid**; $\mathbf{R_f}$ = 0.30 (SiO_2, Hexane/EtOAc = 8:2); **Purification system**: CombiFlash MPLC (DCM/EtOAc = 95:5); **Yield**: 210 mg (92%); **m.p** = 106 - 107 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.35 (s, 1H), 7.23 (t, *J* = 7.6 Hz, 1H), 7.00 (d, *J* = 8.0 Hz, 1H), 6.97 - 6.89 (m, 2H), 6.29 (d, *J* = 19.2 Hz, 2H), 5.14 (s, 2H), 4.52 (s, 2H) ppm; **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ = 154.6, 142.3, 142.1, 128.9, 123.4, 122.4, 121.7, 121.0, 110.3, 107.2, 67.5, 38.7 ppm; **HRMS** (**ESI-QTOF,** $[M + H]^+$): calculated for $C_{13}H_{13}N_2O_2$: 229.0977; found: 229.0973.

Synthesis of *N*-propyl-4*H*-benzo[*d*][1,3]oxazin-2-amine (4am)

According to the general procedure, reactions between 2-aminobenzyl alcohol (**1a**) (1.0 mmol, 123 mg), propyl isothiocyanate (**2m**) (1.0 mmol, 101 mg), Et_3N (2.0 mmol, 202 mg), I_2 (1.1 mmol, 140 mg) in 2 mL THF were performed to obtain the desired *N*-propyl-4*H*-benzo[*d*][1,3]oxazin-2-amine (**4am**) in 80% (152 mg) yield as viscous liquid.

***N*-propyl-4*H*-benzo[*d*][1,3]oxazin-2-amine (4am)** (Scheme 3): **Viscous liquid**; $\mathbf{R_f}$ = 0.50 (SiO_2, Hexane/EtOAc = 8:2); **Purification system**: CombiFlash MPLC (Hexane/EtOAc = 80:20); **Yield**: 152 mg (80%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.25 - 7.18 (m, 1H), 6.98 (d, *J* = 8.0 Hz, 1H), 6.92 - 6.88 (m, 2H), 5.12 (s, 2H), 4.44 (bs, 1H), 3.29 (t, *J* = 6.80 Hz, 2H), 1.62 - 1.56 (m, 2H), 0.96 (t, *J* = 7.20 Hz, 3H) ppm; **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ = 155.2, 142.7, 128.9, 123.4, 122.1, 121.5, 120.9, 67.4, 43.3, 23.0, 11.2 ppm; **MS** (APCI): $[M + 1]^+$ = 191.3 (98.53%); **HRMS** (**ESI-QTOF,** $[M + H]^+$): calculated for $C_{11}H_{15}N_2O$: 191.1184; found: 191.1180.

Synthesis of *N*-isopropyl-4*H*-benzo[*d*][1,3]oxazin-2-amine (4an)

According to the general procedure, reactions between 2-aminobenzyl alcohol (**1a**) (1.0 mmol, 123 mg), isopropyl isothiocyanate (**2n**) (1.0 mmol, 101 mg), Et_3N (2.0 mmol, 202 mg), I_2 (1.1 mmol, 140 mg) in 2 mL THF were performed to obtain the desired *N*-isopropyl-4*H*-benzo[*d*][1,3]oxazin-2-amine (**4an**) in 82% (156 mg) yield as viscous liquid.

***N*-isopropyl-4*H*-benzo[*d*][1,3]oxazin-2-amine (4an)** (Scheme 3): **Viscous liquid**; $\mathbf{R_f}$ = 0.45 (SiO_2, Hexane/EtOAc = 8:2); **Purification system**: CombiFlash MPLC (Hexane/EtOAc = 80:20); **Yield**: 152 mg (80%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.24 - 7.17 (m, 1H), 6.97 (d, *J* = 7.6 Hz, 1H), 6.91 - 6.88 (m, 2H), 5.09 (s, 2H), 4.01 - 3.98 (m, 1H), 1.20 (d, *J* = 6.80 Hz, 6H) ppm; **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ = 154.4, 142.7, 128.9, 123.4, 122.0, 121.4, 120.9, 67.3, 43.2, 23.1 ppm; **MS** (APCI): $[M + 1]^+$ = 191.3 (94.55%); **HRMS** (**ESI-QTOF,** $[M + H]^+$): calculated for $C_{11}H_{15}N_2O$: 191.1184; found: 191.1181.

Experimental procedures and analytical data of synthesized 2-amino-1,3-benzothiazines (5aa-ia, 5ab-al, **5ao-ar)**

Synthesis of *N*-(4*H*-benzo[*d*][1,3]thiazin-2-yl)benzamide (5aa)

According to the general procedure, reactions between 2-aminobenzyl alcohol (**1a**) (1.0 mmol, 123 mg), benzoyl isothiocyanate (**2a**) (1.0 mmol, 163 mg), Et_3N (2.2 mmol, 222 mg), T3P anhydride solution (≥50 wt. % in ethyl acetate) in 2 mL MeCN were performed to obtain the desired *N*-(4*H*-benzo[*d*][1,3]thiazin-2-yl)benzamide (**5aa**) in 98% (263 mg) yield as white solid.

***N*-(4*H*-benzo[*d*][1,3]thiazin-2-yl)benzamide (5aa)**[23] (Table 1, Scheme 4): **White solid**; $\mathbf{R_f}$ = 0.60 (SiO_2, Hexane/EtOAc = 8:2); **Purification system**: CombiFlash MPLC (Hexane/EtOAc = 87:13); **Yield**: 263 mg (98%); **m.p** = 123 - 124 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 12.0 (bs, 1H), 8.17 (d, *J* = 7.6 Hz, 2H), 7.53 (t, *J* = 7.2 Hz, 1H), 7.44 (t, *J* = 7.6 Hz, 2H), 7.32 - 7.27 (m, 1H), 7.17 (d, *J* = 4.0 Hz, 2H), 7. 2 (d, *J* = 8.0 Hz, 1H), 4.02 (s, 2H) ppm; **^{13}C{^{1}H} NMR** (100 MHz, DMSO-d_6) δ = 172.4, 164.5, 138.4, 135.7, 132.5, 129.3, 128.7, 128.5, 127.3, 125.2, 121.6, 119.6, 28.2 ppm; **HRMS** (**ESI-QTOF,** $[M + H]^+$): calculated for $C_{15}H_{13}N_2OS$: 269.0748; found: 269.0751.

Synthesis of *N*-(7-methyl-4*H*-benzo[*d*][1,3]thiazin-2-yl)benzamide (5ba)

According to the general procedure, reactions between 2-amino-4-methylbenzyl alcohol (**1b**) (1.0 mmol, 137 mg), benzoyl isothiocyanate (**2a**) (1.0 mmol, 163 mg), Et_3N (2.2 mmol, 222 mg), T3P anhydride solution (≥50 wt. % in

ethyl acetate) in 2 mL MeCN were performed to obtain the desired *N*-(7-methyl-4*H*-benzo[*d*][1,3]thiazin-2-yl)benzamide (**5ba**) in 95% (268 mg) yield as off-white solid.

***N*-(7-methyl-4*H*-benzo[*d*][1,3]thiazin-2-yl)benzamide (5ba)** (Scheme 4): **Off-white solid**; $\mathbf{R_f}$ = 0.60 (SiO_2, Hexane/EtOAc = 8:2); **Purification system**: CombiFlash MPLC (Hexane/EtOAc = 90:10); **Yield**: 268 mg (95%); **m.p** = 145 - 146 °C; **^{1}H NMR** (400 MHz, DMSO-d_6) δ = 11.61 (br, 1H), 8.09 (d, *J* = 7.2 Hz, 2H), 7.55 (t, *J* = 7.2 Hz, 1H), 7.47 (t, *J* = 7.6 Hz, 2H), 7.12 (d, *J* = 8.0 Hz, 1H), 7.01 (s, 1H), 6.94 (d, *J* = 7.6 Hz, 1H), 3.90 (s, 2H), 2.27 (s, 3H) ppm; **^{13}C{^{1}H} NMR** (100 MHz, DMSO-d_6) δ = 170.2 (less intense), 137.9, 135.8, 132.5, 129.3, 128.7, 127.1, 125.8, 119.8, 118.6, 28.0, 21.2 ppm; **MS** (APCI): $[M + 1]^+$ = 283.1 (100%); **HRMS** (**ESI-QTOF,** $[M + H]^+$): calculated for $C_{16}H_{15}N_2OS$: 283.0905; found: 283.0900.

Synthesis of *N*-(8-methyl-4*H*-benzo[*d*][1,3]thiazin-2-yl)benzamide (5ca)

According to the general procedure, reactions between 2-amino-3-methylbenzyl alcohol (**1c**) (1.0 mmol, 137 mg), benzoyl isothiocyanate (**2a**) (1.0 mmol, 163 mg), Et_3N (2.2 mmol, 222 mg), T3P anhydride solution (≥50 wt. % in ethyl acetate) in 2 mL MeCN were performed to obtain the desired *N*-(8-methyl-4*H*-benzo[*d*][1,3]thiazin-2-yl)benzamide (**5ca**) in 90% (254 mg) yield as off-white solid.

***N*-(8-methyl-4*H*-benzo[*d*][1,3]thiazin-2-yl)benzamide (5ca)** (Scheme 4): **Off-white solid**; $\mathbf{R_f}$ = 0.60 (SiO_2, Hexane/EtOAc = 8:2); **Purification system**: CombiFlash MPLC (Hexane/EtOAc = 90:10); **Yield**: 254 mg (90%); **m.p** = 127 - 128 °C; **^{1}H NMR** (400 MHz, DMSO-d_6) δ = 11.54 (br, 1H), 8.04 (d, *J* = 7.2 Hz, 2H), 7.59 (t, *J* = 7.2 Hz, 1H), 7.49 (t, *J* = 7.6 Hz, 2H), 7.16 (t, *J* = 4.8 Hz, 1H), 7.06 (d, *J* = 4.8 Hz, 2H), 3.93 (s, 2H), 2.32 (s, 3H) ppm; **^{13}C{^{1}H} NMR** (100 MHz, DMSO-d_6) δ = 170.1 (less intense), 138.7, 134.5, 132.8, 130.0, 129.1, 128.7, 125.7, 125.0, 121.9, 28.8, 17.7 ppm; **MS** (APCI): $[M + 1]^+$ = 283.1 (100%); **HRMS** (**ESI-QTOF,** $[M + H]^+$): calculated for $C_{16}H_{15}N_2OS$: 283.0905; found: 283.0902.

Synthesis of *N*-(6-fluoro-4*H*-benzo[*d*][1,3]thiazin-2-yl)benzamide (5da)

According to the general procedure, reactions between 2-amino-5-fluorobenzyl alcohol (**1d**) (1.0 mmol, 141 mg), benzoyl isothiocyanate (**2a**) (1.0 mmol, 163 mg), Et_3N (2.2 mmol, 222 mg), T3P anhydride solution (≥50 wt. % in ethyl acetate) in 2 mL MeCN were performed to obtain the desired *N*-(6-fluoro-4*H*-benzo[*d*][1,3]thiazin-2-yl)benzamide (**5da**) in 98% (280 mg) yield as off-white solid.

***N*-(6-fluoro-4*H*-benzo[*d*][1,3]thiazin-2-yl)benzamide (5da)** (Scheme 4): **Off-white solid**; $\mathbf{R_f}$ = 0.50 (SiO_2, Hexane/EtOAc = 8:2); **Purification system**: CombiFlash MPLC (Hexane/EtOAc = 85:15); **Yield**: 280 mg (98%); **m.p** = 106 - 107 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 11.00 (br, 1H), 8.09 (d, *J* = 7.2 Hz, 2H), 7.57 - 7.53 (m, 1H), 7.46 (t, *J* = 8.0 Hz, 2H), 7.01 (d, *J* = 6.8 Hz, 2H), 6.90 (d, *J* = 7.6 Hz, 1H), 3.97 (s, 2H) ppm; **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ = 172.1 (less intense), 162.5, 160.3 (d, *J* = 250.50 Hz), 134.9, 132.5, 128.7, 128.4, 122.5, 121.9, 121.8, 115.4 (d, *J* = 22.8 Hz), 114.1 (d, *J* = 23.7 Hz), 28.9 ppm; **MS** (APCI): $[M + 1]^+$ = 287.0 (100%); **HRMS** (**ESI-QTOF,** $[M + H]^+$): calculated for $C_{15}H_{12}FN_2OS$: 287.0654; found: 287.0651.

Synthesis of *N*-(7-fluoro-4*H*-benzo[*d*][1,3]thiazin-2-yl)benzamide (5ea)

According to the general procedure, reactions between 2-amino-4-fluorobenzyl alcohol (**1e**) (1.0 mmol, 141 mg), benzoyl isothiocyanate (**2a**) (1.0 mmol, 163 mg), Et_3N (2.2 mmol, 222 mg), T3P anhydride solution (≥50 wt. % in ethyl acetate) in 2 mL MeCN were performed to obtain the desired *N*-(7-fluoro-4*H*-benzo[*d*][1,3]thiazin-2-yl)benzamide (**5ea**) in 90% (258 mg) yield as off-white solid.

***N*-(7-fluoro-4*H*-benzo[*d*][1,3]thiazin-2-yl)benzamide (5ea)** (Scheme 4): **Off-white solid**; $\mathbf{R_f}$ = 0.50 (SiO_2, Hexane/EtOAc = 8:2); **Purification system**: CombiFlash MPLC (Hexane/EtOAc = 85:15); **Yield**: 258 mg (90%); **m.p** = 108 - 109 °C; **^{1}H NMR** (400 MHz, DMSO-d_6) δ = 11.65 (br, 1H), 8.07 (d, *J* = 7.6 Hz, 2H), 7.56 (t, *J* = 7.2 Hz, 1H), 7.47 (t, *J* = 7.6 Hz, 2H), 7.28 (t, *J* = 7.2 Hz, 1H) 7.00 - 6.94 (m, 2H), 3.94 (s, 2H) ppm; **^{13}C{^{1}H} NMR** (100 MHz, DMSO-d_6) δ = 172.0 (less intense), 162.1 (d, *J* = 242.2 Hz), 140.6, 135.2, 132.7, 129.3, 128.9, 128.8, 117.6, 111.7 (d, *J* = 20.1 Hz), 106.9, 27.6 ppm; **HRMS** (**ESI-QTOF,** $[M + H]^+$): calculated for $C_{15}H_{12}FN_2OS$: 287.0654; found: 287.0653.

Synthesis of *N*-(8-fluoro-4*H*-benzo[*d*][1,3]thiazin-2-yl)benzamide (5fa)

According to the general procedure, reactions between 2-amino-3-fluorobenzyl alcohol (**1f**) (1.0 mmol, 141 mg), benzoyl isothiocyanate (**2a**) (1.0 mmol, 163 mg), Et_3N (2.2 mmol, 222 mg), T3P anhydride solution (≥50 wt. % in ethyl acetate) in 2 mL MeCN were performed to obtain the desired *N*-(8-fluoro-4*H*-benzo[*d*][1,3]thiazin-2-yl)benzamide (**5fa**) in 89% (255 mg) yield as off-white solid.

***N*-(8-fluoro-4*H*-benzo[*d*][1,3]thiazin-2-yl)benzamide (5fa)** (Scheme 4): **Off-white solid**; $\mathbf{R_f}$ = 0.50 (SiO_2, Hexane/EtOAc = 8:2); **Purification system**: CombiFlash MPLC (Hexane/EtOAc = 85:15); **Yield**: 255 mg (89%); **m.p** = 124 - 125 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 11.25 (br, 1H), 8.13 (d, *J* = 6.8 Hz, 2H), 7.53 (d, *J* = 6.8 Hz, 1H), 7.46 (t, *J* = 6.4 Hz, 2H), 7.10 (d, *J* = 7.6 Hz, 2H), 6.97 (d, *J* = 6.6 Hz, 1H), 4.02 (s, 2H) ppm; **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ = 172.0 (less intense), 164.0, 153.8 (d, *J* = 251.75 Hz), 134.7, 132.6, 128.9, 128.4, 125.8 (d, *J* = 8.40 Hz), 122.45, 122.1, 115.2 (d, *J* = 19.40 Hz), 28.7 ppm; **MS** (APCI): $[M + 1]^+$ = 287.0 (100%); **HRMS** (**ESI-QTOF,** $[M + H]^+$): calculated for $C_{15}H_{12}FN_2OS$: 287.0654; found: 287.0650.

Synthesis of *N*-(6-chloro-4*H*-benzo[*d*][1,3]thiazin-2-yl)benzamide (5ga)

According to the general procedure, reactions between 2-amino-5-chlorobenzyl alcohol (**1g**) (1.0 mmol, 157.6 mg), benzoyl isothiocyanate (**2a**) (1.0 mmol, 163 mg), Et_3N (2.2 mmol, 222 mg), T3P anhydride solution (≥50 wt. % in ethyl acetate) in 2 mL MeCN were performed to obtain the desired *N*-(6-chloro-4*H*-benzo[*d*][1,3]thiazin-2-yl)benzamide (**5ga**) in 95% (287 mg) yield as white solid.

***N*-(6-chloro-4*H*-benzo[*d*][1,3]thiazin-2-yl)benzamide (5ga)** (Scheme 4): **White solid**; $\mathbf{R_f}$ = 0.50 (SiO_2, Hexane/EtOAc = 8:2); **Purification system**: CombiFlash MPLC (Hexane/EtOAc = 85:15); **Yield**: 287 mg (95%); **m.p** = 148 - 149 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 11.02 (br, 1H), 8.04 (d, *J* = 7.2 Hz, 2H), 7.51 (t, *J* = 7.6 Hz, 1H), 7.41 (t, *J* = 7.6 Hz, 2H), 7.21 (dd, *J* = 2.0, 8.4 Hz, 1H) 7.13 (s, 1H), 6.92 (d, *J* = 7.6 Hz, 1H), 3.91 (s, 2H) ppm; **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ = 172.1 (less intense), 162.4 (less intense), 137.3, 134.4, 132.6, 130.8, 128.7, 128.6, 128.4, 127.0, 122.3, 121.6, 28.7 ppm; **HRMS** (**ESI-QTOF,** $[M + H]^+$): calculated for $C_{15}H_{12}ClN_2OS$: 303.0358; found: 303.0350.

Synthesis of *N*-(7-chloro-4*H*-benzo[*d*][1,3]thiazin-2-yl)benzamide (5ha)

According to the general procedure, reactions between 2-amino-4-chlorobenzyl alcohol (**1h**) (1.0 mmol, 157.6 mg), benzoyl isothiocyanate (**2a**) (1.0 mmol, 163 mg), Et_3N (2.2 mmol, 222 mg), T3P anhydride solution (≥50 wt. % in ethyl acetate) in 2 mL MeCN were performed to obtain the desired *N*-(7-chloro-4*H*-benzo[*d*][1,3]thiazin-2-yl)benzamide (**5ha**) in 90% (272 mg) yield as white solid.

-(7-chloro-4*H*-benzo[*d*][1,3]thiazin-2-yl)benzamide (5ha) (Scheme 4): **White solid**; $\mathbf{R_f}$ = 0.50 (SiO_2, Hexane/EtOAc = 8:2); **Purification system**: CombiFlash MPLC (Hexane/EtOAc = 85:15); **Yield**: 272 mg (90%); **m.p** = 151 - 152 °C; **^{1}H NMR** (400 MHz, DMSO-d_6) δ = 11.72 (br, 1H), 8.06 (d, *J* = 7.6 Hz, 2H), 7.57 (t, *J* = 7.2 Hz, 1H), 7.48 (t, *J* = 7.6 Hz, 2H), 7.28 (d, *J* = 7.6 Hz, 1H) 7.19 (d, *J* = 8.0 Hz, 2H), 3.95 (s, 2H) ppm; **^{13}C{^{1}H} NMR** (100 MHz, DMSO-d_6) δ = 136.3(less intense), 132.7, 132.6, 129.3, 128.9, 128.8, 124.9, 120.5, 27.7 ppm; **MS** (APCI): $[M + 1]^+$ = 303.0 (100%); **HRMS** (**ESI-QTOF,** $[M + H]^+$): calculated for $C_{15}H_{12}ClN_2OS$: 303.0358; found: 303.0354.

Synthesis of *N*-(7-(trifluoromethyl)-4*H*-benzo[*d*][1,3]thiazin-2-yl)benzamide (5ia)

According to the general procedure, reactions between 2-amino-4-(trifluoromethyl)benzyl alcohol (**1i**) (1.0 mmol, 191 mg), benzoyl isothiocyanate (**2a**) (1.0 mmol, 163 mg), Et_3N (2.2 mmol, 222 mg), T3P anhydride solution (≥50 wt. % in ethyl acetate) in 2 mL MeCN were performed to obtain the desired *N*-(7-(trifluoromethyl)-4*H*-benzo[*d*][1,3]thiazin-2-yl)benzamide (**5ia**) in 90% (303 mg) yield as white solid.

***N*-(7-(trifluoromethyl)-4*H*-benzo[*d*][1,3]thiazin-2-yl)benzamide (5ia)** (Scheme 4): **White solid**; $\mathbf{R_f}$ = 0.50 (SiO_2, Hexane/EtOAc = 8:2); **Purification system**: CombiFlash MPLC (Hexane/EtOAc = 86:14); **Yield**: 303 mg (90%); **m.p** = 116 - 117 °C; **^{1}H NMR** (400 MHz, DMSO-d_6) δ = 11.82 (br, 1H), 8.05 (d, *J* = 7.2 Hz, 2H), 7.57 (t, *J* = 7.2 Hz, 1H), 7.50 - 7.47 (m, 5H), 4.05 (s, 2H) ppm; **^{13}C{^{1}H} NMR** (100 MHz, DMSO-d_6) δ = 134.8, 132.8, 129.3, 129.2 (q,

J = 31.8 Hz), 128.5, 126.1, 124.7 (q, *J* = 272.1 Hz),121.7, 116.3, 27.9 ppm; **MS** (APCI): $[M + 1]^+$ = 337.0 (98.57%); **HRMS** (**ESI-QTOF,** $[M + H]^+$): calculated for $C_{16}H_{12}F_3N_2OS$: 337.0622; found: 337.0618.

Synthesis of *N*-phenyl-4*H*-benzo[*d*][1,3]thiazin-2-amine (5ab)

According to the general procedure, reactions between 2-aminobenzyl alcohol (**1a**) (1.0 mmol, 123 mg), phenyl isothiocyanate (**2b**) (1.0 mmol, 135 mg), Et_3N (2.2 mmol, 222 mg), T3P anhydride solution (≥50 wt. % in ethyl acetate) in 2 mL MeCN were performed to obtain the desired *N*-phenyl-4*H*-benzo[*d*][1,3]thiazin-2-amine (**5ab**) in 96% (231 mg) yield as white solid.

***N*-phenyl-4*H*-benzo[*d*][1,3]thiazin-2-amine (5ab)**[24] (Scheme 5 and 7): **White solid**; $\mathbf{R_f}$ = 0.60 (SiO_2, Hexane/EtOAc = 8:2); **Purification system**: CombiFlash MPLC (Hexane/EtOAc = 88:12); **Yield**: 231 mg (96%); **m.p** = 201 - 202 °C (Lit[24] 203 °C); **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.41 (d, *J* = 7.2 Hz, 2H), 7.35 (t, *J* = 8.0 Hz, 2H), 7.25 (t, *J* = 7.2 Hz, 1H), 7.12 (d, *J* = 7.6 Hz, 1H), 7.09 - 7.03 (m, 3H), 3.92 (s, 2H) ppm; **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ = 152.0, 142.9, 142.5, 128.9, 128.4, 126.6, 123.7, 122.1, 121.1, 120.0, 29.9 ppm; **MS** (APCI): $[M + 1]^+$ = 241.1 (94.62%); **HRMS** (**ESI-QTOF,** $[M + H]^+$): calculated for $C_{14}H_{13}N_2S$: 241.0799; found: 241.0790.

Synthesis of *N*-(2,4-dimethylphenyl)-4*H*-benzo[*d*][1,3]thiazin-2-amine (5ac)

According to the general procedure, reactions between 2-aminobenzyl alcohol (**1a**) (1.0 mmol, 123 mg), 2,4-dimethylphenyl isothiocyanate (**2c**) (1.0 mmol, 163 mg), Et_3N (2.2 mmol, 222 mg), T3P anhydride solution (≥50 wt. % in ethyl acetate) in 2 mL MeCN were performed to obtain the desired *N*-(2,4-dimethylphenyl)-4*H*-benzo[*d*][1,3]thiazin-2-amine (**5ac**) in 89% (239 mg) yield as off-white solid.

***N*-(2,4-dimethylphenyl)-4*H*-benzo[*d*][1,3]thiazin-2-amine (5ac)** (Scheme 5): **Off-white solid**; $\mathbf{R_f}$ = 0.40 (SiO_2, Hexane/EtOAc = 8:2); **Purification system**: CombiFlash MPLC (Hexane/EtOAc = 85:15); **Yield**: 239 mg (89%); **m.p** = 176 - 177 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.22 (d, *J* = 8.0 Hz, 1H), 7.17 (s, 1H), 7.12 - 7.07 (m, 2H), 7.02 (d, *J* = 7.2 Hz, 1H), 6.97 (t, *J* = 8.0 Hz, 1H), 6.88 (d, *J* = 7.2 Hz, 1H), 3.89 (s, 2H), 2.32 (s, 3H), 2.21 (S, 3H) ppm; **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ = 153.6, 142.6, 142.0, 136.0, 130.2, 128.3, 127.2, 126.6, 125.2, 123.9, 122.8, 120.2, 29.7, 21.0, 17.5 ppm; **MS** (APCI): $[M + 1]^+$ = 269.1 (98.91%); **HRMS** (**ESI-QTOF,** $[M + H]^+$): calculated for $C_{16}H_{17}N_2S$: 269.1112; found: 269.1108.

Synthesis of *N*-(*p*-tolyl)-4*H*-benzo[*d*][1,3]thiazin-2-amine (5ad)

According to the general procedure, reactions between 2-aminobenzyl alcohol (**1a**) (1.0 mmol, 123 mg), *p*-tolyl isothiocyanate (**2d**) (1.0 mmol, 149 mg), Et_3N (2.2 mmol, 222 mg), T3P anhydride solution (≥50 wt. % in ethyl acetate) in 2 mL MeCN were performed to obtain the desired *N*-(*p*-tolyl)-4*H*-benzo[*d*][1,3]thiazin-2-amine (**5ad**) in 91% (231 mg) yield as off-white solid.

***N*-(*p*-tolyl)-4*H*-benzo[*d*][1,3]thiazin-2-amine (5ad)**[25] (Scheme 5): **Off-white solid**; $\mathbf{R_f}$ = 0.60 (SiO_2, Hexane/EtOAc = 8:2); **Purification system**: CombiFlash MPLC (Hexane/EtOAc = 90:10); **Yield**: 231 mg (91%); **m.p** = 186 - 188 °C (Lit[25] 188 - 189 °C); **^{1}H NMR** (400 MHz, DMSO-d_6) δ = 9.32 (br, 1H), 7.71 (s, 2H), 7.24 - 7.15 (m, 2H), 7.08 (d, *J* = 8.0 Hz, 2H) 7.02 (d, *J* = 7.2 Hz, 2H), 4.00 (s, 2H), 2.24 (s, 3H) ppm; **^{13}C{^{1}H} NMR** (100 MHz, DMSO-d_6) δ = 150.7, 145.0, 139.3, 131.7, 129.4, 128.3, 127.2, 123.5, 120.7, 120.5, 29.1, 20.8 ppm; **MS** (APCI): $[M + 1]^+$ = 255.1 (99.61%); **HRMS** (**ESI-QTOF,** $[M + H]^+$): calculated for $C_{15}H_{15}N_2S$: 255.0955; found: 255.0950.

Synthesis of *N*-(2-methoxyphenyl)-4*H*-benzo[*d*][1,3]thiazin-2-amine (5ae)

According to the general procedure, reactions between 2-aminobenzyl alcohol (**1a**) (1.0 mmol, 123 mg), 2-methoxyphenyl isothiocyanate (**2e**) (1.0 mmol, 165 mg), Et_3N (2.2 mmol, 222 mg), T3P anhydride solution (≥50 wt. % in ethyl acetate) in 2 mL MeCN were performed to obtain the desired *N*-(2-methoxyphenyl)-4*H*-benzo[*d*][1,3]thiazin-2-amine (**5ae**) in 90% (243 mg) yield as white solid.

***N*-(2-methoxyphenyl)-4*H*-benzo[*d*][1,3]thiazin-2-amine (5ae)**[25] (Scheme 5): **White solid**; $\mathbf{R_f}$ = 0.60 (SiO_2, Hexane/EtOAc = 8:2); **Purification system**: CombiFlash MPLC (Hexane/EtOAc = 90:10); **Yield**: 243 mg (90%); **m.p** = 116 - 118 °C (Lit[25] 116 - 117 °C); **^{1}H NMR** (400 MHz, DMSO-d_6) δ = 10.15 (br, 1H), 8.20 (br, 1H), 7.21 -

7.15 (m, 2H), 7. 01 - 6.88 (m, 5H), 3.94 (s, 2H), 3.75 (s, 3H) ppm; **$^{13}C\{^1H\}$ NMR** (100 MHz, DMSO-d_6) δ = 152.1, 151.0, 143.23, 128.3, 127.2, 124.3, 123.2, 122.9, 120.9, 120.7, 111.8, 55.9, 28.9 ppm; **MS** (APCI): $[M + 1]^+$ = 271.1 (98.42%); **HRMS** (**ESI-QTOF,** $[M + H]^+$): calculated for $C_{15}H_{15}N_2OS$: 271.0905; found: 271.0900.

Synthesis of *N*-(4-methoxyphenyl)-4*H*-benzo[*d*][1,3]thiazin-2-amine (5af)

According to the general procedure, reactions between 2-aminobenzyl alcohol (**1a**) (1.0 mmol, 123 mg), 4-methoxyphenyl isothiocyanate (**2f**) (1.0 mmol, 165 mg), Et_3N (2.2 mmol, 222 mg), T3P anhydride solution (≥50 wt. % in ethyl acetate) in 2 mL MeCN were performed to obtain the desired *N*-(4-methoxyphenyl)-4*H*-benzo[*d*][1,3]thiazin-2-amine (**5af**) in 94% (254 mg) yield as pink solid.

***N*-(4-methoxyphenyl)-4*H*-benzo[*d*][1,3]thiazin-2-amine (5af)**[25] (Scheme 5): **Pinkish solid**; $\mathbf{R_f}$ = 0.50 (SiO_2, Hexane/EtOAc = 8:2); **Purification system**: CombiFlash MPLC (Hexane/EtOAc = 85:15); **Yield**: 254 mg (94%); **m.p** = 180 - 181 °C (Lit[25] 179 - 180 °C); **^{1}H NMR** (400 MHz, DMSO-d_6) δ = 9.27 (br, 1H), 7.74 (s, 2H), 7.24 - 7.14 (m, 2H), 7. 00 (d, *J* = 7.6 Hz, 2H), 6.86 (d, *J* = 7.6 Hz, 2H), 3.98 (s, 2H), 3.71 (s, 3H) ppm; **$^{13}C\{^1H\}$ NMR** (100 MHz, DMSO-d_6) δ = 155.2, 150.7, 145.0, 135.4, 128.3, 127.2, 123.3, 121.9, 120.8, 114.8, 114.2, 113.5, 55.6, 29.1 ppm; **MS** (APCI): $[M + 1]^+$ = 271.1 (99.78%); **HRMS** (**ESI-QTOF,** $[M + H]^+$): calculated for $C_{15}H_{15}N_2OS$: 271.0905; found: 271.0903.

Synthesis of *N*-(3-fluorophenyl)-4*H*-benzo[*d*][1,3]thiazin-2-amine (5ag)

According to the general procedure, reactions between 2-aminobenzyl alcohol (**1a**) (1.0 mmol, 123 mg), 3-fluorophenyl isothiocyanate (**2g**) (1.0 mmol, 153 mg), Et_3N (2.2 mmol, 222 mg), T3P anhydride solution (≥50 wt. % in ethyl acetate) in 2 mL MeCN were performed to obtain the desired *N*-(3-fluorophenyl)-4*H*-benzo[*d*][1,3]thiazin-2-amine (**5ag**) in 93% (240 mg) yield as white solid.

***N*-(3-fluorophenyl)-4*H*-benzo[*d*][1,3]thiazin-2-amine (5ag)** (Scheme 5): **White solid**; $\mathbf{R_f}$ = 0.50 (SiO_2, Hexane/EtOAc = 8:2); **Purification system**: CombiFlash MPLC (Hexane/EtOAc = 87:13); **Yield**: 240 mg (93%); **m.p** = 189 - 190 °C; **^{1}H NMR** (400 MHz, DMSO-d_6) δ = 9.66 (br, 1H), 7.94 (br, 1H), 7.52 (br, 1H), 7.32 - 7.17 (m, 3H), 7.08 - 7.04 (m, 2H), 6.79 (t, *J* = 7.6 Hz, 1H), 4.03 (s, 2H) ppm; **$^{13}C\{^1H\}$ NMR** (100 MHz, DMSO-d_6) δ = 162.6 (d, *J* = 240.9 Hz), 151.0, 144.4, 130.5 (d, *J* = 10.1 Hz), 128.45, 127.3, 124.7, 120.7, 116.0, 109.2 (d, *J* = 20..9 Hz), 106.9, 29.0 ppm; **HRMS** (**ESI-QTOF,** $[M + H]^+$): calculated for $C_{14}H_{12}FN_2S$: 259.0705; found: 259.0703.

Synthesis of *N*-(3,5-bis(trifluoromethyl)phenyl)-4*H*-benzo[*d*][1,3]thiazin-2-amine (5ah)

According to the general procedure, reactions between 2-aminobenzyl alcohol (**1a**) (1.0 mmol, 123 mg), 3,5-bis(trifluoromethyl)phenyl isothiocyanate (**2h**) (1.0 mmol, 271 mg), Et_3N (2.2 mmol, 222 mg), T3P anhydride solution (≥50 wt. % in ethyl acetate) in 2 mL MeCN were performed to obtain the desired *N*-(3,5-bis(trifluoromethyl)phenyl)-4*H*-benzo[*d*][1,3]thiazin-2-amine (**5ah**) in 91% (342 mg) yield as white solid.

***N*-(3,5-bis(trifluoromethyl)phenyl)-4*H*-benzo[*d*][1,3]thiazin-2-amine (5ah)** (Scheme 5): **White solid**; $\mathbf{R_f}$ = 0.50 (SiO_2, Hexane/EtOAc = 8:2); **Purification system**: CombiFlash MPLC (Hexane/EtOAc = 85:15); **Yield**: 342 mg (91%); **m.p** = 139 - 140 °C; **^{1}H NMR** [VT@90deg] (400 MHz, DMSO-d_6) δ = 9.90 (br, 1H), 8.59 (br, 2H), 7.58 (s, 1H), 7.27 (t, *J* = 7.6 Hz, 1H), 7.21 (d, *J* = 6.8 Hz, 1H), 7.08 - 7.03 (m, 2H), 4.08 (s, 2H) ppm; **$^{13}C\{^1H\}$ NMR** (100 MHz, DMSO-d_6) δ = 150.9, 144.5, 142.7, 131.0 (q, *J* = 32.5 Hz), 128.6, 127.4, 125.1, 123.8 (q, *J* = 232.5 Hz), 120.5, 119.2, 114.9, 29.0 ppm; **MS** (APCI): $[M + 1]^+$ = 377.0 (99.85%); **HRMS** (**ESI-QTOF,** $[M + H]^+$): calculated for $C_{16}H_{11}F_6N_2S$: 377.0547; found: 377.0540.

Synthesis of *N*-(4-(trifluoromethyl)phenyl)-4*H*-benzo[*d*][1,3]thiazin-2-amine (5ai)

According to the general procedure, reactions between 2-aminobenzyl alcohol (**1a**) (1.0 mmol, 123 mg), 4-(trifluoromethyl)phenyl isothiocyanate (**2i**) (1.0 mmol, 203 mg), Et_3N (2.2 mmol, 222 mg), T3P anhydride solution (≥50 wt. % in ethyl acetate) in 2 mL MeCN were performed to obtain the desired *N*-(4-(trifluoromethyl)phenyl)-4*H*-benzo[*d*][1,3]thiazin-2-amine (**5ai**) in 90% (277 mg) yield as white solid.

***N*-(4-(trifluoromethyl)phenyl)-4*H*-benzo[*d*][1,3]thiazin-2-amine (5ai)** (Scheme 5): **White solid**; $\mathbf{R_f}$ = 0.50 (SiO_2, Hexane/EtOAc = 8:2); **Purification system**: CombiFlash MPLC (Hexane/EtOAc = 85:15); **Yield**: 277 mg (90%); **m.p** = 228 - 229 °C; **^{1}H NMR** [VT@90deg] (400 MHz, DMSO-d_6) δ = 9.50 (br, 1H), 8.01 (br, 2H), 7.59 (d, J = 7.6 Hz, 2H), 7.23 (t, J = 7.6 Hz, 1H), 7.21 (d, J = 8.0 Hz, 1H), 7.11 (d, J = 7.6 Hz, 1H), 7.05 - 7.01 (m, 1H), 4.03 (s, 2H) ppm; **^{13}C{^{1}H} NMR** (100 MHz, DMSO-d_6) δ = 150.5, 145.0, 144.5, 129.0, 127.3, 126.3, 126.2, 124.7 (q, J = 242.57 Hz), 122.8 (q, J = 32.3 Hz), 122.4, 120.9, 120.6, 119.6, 29.0 ppm; **HRMS** (**ESI-QTOF,** $[M + H]^+$): calculated for $C_{15}H_{12}F_3N_2S$: 309.0673; found: 309.0680.

Synthesis of *N*-(2-methyl-4-nitrophenyl)-4*H*-benzo[*d*][1,3]thiazin-2-amine (5aj)

According to the general procedure, reactions between 2-aminobenzyl alcohol (**1a**) (1.0 mmol, 123 mg), 2-methyl-4-nitrophenyl isothiocyanate (**2j**) (1.0 mmol, 194 mg), Et_3N (2.2 mmol, 222 mg), T3P anhydride solution (≥50 wt. % in ethyl acetate) in 2 mL MeCN were performed to obtain the desired *N*-(2-methyl-4-nitrophenyl)-4*H*-benzo[*d*][1,3]thiazin-2-amine (**5aj**) in 88% (263 mg) yield as yellow solid.

***N*-(2-methyl-4-nitrophenyl)-4*H*-benzo[*d*][1,3]thiazin-2-amine (5aj)** (Scheme 5): **Yellow solid**; $\mathbf{R_f}$ = 0.35 (SiO_2, Hexane/EtOAc = 8:2); **Purification system**: CombiFlash MPLC (Hexane/EtOAc = 80:20); **Yield**: 263 mg (88%); **m.p** = 243 - 245 °C; **^{1}H NMR** (400 MHz, DMSO-d_6) δ = 10.65 (br, 1H), 8.09 (s, 1H), 7.98 (d, J = 7.2 Hz, 1H), 7.21 (d, J = 7.6 Hz, 2H), 7.08 (d, J = 7.2 Hz, 1H), 6.94 - 6.92 (m, 2H), 4.01 (s, 2H), 2.20 (s, 3H) ppm; **^{13}C{^{1}H} NMR** (100 MHz, DMSO-d_6) δ = 155.1, 153.3, 142.9, 139.9, 131.5, 128.5, 127.3, 125.6, 123.4, 122.8, 122.5, 122.5, 120.8, 117.6, 28.6, 18.1 ppm; **HRMS** (**ESI-QTOF,** $[M + H]^+$): calculated for $C_{15}H_{14}N_3O_2S$: 300.0806; found: 300.0800.

Synthesis of ethyl (4*H*-benzo[*d*][1,3]thiazin-2-yl)carbamate (5ak)

According to the general procedure, reactions between 2-aminobenzyl alcohol (**1a**) (1.0 mmol, 123 mg), ethoxycarbonyl Isothiocyanate (**2k**) (1.0 mmol, 131 mg), Et_3N (2.2 mmol, 222 mg), T3P anhydride solution (≥50 wt. % in ethyl acetate) in 2 mL MeCN were performed to obtain the desired ethyl (4*H*-benzo[*d*][1,3]thiazin-2-yl)carbamate (**5ak**) in 93% (220 mg) yield as white crystalline solid.

Ethyl (4*H*-benzo[*d*][1,3]thiazin-2-yl)carbamate (5ak) (Scheme 5): **White crystalline solid**; $\mathbf{R_f}$ = 0.60 (SiO_2, Hexane/EtOAc = 8:2); **Purification system**: CombiFlash MPLC (Hexane/EtOAc = 90:10); **Yield**: 220 mg (93%); **m.p** = 93 - 94 °C; **^{1}H NMR** (400 MHz, DMSO-d_6) δ = 7.30 - 7.26 (m, 1H), 7.15 - 7.11 (m, 2H), 6.97 (d, J = 8.0 Hz, 1H), 4.21 (q, J = 7.2 Hz, 2H), 3.97 (s, 2H), 1.32 (t, J = 6.8 Hz, 3H) ppm; **^{13}C{^{1}H} NMR** (100 MHz, DMSO-d_6) δ = 161.3, 157.6, 140.0, 128.5, 127.2, 125.1, 120.9, 61.3, 28.1, 14.8 ppm; **HRMS** (**ESI-QTOF,** $[M + H]^+$): calculated for $C_{11}H_{13}N_2O_2S$: 237.0697; found: 237.0695.

Synthesis of *N*-(furan-2-ylmethyl)-4*H*-benzo[*d*][1,3]thiazin-2-amine (5al)

According to the general procedure, reactions between 2-aminobenzyl alcohol (**1a**) (1.0 mmol, 123 mg), 2-(isothiocyanatomethyl)furan (**2l**) (1.0 mmol, 139 mg), Et_3N (2.2 mmol, 222 mg), T3P anhydride solution (≥50 wt. % in ethyl acetate) in 2 mL MeCN were performed to obtain the desired *N*-(furan-2-ylmethyl)-4*H*-benzo[*d*][1,3]thiazin-2-amine (**5al**) in 85% (208 mg) yield as off-white solid.

***N*-(furan-2-ylmethyl)-4*H*-benzo[*d*][1,3]thiazin-2-amine (5al)** (Scheme 5): **Off-white solid**; $\mathbf{R_f}$ = 0.40 (SiO_2, Hexane/EtOAc = 8:2); **Purification system**: CombiFlash MPLC (Hexane/EtOAc = 85:15); **Yield**: 208 mg (85%); **m.p** = 104 - 105 °C; **^{1}H NMR** (400 MHz, DMSO-d_6) δ = 7.75 (s, 1H), 7.55 (s, 1H), 7.15 (t, J = 7.6 Hz, 1H), 7.10 (d, J = 7.6 Hz, 1H), 6.93 (t, J = 7.6 Hz, 2H), 6.36 (s, 1H), 6.29 (s, 1H), 4.54(s, 2H), 3.89 (s, 2H) ppm; **^{13}C{^{1}H} NMR** (100 MHz, DMSO-d_6) δ = 153.3, 152.8, 146.2 142.3, 128.2, 127.1, 124.3, 122.9, 120.6, 110.9, 107.7, 38.5, 29.0 ppm; **MS** (APCI): $[M + 1]^+$ = 245.1 (99.73%); **HRMS** (**ESI-QTOF,** $[M + H]^+$): calculated for $C_{13}H_{13}N_2OS$: 245.0748; found: 245.0743.

Synthesis of *N*-(*o*-tolyl)-4*H*-benzo[*d*][1,3]thiazin-2-amine (5ao)

According to the general procedure, reactions between 2-aminobenzyl alcohol (**1a**) (1.0 mmol, 123 mg), *o*-tolyl isothiocyanate (**2o**) (1.0 mmol, 149 mg), Et_3N (2.2 mmol, 222 mg), T3P anhydride solution (≥50 wt. % in ethyl acetate)

in 2 mL MeCN were performed to obtain the desired *N*-(*o*-tolyl)-4*H*-benzo[*d*][1,3]thiazin-2-amine (**5ao**) in 95% (241 mg) yield as white solid.

***N*-(*o*-tolyl)-4*H*-benzo[*d*][1,3]thiazin-2-amine (5ao)**[25] (Scheme 5): **White solid**; $\mathbf{R_f}$ = 0.60 (SiO_2, Hexane/EtOAc = 8:2); **Purification system**: CombiFlash MPLC (Hexane/EtOAc = 86:14); **Yield**: 241 mg (95%); **m.p** = 168 - 169 °C (Lit[25] 169 - 170 °C); **^{1}H NMR** (400 MHz, DMSO-d_6) δ = 10.15 (br, 1H), 7.19 - 7.15 (m, 3H), 7.09 (t, *J* = 7.2 Hz, 1H) 7.04 - 6.90 (m, 3H), 3.93 (s, 2H), 2.13 (s, 3H) ppm; **^{13}C{^{1}H} NMR** (100 MHz, DMSO-d_6) δ = 152.5, 142.2, 130.5, 128.3, 127.1, 126.4, 124.1, 123.5, 122.3, 120.9, 119.3, 28.8, 18.3 ppm; **MS** (APCI): $[M + 1]^+$ = 254.82 (99.74%); **HRMS** (**ESI-QTOF,** $[M + H]^+$): calculated for $C_{15}H_{15}N_2S$: 255.0955; found: 255.0948.

Synthesis of ethyl 3-((4*H*-benzo[*d*][1,3]thiazin-2-yl)amino)propanoate (5ap)

According to the general procedure, reactions between 2-aminobenzyl alcohol (**1a**) (1.0 mmol, 123 mg), ethyl 3-(furfurylthio)propionate (**2p**) (1.0 mmol, 214 mg), Et_3N (2.2 mmol, 222 mg), T3P anhydride solution (≥50 wt. % in ethyl acetate) in 2 mL MeCN were performed to obtain the desired ethyl 3-((4*H*-benzo[*d*][1,3]thiazin-2-yl)amino)propanoate (**5ap**) in 93% (246 mg) yield as white solid.

Ethyl 3-((4*H*-benzo[*d*][1,3]thiazin-2-yl)amino)propanoate (5ap) (Scheme 5): **White solid**; $\mathbf{R_f}$ = 0.60 (SiO_2, Hexane/EtOAc = 8:2); **Purification system**: CombiFlash MPLC (Hexane/EtOAc = 90:10); **Yield**: 246 mg (93%); **m.p** = 59 - 60 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.25 (d, *J* = 7.6 Hz, 1H), 7.08 (t, *J* = 8.0 Hz, 2H), 7.0 (d, *J* = 7.6 Hz, 1H), 4.16 (q, *J* = 7.2 Hz, 2H), 3.86 (s, 2H), 3.67 (t, *J* = 6.8 Hz, 2H), 3.60 (t, *J* = 6.6 Hz, 2H), 1.27 (t, *J* = 6.8 Hz, 3H) ppm; **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ = 172.5, 153.4, 145.7, 128.2, 126.5, 124.4, 123.3, 119.9, 60.6, 37.8, 34.1, 29.9, 14.1 ppm; **MS** (APCI): $[M + 1]^+$ = 265.1 (99.36%); **HRMS** (**ESI-QTOF,** $[M + H]^+$): calculated for $C_{13}H_{17}N_2O_2S$: 265.1010; found: 265.1009.

Synthesis of *N*-(pyridin-3-yl)-4*H*-benzo[*d*][1,3]thiazin-2-amine (5aq)

According to the general procedure, reactions between 2-aminobenzyl alcohol (**1a**) (1.0 mmol, 123 mg), 3-pyridyl isothiocyanate (**2q**) (1.0 mmol, 136 mg), Et_3N (2.2 mmol, 222 mg), T3P anhydride solution (≥50 wt. % in ethyl acetate) in 2 mL MeCN were performed to obtain the desired *N*-(pyridin-3-yl)-4*H*-benzo[*d*][1,3]thiazin-2-amine (**5aq**) in 90% (217 mg) yield as brown solid.

***N*-(pyridin-3-yl)-4*H*-benzo[*d*][1,3]thiazin-2-amine (5aq)** (Scheme 5): **Brown solid**; $\mathbf{R_f}$ = 0.15 (SiO_2, Hexane/EtOAc = 8:2); **Purification system**: CombiFlash MPLC (Hexane/EtOAc = 70:30); **Yield**: 217 mg (90%); **m.p** = 145 - 146 °C; **^{1}H NMR** (400 MHz, DMSO-d_6) δ = 9.68 (br, 1H), 8.92 (br, 1H), 8.32 (br, 1H), 8.20 (d, *J* = 4.0 Hz, 1H), 7.32 - 7.30 (m, 1H), 7.30 - 7.17 (m, 2H), 7.08 (d, *J* = 7.6 Hz, 1H), 7.02 - 6.98 (m, 1H), 4.03 (s, 2H) ppm; **^{13}C{^{1}H} NMR** (100 MHz, DMSO-d_6) δ = 150.8 (less intense), 144.8, 143.6, 141.7, 137.9, 128.5, 127.3, 123.9, 120.7, 29.02 ppm; **HRMS** (**ESI-QTOF,** $[M + H]^+$): calculated for $C_{13}H_{12}N_3S$: 242.0751; found: 242.0753.

Synthesis of *N*-methyl-4*H*-benzo[*d*][1,3]thiazin-2-amine (5ar)

The reactions of *N*-(4*H*-benzo[*d*][1,3]thiazin-2-yl)benzamide (**5aa**) (1.0 mmol, 268 mg) was perfomed using K_2CO_3 (2.0 mmol, 276 mg) in 2 mL MeOH at 80 °C for 2 h to obtain 4*H*-benzo[*d*][1,3]thiazin-2-amine (**9aa**) in 95% (156 mg) yield as off-white solid.

The reactions of 4*H*-benzo[*d*][1,3]thiazin-2-amine (**9aa**) (0.75 mmol, 123 mg), methyl iodide (0.9 mmol, 128 mg), K_2CO_3 (1.5 mmol, 276 mg) in 2 mL MeOH at 80 °C for 12 h to obtain *N*-methyl-4*H*-benzo[*d*][1,3]thiazin-2-amine (**5ar**) in 30% (40 mg) yield as off-white solid.

***N*-methyl-4*H*-benzo[*d*][1,3]thiazin-2-amine (5ar)**[26] (Scheme 6): **Off-white solid**; $\mathbf{R_f}$ = 0.40 (SiO_2, Hexane/EtOAc = 8:2); **Purification system**: CombiFlash MPLC (DCM/EtOAc = 95:5); **Yield**: 40 mg (30%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.24 (t, *J* = 7.8 Hz, 1H), 7.13 (d, *J* = 8.0 Hz, 1H), 7.08 (d, *J* = 7.8 Hz, 1H), 7.01 (t, *J* = 7.1 Hz, 1H), 3.86 (s, 2H), 3.08 (s, 3H) ppm; **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ = 154.5, 145.9, 128.35, 126.5, 124.5, 123.3, 120.0, 30.0, 29.4 ppm; **MS** (APCI): $[M + 1]^+$ = 179.1 (99.36%); **HRMS** (**ESI-QTOF,** $[M + H]^+$): calculated for $C_9H_{11}N_2S$: 179.0642; found: 179.0640.

Synthesis of *N*-phenyl-4*H*-benzo[*d*][1,3]selenazin-2-amine (8aa)

According to the general procedure, reactions between 2-aminobenzyl alcohol (**1a**) (1.0 mmol, 123 mg), phenyl isoselenocyanate (**6a**) (1.0 mmol, 182 mg), Et_3N (2.2 mmol, 222 mg), T3P anhydride solution (≥50 wt. % in ethyl acetate) in 2 mL MeCN were performed to obtain the desired *N*-phenyl-4*H*-benzo[*d*][1,3]selenazin-2-amine (**8aa**) in 90% (259 mg) yield as off-white solid.

***N*-phenyl-4*H*-benzo[*d*][1,3]selenazin-2-amine (8aa)** (Scheme 6): **Off-white solid**; $\mathbf{R_f}$ = 0.50 (SiO_2, Hexane/EtOAc = 8:2); **Purification system**: CombiFlash MPLC (Hexane/EtOAc = 90:10); **Yield**: 259 mg (90%); **m.p** = 211 - 212 °C; **^{1}H NMR** (400 MHz, DMSO-d_6) δ = 10.36 (br, 2H), 9.45 (br, 1H), 7.85 (br, 1H), 7.28 (t, *J* = 8.0 Hz, 2H), 7.21 (t, *J* = 7.6 Hz, 2H), 7.06 (d, *J* = 7.6 Hz, 1H), 7.00 (t, *J* = 7.2 Hz, 2H), 3.97 (s, 2H) ppm; **^{13}C{^{1}H} NMR** (100 MHz, DMSO-d_6) δ = 147.9 (less intense), 146.8 (less intense), 141.3(less intense), 129.0, 128.1, 127.3, 125.1, 123.9, 122.9, 121.0, 120.0, 23.3 ppm; **HRMS** (**ESI-QTOF,** $[M + H]^+$): calculated for $C_{14}H_{13}N_2Se$: 289.0243; found: 289.0240.

ASSOCIATED CONTENT

The crystallographic data, copies of ^{1}H NMR, ^{13}C{H} NMR and LC-MS spectra for all synthesized compounds are available free of charge *via* the Internet at http://pubs.acs.org.

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Notes

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REFERENCES:

(1) (a) Hays, S. J.; Caprathe, B. W.; Gilmore, J. L.; Amin, N.; Emmerling, M. R.; Michael, W.; Nadimpalli, R.; Nath, R.; Raser, K. J.; Stafford, D.; Watson, D.; Wang, K.; Jaen, J. C. 2-Amino-4*H*-3,1-benzoxazin-4-ones as Inhibitors of C1r Serine Protease. *J. Med. Chem.* **1998**, *41*, 1060. (b) Zhang, P.; Terefenko, E. A.; Fensome, A.; Zhang, Z.; Zhu, Y.; Cohen, J.; Winnerker, R.; Wrobel, J.; Yardley, J. Potent Nonsteroidal Progesterone Receptor Agonists: Synthesis and SAR Study of 6-Aryl Benzoxazines. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 787. (c) Dias, N. Goossens, J.-F.; Baldeyrou, B.; Lansiaux, A.; Colson, P.; Di Salvo, A.; Bernal, J.; Turnbull, A.; Mincher, D. J.; Bailly, C. Oxoazabenzo[*de*]anthracenes Conjugated to Amino Acids: Synthesis and Evaluation as DNA-Binding Antitumor Agents. *Bioconjugate Chem.* **2005**, *16*, 949. (d) Jana, S.; Ashokan, A.; Kumar, S.; Verma, A.; Kumar, S. Copper-catalyzed trifluoromethylation of alkenes: synthesis of trifluoromethylated benzoxazines. *Org. Biomol. Chem.* **2015**, *13*, 8411. (e) Feng, M.; Tang, B.; Wang, N.; Xu, H.-X.; Jiang, X. Ligand Controlled Regiodivergent C_1 Insertion on Arynes forConstruction of Phenanthridinone and Acridone Alkaloids. *Angew. Chem. Int. Ed*. **2015**, *54*, 14960. (f) Shuler, S. A.; Yin, G.;

Krause, S. B.; Vesper, C. M.; Watson, D. A. Synthesis of Secondary Unsaturated Lactams via an Aza-Heck Reaction. *J. Am. Chem. Soc*. **2016**, *138*, 5218. (g) Ding, D.; Zhu, G.; Jiang, X. Ligand Controlled Pd(II)-Catalyzed Regiodivergent Carbonylation of Alkynes for Syntheses of Indolo[3,2-c]coumarins and Benzofuro[3,2-c]quinolinones. *Angew. Chem. Int. Ed*., **2018**, *57*, 9028.

(2) (a) Dondoni, A.; Battaglia, A.; Giorgianni, P.; Gilli, G.; Sacerdoti, M. Cycloaddition of *N*-Arylketenimines to Thiobenzophenones. Formation of 4*H*-3,1-Benzothiazine and 2-1minothietan Derivatives. *J. Chem. Soc., Chem. Commun.* **1977**, 43. (b) Dondoni, A.; Battaglia, A.; Giorgianni P. Selectivity in Ketenimine-Thioketone Cycloadditions. 1. 1,4- and 1,2-Addition Pathways and the Synthesis of 4*H*-3,1-Benzothiazines, 2-Iminothietanes, and Thioacrylamides. *J. Org. Chem*. **1980**, *45*, 3766. (c) Nomura, Y.; Hayama, T.; Takeuchi, Y.; Tomoda, S.; Kato, Y. The Willgerodt-Kindler Reaction between Polycyclic Aromatic Amines and Benzaldehyde. Formation of 1,3-Thiazines. *Bull. Chem. Soc. Jpn.* **1984**, *57*, 1276. (d) Carisi, P.; Mazzanti, G.; Zani, P.; Barbaro, G.; Battaglia, A.; Giorgianni, P. Chemistry of Silyl Thioketones. Part 3. Cycloaddition Reactions with Heterodienes (α-Nitrosostyrene and Ketene Imines), *J. Chem. Soc., Perkin Trans. 1* **1987**, 2647. (e) Nishio, T. Reaction of (1,ω)-*N*-Acylamino Alcohols with Lawesson's Reagent: Synthesis of Sulfur-Containing Heterocycles. *J. Org. Chem*. **1997**, *62*, 1106. (f) Nishio, T.; Sekiguchi, H.; Sulfur-containing Heterocycles Derived by Reaction of *N*-Thioacylamino Alcohols with Lawesson's Reagent and Saponification of *N*-Thioacylamino Esters. *Heterocycles* **2002**, *58*, 203. (g) Csomós, P.; Fodor, L.; Bernáth, G.; Sinkkonen, J.; Salminen, J.; Wiinamäki, K.; Pihlaja, K. Novel β-lactam condensed 3-thiaquinolines: An efficient synthesis and structural characterization. *Tetrahedron* **2008**, *64*, 1002. (h) Abaev, V. T.; Tsiunchik, F. A,; Gutnov, A. V.; Butin, A. V. Synthesis of 2,4-Difuryl-4*H*-3,1-benzothiazines *via* a Furan Ring Migration Reaction. *J. Heterocycl. Chem.* **2008**, *45*, 475. (i) Gimbert, C.; Vallribera, A. A Straightforward Synthesis of Benzothiazines. *Org. Lett.* **2009**, *11*, 269.

(3) (a) Hoechst, A. G. 3,1-Benzothiazine derivatives and process for their manufacture. GB1214000, **1970-11-25**. (b) Dreikorn, B. A. Tetrazolo- and triazolobenzothiazines. US Patent 4001227, **1975-12-22**. (c) El-Desoky, S. I.; Kandeel, E. M.; Abd-el-Rahman, A. H.; Schmidt, R. R. Synthesis and Reactions of 4*H*-3,1-Benzothiazines. *J. Heterocycl. Chem*. **1999**, *36*, 153. (d) Matysiak, J. Synthesis, antiproliferative and antifungal activities of some 2-(2,4-dihydroxyphenyl)-4*H*-3,1-benzothiazines. *Bioorg. Med. Chem*. **2006**, *14*, 2613. (e) Jie, H.; Yong, Y.; Lu, H.; ZhiGang, Y.; Fan, X.; Qi, S. Tandem addition-cyclization reaction catalyzed by ytterbium chloride: An efficient one-step synthesis of 2-amino-4*H*-3,1-benzothiazine. *Chin. Sci. Bull.* **2013**, *58*, 717.

(4) (a) Pelosi, S. S. 2-(3-Chloroanilino)-4*H*-3,1-benzothiazine. US 4002622, **1975-10-30**. (b) Rieu, J. P. Patoiseau, J. F.; John, G. W. Heterocyclic compounds for treating myocardial ischemia. US 6011032, **2000-1-4**. (c) Su, Y.; Guo, Q.; Wang, G. l. 2-Imino-tetrahydro-1,3-benzothiazine derivative and its preparing method. CN 1683349, **2005-02-28**. (d) Anzini, M.; Giordani, A.; Makovec, F. Amidine, thiourea and guanidine derivatives of 2-aminobenzothiazoles and aminobenzothiazines, novel pharmacological agents for the treatment of neurodegenerative pathologies. WO 2009/040331A2, **2009-4-2**.

(5) (a) Hari, A.; Miller, B. L. Rapid and Efficient Synthesis of 2-Amino-4*H*-benzothiazines. *Org. Lett*. **2000**, *2*, 3667. (b) Häcker, H.-G.; Grundmann, F.; Lohr, F.; Ottersbach, P. A.; Zhou, J.; Schnakenburg, G.; Gütschow, M. 2-Amino- and 2-Alkylthio-4*H*-3,1-benzothiazin-4-ones: Synthesis, Interconversion and Enzyme Inhibitory Activities. *Molecules* **2009**, *14*, 378. (c) Belz, T.; Ihmaid, S.; Al-Rawi, J.; Petrovski, S. Synthesis Characterization and Antibacterial, Antifungal Activity of N-(Benzyl Carbamoyl or Carbamothioyl)-2-hydroxy Substituted Benzamide and 2-Benzyl Amino-Substituted Benzoxazines. *Int. J. Med. Chem*. 2013, 1. http://dx.doi.org/10.1155/2013/436397. (d) Roydeva, P. G.; Beckmann, A.-M.; Stirnberg, M.; Cesar, J.; Kikelj, D.; Ilaš, J.; Gütschow, M. 3,1-Benzothiazines, 1,4-Benzodioxines and 1,4-Benzoxazines as Inhibitors of Matriptase-2: Outcome of a Focused Screening Approach. *Pharmaceuticals* **2016**, *9*, 2.

(6) (a) Larksarp, C.; Alper, H. A Simple Synthesis of 2-Substituted-4*H*-3,1-benzoxazin-4-ones by Palladium-Catalyzed Cyclocarbonylation of *o*-Iodoanilines with Acid Chlorides. *Org. Lett*. **1999**, *1*, 1619. (b) Costa, M.; Cà, M. D.; Gabriele, B.; Massera, C.; Salerno, G. Soliani, M. Synthesis of 4*H*-3,1-Benzoxazines, Quinazolin-2-ones, and Quinoline-4-ones by Palladium-Catalyzed Oxidative Carbonylation of 2-Ethynylaniline Derivatives. *J. Org. Chem*. **2004**, *69*, 2469. (c) Ding, Q.; Wu, J. A Facile Route to 2,4-Dihydro-1*H*-benzo[*d*][1,3]thiazines *via* Silver-Catalyzed Tandem Addition-Cyclization Reactions. *J. Comb. Chem*. **2008**, *10*, 541. (d) Ding, Q.; Liu, X.; Yu, J.; Zhang, Q.; Wang, D.; Cao, B.; Peng, Y. Access to functionalized 4-benzylidene-4*H*-benzo[*d*][1,3]thiazines *via* tandem addition-cyclization/cross-coupling reactions. *Tetrahedron* **2012**, *68*, 3937. (e) Han, B.; Yang, X.-L.; Wang, C.; Bai,Y.-W.; Pan, T.-C.; Chen, X.; Yu, W. CuCl/DABCO/4-HO-TEMPO-Catalyzed Aerobic Oxidative Synthesis of 2-Substituted Quinazolines and 4*H*-3,1-Benzoxazines. *J. Org. Chem*. **2012**, *77*, 1136. (f) Hua, L.; Yao, Z.; Xu, F.; Shen, Q. Chemoselective reactions under solvent-free conditions: lanthanide-catalyzed syntheses of 2-amino-3,1-benzothiazines and 3,4-dihydroquinazoline-2-thiones. *RSC Adv*. **2014**, *4*, 3113. (g) Saunthwal, R. K.; Patel, M.; Kumar, S.; Verma, A. K. Cu(II)-catalyzed tandem synthesis of 2-imino[1,3]benzothiazines from 2-aminoaryl acrylates *via* thioamidation and concomitant chemoselective thia-Michael addition. *Tetrahedron Lett*. **2015**, *56*, 677.

(7) (a) Ghosh, H.; Yella, R.; Nath, J.; Patel. B. K. Desulfurization Mediated by Hypervalent Iodine(III): A Novel Strategy for the Construction of Heterocycles. *Eur. J. Org. Chem*. **2008**, 6189. (b) Yella, R.; Patel. B. K. One-Pot Synthesis of Five and Six Membered N, O, S-Heterocycles Using a Ditribromide Reagent. *J. Comb. Chem*. **2010**, *12*, 754. (c) Spitz, C.; Lohier, J.-F.; Santos, J. S. O.; Reboul, V.; Metzner, P. Fluoride Ion and Phosphines as Nucleophilic Catalysts: Synthesis of 1,4-Benzothiazepines from Cyclic Sulfenamides. *J. Org. Chem*. **2009**, *74*, 3936. (d) Maheswari, C. U.; Kumar, G. S.; Venkateshwar, M.; Kumar, R. A.; Kantam, M. L.; Reddy, K. R. Highly Efficient One-Pot Synthesis of 2-Substituted Quinazolines and 4*H*-Benzo[*d*][1,3]oxazines *via* Cross Dehydrogenative Coupling using Sodium Hypochlorite. *Adv. Synth. Catal*. **2010**, *352*, 341. (e) Qiu, G.; Hu, Y.; Ding, Q.;

Peng, Y.; Hu, X.; Wu, J. Synthesis of 4-methylene-4*H*-benzo[d][1,3]thiazines *via* a tandem reaction of 1-(2-alkynylphenyl)ketoximes with Lawesson's reagent. *Chem. Commun*. **2011**, *47*, 9708. (f) Murata, Y.; Matsumoto, N.; Miyata, M.; Kitamura, Y.; Kakusawa, N.; Matsumura, M.; Yasuike, S. One-pot reaction for the synthesis of *N*-substituted 2-aminobenzoxazoles using triphenylbismuth dichloride as cyclodesulfurization reagent. *J. Organomet. Chem*. **2018**, *859*, 18.

(8) (a) KamaI, A.; Sattur, P. K. Catalase-mediated cyclization: Synthesis of 3-allyl-4-imino substituted 2(1*H*)-quinazolinones and 1,3-benzoxazine-2(3*H*)-ones. *Tetrahedron Lett.* **1989**, *30*, 1133. (b) Bonne, D.; Dekhane, M.; Zhu, J. Exploiting the Dual Reactivity of *o*-Isocyanobenzamide: Three-Component Synthesis of 4-Imino-4*H*-3,1-benzoxazines. *Org. Lett*. **2005**, *7*, 5285. (c) Kiskan, B.; Koz, B.; Yagci, Y. Synthesis and Characterization of Fluid 1,3-Benzoxazine Monomers and Their Thermally Activated Curing. *J. Polym. Sci., Part A: Polym. Chem.* **2009**, *47*, 6955. (d) Ding, Q.; Cao, B.; Zong, Z.; Peng, Y. Silica Gel-Promoted Tandem Addition-Cyclization Reactions of 2-Alkynylbenzenamines with Isothiocyanates. *J. Comb. Chem*. **2010**, *12*, 370. (e) Sashida, H.; Kaname, M.; Minoura, M. Studies on chalcogen-containing heterocycles. Part 38: Regio- and stereoselective tandem additioneiodocyclization of 2-ethynylphenyl isothiocyanates with N- and O-nucleophiles affording 4-(iodoalkylidene)benzo[*d*][1,3]thiazines. *Tetrahedron* **2013**, *69*, 6478. (f) Zhang, Q.; Yang, P.; Deng, Y.; Zhang, C,; Zhu, R.; Gu, Y. Effect of phenol on the synthesis of benzoxazine. *RSC Adv*. **2015**, *5*, 103203. (g) Xie, T.; Xiao, Y.; Zhao, S.; Hu, X.-Q.; Xu, P.-F. Catalyst-Free Chemoselective Synthesis of 3,4-Dihydroquinazoline-2- thiones and 2-Imino[1,3]benzothiazines. *J. Org. Chem*. **2016**, *81*, 10499. (h) Jun, H.-G.; Kim, E.-M.; Yoon, H.-J.; Gong, Y.-D. Microwave-assisted Solid-phase Synthesis of *N*-substituted-2- aminobenzo[*d*][1,3] Thiazine Derivatives from a BOMBA Resin. *Bull. Korean Chem. Soc.* **2017**, *38*, 334. (i) Dong, J.-L.; Wei, P.-S.; Yu, L.-S.-H.; Xie, J.-W. Chemoselective Synthesis of Structurally Diverse 3,4- Dihydroquinazoline-2(1*H*)-thiones and 4*H*-Benzo[*d*][1,3]thiazines. *J. Org. Chem*. **2018**, *83*, 2219.

(9) Quinton, J.; Kolodych, S.; Chaumonet, M.; Bevilacqua, V.; Nevers, M.-C.; Volland, H.; Gabillet, S.; Thuéry, P.; Créminon, C.; Taran, F. Reaction Discovery by Using a Sandwich Immunoassay. *Angew. Chem., Int. Ed*. **2012**, *51*, 6144.

(10) Ogura, H.; Mineo, S.; Nakagawa, K. Studies on Heterocyclic Compounds. XXXIV. Synthesis of 2-Substituted Aminobenzoxazoles with Nickel Peroxide. *Chem. Pharm. Bull*. **1981**, *29*, 1518.

(11) (a) Janssens, F. E.; van Offenwert, T. T.; Stokbroekx, R. A.; Boar, B. R. Eur. Pat. Appl. EP 199400, **1986**. (b) Stokbroekx, R. A.; Luyckx, M. G. M.; Janssens, F. E. Eur. Pat. Appl. EP 184257, **1986**. (c) Qian, X. H.; Song, G. H.; Li, Z. B. Gangkai Shuomingshu, 1294126, **2001**.

(12) (a) Zhang, X.; Jia, X.; Wang, J.; Fan, X. An economically and environmentally sustainable synthesis of 2-aminobenzothiazoles and 2-aminobenzoxazoles promoted by water. *Green Chem*. **2011**, *13*, 413. (b) Zhang, Z.; Wang, F.-J.; Wu, H.-H.; Tan, Y.-J. Straightforward Synthesis of 2-Anilinobenzoxazoles and -benzothiazoles *via* Mechanochemical Ball-milling-promoted One-pot Reactions. *Chem. Lett*. **2015**, *44*, 440.

(13) Yoon, J. H.; Song, H.; Kim, S. W.; Han, G.; Choo, H.-Y. P. A Facile Synthesis of 2-Aminothiazolo[5,4-b]pyridines and 2-Aminobenzoxazoles *via* Cyclization of Thioureas. *Heterocycles* **2005**, *65*, 2729.

(14) Khatik, G.L.; Dube, N.; Pal, A.; Nair, V.A. Highly Efficient One-Pot Synthesis of 2- Aminobenzoxazoles Using Triflic Acid as a Cyclodesulfurizing Reagent. *Synth. Commun*. **2011**, *41*, 2631.

(15) Heinelt, U.; Schultheis, D.; Jäger, S.; Lindenmaier, M.; Pollex, A.; Beckmann, H. S.g. A convenient method for the synthesis of 2-amino substituted aza-heterocycles from *N,N'*-disubstituted thioureas using TsCl/NaOH. *Tetrahedron* **2004**, *60*, 9883.

(16) Tian, Z.; Plata, D. J.; Wittenberger, S. J.; Bhatia, A. V. A general synthesis of *N*-aryl- and *N*-alkyl-2-aminobenzoxazoles. *Tetrahedron Lett*. **2005**, *46*, 8341.

(17) Cee, V. J.; Downing, N. S. A one-pot method for the synthesis of 2-aminobenzimidazoles and related heterocycles. *Tetrahedron Lett*. **2006**, *47*, 3747.

(18) (a) Raghavendra, G. M.; Kumar, C. S. P.; Suresha, G. P.; Rangappa, K. S.; Mantelingu, K. T3P catalyzed one pot three-component synthesis of 2,3-disubstituted 3*H*-quinazolin-4-ones. *Chin. Chem. Lett*. **2015**, *26*, 963. (b) Milen, M.; Dancsó, A.; Földesi, T.; Slégel, P.; Volk, B. Propylphosphonic anhydride (T3P) mediated one-pot three-component synthesis of racemic dialkyl (2-substituted3-oxo-2,3-dihydro-1*H*-isoindol-1-yl)phosphonates. *Tetrahedron* **2016**, *72*, 5091. (c) Putta, V. P. R. K.; Gujjarappa, R.; Tyagi, U.; Pujar, P. P.; Malakar, C. C. A Metal- and Base-Free Domino Protocol for the Synthesis of 1,3-Benzoselenazines, 1,3-Benzothiazines and Related Scaffolds. *Org. Biomol. Chem.* **2019**, *17*, 2516 and references cited there in.

(19) (a) Kim, S.; Yi, K. Y. Di-2-Pyridyl Sulfite. A New Useful Reagent for the Preparation of *N*-Sulfinylamines, Nitriles, Isocyanides, and Carbodiimides under Mild Conditions. *Tetrahedron Lett*. **1986**, *27*, 1925. (b) Chen, C.-Y.; Wong, F. F.; Huang, J.-J.; Lin, S.-K.; Yeh, M.-Y. Desulfurization and transformation of isothiocyanates to cyanamides by using sodium bis(trimethylsilyl)amide. *Tetrahedron Lett*. **2008**, *49*, 6505. (c) Nath, J.; Patel, B. K.; Jamir, L.; Sinha, U. B.; Satyanarayana, K. V. V. V. A one-pot preparation of cyanamide from dithiocarbamate using molecular iodine. *Green Chem*. **2009**, *11*, 1503.

(20) (a) Khorana, H. G. The Chemistry of Carbodiimides. *Chem. Rev*. **1953**, *53*, 145. (b) Kurzer, F.; Douraghi-Zadeh, K. Advances in the Chemistry of Carbodiimides. *Chem. Rev*. **1967**, *67*, 107. (c) Omar, A.-M. M. E.; Habib, N. S.; Aboulwafa, O. M. The Cyclodesulfurization of Thio Compounds; XVI. Dicyclohexylcarbodiimide as an Efficient Cyclodesulfurizing Agent in the Synthesis of Heterocyclic Compounds from Various Thio Compounds. *Synthesis* **1974**, 864. (d) Williams, A.; Ibrahim, I. T. Carbodiimide Chemistry: Recent Advances. *Chem. Rev*. **1981**, *81*, 589. (e) Kim, S.; Yi, K. Y. 1,l'-ThiocarbonyldL2,2'-pyridone. A New Useful Reagent for Functional Group Conversions under Essentially Neutral Conditions. *J. Org. Chem*. **1986**, *51*, 2613. (f) Isobe, T.; Ishikawa, T. 2-Chloro-1,3-dimethylimidazolinium Chloride. 1. A Powerful Dehydrating Equivalent to DCC. *J. Org. Chem*. **1999**, *64*, 6984. (g) Ali, A. R.; Ghosh, H.; Patel, B. K. A greener synthetic protocol for the preparation of carbodiimide. *Tetrahedron Lett*. **2010**, *51*, 1019.

(21) Ueng, S.-H.; Yeh, S.-H.; Loh, H.; Chao, Y.-S. WO201739778A1, **2017-03-09**.

(22) Molina, P.; Arques, A.; Molina, A. A Novel and Efficient Synthesis of 4*H*-3,1-Benzoxazines by a Tandem Aza-Wittig/Heterocumulene-Mediated Annulation Strategy. *Synthesis* **1991**, 21.

(23) Shah, S. K.; Grant, S. K.; Maccoss, M.; Shankaran, K.; Qi, H.; Guthikonda, R. N. Substituted Heterocycles as Inhibitors of Nitric Oxide Synthase. WO1996014842A1, **1996-05-23**.

(24) Corbett, M. T.; Caille, S. A Bench-Stable Vilsmeier Reagent for in situ Alcohol Activation: Synthetic Application in the Synthesis of 2-Amino-2-Thiazolines. *Synlett* **2017**, *28*, 2845.

(25) Gonda, J.; Kristian, P. 2-Isothiocyanatobenzylpyridinium Bromidean Intermediate for the Synthesis of 2-Arylamino-4*H*-Benzo[*d*) [l,3)Thiazines. *Collect. Czech. Chem. Commun*. **1986**, *51*, 2810.

(26) Söederbaum, H. G; Widman, O. *Chem. Ber*. **1889**, *22*, 2939.